UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

School of Chemistry

The Synthesis of Polyfluorinated Carbohydrates

by

Clément Quentin Fontenelle

Thesis for the degree of Doctor of Philosophy

December 2014

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

Chemistry

Thesis for the degree of Doctor of Philosophy

THE SYNTHESIS OF POLYFLUORINATED CARBOHYDRATES

Clément Quentin Fontenelle

Carbohydrates are essential to many fundamental biological processes throughout Nature. Although generally specific for their cognate protein receptors, typical protein-carbohydrate affinities are only in the micromolar to millimolar range. Polyfluorination has emerged as an attractive strategy to enhance this affinity in order to develop carbohydrate-based inhibitors and therapeutics. This thesis describes three syntheses of 3,4-dideoxy-3,3,4,4-tetrafluoro-D-mannopyranose and D-glucopyranose.

Polyfluorination of carbohydrates has important consequences on the hydrogen bond properties of the adjacent alcohols and particularly, difluorination in the β-position of an alcohol group is expected to significantly reduce its hydrogen bond acceptor capacity. For these cases, the substitution of the alcohol group for the intrinsically more nucleophilic amino group is proposed in order to restore this hydrogen bond accepting capacity. Hence, the synthesis of 2-amino-2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-mannopyranose, D-glucopyranose, 4-amino-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-galactopyranose and D-glucopyranose as well as 3-amino-2,3-dideoxy-2,2-difluoro-D-galactopyranose is reported in this thesis.

In the course of this work, a novel diastereoselective Honda-Reformatsky addition reaction of ethyl bromodifluoroacetate to various α-chiral α-oxygenated *N-tert*-butanesulfinylimines is described to access to α,α-difluoro-β-amino acids and 2,2-difluoro-3-amino carbohydrate analogues. In addition, an extension of the Konno procedure to introduce a tetrafluoroalkylidene moiety was developed.

Table of Contents

List of tables

List of figures

DECLARATION OF AUTHORSHIP

I, Clément Quentin Fontenelle

declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

The Synthesis of Polyfluorinated Carbohydrates

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. 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;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. 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;
5. I have acknowledged all main sources of help;
6. 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;
7. Parts of this work have been published as:

Fontenelle, C. Q.; Conroy, M.; Light, M.; Poisson, T.; Pannecoucke, X.; Linclau, B. *J. Org. Chem.* **2014**, *79*, 4186-4195.
Fontenelle, C. Q.; Tizzard, G. J.; Linclau, B. *J. Fluorine Chem.* **2014**.
http://dx.doi.org/10.1016/j.jfluchem.2014.07.015

Signed:.....

Date:.....

Acknowledgements

First of all, I would like to thank Dr. Bruno Linclau for giving me the opportunity to do my PhD within his group during the last four years. His patience, support and ideas were a valuable help throughout the course of these studies. I also thank Prof. Peter Roach for the feedback he gave to me.

I want to thank all the group members, past and present for their help and for bringing generally a good atmosphere in the lab. As I have stayed four years in this lab, the list is long but I will bother making it:

Konrad, Kylie, Nathan and Samuel Golten for helping me starting in the beginning, Carole and Lewis who started the same year and with whom I went through the important milestones, Olivier for bringing his Belgian craziness, Craig for tuning my ear to the Glaswegian accent, Leona for being herself, Florent Larnaud for making this lab more French at times, Florent Péron for introducing "la Minimale" in the lab, Julien aka King Julian, my fumehood neighbour, for all the laugh and all his "good" ideas (Chimie Passion , the *a cappella* album, the naphthyl oxidation…), Cindy, Zara, Zhong, Krunal and Joe for always being cheerful, Guillaume for being Jean-Paul or Barnabé, Gemma for tuning my ear to the Yorkshire accent (and those cat videos), Stéphanie for taking care of the lab and being very supportive and Lucas with whom I have shared my fumehood only briefly unfortunately. I thank all the English for coping with the French Colonialism that occurred in the lab over the years.

I do not forget Emma, Jason, Niall, Sam Watkin, Angus, Frank who made me feel welcome from the beginning. I generally thank everyone in the Harrowven, Brown and Whitby labs for the good moments I had with them and the chemicals I may have borrowed, as well as the people on the 4th and 5th floor that I have met, especially Ana and Agnes.

I thank all the staff members without whom this PhD would have been impossible, Neil for the NMR, John and Julie for the Mass Spec, Mark and Graham for the X-ray, Karl, Keith and Mark for running the stores and waste disposal, the glassblowing workshop and Sally for always having an answer.

I am grateful to the European Union for providing the financial support through the INTERREG IVa Channel Programme, IS:CE-Chem, project 4061 and AI-CHEM. Thanks must go to Karen and Robin for coordinating this project here at the University of Southampton.

Special mentions go to all my housemates who happened to be my colleagues most of the time. Mara, Aurélien, Boris, both Florent, Martina, Alexandre and Ayham, it's been a pleasure for me, thanks for making 29 Castle Street and 82 Welbeck Avenue so memorable.

I would also like to thank the Southampton Rugby Football Club for the warm welcome and for allowing me to meet the phenomenon Ben Ardaillon as well as all the friends I have henceforth. Rugby has been a great stress release much needed at times.

I must thank my family for the financial and genuine support that have brought me to this level of studies. Finally, I dedicate this thesis to my dad who passed on me his thirst of knowledge and culture.

Abbreviations

BHT	Butylated Hydroxytoluene
Boc	*tert*-Butyloxycarbonyl
Cbz	Carboxybenzyl
DDQ	Dichlorodicyanoquinone
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
EBDFA	Ethyl Bromodifluoroacetate
EVE	Ethyl Vinyl Ether
FDG	Fluoro Deoxy Glucose
FT-IR	Fourier Transform Infrared
Glc	Glucose
GlcNAc	2-*N*-Acetylglucosamine
GOase	Galactose Oxidase
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
k_{cat}	Turnover number (s^{-1})
K_d	Dissociation constant (M)
K_f	Formation constant ($dm^3.mol^{-1}$)
K_i	Inhibition constant (M)
K_M	Michaelis constant (M)
Man	Mannose
ManNAc	2-*N*-Acetylmannosamine
Nap	Naphthylidene
NAP	Naphthylmethyl
NMR	Nuclear Magnetic Resonance
pK_{AHY}	Hydrogen-bond acidity
pK_{HB}[22]	Hydrogen-bond basicity
pK_{BHX}[52]	Hydrogen-bond basicity (same as pK_{HB}, renamed later)
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
PTSA	*p*-Toluenesulphonic acid
RDA	Retro Diels-Alder
R*f*	Retention factor
SET	Single Electron Transfer
STD	Saturation Transfer Difference
TBAF	Tetrabutylammonium Fluoride
TBAI	Tetrabutylammonium Iodide
TBDMS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
UDP	Uridine Diphosphate
UGM	UDP-galactose mutase

Chapter 1: Introduction

1.1 The introduction of fluorine in organic compounds

1.1.1 Properties of fluorinated compounds

According to the Pauling scale fluorine is the most electronegative element before oxygen, chlorine and nitrogen.[1] This results in the three non-bonding lone pairs being strongly attracted to the nucleus resulting in one of the smallest Van der Waals radii of 1.47 Å, and a very poor polarisability.[2] In addition, the electronegativity of fluorine confers a high level of polarisation to the C—F bond, which gives it a strong ionic character, leading to a short length and the greatest (single) bond strength to carbon. The strongly ionic C—F bond can even influence the adjacent bonds, strengthening C—C single bonds while weakening C=C bonds in allylic systems.[3]

The ionic C–F bond also has an effect on molecular conformation. Stabilising polar interactions with a formal positive charge, such as in various β-fluorinated ammonium (and oxonium) species, leads to a preferred conformation in which the fluorine is close to the charged atom, resulting in 5.4 to 7.2 kcal.mol^{-1} more stable structures.[4] Although weaker, similar interactions were reported in the case of tetraalkyl ammonium[5] and pyridinium[6] species suggesting that the stabilisation occurs through charge-dipole C—F···X^{+} contacts rather than through H-bonding. The strong C—F dipole also tends to interact with other dipoles. For example, in α-fluoro carbonyl compounds, especially amides or esters, the C—F bond prefers to be *anti*-planar to the carbonyl group so that the dipoles point in opposite directions. These dipole-dipole interactions can be energetically as strong as the charge-dipole ones[4]

Fluorination of bioactive compounds can introduce many more beneficial effects such as improving absorption and resistance to metabolism, which generally leads to a greater bioavailability. It has also given rise to mechanism based inhibitors and allowed the development of a broad range of new tracers for Positron Emission Tomography as its ^{18}F derivative.[7] In addition, fluorine introduction can influence not only the lipophilicity of a molecule but also the pKa and the hydrogen bonding properties of adjacent functional groups. These latter properties will be discussed later (see **1.2.2**).

Given these interesting properties allow researchers to tune the biopotency or bioavailability of target molecules, it is not surprising that approximately 30-40% of agrochemicals and 25%

of pharmaceuticals on the market possess at least one fluorine atom.[8,9] Moreover, in 2008, a third of the top 30 best-selling pharmaceutical products in the US were at least monofluorinated.[10]

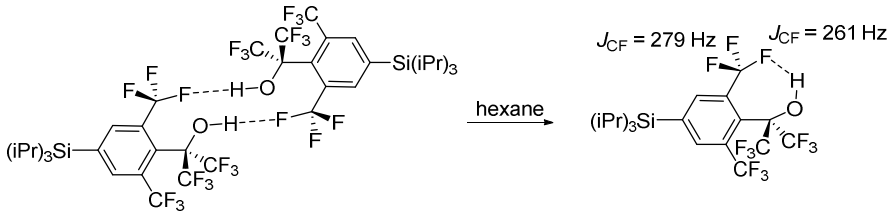
1.1.2 Fluorine as a Hydrogen Bond Acceptor

A recent IUPAC definition of the hydrogen bond is as follows: "**The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation**".[11,12] Typical criteria include that for a hydrogen bond X—H···Y—Z, X and H are covalently bonded and the increase in electronegativity of X results in a greater H···Y bond strength. The X—H bond length increases upon hydrogen bond formation and strong hydrogen bonds are therefore usually characterised by a long X—H distance, a short H···Y distance and an X—H···Y angle close to 180°. These physical variations generally result in an observable red shift in the infrared X—H stretching frequency and a pronounced X–H proton deshielding.

The capability of organofluorine to act as an H-bond acceptor has been, and still is, a source of debate among the scientific community. Although fluorine displays favourable characteristics (high electronegativity and three lone pairs), it is evident that the C—F bond is only a weak H-bond acceptor. If the fluorine in a C—F bond could indeed form short intra or intermolecular contacts with the hydrogen of an H—X group (X = N, O), the interactions were much weaker than with other common heteroatoms such as nitrogen or oxygen. This was attributed to the low proton affinity and polarisability of the fluorine.[13] Nonetheless, in the solid state such interactions could be examined using X-ray diffraction and as the Cambridge Structural Database revealed, 0.6% of all CF groups were found involved as H-bond acceptors of X—H.[14] This was usually observed together with a lack of competing heteroatoms as otherwise, X—H···X—H H-bond formation was favoured. Interestingly, this proportion increased to 10% when searching the Protein Data Bank,[15] perhaps revealing already the underestimated importance of X—H···F—C H-bonds. It should be noted that whether these contacts are real H-bonds or rather dipolar or Van der Waals interactions is often disputed. However, a recent review from Schneider[16] has shown that the study of these kind of weak interactions in the solid state was not the most appropriate. These are probably best assigned in the gas state, by computational methods, or in the liquid state, by means of IR and NMR spectroscopy. In fact, the weak interactions are so numerous in a crystal lattice, even involving the more polarisable C—H bond, that it becomes difficult to ensure that a C—F···H—X contact was indeed one of the

determinant interaction leading to a certain spatial arrangement. In addition, some weak intermolecular interactions occurring in the solid state may not always be the predominant ones in solution.

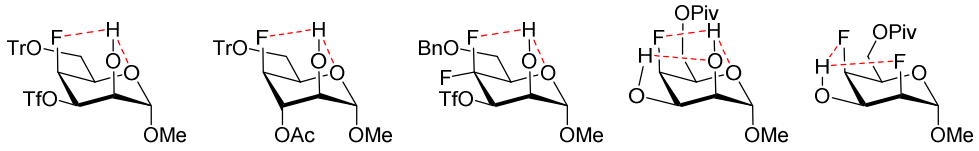
Scheme 1.1 Intermolecular (solid state) *vs* intramolecular (hexane solution) hydrogen bonds involving fluorine[17]



1.1 solid state ν(OH) = 3582 cm^{-1} **1.1** hexane solution ν(OH) = 3616 cm^{-1}

For instance, **Scheme 1.1** shows that once dissolved in hexane, **1.1** exhibits an intramolecular C—F···H—O H-bond rather than the intermolecular ones observed in the solid state. This is also the first example of a compound with a C—F···H—O H-bond for which the changes in conformation were experimentally observed by IR and NMR.

More recently, Vasella, Bernet and co-workers found evidence of divalent or trivalent (bifurcated) intramolecular C—F···H—O H-bonds among fluorinated *myo*-inositols[18,19] and levoglucosans[20] through analysis of both $^{1h}J_{OH,F}$ and $^{3}J_{H\text{-}OH}$. In 2013, Bernet and Gouverneur extended these conclusions to the less strained fluorinated carbohydrates shown in **Figure 1.1**.[21]



	1.2	**1.3**	**1.4**	**1.5**	**1.6**
$^{1h}J_{2\text{-}OH,F}$	10.5	5.7	4.2	8.1	<1.5
$^{3}J_{2,OH}$	11.6	10.5	10.2	12.0	$^{3}J_{3,OH}$ = 12.1

Figure 1.1 Observed C—F···H—O H-bonds in fluorinated carbohydrates in $CDCl_3$[21]

The proton NMR spectrum of the compounds **1.2**-**1.4** in an apolar solvent ($CDCl_3$) revealed H-bonding between 2-OH and 4-F as evidenced by the scalar coupling $^{1h}J_{2\text{-}OH,F}$ (4.2 to 10.5 Hz). Additionally, the high $^{3}J_{H,OH}$ values (11.6, 12.0 Hz) suggested a dihedral angle $\theta_{H\text{-}C2\text{-}O\text{-}H}$ around 180° meaning that the alcohol proton was positioned in between 4-F and the ring oxygen. As

observed previously for *myo*-inositols and levoglucosans, 2-OH was involved in a trivalent bifurcated H-bond with 4-F and the ring oxygen, pointing towards which ever proved to be the best acceptor. For example, if the presence of an equatorial electron-withdrawing group on the vicinal carbon had a negligible influence (compare the triflate in **1.2** with the 3-OH in **1.5**), the strength of the H-bond to the fluorine was considerably reduced when such a group was in axial position as shown by the decreased $^{1h}J_{2\text{-}OH,F}$ of 5.7 Hz (**1.3**). This was explained by a reduction of electron density at the fluorine atom, reducing its hydrogen bond accepting capacity, causing the 2-OH to move towards the better acceptor ring oxygen. According to the authors, the small scalar coupling observed for **1.4** suggested that a CF_2 is a poorer acceptor than a CHF, although we believe a change in magnitude of the coupling constants caused by the addition of a second electronegative fluorine atom, changing other parameters in the molecule, cannot be excluded. It should be noted that these C—F···H—O H-bonds were gradually replaced by intermolecular H-bonds to the solvent when increasing its polarity ($CDCl_3$, CD_3CN, THF-*d*8, acetone-*d*6 and DMSO-*d*6). Remarkably, some of the bifurcated H-bonds observed were only partially disrupted in solvents as polar as acetone. Similarly, the bifurcated H-bond observed for **1.6** (3-OH to 2-F and 4-F) persisted to about 35-40% even in DMSO.

Perhaps more importantly, the C—F bond was shown to form intermolecular H-bonds with an external donor in CCl_4. In 1999, Laurence *et al.* developed a general H-bond basicity scale for acceptors.[22] The formation of the complex between an acceptor and a reference H-bond donor 4-fluorophenol could be observed by FT-IR as the donor ν_{OH} band shifted upon addition of the acceptor and subsequent complex formation. The concentrations of complex, free donor and free acceptor could be deduced from the IR spectrum leading to the formation constants K_f for several halogenoalkanes at 298 K (K_f ($dm^3.mol^{-1}$) = [complex]/[B][4-FC_6H_4OH]). From these constants, a logarithmic scale of hydrogen-bond basicity, $pK_{HB} = \log K_f$, was defined to measure the relative hydrogen-bond acceptor strength of the halogens. Though much weaker than amines, alcohols or ethers, the fluoroalkanes proved the best acceptors among the halogenoalkanes with a maximum pK_{HB} of 0.26 for the electron-rich fluorine of 1-fluoroadamantane. As fluoroalkanes are better H-bond bases than the chloro, bromo and iodo counterparts, the low polarisability of the C—F bond may be compensated by the high electronegativity of fluorine.

More recently, Dalvit, Vulpetti *et al.* compared the hydrogen bond acceting capacity of mono-, di- and trifluoromethylbenzene to the well-documented acceptor acetophenone.[23] The association constants were deduced in a similar manner as above but this time by monitoring

the NMR chemical shifts of either the fluorine or the alcohol proton of the reference donor *p*-fluorophenol which both vary upon complexation. The authors concluded that the fluorine in RCH_2F is a better H-bond acceptor than those in $RCHF_2$ and RCF_3. However, the free energy associated with the formation of the complex with fluoromethylbenzene was disfavoured by 1.76 $kcal.mol^{-1}$ compared to that associated with the formation of the complex with acetophenone, suggesting that intermolecular C—F···H—X hydrogen bonds would only be possible in the absence of competing acceptors. These results were further corroborated by a third NMR technique and computational calculations.

Thus, although previous considerations, mainly deduced from analyses in the solid state, had shown that fluorine is hardly ever an H-bond acceptor, more recent studies in solution clearly account for its implication in intramolecular as well as intermolecular H-bonds in apolar solvents. If these interactions become negligible in polar solvents such as DMSO (and in no doubt water), they may well become significant in protein pockets where competing water molecules can be absent, especially if the fluorine is predisposed towards an H-bond donor. Nevertheless, it is clear that organofluorine is only a weak to very weak hydrogen bond acceptor.

1.2 Fluorinated Carbohydrates

1.2.1 Carbohydrates

Carbohydrates are the most abundant natural products on Earth. They are the building blocks of glycans, a generic term referring to monosaccharides, oligosaccharides, polysaccharides and their conjugates such as glycolipids or glycoproteins. Although the structure determination of most carbohydrates was achieved by Emil Hermann Fisher and others around the end of the 19th century, the recognition of the importance of carbohydrates and particularly their glycoconjugates, has long been undermined by the at the time preferred study for DNA and proteins. However, for the last 40 years, their prominence has been continuously heightened and has led to a new field of research, Glycobiology, coined by Dwek *et al.* in 1988.[24] In all their different forms, glycans are now known to be involved in a multitude of vital biological processes related to development, hormonal function, cell proliferation and organisation, host-pathogen interactions, and inflammatory and immune responses.[25,26] Half of all human proteins are glycosylated and the diverse glycones are deemed crucial for the proteins' stability, solubility and activity. These various involvements have led to the discovery and

development of glycosylated compounds as potent antitumor and antifungal agents, antibiotics, antiparasitics and antivirals.

The main mode of binding of carbohydrates is *via* hydrogen bonds to polar residues in the protein such as the carbonyl or NH groups of a backbone amide, or a bidentate hydrogen-bonding side chain such as a guanidinium moiety. Sometimes, the presence of a metal (alkali or alkaline earth) is required while ionic interactions are invoked in the case of aminosugars.[27] As they are highly directional (stronger H-bonds are linear) and given that they engage stereochemically defined hydroxyl groups, hydrogen bonds generally account for the high selectivity of a glycan for its receptor.[28] Conversely, hydrophobic interactions play a major role in the affinity of a ligand for its receptor. This is mainly thought to be due to the desolvation of high energy water molecules by hydrophobic parts of the ligand. Due to unfavoured contacts with non polar or polyamphiphilic surfaces, these water molecules are perturbed and their release in the bulk results in a beneficial decrease of the free energy of binding;[29] these hydrophobic interactions are also promoted through C—H···π contacts. They are even thought to bring additional specificity as these hydrophobic domains have to be accommodated by well disposed non polar surfaces or aromatic fragments in the protein receptor.[30] Although carbohydrates are very hydrophilic with many hydroxyl groups, they display hydrophobic patches above and/or below the ring as shown in **Figure 1.2**.

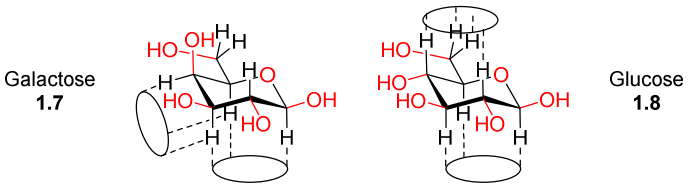


Figure 1.2: Representation of hydrophobic patches of galactose and glucose

As illustrated, the axial 4-OH of galactose **1.7** leads to a much more hydrophobic bottom face than for glucose **1.8**, which tends to exhibit a hydrophobic domain on each face of the ring. This is clearly demonstrated by the crystal structure of the *E. coli* galactose transport protein (**Figure 1.3**) where glucose is sandwiched between aromatic tryptophan and phenylalanine residues.[31]

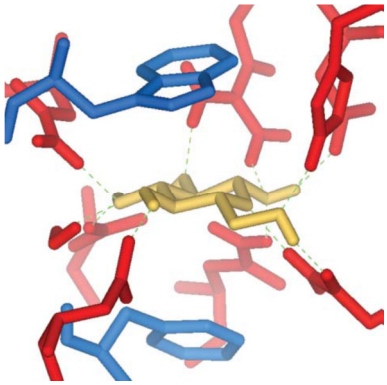


Figure 1.3: Binding site of the *E. coli* galactose chemoreceptor protein, with glucose substrate (yellow).[31] Aromatic tryptophan and phenylalanine residues are shown in blue, polar residues in red.

Nonetheless, the lack of hydrophobic surfaces and the tough competition of carbohydrates with the aqueous solvent usually results in affinities for their protein receptors mostly within the millimolar range, with some exceptions in the micromolar range.[27] This is put into perspective by the fact that Nature exploits such protein-carbohydrate interactions for a range of communication events, with the transient nature of the interactions essential to ensure the operation of a living organism. Inversely, in the interest of developing therapeutics or probes to determine the biosynthesis and the biological roles of glycans, the synthesis of analogues or inhibitors with improved affinity and drug-like properties is required. Indeed, many natural saccharides are rapidly degraded by glycosidases and then excreted through renal filtration. For years, our group has grown a strong interest in polyfluorinated carbohydrates as potentially more stable and bioavailable analogues. With regard to the concept of "polar hydrophobicity", such structures could also exhibit greater affinities for receptors and lead to the development of inhibitors and potentially therapeutics.

1.2.2 Fluorinated Carbohydrate Analogues as Probes to Investigate the Polar Hydrophobicity Effect

1.2.2.1 Hydrophobicity

As discussed above, the desolvation of high energy water molecules from non polar surfaces that occurs when hydrophobic domains come into contact is energetically favourable and is the main driving force for carbohydrate binding to proteins. In 1995 and later in 2011, Whitesides *et al.* demonstrated that ligands with perfluoroalkyl chains showed greater affinities for bovine and human carbonic anhydrase II than their corresponding perproteoalkyl counterparts.[32,33] They found that the intrinsic hydrophobicity (per unit area) appeared almost

identical for both categories of compounds and that an analogous hydrophobic effect (desolvation) was observed for a comparable solvent accessible surface area. However, for the same number of carbons, this surface area is larger for perfluoroalkyl chains than for alkyl ones; this leads to a greater desolvation upon binding resulting in the enhanced affinities observed for the fluorinated analogues.

1.2.2.2 Multipolar interactions

It has been discussed previously that fluorine can behave as a weak H-bond acceptor (cf. **1.1.2**). Perhaps more importantly, in 2003, when Diederich *et al.* studied the activities of thrombin inhibitors by a phenyl fluorine scan,[34] he found that the 4-F analogue **1.10** proved fivefold more potent than the parent compound **1.9**, while regioisomers **1.11** and **1.12** showed similar affinities (**Figure 1.4**).

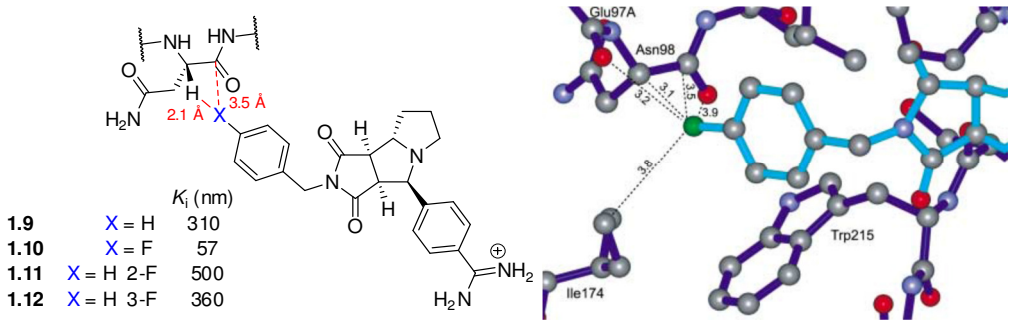


Figure 1.4: Activities of fluorinated thrombin inhibitors and crystal structure of **1.10** in the thrombin D pocket showing the binding mode[34]

The introduction of the fluorine decreases the polarisability of the aromatic ring which makes it more hydrophobic and should result in better affinities. However, **1.11** (2-F) and **1.12** (3-F) must suffer from repulsive interactions with some protein residues leading to larger inhibition constants than **1.9**. Conversely, **1.10** (4-F) is the only analogue that can accommodate attractive $^{\delta+}C—F^{\delta-}\cdots{}^{\delta+}H—C_{\alpha}{}^{\delta-}$ and $^{\delta+}C—F^{\delta-}\cdots{}^{\delta+}C{=}O^{\delta-}$ dipole-dipole interactions with the backbone amide of Asn98 (**Figure 1.4**) that could explain the enhanced activity. Study of both the CSD and PDB actually revealed that many fluorinated structures or ligands presented C—F···H—N,

C—F···C=O and C—F···H—C_{α} interactions that helped stabilise the complexes.[13] It is worth noting that when classifying the fluorinated ligands found in the PDB according to their ^{19}F NMR chemical shifts, Vulpetti *et al.* noticed an empirical correlation between the chemical shift and the type of fluorine-protein interactions observed in the X-ray structures. According

to the "rule of shielding", while shielded electron-rich fluorines (e.g. primary or secondary alkyl fluorines) tend to form close contacts with hydrogen bond donors (OH, NH), and deshielded electron-poor fluorines (e.g. OCF_3, SCF_3) will prefer hydrophobic and F···C=O interactions.[35,36] This correlation could be considered in the design of ligands with incorporation of judicious fluorinated moieties depending on the nature of the residues found in protein cavities.

The strength of these interactions relies on the fact that they are negligible in the aqueous bulk and appear only upon positioning of the ligand in the receptor. Thus, however weak they may be, these interactions overall result in a 'real' gain in association energy, not to mention that they remain to a certain extent directional and are therefore expected to promote specificity.

1.2.2.3 Polar Hydrophobicity and Pioneering Studies

The combination of perfluoroalkyl hydrophobicity and possible attractive charge-dipole and dipole-dipole interactions or even hydrogen bonds with various protein residues has been termed "Polar Hydrophobicity" by DiMagno in 1998 as an attractive strategy for increasing the affinity of carbohydrates to their physiological receptor.[37,38]

Within hindsight, one of the first examples consistent with this concept was published in 1986 by Withers *et al.*, who analysed the inhibition of certain enzymes by various mono and difluorinated monosaccharides. Structures and inhibition constants for glycogen phosphorylase are shown below in **Figure 1.5**.[39,40]

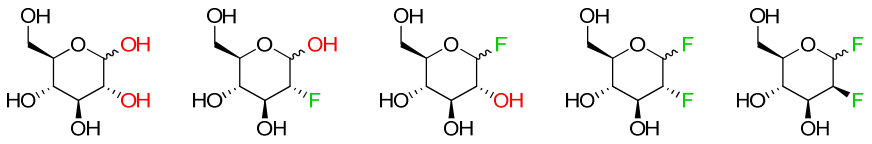


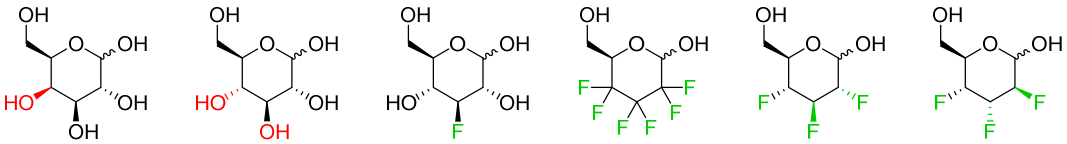
Figure 1.5: Inhibitors of glycogen phosphorylase (**1.8**-**1.15**)[39] and β-glycosidases (**β1.15** and **β1.16**)[40]
K_i values are inhibition constants for glycogen phosphorylase

D-Glucose anomeric mixture **1.8** averaged a K_i value of 2 mM and deoxofluorination at C-2 (**1.13**) had no major effect with 1.9 mM, although it did show that the enzyme could readily accommodate the fluorine at C-2. Substitution for fluorine at the anomeric position proved similar as no significant energetic consequence could be observed with K_is of 3.8 mM for **β1.14**

and 0.6 mM for **α1.14**. Vicinal difluorination proved more remarkable as increased affinities (lower K_i) were obtained for both anomers, leading to a 1.9-fold decrease for **β1.15** and a fivefold for **α1.15** and therefore showing the fluorines' synergetic effect. Although not discussed at the time by the authors, a reason may be that the dual substitution resulted in the apparition of a larger hydrophobic domain that promoted binding. Both C—F bonds were probably involved in some attractive interactions as the 1-deoxy, 2-deoxy and 1,2-dideoxy-D-glucose all exhibited lower affinities (not shown) while being more hydrophobic too. Additionally, the enzyme was able to recognise the stereogenicity of the fluorinated substrate as the epimer **1.16** proved much weaker.

In later work by the same group, **β1.15** and **β1.16** were also found to be potent inhibitors of β-glucosidase and β-mannosidase respectively in brain, spleen, liver and kidney tissues.[40] This indicates that these compounds were able to pass through the different membranes in the body and notably, the blood-brain barrier, to reach the target organs without substantial degradation.

The first example of a heavily fluorinated carbohydrate was published to exemplify the concept of polar hydrophobicity. DiMagno's group synthesised hexafluorohexopyranose **1.18** and studied its transport across the erythrocyte membrane by the glucose transporter protein Glut1.[37] Previously, Riley had established by an optical method that D-glucose **1.8** and 3-fluoro-3-deoxy-D-glucose **1.17** (3FDG) binds similarly to Glut1 resulting in comparable transport kinetics across the red blood cells membrane (**Figure 1.6**).[41] Later investigations succeeded in measuring the different transport of both 3FDG anomers by means of ^{19}F NMR which allows the distinction of intracellular and extracellular resonances for both anomers.[42,43] Using the same technique, London *et al.* extended the results to 2FDG **1.13**, which was transported at the same rate as 3FDG while the rates for 4FDG and 6FDG were roughly halved (not shown).[44]



1.7 ≈0.1 | **1.8** 1 | **1.17**[41] ≈1 | **1.18**[37] ≈10 | **1.19**[45] ≈0.7 | **1.20**[45] ≈0.3

Figure 1.6: Relative transport rates across the erythrocytes membrane[37,41,45]

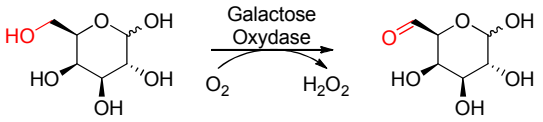
When DiMagno repeated the experiment with hexafluorosugar **1.18**, he found that it was transported approximately ten times faster than 3FDG and by inference, D-glucose. Several control experiments accounted for the fact that **1.18** was most likely crossing the membrane through interaction with the protein transporter and not just by increased diffusion due to higher lipophilicity. An experiment conducted at 25 °C instead of 37 °C saw the complete interruption of the transport where a diffusion mechanism would have been reduced by only 4% in response to the temperature decrease. Also, addition of D-glucose or phroetin, a known inhibitor of glucose efflux, both resulted in an impaired transfer. This suggests that **1.18** benefited from an enhanced binding to Glut1 despite the complete loss of stereochemistry at C-2, C-3 and C-4. It is quite remarkable as the epimer D-galactose **1.7** was transported ten times slower than glucose, showing the importance of the stereochemistry. Later on, O'Hagan *et al.* synthesised the trifluorinated hexoses **1.19** and **1.20**, first of which respected the glucose stereochemistry while the second had two stereocenters inverted.[45] Although the glucose stereochemical information was preserved in **1.19**, the relative rate of transport was only 70% and 21% of that of the natural ligand **1.8** for the α and β anomer respectively. The α anomer was transported faster for all the analysed fluorinated carbohydrate analogues but this was the greatest difference ever observed. This suggests that the protein was able to recognise the stereochemistry at the anomeric centre despite the various substitutions for fluorine. The altrose analogue **1.20** was found to cross the membrane at around 30% of the rate of **1.8**, implying that the protein Glut1 could distinguish the different stereogenicity associated with the C—F bonds.

However, it should be appreciated that the erythrocyte membrane experiments do not *prove* the existence of a polar hydrophobic effect, given the unclear relationship between transport rate and actual binding affinity with the transporter protein.

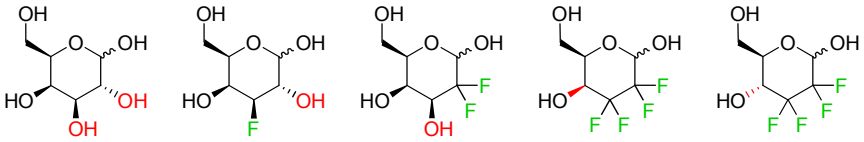
1.2.2.4 Kinetic and binding data of tetrafluorinated carbohydrate derivatives

Our group has developed an interest for various tetrafluorinated carbohydrates which include a polar hydrophobic CF_2CF_2 motif to improve the sugar affinity while retaining a stereochemically defined hydrogen bond donating/accepting hydroxyl group to maintain a certain level of specificity.[46-48] *Galacto* configured mono, di and tetrafluorinated **1.22**–**1.24** as well as the epimer **1.25** were tested for oxidation of the primary 6-OH group by the enzyme galactose oxidase (GOase) (**Scheme 1.2**).[49]

Scheme 1.2: Oxidation of D-galactose and fluorinated analogues by wild type galactose oxidase[49]



1.7 **1.21**

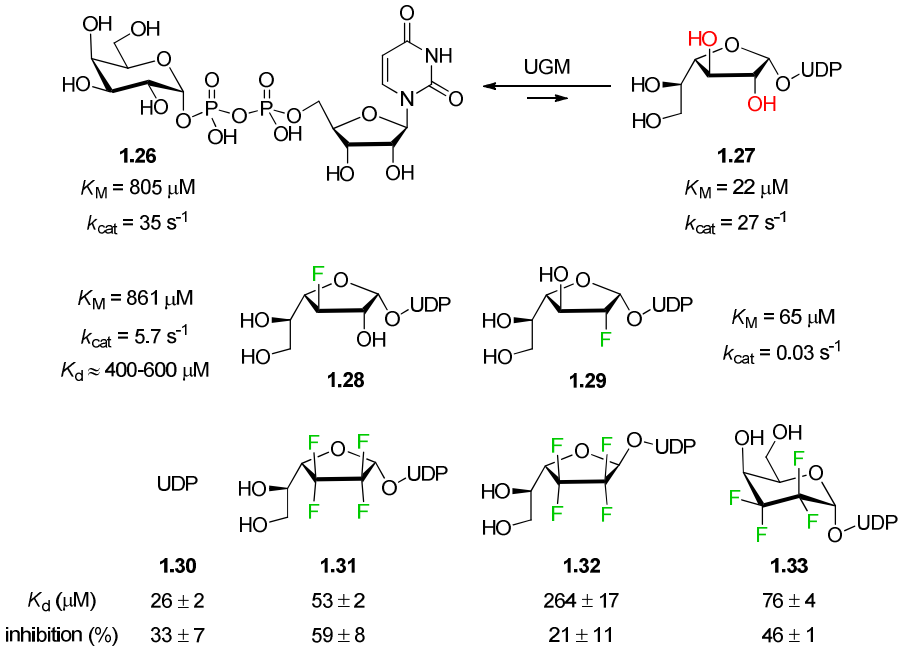


	1.7	**1.22**	**1.23**	**1.24**	**1.25**
K_M (M)	0.05	0.03	0.06	0.44	–
k_{cat} (s^{-1})	362	79	107	29	–

Although the k_{cat} values were slightly reduced, **1.22** and **1.23** were found to be good substrates for the enzyme, with an even lower K_M for **1.22** compared to the parent compound. Given these satisfactory results for analogues fluorinated at C-2 or C-3, similar or better results could have been expected for the tetrafluoro analogue **1.24** but the latter exhibited a ninefold higher K_M for a 12.5-fold decrease in k_{cat}. However, it is noteworthy that despite the introduction of four fluorines, **1.24** was indeed recognised by GOase and oxidised with a low but significant activity. In fact, this work represented the first reported example of an enzymatic biotransformation of a heavily fluorinated carbohydrate. Interestingly, the *gluco* configured analogue **1.25** was rejected by GOase meaning that the tetrafluoroethylene moiety did not reflect on the discrimination ability of the enzyme concerning the 4-OH orientation (parent D-Glc is also not turned over, not shown). The loss in binding and activity was attributed to the fluorines' strong electronegative effect that depletes the oxygen electron density and impairs its ability to accept hydrogen bonds, thereby hampering a crucial interaction with a guanidinium residue.

Motivated by the aforementioned results, our group pursued the synthesis and assay of novel carbohydrate mimetics and described the first enzyme inhibitor based on a heavily fluorinated carbohydrate. Both UDP-F_4-Gal*f* (**1.31**) and UDP-F_4-Gal*p* (**1.33**) proved to inhibit UDP-galactopyranose mutase (UGM), a crucial enzyme for the synthesis of the mycobacterial cell wall. Its inhibition prevents the isomerisation of UDP-galactopyranose (UDP-Gal*p*) to UDP-galactofuranose (UDP-Gal*f*), which is essential to mycobacterial proliferation (**Scheme 1.3**). Such inhibitors are of great therapeutic interest against pathogens such as *Mycobacterium tuberculosis*, though in the context of our research this enzyme was regarded as a model system.[50]

Scheme 1.3: Role of UGM, monofluorinated substrates and tetrafluorinated inhibitors[50]



The pyranose form **1.26** has a much higher K_M than the furanose form **1.27** for a similar k_{cat}. Despite the monosubstitution for fluorine at C-2 or C-3, **1.28** and **1.29** remained substrates for UGM and were indeed isomerised to their respective pyranose form (not shown). The fortyfold increase of K_M for **1.28** compared to the threefold increase for **1.29** suggested that either the 3-OH is implicated in a strong interaction with the enzyme or the fluorine led to unfavourable repulsions. The considerably lower k_{cat} for **1.29** agreed with a cationic transition state that would be disfavoured by the electron withdrawing fluorine. For analogous reasons, and exacerbated by the presence of four fluorines, neither **1.31** nor **1.33** were substrates for the enzyme under reducing conditions, even at a very high enzyme concentration. Their dissociation constants were compared to the UDP moiety alone, which is a well-known inhibitor of UGM. UDP proved the most affine ligand followed by **1.31** and **1.33** within the same order of magnitude. Interestingly, **1.32**, which displayed the wrong stereochemistry at the anomeric centre, exhibited a tenfold higher K_d than UDP. This indicated that the binding process is strongly dependent on the anomeric configuration, even with tetrafluorinated sugars, suggesting these bind the same pocket as the natural substrate. The capacity of compounds **1.31**-**1.33** to inhibit the isomerisation of **1.27** was then evaluated and **1.31** and **1.33** were found to be significantly better inhibitors than UDP. Analysis of the **1.31**-UGM binding by STD ^{1}H NMR experiments showed that the parent substrate **1.27** and **1.31** have a similar binding mode for the three different units, galactose, ribose and uracil. A stronger

response was observed for the F_4-Gal*f* moiety of **1.31** than for the unfluorinated Gal*f* of **1.27**, which is supportive of a greater importance of F_4-Gal*f* in the binding event to UGM. Finally, STD competition experiments further confirmed that **1.31** clearly exhibits an enhanced affinity for UGM compared to both UDP and natural **1.27**, yielding an estimated K_d of 5-10 µM.

These examples show the potential of the concept of increasing the polar hydrophobicity of a saccharide as a strategy to enhance its affinity for a receptor, and a promise to potential therapeutics. However, the introduction of a polyfluorinated moiety has consequences on the properties of adjacent functional groups such as alcohols or amines. A strong variation of the hydrogen bond donating or accepting capacity as well as the p*K*a is expected and a good understanding of these changes is necessary in order to design potent carbohydrate mimetics.

1.3 Influence of Fluorination on Adjacent Functional Groups

1.3.1 Hydrogen bond donating capacity

The introduction of one or several strongly electronegative fluorine atoms is expected to modify the H-bond properties of an adjacent functional group such as an alcohol. The H-bond donating capacity is also termed H-bond acidity. By inference, many scientists made a correlation with the Brønsted acidity of the FG. The p*K*a of alcohols decreases upon fluorination, for instance, the p*K*a drops 3.5 units from 15.9 for ethanol **1.47** to 12.4 for 2,2,2-trifluoroethanol **1.48** (**1.3.2**, **Table 1.1**) and in fact, **1.48** is a better H-bond donor than **1.47**. Due to the strong inductive effect of the fluorine, the C—O bond shortens while the O—H bond stretches, the alcohol hydrogen atom becomes more electropositive leading to a greater susceptibility to deprotonation by a base or H-bond formation with an acceptor. Until recently, the inductive effect was the only parameter considered and fluorination was thought to always increase the H-bond donating capacity. However, through the work with fluorinated carbohydrates, our group became interested in a more detailed investigation of this topic. The effect of adjacent fluorination was studied depending on the position and relative configuration of the fluorine and alcohol, in simple model systems such as locked 4-*tert*-butylcyclohexanols. For this purpose, the relative H-bond acidities pK_{AHY} of donor compounds **1.36**-**1.46** were determined by FT-IR, similarly to pK_{BHX}, but using *N*-methylpyrrolidinone (NMP) as the H-bond acceptor in CCl_4 (pK_{AHY} = log K_f, K_f ($dm^3.mol^{-1}$) = [complex]/[AH][NMP]). The values obtained were compared with those of the nonfluorinated references **1.34** and **1.35**.

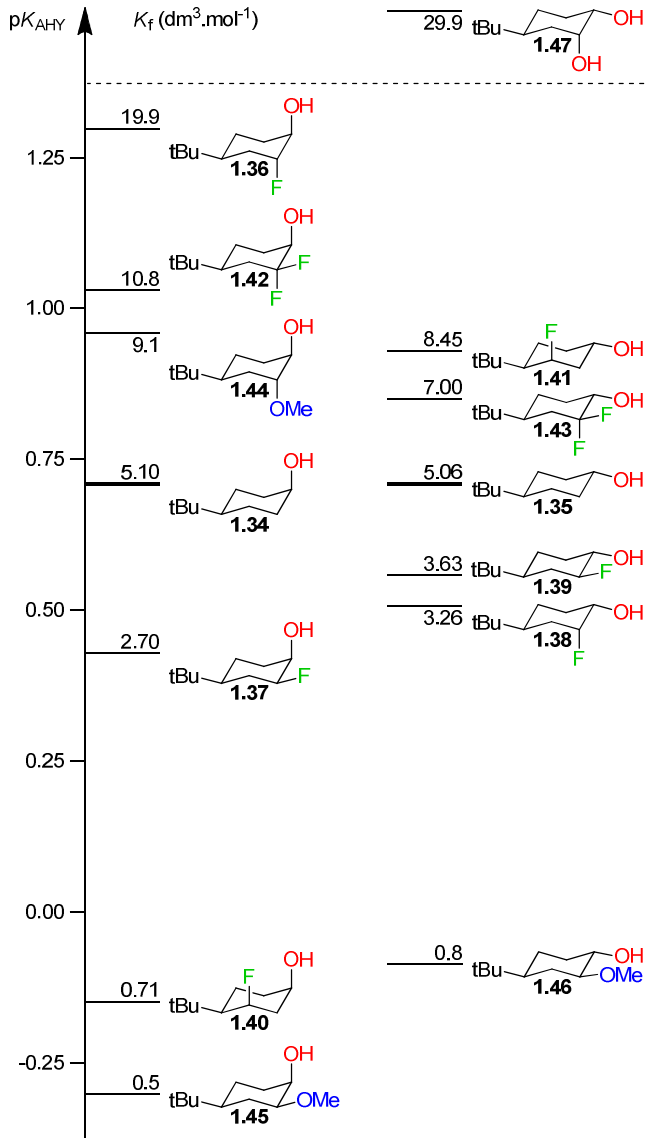


Figure 1.7: Visualisation of the H-bond acidity range of compounds **1.34**-**1.47**, as measured by an equilibrium constant with a standard hydrogen bond acceptor.[51]

The results summarised in **Figure 1.7** proved that the strong inductive effect of fluorine is clearly not the only factor to take into account as fluorination sometimes led to decreased H-bond acidities.[51] If the transdiaxial configuration in **1.36** did result in an important fourfold increase, all the other vicinal fluorinations (**1.37**-**1.39**) decreased the H-bond acidity of the alcohol, the worst of which was found to be halved compared to the nonfluorinated alcohols. *Cis*-1,3-diaxial fluorohydrin **1.40** virtually lost its capacity to act as an H-bond donor while the *trans* isomer **1.41** proved a better donor than its parent **1.35**. Difluorination led to an increased H-bond acidity although **1.42** and **1.43** remained less potent than some 1,2- and 1,3-monofluorohydrins respectively. Conformational analysis showed that compounds **1.37**-**1.40**, **1.42** and **1.43** adopted almost exclusively the conformation allowing a close contact between the labile hydrogen and the fluorine atoms. This suggested the presence of intramolecular F···H—O interactions that compete with the formation of intermolecular H-bonds, hence the observed reduction in H-bond acidity.

Thus, injudicious fluorination may decrease the hydrogen bond donating capacity of an adjacent functional group. However, this must be placed in the context of carbohydrates. Indeed, carbohydrates contain many hydroxyl groups which form strong intramolecular H-bonds. These probably impair the formation of intermolecular H-bonds in a similar manner to fluorine and therefore, the comparison of fluorocyclohexanols to methoxycyclohexanols may be more appropriate in the context of sugars. Recent unpublished results for compounds **1.44**-

1.46 are shown in **Figure 1.7** and perhaps restore the interest of fluorination to improve the H-bond acidity. In fact, when comparing **1.36** to **1.44**, **1.37** to **1.45** and **1.39** to **1.46**, the fluorohydrins all exhibit greater H-bond acidities than the methoxy analogues. When intramolecular contacts are not possible, the higher electronegativity of fluorine is responsible for doubling the H-bond acidity of **1.36**. By contrast, when such contacts are possible, because the methoxy oxygen atom is a much better H-bond acceptor than fluorine, the alcohol in **1.45** and **1.46** becomes unable to engage in intermolecular interactions while the hydroxyls of **1.37** and **1.39** were satisfactory donors. However, one should appreciate the importance of the vicinal diol example **1.47**. Remarkably, the H-bond donating capacity of one of the alcohols is multiplied by six compared to **1.34** and **1.35**. In fact, when a hydroxyl is involved in a hydrogen bond as an acceptor, it becomes a much superior donor compared to the best donating fluorohydrin **1.36**. One alcohol is sacrificed for the other as it becomes a weak intermolecular donor to make the second alcohol a strong donor (**Figure 1.8**). The H-bond acidity of each alcohol independently could not be determined by IR as the ν_{OH} bands overlapped. The observed constant is an average for the two alcohols as no conformation is expected to be favoured.

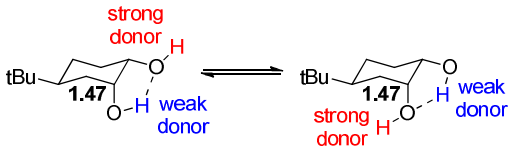


Figure 1.8: Interconversion of the intramolecular H-bonds in **1.47**

As a result, in the context of carbohydrates, the consequences of the introduction of CHF, CF_2 or CF_2CF_2 moieties may vary. Fluorine is a weaker acceptor than alcohols and therefore its introduction should increase the availability of an adjacent alcohol to form intermolecular H-bonds as the existing intramolecular H-bonds are less competitive. The strong inductive effect of fluorine is also expected to increase the H-bond acidity of the adjacent hydroxyls. However, the synergetic effect observed for a vicinal diol will always be larger than the potential gain obtained upon fluorination. Interestingly, the tetrafluorinated carbohydrates **1.24** and **1.25** retain the possibility for this synergistic effect to happen between 4-OH and 6-OH while DiMagno's hexafluorohexose **1.18** and O'Hagan's trifluorohexoses **1.19** and **1.20** have completely lost this opportunity.

1.3.2 Hydrogen bond accepting capacity

The hydroxyl groups in carbohydrates can each accept two hydrogen bonds so their hydrogen bond accepting capacities are fundamental for the effective binding to a receptor. In a similar manner, it is also referred to as H-bond basicity. As for the H-bond acidity, the analogy between H-bond basicity and Brønsted basicity appears often and until recently in the literature. The pK_{BHX} scale is a measure of H-bond basicity obtained by FT-IR through analysis of the ν_{OH} shift of 4-fluorophenol upon addition of an H-bond acceptor.[52] A comparison of the pK_{BHX} and the pK_a(H) clearly showed the absence of correlation between H-bond and Brønsted basicities. Nevertheless, within a same family of compounds such as alcohols or primary amines, a relationship can be observed and if the pK_a decreases from ethanol **1.48** to trifluoroethanol **1.50**, it proves also true for the pK_{BHX} which drops from 0.96 to –0.28 (**Table 1.1**).

Table 1.1: Brønsted acidity (pKa) and H-bond basicity (pK_{BHX}) of compounds **1.48**-**1.53**

	pK_a	pK_{BHX}[53]		$pK_{a(H)}$	pK_{BHX}[54]
CH_3CH_2**OH** (**1.48**)	15.9[55]	0.96	CH_3CH_2**NH_2** (**1.51**)	10.6[56]	2.17
H**CF_2CF_2**CH_2**OH** (**1.49**)	12.7[55]	-	H**CF_2CF_2**CH_2**NH_2** (**1.52**)	5.85[57]	-
CF_3 CH_2**OH** (**1.50**)	12.4[55]	–0.28	**CF_3**CH_2**NH_2** (**1.53**)	5.7[58]	0.67

Although the pK_{BHX} of tetrafluoropropanol (**1.49**) has not been measured, the pK_a of 12.7, similar to that of trifluoroethanol (**1.50)**, suggests the incapacity of its alcohol to act as an H-bond acceptor. Returning to the fluorinated carbohydrate case, this means that an alcohol vicinal to a CF_2CF_2 moiety, such as 4-OH in **1.24** (**1.2.2.3**, p. 10), is expected to be a better H-bond donor but it has most likely lost all H-bond accepting capacity. This capacity was crucial for an attractive interaction with a guanidinium residue in GOase, and therefore, **1.24** proved a poor substrate for that enzyme (see **1.2.2.4**).

To restore this capacity, a substitution of the alcohol for an amine may appear judicious. Indeed, considering ethylamine **1.51**, the same effects are observed upon trifluorination (**1.53**); the $pK_{a(H)}$ drops almost five units from 10.6 to 5.7 and the pK_{BHX} decreases from 2.17 to 0.67. However, because an amine is intrinsically more nucleophilic (compare **1.48** to **1.51**), the

nitrogen atom in **1.53** remains an H-bond acceptor ($pK_{BHX} > 0$) despite the inductive effect of the fluorines. The value of 0.71 is close to that of ethanol **1.48** so similar H-bond accepting capacities are expected for alcohols and α-polyfluorinated amines. Likewise, the comparable $pK_{a(H)}$ value of 5.85 for tetrafluoropropylamine (**1.52**) suggests a behaviour akin to **1.53**. Additionally, the $pK_{a(H)}$ values of 5.7 and 5.85 attest that **1.53** and **1.52** should not be protonated at physiological pH (7.4). This means that the replacement for an amine will not introduce a positive charge in the molecule and that the lone pair will indeed have the potency to accept a hydrogen bond. In summary, a CF_2—$CHNH_2$ may be a CHOH—CHOH H-bond acceptor mimic of choice.

1.4 Aims and Objectives

The synthesis of tetrafluorinated carbohydrates will be extended to substrates with the fluorines in position 3 and 4. In an effort to assess the difference between a CH_2 and a CF_2 group, 2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hexopyranose (**1.54**, **Figure 1.9**) had been synthesised previously within the group[46] in order to be compared with DiMagno's hexafluorohexopyranose **1.18**. However, only the synthesis of enantioenriched **1.54** was possible at the time and the first aim will be to obtain the enantiopure form.

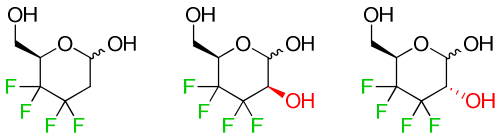


Figure 1.9: 3,3,4,4-tetrafluorinated carbohydrate analogues

Then, the synthesis of 3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose (**1.55**) as well as 3,4-dideoxy-3,3,4,4-tetrafluoro-D-ery*thro*-hexopyranose (**1.56**) will be attempted *via* different routes. For the sake of simplicity, **1.55** and **1.56** may be referred to as tetrafluoro-D-mannopyranose and tetrafluoro-D-glucopyranose respectively later in this thesis.

A second main goal involved the synthesis of a series of polyfluorinated aminosugars (**1.57**-**1.61**, **Figure 1.10**) as analogues of polyfluorinated carbohydrates **1.24**, **1.25**, **1.55**, **1.56** and **1.23** respectively, with a potentially restored hydrogen bond accepting capacity.

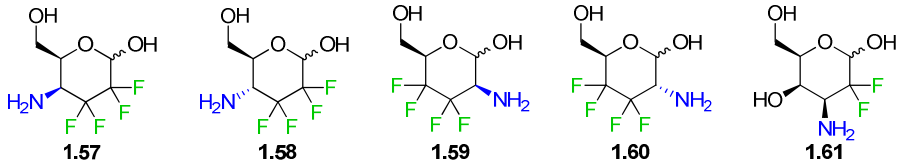
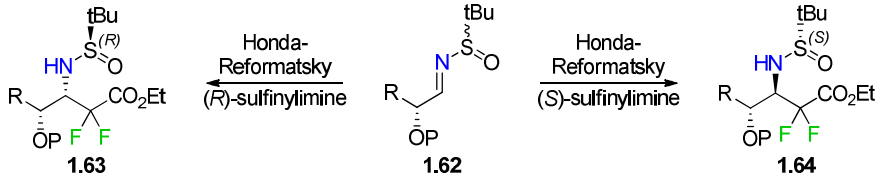


Figure 1.10: 2,2,3,3- and 3,3,4,4-tetrafluoroaminosugars and 2,2-difluoro-3-amino-D-galactose

All of these new carbohydrates analogues will have their biological activity and/or inhibition properties assessed for certain enzymes. In particular, **1.57** and **1.61**, the amino analogues of **1.24** and **1.23** respectively, will be tested as potential substrates for GOase (*cf.* **1.2.2.4**) so as to determine whether the presence of the better hydrogen bond acceptor amino group at position 3 or 4 does lead to more potent substrates.

In order to synthesise 3-amino-2,3-dideoxy-2,2-difluoro-D-*lyxo*-hexopyranose **1.61**, a new methodology based on the Honda-Reformatsky reaction will be developed and applied to various α-alkoxy sulfinylimines **1.62** (**Scheme 1.4**).

Scheme 1.4: New Honda-Reformatsky reaction with α-alkoxy sulfinylimines



1.5 Previous syntheses of tetrafluorinated sugars

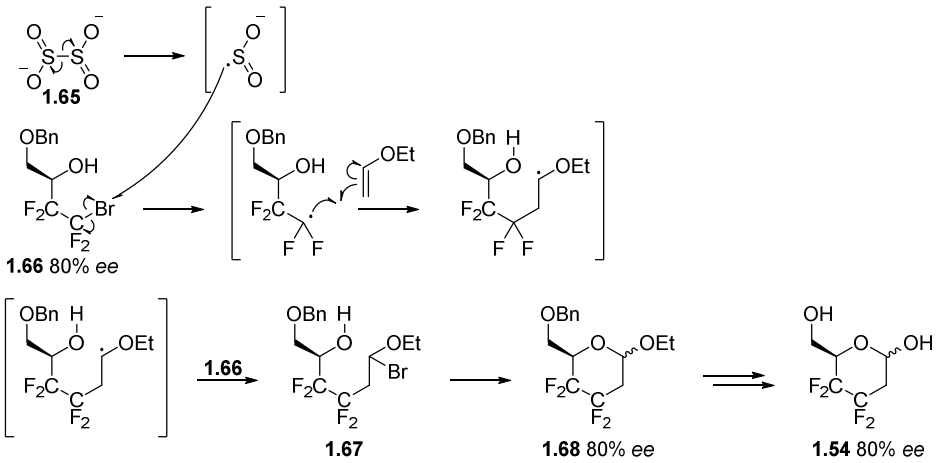
The synthetic routes to the fluorinated carbohydrate targets drew from three main precedents using radical and anionic processes described below.

1.5.1 Radical addition

In 2004, our group reported the synthesis of the enantioenriched tetrafluorinated hexopyranose **1.54**.[46] As shown in **Scheme 1.5**, the crucial step was a sodium dithionite (**1.65**) mediated radical coupling to ethyl vinyl ether (EVE) which mechanism is as follows. The $SO_2^{-\bullet}$ formed by S—S bond homolysis of **1.65** gives an electron to the bromine atom of starting material **1.66** rapidly generating a bromide ion and the CF_2 centered radical. Addition of EVE to

this radical followed by bromine atom transfer from another molecule of starting material **1.66** gives the α-bromoether **1.67** which spontaneously cyclises via an S_N1 or S_N2 process to form the ethyl glycoside **1.69**.

Scheme 1.5: Mechanism of the radical addition/cyclisation reaction en route to **1.54**

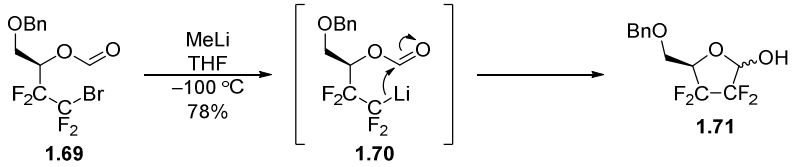


This route will be followed to synthesise enantiopure D-hexopyranose **1.54** then will be adapted for the synthesis of tetrafluorinated mannose and glucose analogues **1.55** and **1.56**.

1.5.2 Anionic intramolecular addition

At the same time, a Br-Li exchange mediated anionic cyclisation was developed within our group in order to obtain tetrafluorinated pentoses such as **1.71**.[46,48] After optimisation, the use of MeLi in THF at –100 °C emerged as the best conditions to realise bromine/lithium exchange on **1.69** to give **1.70**, the latter spontaneously cyclising in a 5-*exo*-trig fashion to afford the hemiacetal **1.71** in 78% yield (**Scheme 1.6**).

Scheme 1.6: Formation of tetrafluoropentofuranose **1.71** by Li-Br exchange mediated anionic cyclisation

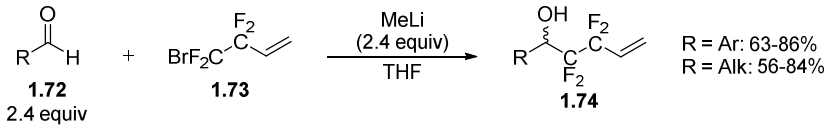


In a similar fashion, 6-*exo*-trig cyclisations were performed on formate or benzyloxyacetate derivatives leading to fluorinated glucose, galactose and fructose analogues in comparable yields.[47,48] Analogous anionic cyclisation will be performed on different substrates in order to synthesise mannose and glucose derivatives **1.54** and **1.55**.

1.5.3 Konno's anionic intermolecular addition

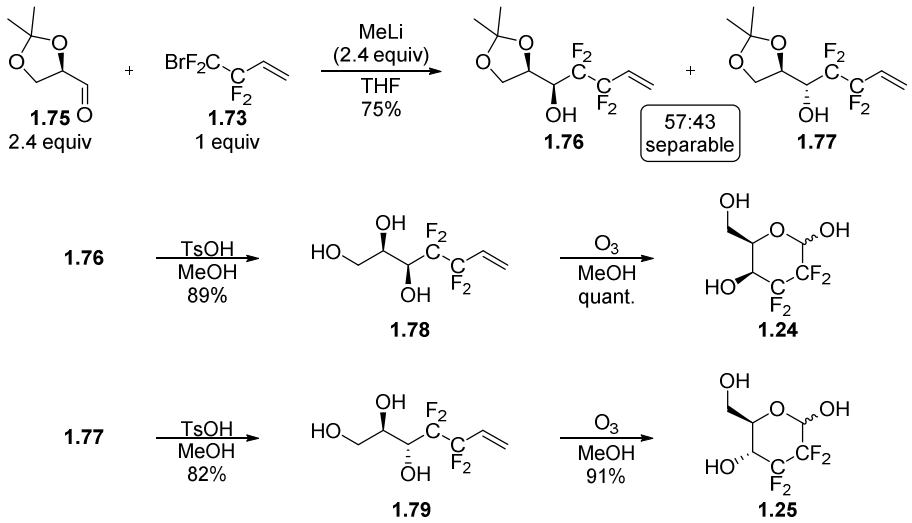
In 2011, Konno *et al.* showed that when treated with MeLi, **1.73** underwent bromine/lithium exchange and the newly formed lithiated tetrafluorobutene readily added to various alkyl and aryl electrophiles in an intermolecular fashion, surprisingly without significant β-fluoride elimination (**Scheme 1.7**).[59]

Scheme 1.7: Konno's addition of lithiated tetrafluorobutene to aldehydes.[59]



In 2013, in the wake of his article about the addition of the tetrafluorobutenyl moiety to electrophiles, Konno published a quick 3-step synthesis of the 2,2,3,3-tetrafluoro galactose **1.24** and glucose **1.25**.[60] As shown in **Scheme 1.8**, it consisted in adding the tetrafluorinated unit to the carbonyl of D-glyceraldehyde acetonide **1.75**, coupling that gave the two separable alcohols **1.76** and **1.77** in a 57:43 ratio for a 75% isolated yield. Each alcohol was then deprotected giving the triols **1.78** and **1.79** which after ozonolysis of the alkene afforded the desired tetrafluorinated carbohydrates in excellent yields.

Scheme 1.8: Konno's synthesis of 2,2,3,3-tetrafluoro galactose and glucose **1.24** and **1.25**[60]



The anionic intermolecular addition of different tetrafluorinated moieties to various substrates will be performed to synthesise the fluorinated carbohydrates **1.55** and **1.56** as well as the fluorinated aminosugars **1.57**-**1.60**.

Chapter 2: Synthesis of 3,3,4,4-tetrafluoro carbohydrates

2.1 Target molecules

The synthesis of the 3,3,4,4-tetrafluoro carbohydrate analogues shown in **Figure 2.1** is described in this chapter.

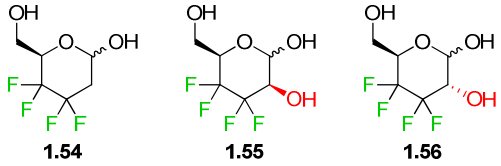


Figure 2.1: 3,3,4,4-tetrafluorinated carbohydrate analogues

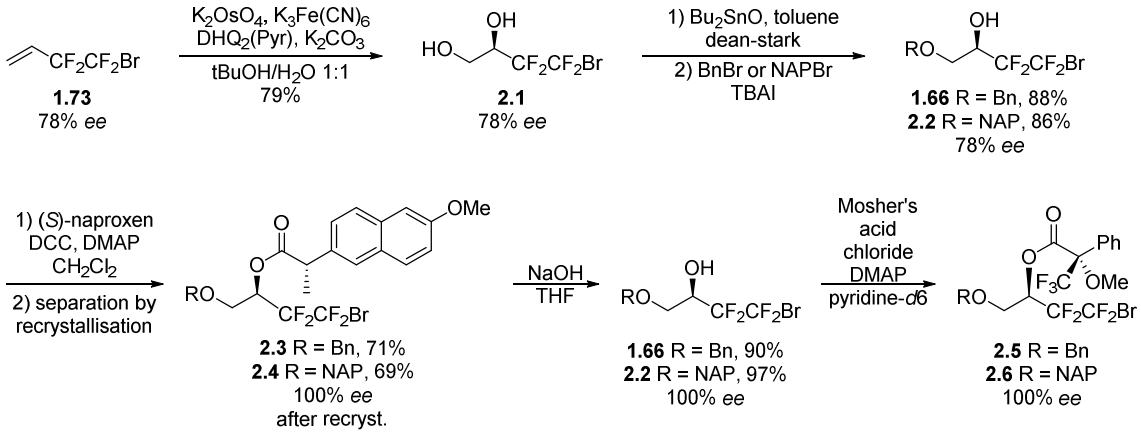
2.2 Synthesis of 2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hexopyranose (1.54)

2.2.1 Preparation of enantiopure starting alcohols 1.66 and 2.2

The D-hexopyranose **1.54** had been previously synthesised in the group, but only with an *ee* of around 80%. This was the maximum excess that could be reached for the Sharpless asymmetric dihydroxylation of alkene **1.73** (**Scheme 2.1**), the first step in the synthesis.[46] In 2009, a kinetic resolution procedure was developed within the group which afforded the enantiopure diol with the primary alcohol protected as a benzyl ether (**1.66**) or a 2-naphthylmethyl ether (**2.2**).[48] Hence, the synthesis of enantiopure **1.54** began by repeating this procedure on large scale (up to 15 g). Hence, the diol **2.1** was transformed into the corresponding dibutyltin acetal (not shown) from which the least hindered primary oxygen reacted with the alkyl halide to give the enantioenriched alcohols **1.66** and **2.2** in excellent yields. The NAP protected diol **2.2** is not needed for the synthesis of **1.54** but will be required later in this thesis (*cf* section **2.3.3.1**). Then, in each case, the secondary alcohol was coupled with (*S*)-naproxen to provide the esters **2.3** and **2.4** in good yields and as single diastereoisomers after recrystallisation from hexane. Finally, cleavage of the chiral auxiliary

afforded the enantiopure benzyl and NAP protected diols **1.66** and **2.2**. The corresponding Mosher's esters were systematically synthesised so as to detect any potential erosion of the enantiomeric excess due to the harsh basic conditions of the saponification. However, ^{19}F NMR analysis typically showed enantiomeric excesses of >99% for both **2.5** and **2.6** (**Figure 2.2**).

Scheme 2.1: Synthesis of starting enantiopure alcohols **1.66** and **2.2**[48]



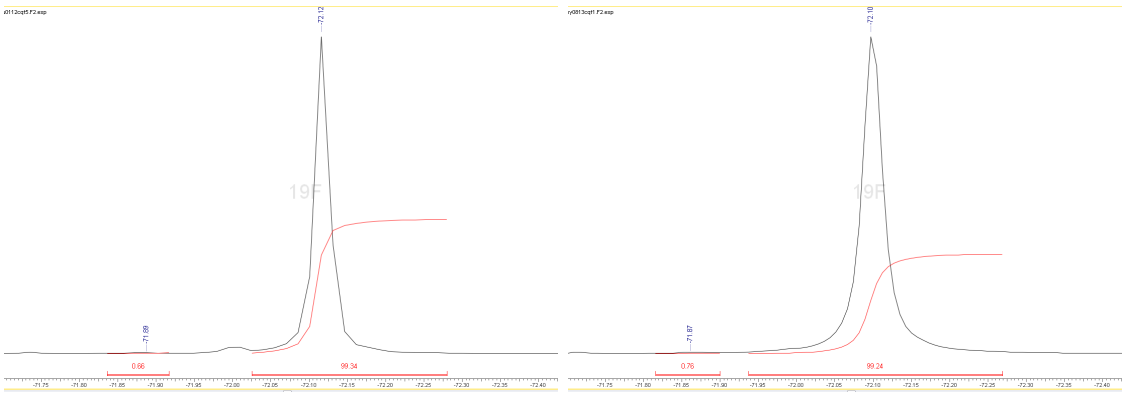


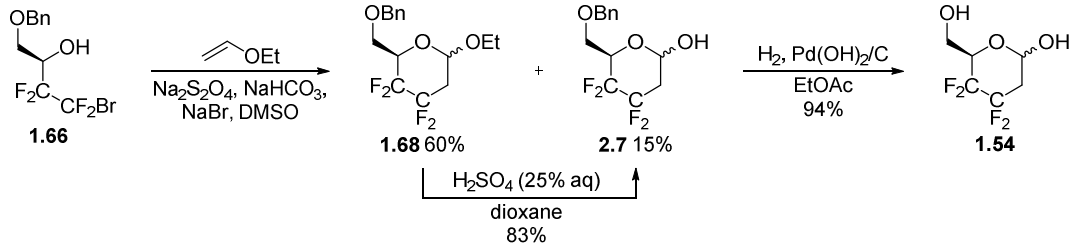
Figure 2.2: Detail of the ^{19}F NMR spectrum centred on the CF_3 peak of Mosher esters **2.5** (left) and **2.6** (right)

2.2.2 Radical Addition and Deprotection

The radical reaction described in **1.5.1** was performed starting from 500 mg of enantiopure alcohol **1.66** and provided the desired ethyl glycoside **1.68** and the corresponding hemiacetal **2.7** in 60% and 15% yield respectively. The unexpected formation of hydrolysed product **2.7** had not been reported before and represented an improvement of the combined yield. Unfortunately, a mechanism consistent with the anhydrous conditions of the reaction is yet to be determined. The reproduction of this reaction proved troublesome and it should be noted

that the initial conditions described in the literature[46] were slightly modified to achieve the reported yields. First, sodium dithionite is a strong reductant which degrades over time and the use of a new batch was absolutely crucial to reach good yields. Instead of being stirred at rt, the reaction was heated at 35 °C and consequently, a sealed tube was used to avoid any evaporation of the volatile ethyl vinyl ether (EVE). Although no explanation emerged for this, the addition of 1.5 equiv of NaBr seemed to promote the formation of **1.68** and **2.7**. Finally, during the work-up, the number of extractions of the aqueous phase was increased as the latter still contained a significant amount of both desired products when following the reported procedure.

Scheme 2.2: Synthesis of D-hexopyranose **1.54**



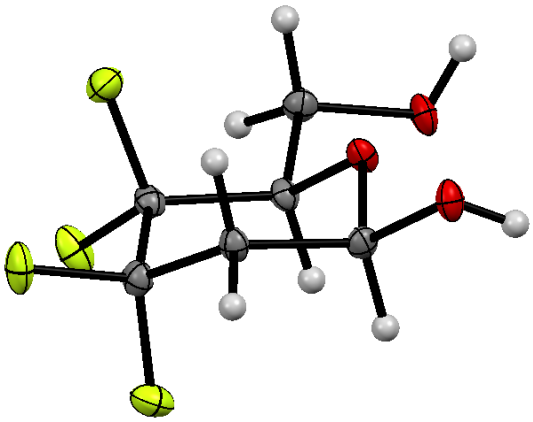


Figure 2.3: X-ray crystallographic analysis of **1.54**

To finish, hydrolysis of the ethyl glycoside followed by debenzylation resulted in the first isolation of enantiopure 2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hexopyranose (**1.54**) as a 1:1 mixture of anomers. This compound was recrystallised and a crystal structure was acquired (**Figure 2.3**). The deoxysugar clearly adopted the $^4C_1$ chair conformation, common for natural carbohydrates, with very little distortion.

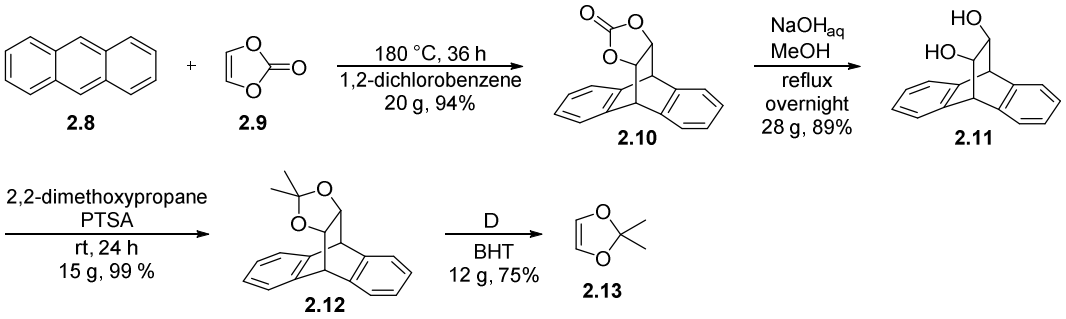
2.3 Synthesis of 3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*- and D-*erythro*-hexopyranoses 1.55 and 1.56

2.3.1 Radical Addition

2.3.1.1 Addition of dimethyldioxole

Given the successful approach shown above, the synthesis of both tetrafluoro- mannose and glucose **1.55** and **1.56** was first envisaged by radical addition/cyclisation reaction using dimethyldioxole (**2.13**) as a source of electron rich enediol. The synthesis[61] of **2.13** (**Scheme 2.3**) employed a Diels-Alder reaction between anthracene and vinylene carbonate in order to protect the double bond, followed by the hydrolysis of the carbonate **2.10** using aqueous sodium hydroxyde in refluxing methanol. The obtained diol **2.11** was then protected as the acetonide **2.12** using dimethoxypropane, catalysed by PTSA. All reactions went successfully on multigram scales with excellent yields matching those of the literature.

Scheme 2.3: Synthesis of 2,2-dimethyl-1,3-dioxole **2.13**[61]



The last and crucial step consisted of a retro Diels-Alder (RDA) reaction. The simpler apparatus (**Figure 2.4**) recently depicted by Vijgen[62] was preferred to Posner's procedure as it resulted in better yields. The adduct **2.12** to which a few crystals of 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) were added, was placed in a flask equipped with a Vigreux column connected to a collecting tube immersed in a dry ice/acetone bath at –50 °C, temperature at which **2.13** remains liquid. The starting material was not freeze-dried as mentioned in the article but the whole apparatus was carefully flame-dried under vacuum and cooled under N_2. The acetonide **2.12** (12 g) was gently heated with a heat gun until the solid had melted then the temperature was increased to 500 °C to initiate both the RDA and the distillation of the freshly formed product affording pure dimethyldioxole in 75% yield.

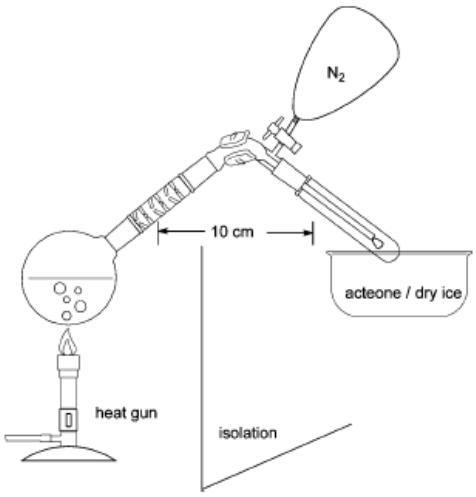


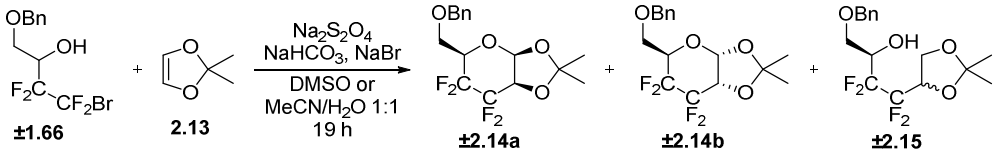
Figure 2.4: Vijgen's procedure for the RDA reaction[62]

With dimethyldioxole in hand, the radical addition reaction was attempted starting from the racemic alcohol **±1.66**. Generally, the crude material appeared to be a complex mixture with the TLC plate revealing around ten spots distributed over its entire length. The desired acetonides **±2.17** could be obtained but in yields not higher than 22%. The reduced adducts **±2.18** were the main by-products being formed approximately in the same proportion as the desired products. They could result from hydrogen abstraction or from a second SET to the newly formed radical leading to the corresponding anion and its subsequent protonation. Evidence of the reduced starting material RCF_2CF_2H could be found by ^{1}H and ^{19}F NMR though not in significant amount. Elution of polar fractions indicated the formation of the hydrolysed product (loss of acetal protecting group) however it could not be separated from impurities of similar R*f*. Optimisation of several parameters are summarised in **Table 2.1** below.

The reaction was first carried out in MeCN/H_2O 1:1 leading to incomplete conversion and the desired product to be isolated in 4% yield, whereas in DMSO the experiment went to completion and gave **±2.14** in 19% yield (entries 1 and 6). Addition of 1.5 equiv of NaBr seemed to vary the **±2.14**/**±2.15** ratio, increasing it from 1:3.8 to 1:1 (entries 2 and 3). However, the different mechanisms leading to the reduced adduct **±2.15** could have been promoted by the increased temperature (45 °C instead of 35 °C). To assess the significance of the temperature, an experiment was conducted at rt which resulted in a longer reaction time (3 days) and a product/by-product ratio in favour of the latter (entry 4). Thus, the temperature is not detrimental to the formation of **±2.14** *vs* that of **±2.15**. The reaction concentration was doubled without improving any of the outcomes (entries 3 and 6). Similarly, decreasing the

number of equivalents of **2.13** had no particular effects on the reaction results (entries 5, 6 and 7).

Table 2.1: Optimisation of the radical addition/cyclisation reaction using dimethyldioxole



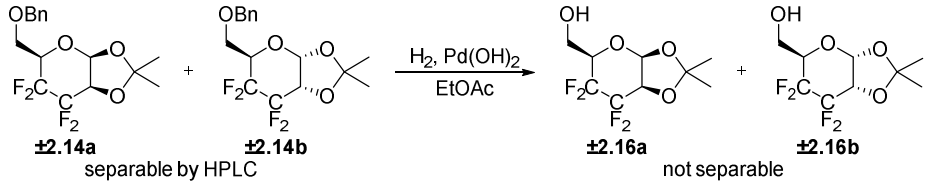
entry	NaBr (equiv)	2.13 (equiv)	temperature (°C)	solvent/concentration (mol.L^{-1})	yield ±2.14 (%)[a]	yield ±2.15 (%)[a]
1	1.5	2	35	MeCN:H_2O/0.38	4	7
2	-	2	45	DMSO/0.2	8	30
3	1.5	1.5	35	DMSO/0.2	18	18
4	1.5	3	rt (3 d)	DMSO/0.25	17	25
5[b]	1.5	3	35	DMSO/0.38	20	13
6[b]	1.5	2	35	DMSO/0.38	19	24
7[b]	1.5	1	35	DMSO/0.38	22	20

[a] Isolated yield. [b] 1.5 mmol of **±1.66** instead of 0.3 mmol.

The use of relatively electron poor enediol derivative such as vinylene carbonate proved unsuccessful as it resulted in a very complex mixture. Evidence of the reduced radical RCF_2CF_2H could be found by ^1H NMR. This corroborates with a failed attempt, previously described in the group, to use the electron poor vinyl acetate instead of ethyl vinyl ether while trying to synthesise trideoxytetrafluorohexose **1.54**, and is explained by the electron poor nature of perfluoroalkyl radicals.

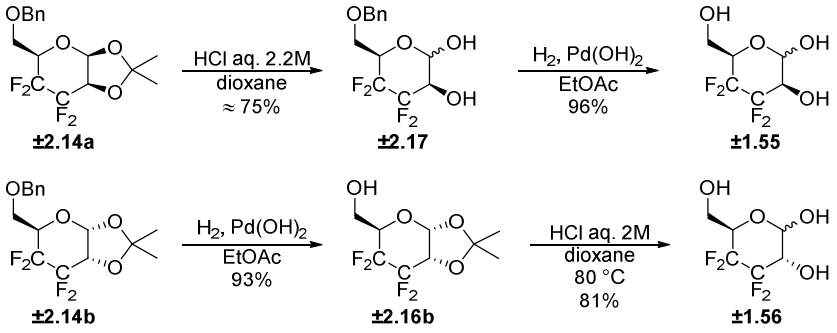
Although yields were low, the decision was taken to continue the synthesis in order to obtain the data for the final compounds **±1.55** and **±1.56**. In this regard, the two diastereoisomers **±2.14a** and **±2.14b** were separated using HPLC as column chromatography did not prove sufficient. Hydrogenolysis of a mixture of **±2.14** leading to the more polar debenzylated compounds **±2.16** failed to improve the separation (**Scheme 2.4**).

Scheme 2.4: Debenzylation of a mixture of the diastereoisomers **±2.14a** and **±2.14b**



The deprotection of **±2.14a** and **±2.14b** consisted of the hydrolysis of the acetonide and the hydrogenolysis of the benzyl protecting group (**Scheme 2.5**). Following a standard procedure,[63] **±2.14a** was treated with 5% (1.4M) aq HCl for 6 h at rt however no reaction occurred as a TLC only showed the starting material. The same reaction mixture was then heated at 60 °C overnight but still proved incomplete. Concentrated aq HCl was then added until an overall concentration of 2.2 M and the heating was increased to 100 °C leading to completion after 3 h. However, the high temperature and/or long reaction time resulted in the formation of by-products which were not separable from the desired hemiacetal **±2.17**. Hydrogenolysis of **±2.17** was carried out with Pearlman's catalyst in EtOAc[46] and afforded the tetrafluoromannose derivative **±1.55** in pure form and excellent yield. The deprotection sequence was reversed for **±2.14b** for no particular reason. Thus, the same hydrogenolysis procedure was performed on **±2.14b** and offered the desired debenzylated compound **±2.16b** in very good yield. Subsequent hydrolysis of **±2.16b** was performed with 2M aq HCl at 80 °C for 2.5 h giving pure tetrafluoroglucose **±1.56** in 81% yield.

Scheme 2.5: Deprotection towards the formation of tetrafluoromannose **±1.55** and glucose **±1.56**

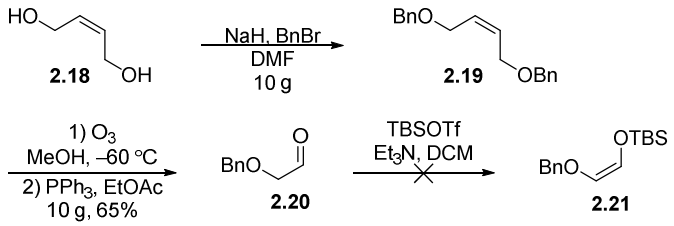


Hence the synthesis of the first samples of tetrafluorinated mannose and glucose as racemates was achieved. Recrystallisation afforded crystals suitable for X-ray diffraction for both compounds (*cf* section **2.3.4**).

2.3.1.2 Addition with Silyl enol ethers

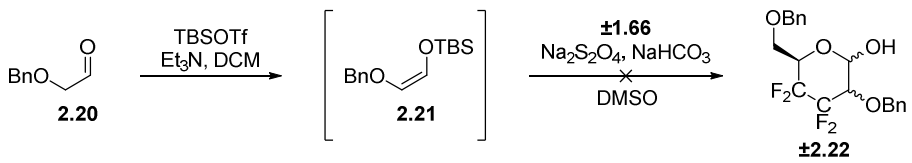
It was decided to investigate whether the sodium dithionite mediated radical reaction using dimethyldioxole could be further improved, as to allow multigram synthesis of the desired sugars. The use of silyl enol ethers as a source of electron rich double bond was considered next. In fact, the C=C bond of alkoxy silyl enol ether derivatives are expected to be more electron rich than that of protected enediols such as dimethyldioxole, leading to an improved reactivity towards the electron poor CF_2 radical. Consequently, the silyl enol ether **2.21** was synthesised to then be engaged in the sodium dithionite induced radical reaction.

Scheme 2.6: Proposed route to silyl enol ether 27



As shown in **Scheme 2.6**, dibenzylation of *cis*-but-2-ene-1,4-diol (**2.18**) following a standard procedure[64] gave **2.19** almost quantitatively. Subsequent ozonolysis afforded pure benzyloxyacetaldehyde **2.20** on large scale and good yield after distillation.[65] However, when attempting the enolisation using two equivalents of triethylamine and *tert*-butyldimethylsilyl triflate in CH_2Cl_2, no product could be isolated. This was explained by the relative instablility of these compounds. As a result, the silyl enol ether formation was attempted *in situ*, followed by direct subjection to the radical addition/cyclisation conditions (**Scheme 2.7**).

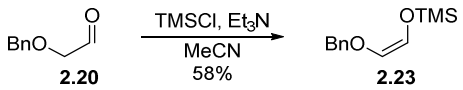
Scheme 2.7: Radical addition/cyclisation reaction using *in situ* formed silyl enol ether **2.21**



This reaction proved unsuccessful with no evidence of the formation of the desired products provided from NMR-analysis. Furthermore, the reduction product RCF_2CF_2H was isolated, suggesting the absence of silyl enol ether in the medium.

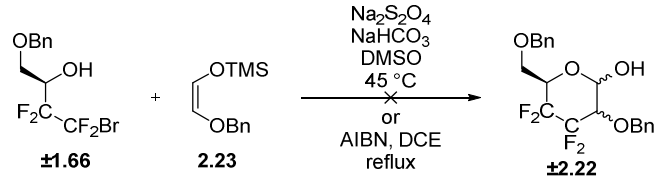
However, following Denmark's procedure, the trimethylsilyl analogue **2.23** could be obtained in 58% yield after distillation (**Scheme 2.8**).[66] The ^{1}H NMR spectrum revealed a *Z*/*E* ratio of 90:10 as the ethylenic protons coupled with a small $^{3}J_{H\text{-}H}$ of 3.4 Hz for the major isomer. Interestingly, theses protons appeared as a singlet for the *E* isomer.

Scheme 2.8: Formation of trimethylsilyl enol ether **2.23**



The trimethyl silyl enol ether **2.23** was then engaged in the radical addition/cyclisation reaction under different initiation conditions (**Scheme 2.9**).

Scheme 2.9: Radical addition/cyclisation reaction with aldehyde derived silyl enol ether **2.23**



Using the standard sodium dithionite conditions, the reaction resulted mainly in the recovery of the starting material, along with a complex mixture of unknown products. The large amount of recovered starting material suggested that in the presence of the silyl enol ether, sodium dithionite might not have transferred an electron to the bromine atom. Thus, the decision was made to use a different initiator. A stoichiometric mixture of the starting materials and 0.25 equiv of AIBN were refluxed in dichloroethane for one day after which the crude ^{19}F NMR showed the presence of a 2.5:1 mixture of starting bromide **±1.66** and an unknown compound. The ^{19}F NMR of this new compound showed peaks centered at δ = –62.3 ppm, a typical chemical shift for the fluorines α to the bromine atom in the CF_2CF_2Br moiety. This suggested that AIBN is probably not a suitable initiator for the formation of CF_2 centered radical under these conditions.

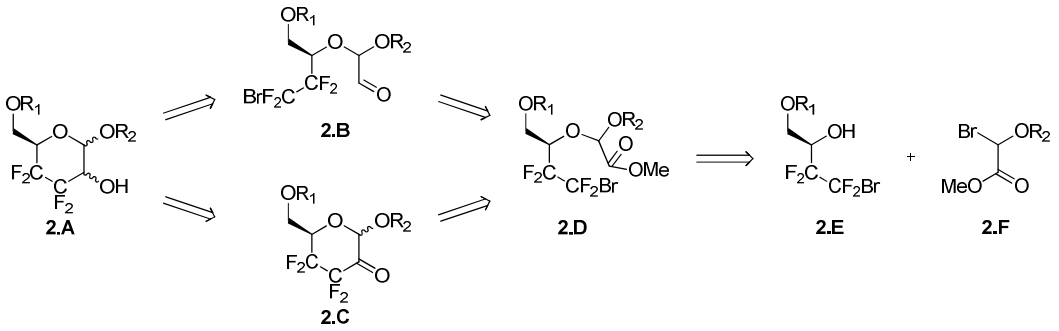
The use of silyl enol ethers clearly did not improve the outcome of the radical addition reaction. Consequently, the route to the synthesis of the tetrafluorinated sugars was reconsidered giving rise to an anionic approach.

2.3.2 Anionic Intramolecular Addition

2.3.2.1 Synthesis

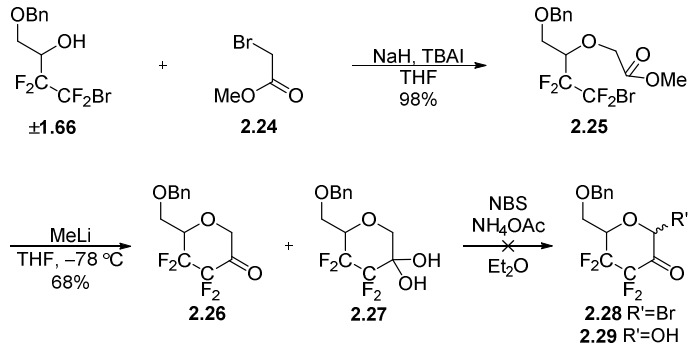
It was then envisioned that the anionic cyclisation pathway described in section **1.5.2** could be applied to the synthesis of F_4-Man and F_4-Glc. As shown in **Scheme 2.10**, two retrosynthetic paths were envisaged. The synthesis of **2.A** could be achieved *via* intramolecular cyclisation of the aldehyde **2.B** obtained by reduction of the ester **2.D**. Alternatively, the cyclisation and reduction could be inverted; the cyclisation of **2.D** could give the 2-hexulose **2.C** which would afford **2.A** after reduction of the ketone. Finally, the precursor **2.D** could be prepared by S_N2 between starting alcohol **2.E** and alkoxybromoacetate **2.F**.

Scheme 2.10: Retrosynthesis of 3,3,4,4-tetrafluorohexoses by anionic cyclisation



Given aldehydes are often not easily purified, and the expected low stereoselectivity of the anionic cyclisation reaction involving **2B**, the ester cyclisation route was selected. As **2.C** is likely to adopt a chair conformation, the reduction of the ketone may illustrate some selectivity depending on the reducing agent used or the configuration of the anomeric substituent.

Scheme 2.11: Attempted anionic cyclisation starting from ester **2.25**



As illustrated in **Scheme 2.11**, the nucleophilic substitution was first tried on methyl bromoacetate (**2.24**) leading to the ester **2.25** in almost quantitative yield. The MeLi mediated cyclisation was then performed and the cyclic ketone hydrate **2.27** was obtained with a promising yield of 68%. Although the ketone **2.26** was first expected, the hydration of the carbonyl was predictable given the presence of the strongly activating fluorine atoms next to it. This hydration was first revealed by the presence of additional peaks in the ^{1}H and ^{19}F NMR spectra and by the appearance of a broad peak around 3400 cm^{-1} on the IR spectrum before being undoubtedly characterised by X-ray diffraction (**Figure 2.5**).

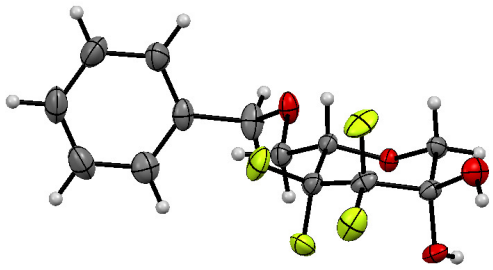
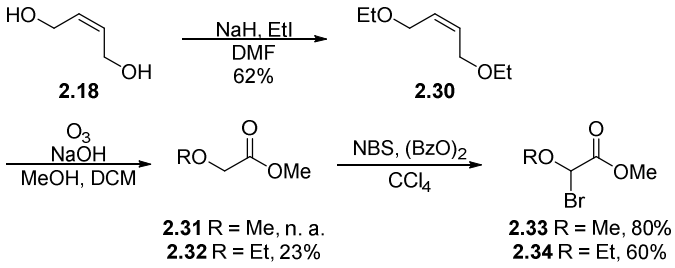


Figure 2.5: X-ray crystallographic analysis of hydrate **2.27** (L-enantiomer)

It was then proposed that α-bromination of the ketone could give the bromide **2.28** which would rapidly hydrolyse to the desired hemiacetal **2.29**. As radical bromination conditions could result in a side-reaction involving the benzylic position being brominated as well, milder conditions using NBS and catalytic ammonium acetate were tried but proved unsuccessful.[67] α-Bromination of 1,1,1-trifluorobutan-2-one and similar substrates was performed using elemental bromine and concentrated sulphuric acid but unfortunately, these conditions were not attempted on this ketone hydrate.[68]

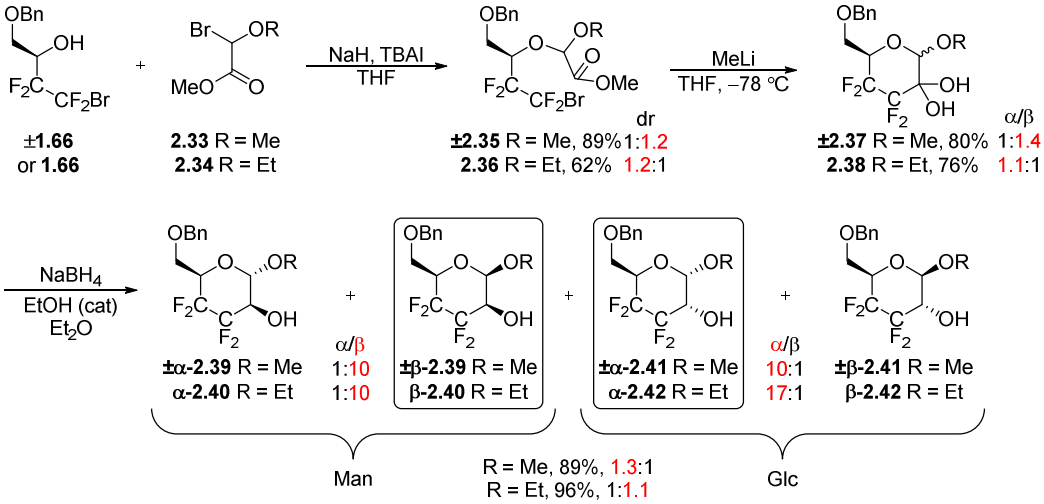
As a result, a route in which the anomeric oxygenated substituent is introduced before the cyclisation step was designed. The bromoacetate **2.24** was substituted for methoxy and ethoxybromoacetate **2.33** and **2.34** in order to obtain the methyl (**2.39**-**2.41**) and ethyl glycosides (**2.40**-**2.42**) respectively (**Scheme 2.13**). At first, only the synthesis of the methyl glycosides was envisaged but upcoming difficulties discussed later in this thesis required the synthesis of the ethyl analogues. Whereas methyl methoxyacetate (**2.31**) was commercially available, the ethoxy equivalent **2.32** had to be synthesised (**Scheme 2.12**).

Scheme 2.12: Preparation of methyl bromoalkoxyacetates **2.33** and **2.34**



As for the dibenzyloxybutene **2.19** described above, **2.30** was obtained following Nishinozo's procedure[64] but using ethyl iodide as the electrophile. Distillation afforded pure **2.30** in 62% yield which was then subjected to ozonolysis in methanolic NaOH to form directly the methyl ester **2.32**. Although this Garofalo ozonolysis procedure[69] was reported to proceed with consistent yields above 60%, an unexpected low yield of 23% was obtained when applying these conditions to the alkene **2.30**. α-Bromination was achieved by refluxing either ester with NBS and a catalytic amount of benzoyl peroxide in CCl_4 leading to the desired alkoxybromoesters **2.33** and **2.34** in 80% and 60% yield respectively after distillation.

Scheme 2.13: Synthesis of methyl and ethyl glycosides **2.39**-**2.42**



As shown in **Scheme 2.13**, nucleophilic substitution of either bromide by the alcoholate of **±1.66** or **1.66** afforded the esters **±2.35** and **2.36** in 89% and 62% yield respectively. It should be noted that for the ethyl analogue, a better yield of 77% was obtained when using the racemic alcohol **±1.66**. Although the reaction was not expected to proceed with any selectivity, **±2.35** was isolated as 1:1.2 mixture of diastereoisomers. The ethyl analogue **2.36** was obtained

as a 1.2:1 mixture of diastereoisomers after chromatography, although analysis of the crude mixture suggested a ratio closer to 1:1. Then, each diastereoisomeric mixture of esters (up to 2.5 g) was subjected to MeLi mediated anionic cyclisation which offered the hydrated hexuloses **±2.37** and **2.38** in 80% and 76% yield respectively. Interestingly, the α/β ratio for the methyl derivative **±2.37** was 1:1.4 whereas for the ethyl derivative **2.38**, the anomeric ratio was 1.1:1. These are the isolated ratios as the ^{1}H and ^{19}F NMR analysis of the crude was prevented by overlapping peaks.

The next step was the reduction of the ketone to the alcohol to obtain the mannose or glucose derivatives. As the ketone was hydrated, a minimum of 2 equiv of reducing agent was systematically used. The first reducing agent used was sodium borohydride. Being a small nucleophile, the attack of the ketone by the hydride is expected to be mainly axial which would afford the glucose derivative. When first attempted on the methyl hexulose **±2.37**, the reaction proved successful with an excellent yield of 89% but led however to both diastereoisomers at C-2 **±2.39** and **±2.41**.

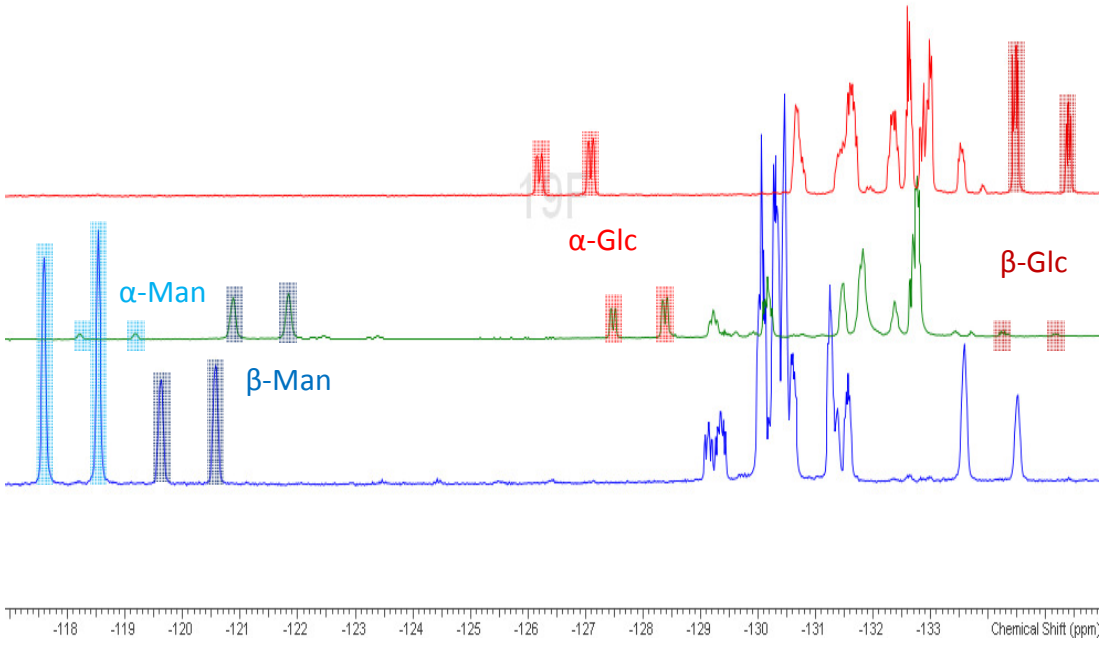


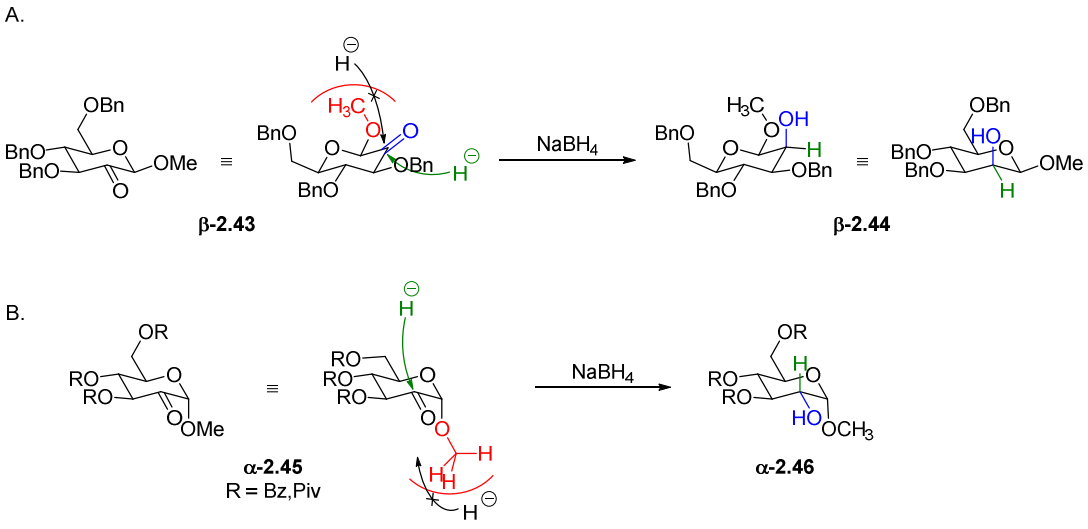
Figure 2.6: ^{19}F NMR spectra of (from top to bottom) tetrafluoroglucose **1.56** (red), the crude mixture after $NaBH_4$ reduction (green) and tetrafluoromannose **1.55** (blue).

Both mannose and glucose derivatives **±2.39** and **±2.41** were obtained in a 1.3:1 ratio as revealed by ^{19}F NMR spectra shown in **Figure 2.6**. Interestingly, the α/β ratio for the mannose derivative **±2.39** was 1:10 while for the glucose derivative **±2.41**, the anomeric ratio was 10:1. Thus, the reduction of the β-anomer of **±2.37** provided mainly the mannose derivative and the reduction of the α-anomer of **±2.37** led mainly to the glucose derivative. Hence, the 1:1.4

anomeric ratio observed for the starting material **±2.37** was retained during the reduction giving a Glc/Man 1:1.3 ratio. Similarly, the reduction of the ethyl derivative **2.38** with sodium borohydride gave the mannose and glucose derivatives **2.40** and **2.42** with the excellent yield of 95%. Interestingly, the selectivity towards the β-Man analogue **β-2.40** and the α-Glc analogue **α-2.42** was retained and the major isomers were isolated in 10:1 and 17:1 ratios respectively compared to the minor ones, The 1.1:1 α/β ratio observed for **2.38** resulted in a 1.1:1 Glc/Man ratio after reduction.

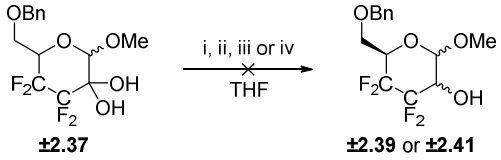
The observed selectivities suggested that the face attacked by the hydride was depending on the configuration of the anomeric methoxy group. In fact, the reduction of various glucosid-2-uloses with sodium borohydride has been reported to proceed with good to excellent selectivities (10:1 to >50:1 in most cases), essentially depending on the orientation of the anomeric substituent, which directs attack of the hydride ion through steric hindrance, regardless of the presence of a bulky protecting group at the adjacent 3-OH. Thus, the reduction of an α anomer of methyl glucosid-2-ulose mainly led to a glucose derivative together with less than 5% of the epimeric mannose while a β anomer resulted almost exclusively in a mannose derivative (**Scheme 2.14**).[70],[71] The selectivity for the β-mannose decreased to around 3:1 when the 3-OH was protected with acyl groups which presumably directed the sodium borohydride to the top-face of the ring through chelation, therefore leading to small amounts of β-glucose. This was later addressed by the use of K or L-selectride® which only afforded the mannose derivative. Interestingly, the selectivity was reversed in favour of β-glucose when reducing with a borane-pyridine complex.[72]

Scheme 2.14: Anomeric dependence of the reduction of methyl glucosid-2-ulose with $NaBH_4$.[70],[71]



The diastereoselectivities obtained with the 3,3,4,4-tetrafluorinated 2-ulose derivatives is in agreement with the above. As the two obtained products were not separable at this stage, it would have been interesting if the reduction could lead to only one type of carbohydrate, either the mannose or the glucose derivative. In this regard, different reducing agents of greater size than sodium borohydride were tried including tributyltin hydride in the presence of TBAF, lithium tri-*sec*-butylborohydride (L-selectride®), diisobutylaluminium hydride (DIBAL) and lithium aluminium hydride (**Scheme 2.15**). Large nucleophiles were expected to attack the ketone preferentially in an equatorial way and therefore might lead to the mannose derivative almost exclusively regardless of the orientation of the anomeric substituent.

Scheme 2.15: Reduction of **±2.37** using larger nucleophiles



±2.37 **±2.39** or **±2.41**

i. 2 equiv Bu_3SnH, 3 equiv TBAF; ii. 2.05 equiv L-selectride®; iii. 3 equiv DIBAL; iv. 2.2 equiv $LiAlH_4$.

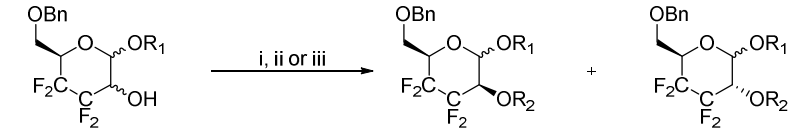
However, the starting material was mainly recovered when attempting to use these four reductants. A small amount of alcohol could be obtained using Bu_3SnH/TBAF or $LiAlH_4$ but in low yields. Interestingly, for both these reactions, the ^{19}F NMR spectrum showed almost exclusively the characteristic peaks of the mannose derivative. This strongly suggested that the attack of larger nucleophiles than $NaBH_4$ was mainly equatorial as expected. However more selective due to their size, these reducing agents were most likely too bulky to be able to reach and reduce the hindered carbonyl, leading to low yields and recovery of the starting material.

2.3.2.2 Separation of the Mannose and Glucose derivatives

Whether for the methyl or ethyl series, the F_4-Man and F_4-Glc diastereoisomers **±2.39**/**±2.41** and **2.40**/**2.42** could not be separated, even by HPLC. In order to achieve the required separation, derivatisation of the mixture was investigated. The first idea was to protect the 2-OH with entities of different size and properties including benzyl, acetyl and benzoyl groups (**Scheme 2.16**). Unfortunately and although obtained in good yields, none of the benzyl ethers **±2.47**-**±2.50** or acetates **±2.51**-**±2.52** could be separated by column chromatography. The benzoates **±2.53** and **±2.54** were gained in a moderate 56% yield and allowed the isolation of pure β-Man **±β-2.53**. However, the other major isomer α-Glc **±α-2.54** remained contaminated

with 7% of the minor α-Man **±α-2.53**. Thus, increasing the bulk at the stereocentre that differs in Man and Glc did not prove successful in improving the separation of the latters.

Scheme 2.16: Protection of the 2-OH with i) NaH, BnBr, THF; ii) Ac_2O, pyridine; iii) BzCl, DMAP, pyridine

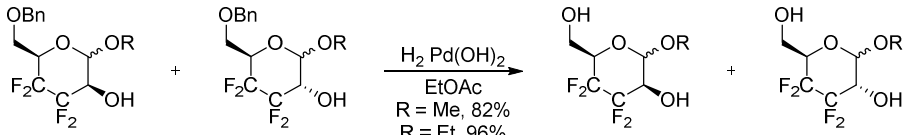


±2.39/±2.41 R_1 = Me
±2.40/±2.42 R_1 = Et

±2.47 R_1 = Me, R_2 = Bn, 64% **±2.48**
±2.49 R_1 = Et, R_2 = Bn, 79% **±2.50**
±2.51 R_1 = Et, R_2 = Ac, 89% **±2.52**
2.53 R_1 = Et, R_2 = Bz, 56% **2.54**

Then, the hydrogenolysis of the benzyl ether at position 6 of compounds **±2.39**-**2.42** was attempted (**Scheme 2.17**) instead. This reaction afforded the desired unprotected methyl **±2.55**-**±2.57** and ethyl **2.56**-**2.58** glycosides in 82% and 96% yields respectively. As revealed by ^{19}F NMR, for the methyl series, column chromatography allowed the isolation of the major β-Man derivative **±β-2.55** from the mixture of four isomers. Another fraction consisted of the α-Glc derivative **±α-2.57**, the other major isomer, along with the α-Man and β-Glc derivatives **±α-2.55** and **±β-2.57**, the two minor isomers. Unfortunately, further purification by HPLC did not permit the isolation of the Glc derivatives alone.

Scheme 2.17: Hydrogenolysis of the 6-*O*-benzyl ether



±2.39 R = Me
2.40 R = Et

±2.41 R = Me
2.42 R = Et

±2.55 R = Me
2.56 R = Et

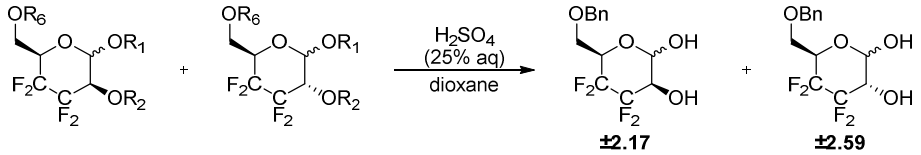
±2.57 R = Me
2.58 R = Et

Remarkably, for the ethyl series, column chromatography allowed the obtaining of pure glucose derivative **2.58** as a 20:1 α/β mixture. The mannose derivative **2.56** was obtained as a 1:10 α/β mixture however along with 5% of α-Glc **α-2.58**. Although a significant mixed fraction of **2.56** and **2.58** was isolated, this was the best separation ever obtained and it was deemed sufficient to pursue the synthesis of at least the tetrafluorinated glucose **1.56**.

2.3.2.3 Hydrolysis of the alkyl glycosides

This strategy afforded the methyl or ethyl glycosides and hydrolysis of the acetal was required as to obtain the unprotected carbohydrates analogues. The hydrolysis conditions that were successfully applied to ethyl hexoside **1.68** (25% aq H_2SO_4 in refluxing dioxane, *cf* section **2.2.2**) were applied to a number of substrates and results are summarised in **Table 2.2**.

Table 2.2: Hydrolysis of alkyl glycosides



entry	substrates Man/Glc	R_1	R_2	R_6	T (°C)	time	products	yield (%)[a] Man/Glc ratio
1	**±2.39/±2.41**	Me	H	Bn	110	5 h	**±2.17/±2.59**	49 / 75:25
2	**±2.39/±2.41**	Me	H	Bn	110	o/n	degradation	-
3	**±2.39/±2.41**	Me	H	Bn	75	5 h	degr.	-
4	**±2.55/±2.57**	Me	H	H	110	5 h	degr.	-
5	**±2.47/±2.48**	Me	Bn	Bn	90-95	5 h	SM	-
6	**±2.40/±2.42** 48:52[c]	Et	H	Bn	70	5 h	**±2.17/±2.59** SM	31 / 85:15 61 / 30:70
7	**±2.40/±2.42** 30:70[c]	Et	H	Bn	100	5 h	**±2.17/±2.59** SM	35 / 58:42 63 / 8:92
8	**±2.40/±2.42**	Et	H	Bn	100	o/n	degr.	-
9	**±2.49/±2.51**	Et	Bn	Bn	100	4.5 h	mainly SM	-
10	**2.53/2.54**	Et	Bz	Bn	100	5 h	SM	-
11[b]	**2.53/2.54**	Et	Bz	Bn	rt	5.5 h	mainly SM	-
12	**±2.51/±2.52** 48:52[c]	Et	Ac	Bn	100	4.5 h	**±2.17/±2.59** **±2.40/±2.42**	53 / 68:32 46 / 14:86

[a] Isolated yields. [b] HBr, AcOH, rt instead of conditions described. [c] ratio

The first attempt conducted at reflux for 5 h starting from methyl glycosides **±2.39**/**±2.41** afforded the desired products **±2.17**/**±2.59** in 49% yield and 75:25 Man/Glc ratio (entry 1). As some starting material was remaining (not isolated), in a second attempt the reaction was left at reflux overnight leading to the degradation of the substrates and products as none of them could be isolated (entry 2). Unexpectedly, when repeating the experiment in entry 1, similar degradation was observed as revealed by the presence of a significant number of spots on the TLC. In fact, the products could be isolated but only in small amounts and along with some inseparable impurities. Thus, to avoid degradation, the temperature was decreased to 75 °C (entry 3). After 5 h, TLC showed almost complete conversion of the starting material but only a small amount of impure product(s) could be isolated after column chromatography suggesting degradation did happen. The hydrolysis of a mixture of the debenzylated derivatives **±2.55** and **±2.57** was tried but after 5 h at reflux, some degradation had already occurred as shown by the presence of many spots on the TLC (entry 4). Lastly, the presence of a benzyl at position 2 resulted in the starting material to be recovered after reaction suggesting an increased stability of the substrate (no degradation) but also a disfavoured hydrolysis as no products were formed (entry 5). The difficulty to perform this hydrolysis most likely arose from the presence of the electronegative fluorine atoms which destabilise the oxonium transition state. Given the good results obtained for the hydrolysis of ethyl 2-deoxyhexoside **1.68**, it was decided to synthesise the ethyl analogues **2.40** and **2.42** described above even though the hydrolysis of 2-deoxyhexoside was known to be easier.

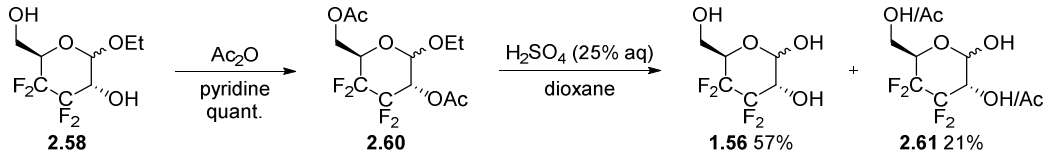
The ethyl glycosides were first heated with 25% aq H_2SO_4 and dioxane at 70 °C for 5 h which afforded the desired hemiacetals **±2.17**/**±2.59** in 31% yield and 85:15 Man/Glc ratio (entry 6). Meanwhile, 61% of unreacted starting material was isolated and consisted of a 30:70 mixture of **±2.40** and **±2.42** respectively. The latter was then treated similarly but at 100 °C for 5 h leading to **±2.17**/**±2.59** in 35% yield for a 58:42 Man/Glc ratio (entry 7). Similarly, 63% of an 8:92 mixture of **±2.40** and **±2.42** was recovered unreacted. The reaction time was increased to 1 d but this resulted in the degradation of the products (entry 8). Once again, the presence of the benzyl at position 2 prevented the reaction from happening as mainly the starting material was recovered after 4.5 h at 100 °C (entry 9). The benzoyl derivatives **2.53**/**2.54** were expected to result in improved yields of hydrolysed products as the carbonyl could stabilise the oxonium transition state by anchimeric effect leading to a very stable benzylic carbocation. On the contrary, the benzoates were left unreacted when treated either with aq H_2SO_4 or with a mixture of HBr and AcOH (entries 10, 11). Finally, a mixture of the acetates **±2.51**/±**2.52** was subjected to the original conditions and after 4.5 h, 53% of the hexoses **±2.17**/**±2.59** were

isolated for a 68:32 Man/Glc ratio (entry 12). The remaining by-products were deacetylated ethyl glycosides **±2.40**/**±2.42** obtained in 46% yield and a 14:86 Man/Glc ratio. The yield improvement is most probably due to the anchimeric effect played by the neighbouring acetate.

Generally, the ethyl glycosides seemed more reactive as 31% of products could be obtained when heating at only 70 °C. They also appeared more stable as the unreacted starting material could be almost entirely recovered in most cases. Larger amounts of Man derivatives were systematically obtained which strongly suggested a greater reactivity of the β anomers compared to the α anomers. In fact, the latter are known to be more stable due to two stabilising anomeric effects (*exo* and *endo*) compared to only one (*exo*) for the β anomers. For example, in entry 6, the proportion of ethyl α-mannoside increased from 10% in the starting mixture to 25% in the recovered starting material (not shown in the table). By calculating the absolute quantities of ethyl α-mannoside before and after the reaction, it can be recognised that virtually none of it has reacted. As the ethyl mannoside **±2.40** was mainly β and the ethyl glucoside **±2.42** mainly α, large amount of hydrolysed Man could be acquired while a significant part of the starting Glc remained unreacted. The neighbouring group participation observed for the acetates did not particularly influence the lack of reactivity of the α anomers as the reaction led to similar Man/Glc ratios for the products and recovered starting materials.

Since satisfactory separation and hydrolysis conditions were now available, the synthesis of F4-Glc **1.56** was achieved as shown in **Scheme 2.18**.

Scheme 2.18: Acetylation and hydrolysis of ethyl glucoside **2.58**



First, standard acetylation of **2.58** gave the 2,6-*O*,*O*-diacetylated glucoside **2.60** which was then subjected without any purification to hydrolysis. After 17 h at 100 °C, fully deprotected enantiopure tetrafluorinated glucose **1.56** was obtained for the first time in 57% yield. Interestingly, the main byproduct was not the expected deacetylated ethyl glucoside **2.58** but presumably the F_4-Glc derivative **2.61** monoacetylated at position 2 or 6. This would mean an extra 21% of desired product after deprotection of the acetyl group. This result was

remarkable as the starting glucoside **2.60** consisted almost exclusively of the α anomer which proved more difficult to hydrolyse in previous experiments. Additionally, no degradation seemed to have occurred even after 17 h at reflux.

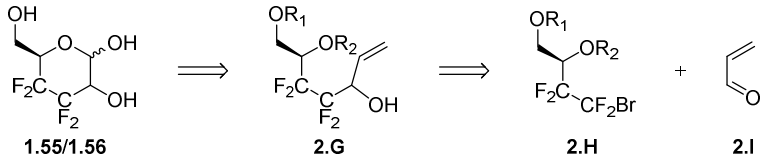
In summary, although tetrafluorinated carbohydrates **1.56** and **1.55** could be accessed *via* intramolecular coupling, due to the difficulties encountered to separate and hydrolyse the F_4-Man and F_4-Glc, a third route was investigated.

2.3.3 Anionic Intermolecular Addition

2.3.3.1 Synthesis

Konno's intermolecular addition of tetrafluorobutenyl lithium to aldehydes and his later short synthesis of 2,2,3,3-tetrafluoro galactose 1.24 and glucose 1.25 inspired us the design of a new retrosynthetic route (*cf* section **1.5.3**). The anomeric aldehyde group would be formed by oxidative cleavage of the double bond of the allylic alcohol **2.G** which would be obtained *via* treatment of known protected tetrafluorobutanediol **2.H** with MeLi in the presence of an α,β-unsaturated aldehyde such as **2.I** (**Scheme 2.19**).

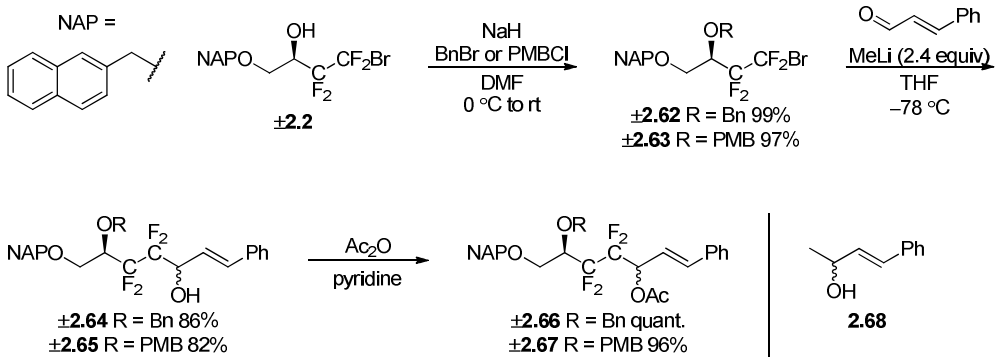
Scheme 2.19: Retrosynthetic route involving an intermolecular addition



In order to follow this route, the secondary alcohol of racemic **±2.2** was protected as the benzyl ether or the *p*-methoxybenzyl ether, the latter allowing its selective deprotection at a later stage (**Scheme 2.20**). For both protections, the alcohol was first deprotonated by NaH in DMF and then reacted with either electrophile resulting in compounds **±2.62** and **±2.63** in almost quantitative yields. The coupling was first tried with the NAP/Bn substrate on a 250 mg scale according to Konno's conditions. It should be noted that for toxicity and reactivity reasons, acrolein **2.I** was substituted for cinnamaldehyde, an electrophile that Konno had successfully reacted with lithiated tetrafluorobutene. Pleasingly, the coupling product **±2.64** was obtained in 82% yield although the separation of the diastereoisomers was not possible, even after quantitative acetylation of the newly formed alcohol (**±2.66**). The coupling reaction starting from 1 g of PMB protected **±2.63** proceeded similarly however the desired product

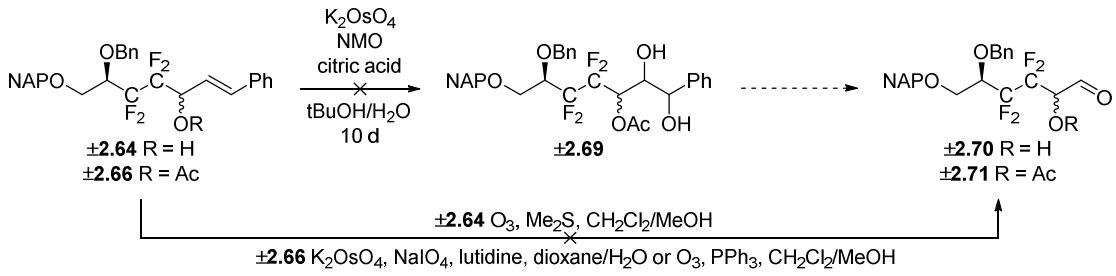
±2.65 and the by-product **2.68** resulting from direct MeLi addition to cinnamaldehyde had similar R*f* which prevented their separation. An estimated yield of 86% could be calculated from the ^{1}H NMR spectrum of the purified mixture. High yielding acetylation allowed the purification of **±2.67** but diastereoisomers remained inseparable.

Scheme 2.20: Coupling reaction with dietheral substrates



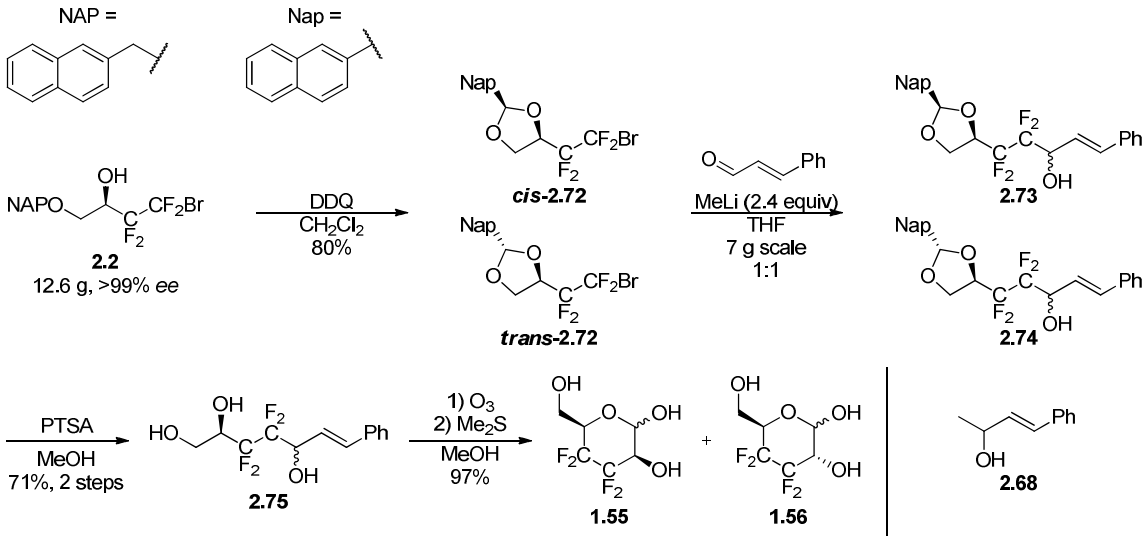
Nevertheless, the oxidative cleavage of the double bond was attempted on the mixtures of diastereoisomers **±2.64** and **±2.66** (**Scheme 2.21**). Both mixtures were first subjected to ozonolysis but this led to the formation of numerous aldehyde-containing products as revealed by ^{1}H NMR analysis of the crude material. It was believed that because of its lower aromaticity, the naphthalene unit could probably have reacted with ozone resulting in numerous by-products. Thus, a one-pot dihydroxylation/oxidative cleavage was tried on the mixture of acetates **±2.66** using dipotassium osmate and sodium periodate. Although no more starting material could be observed after 21 h, the reaction also led to a complex mixture of products. It was then decided to perform the dihydroxylation first, followed by the oxidative cleavage of the obtained diol. Hence, **±2.66** was subjected to the racemic dihydroxylation conditions developed for tetrafluorobutene **1.73** but after ten days at rt, only the starting material was retrieved.

Scheme 2.21: Attempted formations of aldehydes **2.70** and **2.71**



The presence of the naphthyl presented a problem for the ozonolysis reaction as it led to side reactions and its removal prior to subjection to ozone was therefore necessary. It was then envisioned to fully deprotect the diol before the ozonolysis reaction. Hence, the latter would lead directly to the cyclised 6-deprotected carbohydrate derivatives. Consequently, and in the interest of atom economy, it was decided to protect the secondary alcohol *via* conversion of the 2-naphthylmethyl ether **2.2** into the naphthylmethylidene acetal **2.72**, which was expected to be less electron rich compared to a naphthyl methyl ether. In fact, following an adapted procedure from Ishitawa,[73] multigram scale oxidation by DDQ under anhydrous conditions led to the expected benzylic carbocation which was trapped by the vicinal alcohol yielding **2.72** in 80% yield as a crystalline 1:1 mixture of diastereoisomers (**Scheme 2.22**). Interestingly, the acetal diastereoisomers could be easily separated by column chromatography, leading to crystalline solids. Stereochemical assignment of the diastereoisomers was possible after X-ray crystallographic analysis (**Figure 2.7**).

Scheme 2.22: Naphthylmethylidene acetal formation and target analogues synthesis



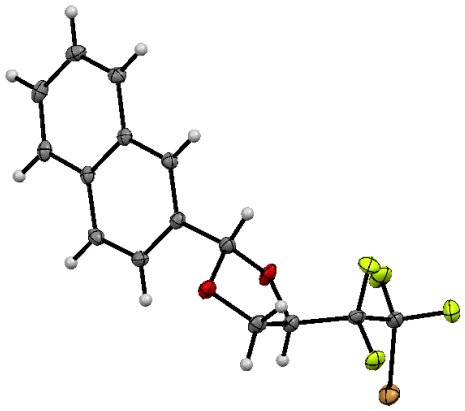


Figure 2.7: X-ray crystallographic analysis of ***trans*-2.72**

Pleasingly, the change in protecting group did not affect the outcome of the coupling reaction, with yields of **2.73/2.74** around 80% obtained again. The reaction proved unselective starting from either acetal diastereoisomer **2.72**, both leading to a 1:1 mixture of alcohol diastereoisomers (**2.73** or **2.74**), which were not separable (not shown). Additionally, the mixture of alcohol diastereoisomers **2.74**, obtained from ***trans*-2.72**, and the inevitable cinnamaldehyde/MeLi addition by-product **2.68**, had similar R*f* values and were therefore not separable. Similarly, the mixture of alcohol diastereoisomers **2.73**, obtained from ***cis*-2.72**, and by-product **2.68** were not easily separable, although the substitution of petroleum ether for toluene as the eluent apolar solvent allowed for a better separation. However, cleavage of the naphthaldehyde acetal of **2.73** afforded the much more polar triol **2.75** which was then readily separated from **2.68**.

Since, the stereochemistry of the acetal did not influence the stereochemical outcome of the coupling reaction, the subsequent coupling reactions were performed on a *cis*/*trans* mixture of **2.72** (up to 7 g) giving the four inseparable diastereoisomers **2.73**/**2.74** and **2.68**. As the purification of the triol **2.75** was much easier, the crude mixture obtained was directly dissolved in MeOH and treated with 10 mol% of PTSA offering the triol **2.75** in 71% yield over the two steps. Unfortunately, the *syn* and *anti* diastereoisomers were not separable at this stage. Ozonolysis was then attempted on the triol and cleanly provided the mixture of tetrafluoromannose **1.55** and glucose **1.56** in 97% yield after separation from the by-products benzaldehyde and DMSO by column chromatography. The reaction was accomplished on a maximum 2.5 g scale affording the desired sugars in a slightly diminished 89% yield.

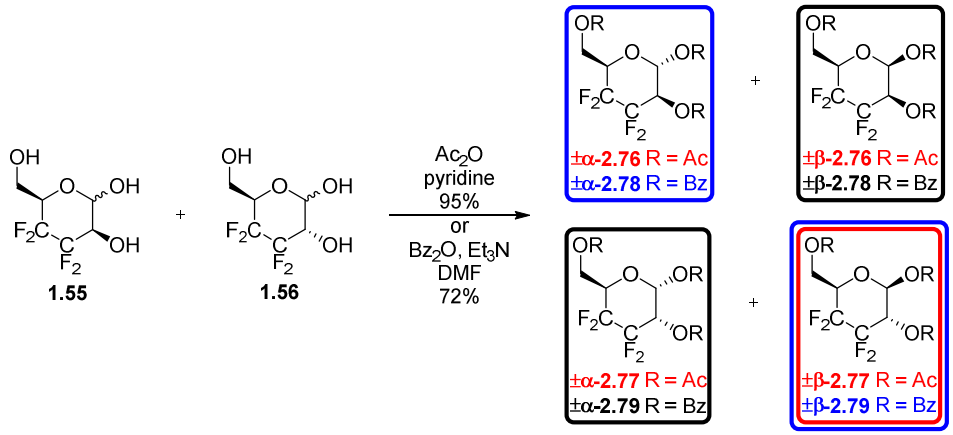
2.3.3.2 Separation

Unfortunately, the mannose and glucose sugars **1.55** and **1.56** could not be separated. Although the latter synthetic strategy was superior over the first two, with a 51% overall yield from enantiopure alcohol **2.2**, the separation of the carbohydrate analogues **1.55** and **1.56** had to be achievable to prove the real benefit of this route. Again, derivatisation reactions were attempted. First, a standard peracetylation (acetic anhydride/pyridine) was carried out which gave the four triacetate diastereoisomers **±2.76** and **±2.77** in 95% yield (**Scheme 2.23**). Column chromatography using $CHCl_3$/EtOAc 96:4 as eluent only allowed the incomplete isolation of glucose derivative **±β-2.77** (red frame) still contaminated with up to 5% of the other anomer **±α-2.77**, leaving a second mixture fraction still containing the four diastereoisomers. After repeated chromatography, 27% of a 4:96 α/β mixture of glucose derivative **±2.77** could be isolated. However, the tri-*O*-acetyl mannose derivative **±2.76** could never be completely

separated from the two anomers of glucose triacetate, even by means of HPLC, leading to a 3:97 Glc/Man mixture at best.

Interestingly, the β-anomer of tetrafluoroglucose triacetate **±β-2.77** could be recrystallised and analysed by X-ray diffraction (**Figure 2.8**). Once again, the tetrafluorinated carbohydrate adopted the $^4C_1$ conformation characteristic of the natural glucose.

Scheme 2.23: Peracylation of tetrafluorinated mannose and glucose



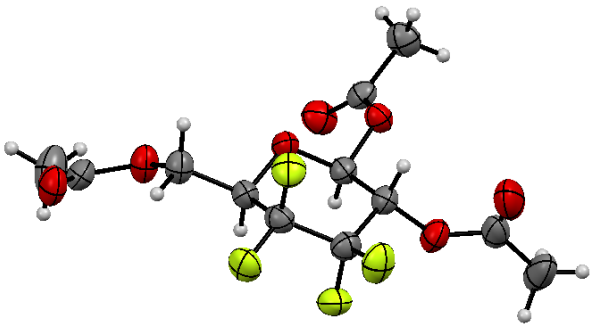


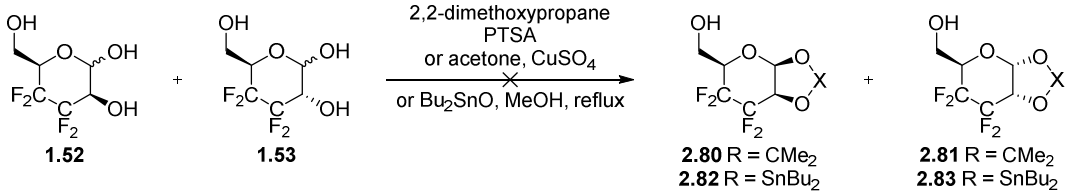
Figure 2.8: X-ray crystallographic analysis of **±β-2.77**

It was then decided to introduce the bulkier benzoyl protecting group using benzoic anhydride and Et_3N which afforded the compounds **±2.78** and **±2.79**.[74] Unfortunately, it only allowed the separation of the 1,2 *syn* isomers i.e. the tribenzoyl β-Man **±β-2.78** and α-Glc **±α-2.79** (black frame) from the 1,2 *anti* isomers i.e. the tribenzoyl α-Man **±α-2.78** and β-Glc **±β2.79** (blue frame).

When investigating the first synthetic route involving the 1,2-acetonides, we reported (**Scheme 2.4**) that the 6-O-benzyl ethers **±2.14a** and **b** were separable by HPLC. Hence, it was attempted to protect **1.55**/**1.56** accordingly. Although evidence of the formation of 1,2-*O*,*O*-

isopropylidene or stannylene acetals was found in the literature for Man and Glc, none of the compounds **2.80**-**2.83** could be obtained under similar conditions (**Scheme 2.24**).[75,76]

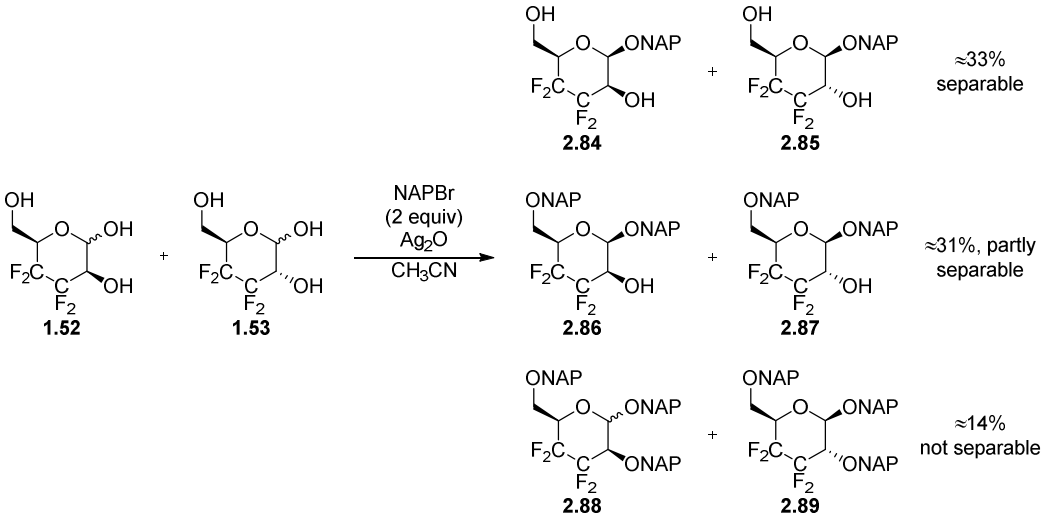
Scheme 2.24: Formation of 1,2-*O*,*O*-isopropylidene and stannylene acetals



Contemplating previous results, the glucose could only be separated from the mannose if the anomeric position was protected (*cf* **±2.55**-**2.58**, section **2.3.2.2**). The pKa of the anomeric alcohol of natural Man and Glc had been measured at 12.1 and 12.5 respectively, and the inductive effect of the fluorine atoms should lead to a further decrease.[77] Although the pKa of the 2-OH should be very similar for **1.55** and **1.56** (*cf.* section **1.3.2**, pKa of F_4-PrOH is 12.7), it was envisioned that the anomeric position could be selectively protected if such sugars were treated with one equivalent of base in the presence of an electrophile e.g. an alkyl bromide. Accordingly, a mixture of deprotected F_4-sugars and two equivalents of 2-bromomethylnaphthalene was dissolved in THF before addition of 1.1 equiv of NaH but after 3 h at rt, no reaction had occurred as indicated by TLC. The number of equivalents of base and electrophile was increased, TBAI was added, the THF was substituted for DMF or NAPBr exchanged for PMBCl but the reaction outcome remained unchanged (not shown). The base was then switched for Ag_2O, which is known to also activate alkyl chlorides or bromides. As the primary alcohol was expected to react substantially, it was decided to treat the mixture of fluorosugars in CH_3CN with 2.2 and 2.5 equiv of NAPBr and Ag_2O respectively. As shown in **Scheme 2.25**, around 45% of disubstituted products were formed among which 31% at position 1 and 6. Interestingly, and as reported for benzyl,[78] the reaction demonstrated a strong β-selectivity which probably accounted for the fact that **2.86** and **2.87** were partly separable. Another 14% mainly consisted of an inseparable 3:1 mixture of trisubstituted β-Glc **2.89** and Man **2.88**. Despite the use of an excess of reagents, a remarkable 33% of 1-*O*-NAP β-Man **2.84** and β-Glc **2.85** could be first isolated and then separated after careful column chromatography ($CHCl_3$/Et_2O). The beta selectivity of the anomeric alkylation process was remarkable, but expected from 'kinetic anomeric effect' considerations which attribute a higher reactivity to the beta oxyanion. As the protection occurred mainly at the anomeric

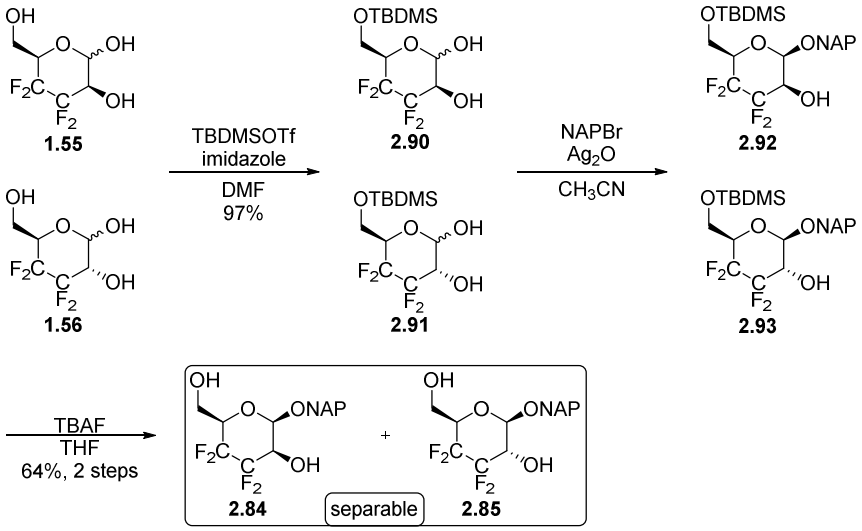
position, the next obvious choice was to try the reaction with a reduced amount of reagents but surprisingly, this resulted in an unselective process leading to a rather complex mixture. Nonetheless, this was a significant step towards the separation of the tetrafluorinated carbohydrates.

Scheme 2.25: Naphthylmethylation of F_4-Man and F_4-Glc



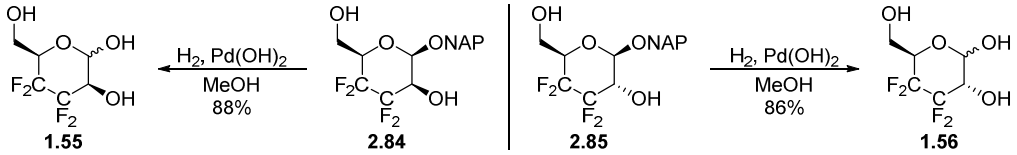
The second most reactive alcohol was clearly the primary 6-OH, and to circumvent the detrimental introduction of NAP at this position, its protection was envisaged before anomeric naphthylmethylation. As orthogonal and easily removable protecting group, the TBDMS group was selected, and was introduced by means of its triflate and imidazole in excellent yield and selectivity (**Scheme 2.26**). The silylated hexoses **2.90** and **2.91** were then subjected to the same anomeric alkylation conditions explained above, which afforded the desired products **2.92** and **2.93** and their isomers in 82% yield on a gram scale. The reaction demonstrated great β- and regio- selectivities as 1-*O*-NAP-β-Glc **2.93** was almost exclusively formed with only 2% of α anomer and no regioisomer observed. For the mannose derivative, the β-selectivity proved similar with 3.5% of α anomer while the regioselectivity significantly decreased as no less than 14% of unwanted 2-*O*-NAP-Man was detected (not shown). An explanation for this might be that the 3-F_{ax}/2-OH transdiaxial relation, only present for the mannose derivative, rendered the 2-OH more acidic compared to the 2-OH of the glucose derivative. Subsequent deprotection of the TBDMS group using TBAF in THF allowed the separation of the products **2.84** and **2.85** *via* column chromatography. The glucose analogue fractions were contaminated with an unknown impurity which seemed not carbohydrate related so the yield could only be estimated to 77%.

Scheme 2.26: Successful separation route



Finally, the NAP groups of the individual glucose and mannose derivatives were removed by hydrogenolysis using Pearlman's catalyst affording each desired tetrafluorinated mannose and glucose analogues in excellent 86% and 88% yields respectively (**Scheme 2.27**).

Scheme 2.27: Hydrogenolysis of the 2-naphthylmethyl protecting groups



In conclusion, while the synthesis of the 3,3,4,4-tetrafluorinated sugar rings was easily achieved, the separation of **1.55** and **1.56**, and of all their precursors obtained after the coupling reaction, proved very difficult. The varying stereochemistry at the anomeric centre precluded any separation due to preferred spatial arrangements of the 1,2-diol. In fact, when fixed, and particularly in the case of the bulky benzoyl protecting groups (**±2.78** and **±2.79**), the *syn* and *anti* isomers could be cleanly separated. The high β-selectivity of the naphthylmethylation fixed the orientation of the anomeric alcohol as a bulky ether allowing the discrimination between the mannose and glucose analogues. This difficult separation had a cost in that it required four extra steps for an overall yield of 27% per sugar. As a consequence, the total yield was approximately 14% for each sugar from the enantiopure diol **2.2**.

2.3.4 Configurational analysis

Recrystallisation of both **1.55** and **1.56** from hexane/acetone afforded crystals suitable for X-ray diffraction (**Figure 2.9**). Both compounds crystallised as the β-anomer and adopted the $^4C_1$ conformation. A slight distortion of the chair was visible probably due to repulsion between O-2 and F-4_{ax} in **1.55** and between O-2 and F-3_{ax} in **1.56**. This means that the introduction of the tetrafluoroethylene moiety does not drastically alter the shape of the natural carbohydrates.

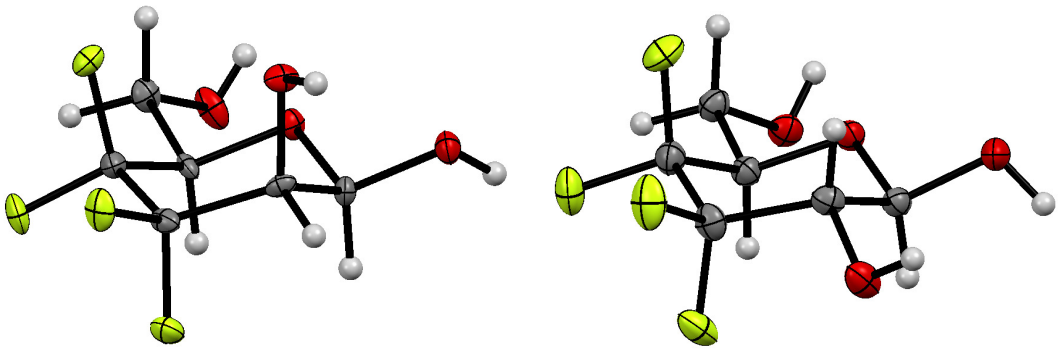


Figure 2.9: X-ray crystallographic analysis of **1.55** (left) and **1.56** (right)

The conformation and configuration at C-2 could also be confirmed in solution in acetone-*d*6 by analysing the coupling constants between C-2 and both F-3_{ax} and F-3_{eq} in the ^{13}C NMR spectra. Indeed, a study of the $^2J_{C\text{-}F}$ coupling constants found in several monodeoxyfluoro carbohydrates has highlighted a trend depending on the orientation of the electroattractive substituent borne by the carbon with respect to the coupled fluorine. As shown in **Figure 2.10**, if the electroattractive substituent on the coupled carbon is *gauche* to the fluorine, the $^2J_{C\text{-}F}$ values are approximately 18 Hz. However, in the case of a *trans* orientation, the magnitude of the $^2J_{C\text{-}F}$ increases to 24 Hz or above.[79]

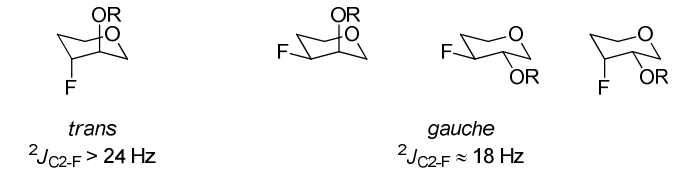


Figure 2.10: Typical $^2J_{C\text{-}F}$ values for various monodeoxyfluorosugars[79]

This trend has been successfully used by our group to determine the configuration and conformation of several polyfluorinated carbohydrates.[48]

For both anomers of **1.55**, the $^{2}J_{C2\text{-}F3}$ values observed were approximately 29 and 19 Hz, indicating that the electronegative substituent at C-2 is *trans* to F-3_{ax} and *gauche* to F-3_{eq} (**Figure 2.11**). The alcohol at C-2 is therefore in axial position which is supportive of a mannose configuration for **1.55**. In contrast, the $^{2}J_{C2\text{-}F3}$ values observed for both anomers of **1.56** were around 18Hz for both axial and equatorial fluorines, indicating a *gauche*/*gauche* orientation of the electronegative substituent at C-2 with respect to the fluorines (**Figure 2.12**). This means that the alcohol at C-2 is in equatorial position which is indicative of a glucose configuration for **1.56**. These values also suggest that both tetrafluoromannose and glucose retain the pyranose form and chair conformation in solution in acetone-*d*6.

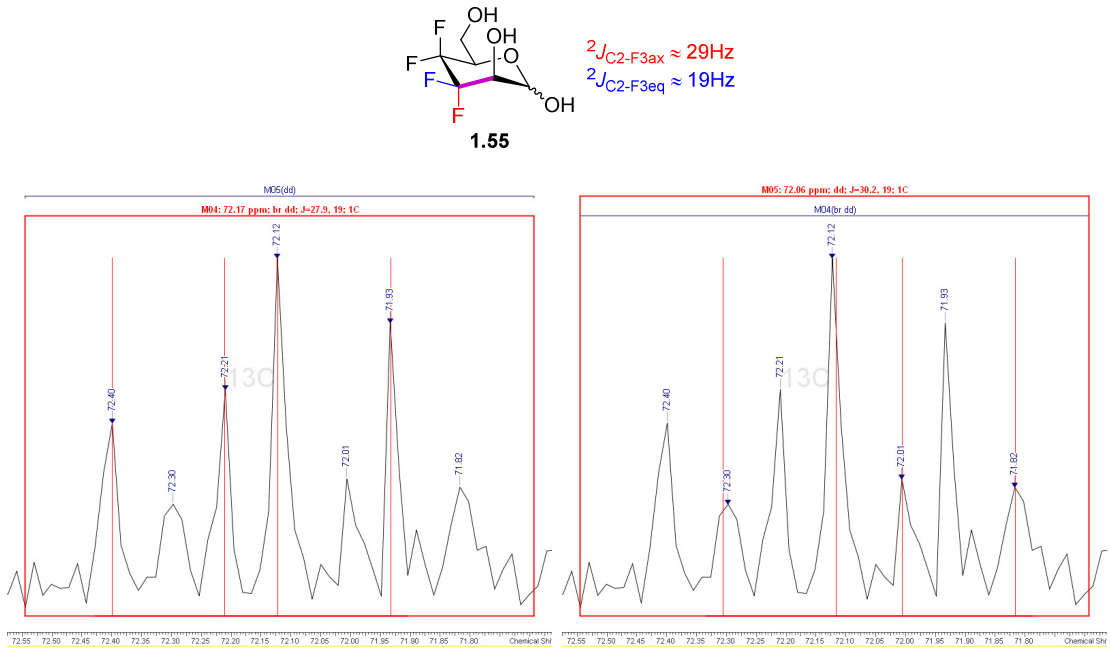


Figure 2.11: Detail of the ^{13}C NMR spectrum of **1.55** centred on C-2, β anomer (left) and α anomer (right)

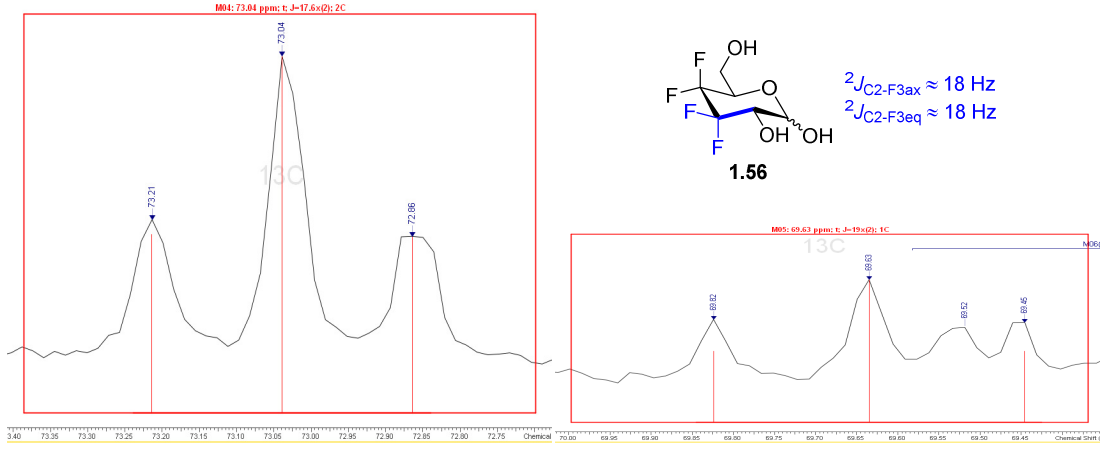


Figure 2.12: Detail of the ^{13}C NMR spectrum of **1.56** centred on C-2, β anomer (left) and α anomer (right)

2.3.5 Summary

The first synthesis relying on the radical addition of **±1.66** to dimethyldioxole was undoubtedly the shortest with three steps from the starting alcohol **1.66**. It also had the advantage to provide the mannose and glucose as the 1,2-acetonide intermediates **±2.14a** and **b** which were directly separable by HPLC. However, the yield for the crucial radical reaction never exceeded 22% resulting in an overall yield of 8% of each carbohydrate **1.55** and **1.56** from the starting bromide **±1.66**.

The second synthesis afforded the anomeric alkyl mannoside and glucoside mixture in good yields over three steps. However, both the separation and the hydrolysis of the anomeric substituent proved capricious and were only possible with the ethyl glycosides, which necessitated a low-yielding synthesis of the methyl bromoethoxyacetate reagent **2.34**, also in three steps. The product separation required the removal of the 6-*O*-benzyl group, which is unfortunate as the 6-OBn protection would have permitted an orthogonal protection of the 2-OH group. In addition, although this strategy allowed the isolation of pure ethyl glucoside derivative **2.58**, the corresponding mannose analogue **2.56** was isolated with 5% of the glucose analogue **2.58**. The hydrolysis required the anchimeric assistance of an ester group to reach good yields. In conclusion, the tetrafluoroglucose **1.56** (and in principle mannose **1.55**) was obtained in 12% overall yield (≈17% with monoacetate **2.61**) in six steps from the starting bromide **1.66**.

Finally, the last route inspired by Konno's work offered each tetrafluorinated carbohydrate in eight steps for an overall yield of approximately 14% per sugar. However, the ease of this synthesis must be considered. First, every step was achievable on gram to multigram scale including the crucial MeLi mediated coupling, which was performed starting from 7 g of bromide **2.72**. Secondly, apart from the final hydrogenolyses which were left overnight, the seven remaining steps required reaction time shorter than 5 h, with an average of 2.6 h per step. Additionally, among the eight steps, one did not necessitate any purification while four benefitted from easy work-up procedures such as filtration or direct evaporation. At last, I believe that this last method has the greatest potential for improvement especially regarding the four steps required to achieve the separation. Further optimisation for the naphthylmethylation reaction, including a solvent and temperature screenings, should be possible, including a one-pot naphthylmethylation/desilylation sequence, since TBAF mediated silyl ether cleavage is possible in CH_3CN. For all these reasons, the last route was deemed the most effective and practical.

Chapter 3: Synthesis of Tetra- and Difluorinated Aminosugars

3.1 Targets

As explained in the introduction, our group has developed an interest in the synthesis of tetrafluorinated aminosugars as analogues of the corresponding tetrafluorinated sugars, in order to restore the hydrogen bond accepting capacity lost by the alcohol upon adjacent introduction of the CF_2CF_2 moiety.

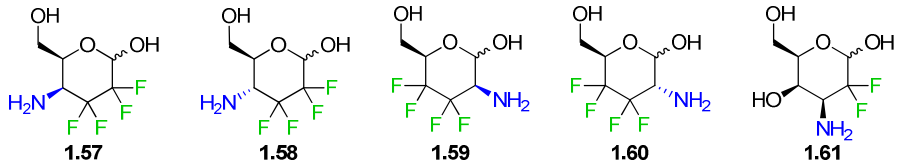


Figure 3.1: 2,2,3,3- and 3,3,4,4-tetrafluoroaminosugars and 2,2-difluoro-3-amino-D-galactose

A synthesis of 2,2,3,3-tetrafluoro galactose **1.24** and glucose **1.25** had been previously developed within our group[47] and in view of our strategy to restore the hydrogen bond accepting capacity at position 4, the corresponding amino analogues **1.57** and **1.58** became of interest (**Figure 3.1**). The galactose configured derivative **1.57**, is a specific target to investigate as substrate for the enzyme galactose oxidase.[49] It had been previously established that 2,2,3,3-tetrafluoro galactose **1.24** is a weak substrate for GOase, but the presence of a H-bond acceptor at position 4 appeared crucial for GOase activity (the glucose derivative **1.25** showed no activity)..

The 2-amino-2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-*threo*- and D-*erythro*-hexopyranose **1.59** and **1.60** will be synthesised as direct analogues of the non aminated tetrafluorinated carbohydrates **1.55** and **1.56** described above. Additionally, their *N*-acetyl derivatives are of interest as analogues of ManNAc and GlcNAc, two crucial sugars found in many biologically relevant saccharides..

Finally, we were interested in synthesising 3-amino-2,3-dideoxy-2,2-difluoro-D-*lyxo*-hexopyranose (**1.61**), an amino analogue of galacto configured difluorosugar **1.23** with an improved hydrogen bond accepting capacity at position 3. The aminosugar **1.61** will also be tested for oxidation by GOase and will be compared not only to the previously reported

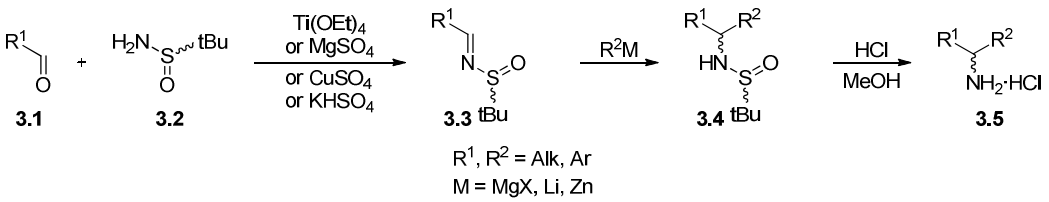
compounds **1.23** and **1.24** but also to the newly synthesised tetrafluoro 4-aminogalactose analogue **1.59**.

3.2 Chiral amine synthesis *via* the Ellman auxiliary

3.2.1 Addition of lithiated nucleophiles

The synthesis of chiral amines has been revolutionised by the introduction of the *N-tert*-butanesulfinylimine system, which appear to undergo many types of highly selective addition reactions.[80] *N-Tert*-butanesulfinylimines **3.3** are readily obtained in high yields by condensation of the corresponding aldehydes and Ellman's *tert*-butanesulfinamide (**3.2**), a chiral molecule of which both enantiomers are commercially available and relatively inexpensive (**Scheme 3.1**).[81] Moreover, the addition of various organometallic nucleophiles to such sulfinylimines is known to afford chiral sulfinamides **3.4** generally with high diastereoselectivity and very good yields. Aryl sulfinylimines usually exhibit greater selectivities than their alkyl counterparts. The auxiliary is then easily removed using HCl in Et_2O or dioxane and MeOH as co-solvent giving the corresponding chiral amines **3.5** as their hydrochloride salt which can be most of the time precipitated in excellent yields.[80]

Scheme 3.1: Condensation of aldehydes with *tert*-butanesulfinamide and organometallic addition



Grignard reagents derived from alkyl or aryl substrates have been found to show the best results in non-coordinating solvents such as CH_2Cl_2 or toluene, which is in agreement with the chelated Zimmerman-Traxler transition state proposed by Ellman, predicting a *Re*-face attack for an *S* configured sulfinylimine (**TS-1**, **Figure 3.2**).[82]

Organolithium reagents typically resulted in lower diastereoselectivities than the Grignard reagents. The outcomes could be improved by the use of Lewis acids additives such as BF_3 or $AlMe_3$ or coordinating solvents like THF which both interfere with chelation control. This is supportive of an open transition state in which the S—O bond is antiperiplanar to the C=N bond allowing a Si-face attack from the least hindered side of the sulphur lone pair (**TS-2**,

Figure 3.2).[83] Remarkably, this means that Grignard and organolithium reagents achieve opposite diastereoselectivities.

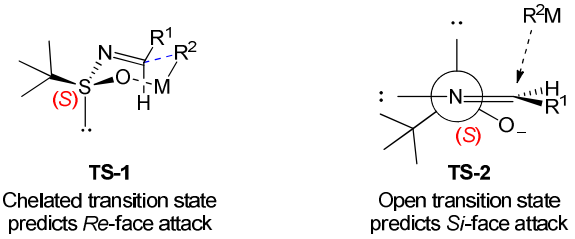
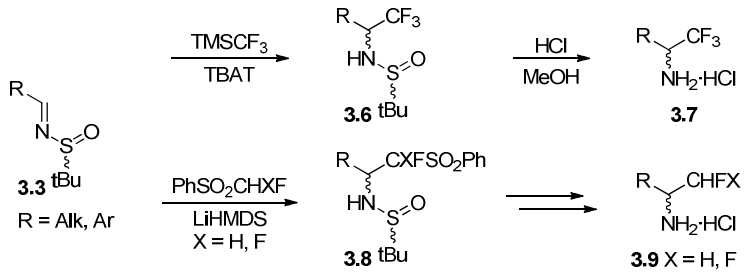


Figure 3.2: Proposed transition states for addition of Grignard *vs* organolithium reagents

Ortholithiation of *N*-Boc anilines and indoles as well as Li-Br exchange performed on heteroaryl and vinyl bromides also afforded the corresponding sulfinamides diastereoselectively according to **TS-2**.

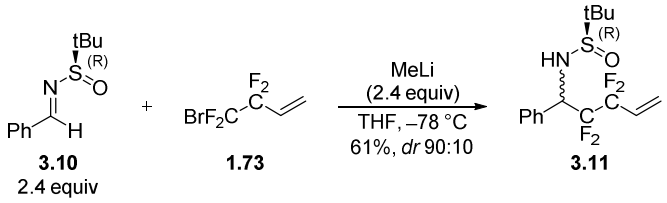
Regarding fluorinated nucleophiles, the diastereoselective addition of the Ruppert-Prakash reagent $TMSCF_3$ was successfully achieved as well as the addition of monofluoro or difluoro-(phenylsulphonyl)-methyl lithium offering the β-fluorinated chiral amines **3.7** and **3.9** (**Scheme 3.2**).[84-86] The diastereoselective outcome of the reactions was also consistent with an open transition state.

Scheme 3.2: Synthesis of β-fluorinated chiral amines



As illustrated in **Scheme 3.3**, Konno *et al.* had successfully described the addition of tetrafluorobutenyl lithium to the benzaldehyde derived *N*-*tert*-butanesulfinylimine **3.10** leading to the fluorinated sulfinamide **3.11** in a 61% isolated yield and a 90:10 diasteroisomeric ratio.[59]

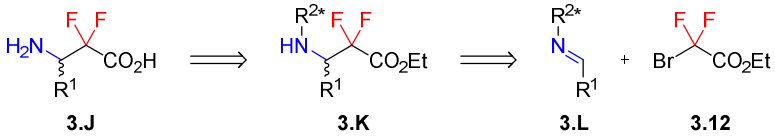
Scheme 3.3: Konno's reductive coupling of **1.73** with benzaldehyde derived *N-tert*-butanesulfinylimine **3.10**[59]



3.2.2 Reformatsky-type reaction

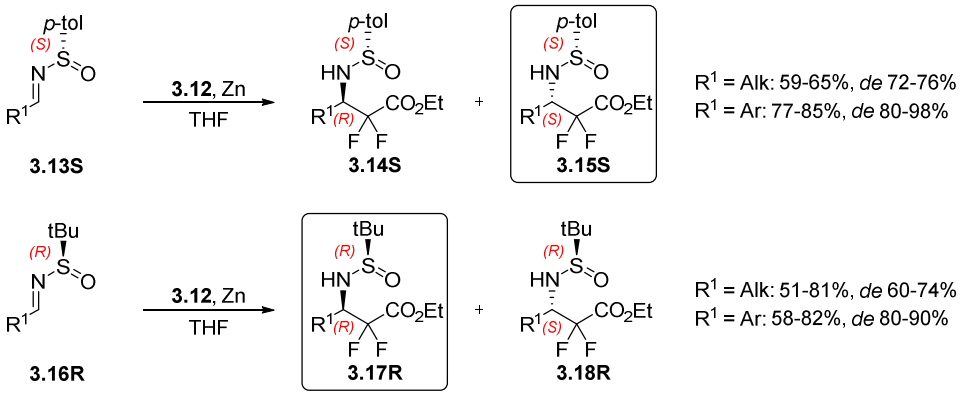
The Reformatsky addition of **3.12** to chiral imines proved the method of choice to access α,α-difluoro-β-aminoacids (**Scheme 3.4**, **3.J**), molecules that have received a great attention for their conformational properties and biological activities.[87]

Scheme 3.4: Retrosynthesis of α,α-difluoro-β-aminoacids *via* Refomatsky reaction with chiral imines



In 2002, Soloshonok and Staas, and their respective colleagues, both pioneered the use of sulfinylimines for Reformatsky reactions involving ethyl bromodifluoroacetate (EBDFA, **3.12**) and Zn dust (**Scheme 3.5**). The suffix *R* or *S* in the numbering refers to the absolute configuration of the sulfinylimine auxiliary. Soloshonok worked with (*S*)-*p*-toluenesulfinylimines **3.13S**[88] while Staas preferred the (*R*)-*tert*-butanesulfinylimines **3.16R**.[89] The sulfinyl auxiliaries had the critical advantage to prevent the cyclisation of the newly formed amine onto the carbonyl of the ester. This spontaneous side-reaction forms undesired β-lactams and is usually observed or is even predominant with other auxiliaries such as those derived from (*R*)-phenylglycinol. As for the Grignard or organolithium reagents, the imines derived from aliphatic aldehydes generally exhibited lower yields and *de* compared to their aromatic counterparts. Both auxiliaries resulted in the same stereoinduction (for the same sulfinyl configuration) proving that they act through the same mechanism, although the *p*-tolyl group seemed to result in slightly higher *de* than the *tert*-butyl.

Scheme 3.5: Diastereoselective Reformatsky reactions with sulfinylimines



The stereochemical outcome of these Reformatsky reactions was consistent with the transition states proposed by Ellman and Davis for other nucleophilic additions to sulfinylimines (e. g. Grignards, lithium or titanium enolates).[82,90] As shown in **Figure 3.3**, both follow a Zimmerman-Traxler type transition state leading to a *Re*-face attack (for an (*S*)-configured sulfinyl auxiliary) but **TS-1** involves a *C*-metallated enolate while **TS-3** accommodates the corresponding *O*-metallated enolate. In both cases, the sulfinylimine adopts the favoured *E* geometry which allows the larger R group to lay in pseudo-equatorial position in **TS-1** while the triple chelation in **TS-3** forces the R group to be in pseudo-axial position.

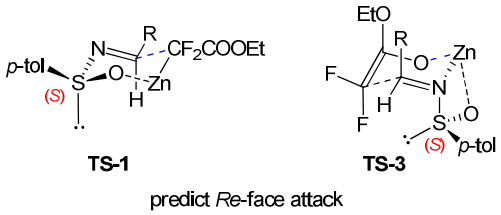


Figure 3.3: Ellman (**TS-1**, **TS-3**) and Davis (**TS-3**) transition state models for the addition to sulfinylimines[82,90]

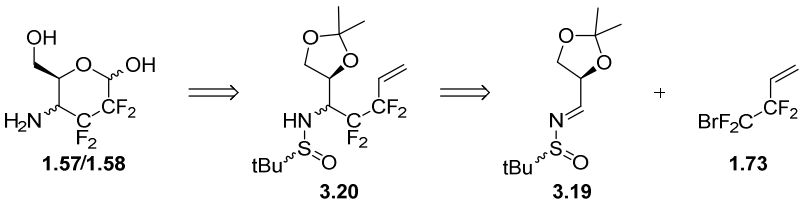
3.3 Synthesis of 2,2,3,3-tetrafluoro-4-aminosugars

3.3.1 Synthesis of 4-amino-2,2,3,3-tetrafluoro-D-*erythro*-hexopyranose 1.58

Konno's synthesis of the tetrafluorinated galactose **1.24** and glucose **1.25** was very efficient (*cf* **Scheme 1.8**) and its application to the synthesis of tetrafluoro 4-aminosugars quite obvious given that lithiated **1.73** successfully added to the sulfinylimine **3.10**. The desired compounds **1.57**-**1.58** would be obtained by the same deprotection/ozonolysis sequence performed on the

sulfinamide **3.20** obtained after coupling between bromotetrafluorobutene **1.73** and the glyceraldehyde acetonide derived *N-tert*-butanesulfinylimine **3.19** (**Scheme 3.6**).

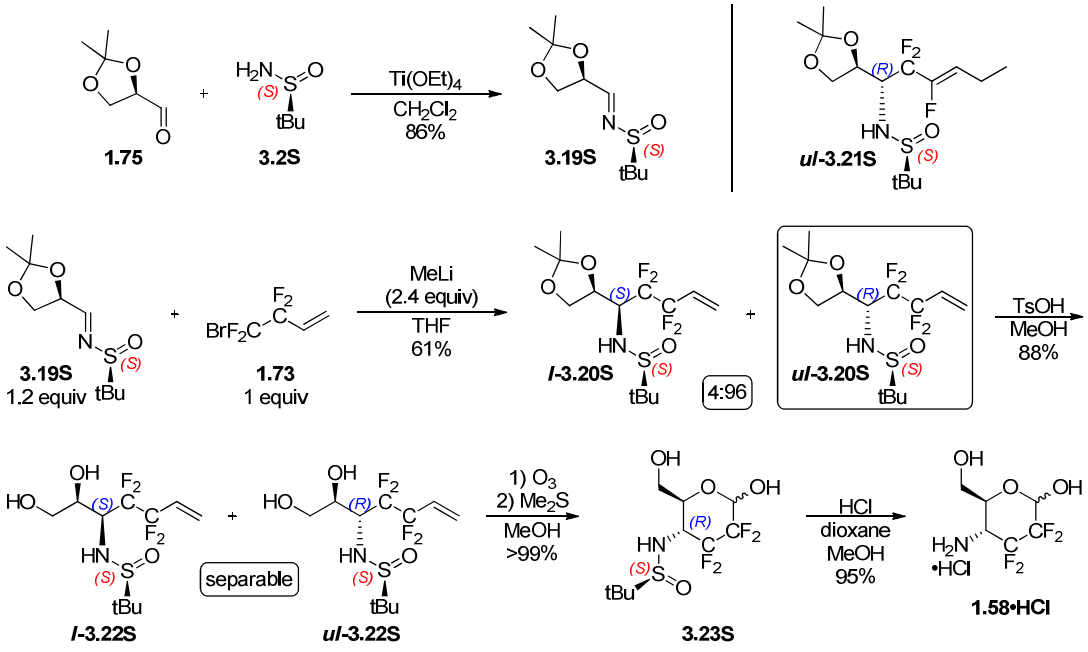
Scheme 3.6: Retrosynthetic route using glyceraldehyde derived *N-tert*-butanesulfinylimine **3.N**



D-Glyceraldehyde acetonide **1.75** was prepared in two steps from D-mannitol following Schmid and Bryant's large scale synthesis (not shown).[91] The (*S*)-*N-tert*-butanesulfinylimine **3.19S** was synthesised in 86% yield with $Ti(OEt)_4$ according to Ellman's procedure from which the work-up was simplified to a single filtration only (**Scheme 3.7**).[92] A single diastereoisomer was obtained, proving that no epimerisation of the aldehyde had taken place as reported by Ellman.and co-workers.[93]

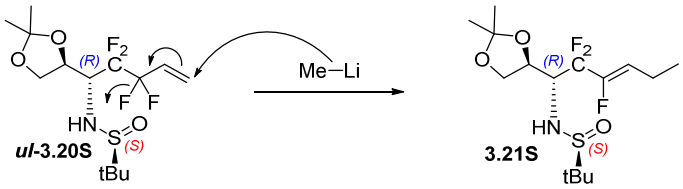
First, Konno's coupling conditions were exactly reproduced by using 2.4 equiv of sulfinylimine **3.19S**. This resulted in an 8:92 mixture of the diastereoisomers ***l*-3.20S** and ***ul*-3.20S** isolated in 78% yield. The prefix *l* (like) indicates that the sulfinyl group and the newly formed amine stereocenter have the same absolute configuration (and otherwise for *ul* (unlike))

Scheme 3.7: Syntheses of *N-tert*-butanesulfinylimine **3.19S** and tetrafluorinated glucosamine **1.58·HCl**



However, three steps were required for the preparation of the sulfinylimine **3.19S** compared to the bromide **1.73** which is commercially available. Hence, the number of equivalents of **3.19S** was reduced to 1.2 in order to increase the isolated quantity of adducts ***l*-** and ***ul*-3.20S**. Starting from no less than 2.5 g of sulfinylimine, this afforded a 4:96 diastereoisomeric mixture isolated in 61% yield. Although the yield was lower, almost 2 g of adducts ***l*-** and ***ul*-3.20S** were obtained, a quantity which would have not been reached following Konno's conditions. Apart from the product of direct MeLi addition to the sulfinylimine (not shown), another by-product was observed which represented *circa* 3% of the addition products ***l*-** and ***ul*-3.20S**. Despite isolation in pure form was not possible, it could be assigned as **3.21S**, the result of a MeLi S_N2' addition to ***ul*-3.20S** (**Scheme 3.8**). The ethyl group as well as the ethylenic proton were clearly observed in the ^{1}H NMR spectrum, and the $^3J_{H-F}$ value of 36.5 Hz indicated a *Z*-substituted fluoroalkene. Three resonances were observed in the ^{19}F NMR spectrum, with two signals showing a large coupling constant of 264.4 Hz representative of a geminal CF_2 group, while the third signal showed the recurrence of the $^3J_{H-F}$ value of 36.5 Hz. This type of by-product, not reported by Konno when performing the reaction with the aldehyde **1.75**, was undoubtedly due to the excess of MeLi relative to the sulfinylimine. This is an interesting S_N2' reaction similar to the C-C bond forming S_N2' process recently described by Paquin *et al*.[94]

Scheme 3.8: Proposed identity and formation of the by-product **3.21S**



Interestingly, this by-product had not been observed when 2.4 equiv of sulfinylimine were employed as the excess of MeLi reacted preferably with the excess of sulfinylimine remaining in the medium.

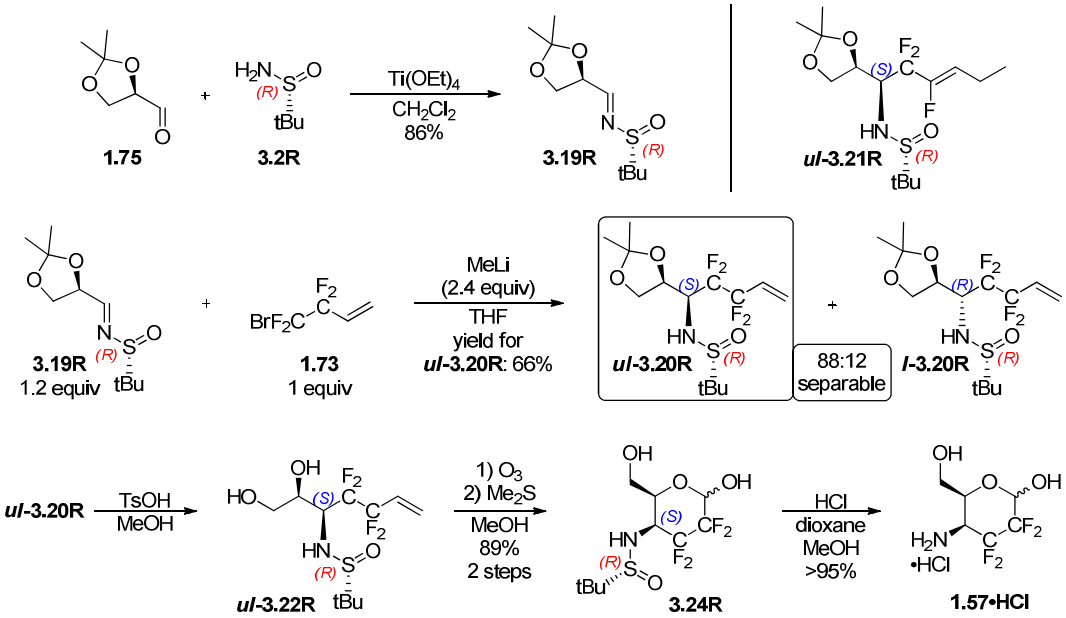
Hydrolysis of the acetonide afforded the corresponding diastereoisomeric diols from which the pure major diastereoisomer ***ul*-3.22S** could be isolated in 88% yield. Alkene ozonolysis performed on 1.6 g of material offered quantitatively the tetrafluorinated *N*-sulfinylglucosamine **3.23S**. Finally, auxiliary removal using 4M HCl in dioxane with MeOH as co-solvent allowed the precipitation from Et_2O of tetrafluoroglucosamine hydrochloride **1.58·HCl**

as pure α anomer. The anomeric equilibrium in CD_3OD consisted of a 75:25 α/β anomeric mixture.

3.3.2 Synthesis of 4-amino-2,2,3,3-tetrafluoro-D-*threo*-hexopyranose 1.57

For the galacto configured derivative **1.57**, the (*R*)-configured sulfinylimine **3.19R** was synthesised in 86% yield following the same procedure as for **3.19S** (**Scheme 3.9**). The coupling reaction was performed starting from 1.2 equiv of sulfinylimine **3.19R** on 500 mg scale which cleanly afforded the two diastereoisomers ***ul*-3.20R** and ***l*-3.20R** in an 88:12 ratio together with *circa* 3% of the MeLi S_N2' by-product ***ul*-3.21R**. Nonetheless, the major diastereoisomer ***ul*-3.20R** was separable at this stage from both the minor one ***l*-3.20R** and the by-product ***ul*-3.21R** and it could then be isolated in 66% yield. Diol deprotection followed by ozonolysis readily afforded the *N*-protected 4-aminotetrafluorogalactose derivative **3.24R** in 89% over the two steps.

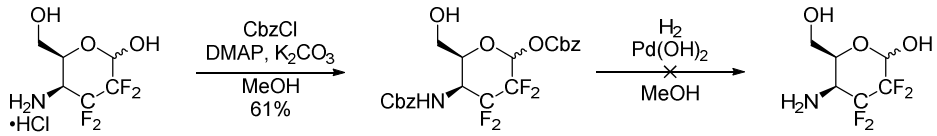
Scheme 3.9: Syntheses of *N-tert*-butanesulfinylimine **3.19R** and tetrafluorinated glucosamine **1.57·HCl**



The auxiliary removal proved troublesome as the hydrochloride salt **1.57·HCl** obtained could not be precipitated, in contrast to the corresponding 4-aminoglucose derivative **1.58·HCl** (see above). This resulted in an incomplete separation from the sulfinate ester byproduct. Any attempt of purification by chromatography proved unsuccessful, leading to a complex mixture.

Protection of both the 4-amino and 1-hydroxy groups as Cbz carbamate allowed purification, but subsequent hydrogenolysis resulted in obtaining a complex mixture (**Scheme 3.10**). As methyl *tert*-butanesulfinate is somewhat volatile (52 °C/16 torr), purification was then attempted by co-evaporating with MeOH carefully keeping the temperature below 40 °C to avoid apparition of impurities. This proved only partially successful, but as described above, after dissolving the salt in water, the impurity could largely be removed by extraction with Et_2O. Hence, **1.57·HCl** was at last obtained in excellent yield.

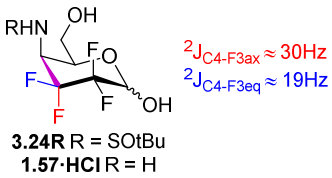
Scheme 3.10: Purification of **1.57·HCl** by protection as the carbamate **3.25**



1.57•HCl **3.25** **1.57**

3.3.3 Configurational analyses and possible transition states

The stereochemical outcome of the addition reaction could be deduced by analysing the multiplicity of the peak observed for C–4 in the ring systems in the ^{13}C NMR spectrom. Thus, the C–4 signals displayed $^{2}J_{C4\text{-}F}$ values of around 30 and 19 Hz for both α and β anomers of both **3.24R** (**Figure 3.4**) and **1.57·HCl** (**Figure 3.5**) indicating an axial electronegative substituent and therefore a galactopyranose configuration for both these molecules in solution.



3.24R R = SOtBu
1.57·HCl R = H

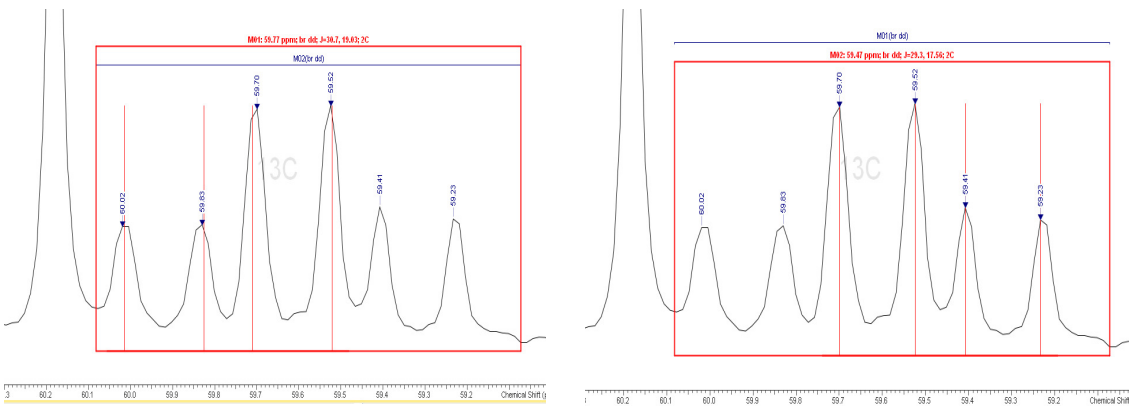


Figure 3.4: Detail of the ^{13}C NMR spectrum of **3.24R**, centred on C-4, α anomer (left) and β anomer (right).

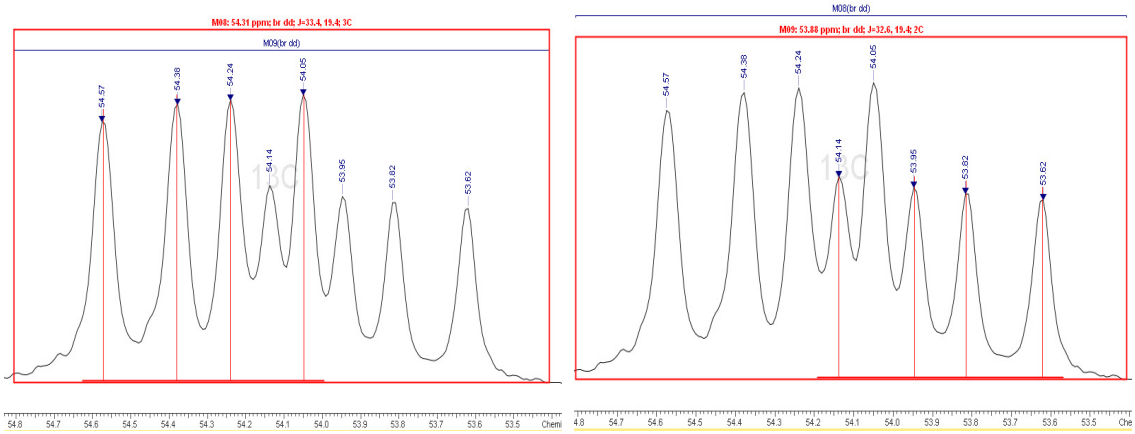


Figure 3.5: Detail of the ^{13}C NMR spectrum of **1.57·HCl** centred on C-4, α anomer (left) and β anomer (right)

Interestingly, X-ray crystallographic analysis of **3.23S** was possible which revealed the adoption of the $^{4}C_{1}$ conformation expected for most hexoses as well as the relative configuration at C–4 (**Figure 3.6**). Both the stereochemistry of the sulphur atom and of C–5 were known from the starting material **3.19S**, leading to the gluco configuration in **3.23S** by deduction.

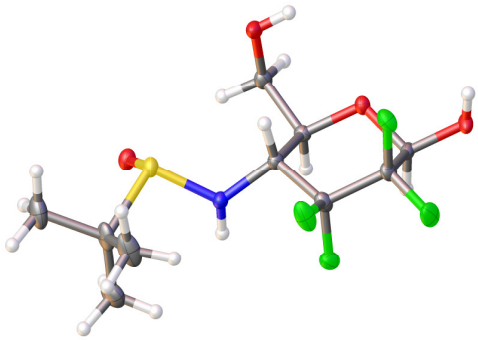


Figure 3.6: X-ray crystallographic analysis of **3.23S**

The ^{13}C NMR analysis of the C–4 signals gave $^{2}J_{C4\text{-}F}$ values of 18 Hz for both axial and equatorial fluorines confirming the existence of the gluco configuration in solution for both anomers (**Figure 3.7**). The same conclusions were drawn for the hydrochloride salt **1.58·HCl** as comparable $^{2}J_{C4\text{-}F}$ values could be extracted from the resonances corresponding to C–4 (**Figure 3.8**).

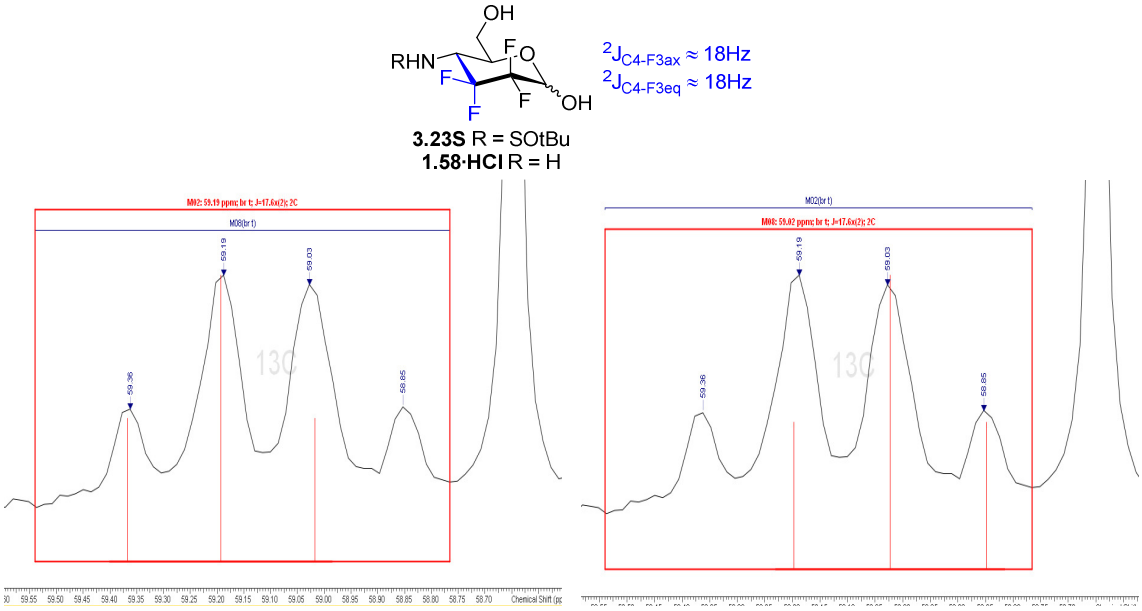


Figure 3.7: Detail of the ^{13}C NMR spectrum of **3.23S** centred on C-4, β anomer (left) and α anomer (right)

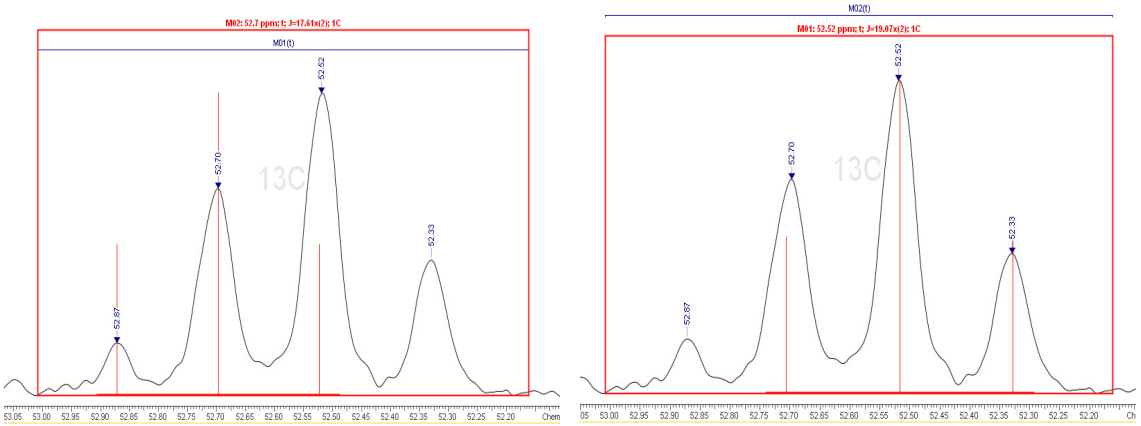


Figure 3.8: Detail of the ^{13}C NMR spectrum of **1.58·HCl** centred on C-4, β anomer (left) and α anomer (right)

The coupling constants mentioned above for both the galactose and glucose analogues also attested that they existed in the pyranose form in solution. This was confirmed by HMBC analysis of **1.57·HCl** and **1.58·HCl** in CD_3OD in which irradiation of the anomeric proton

resulted in a cross peak to C–5. The possible presence of iminosugar isomers was excluded as no such cross peak to C–4 was observed.

The stereochemical outcome of the addition reaction to both glyceraldehyde acetonide derived sulfinylimines showed that the diastereoselectivity was governed by the absolute configuration of the auxiliary rather than the α-oxygenated stereocentre. The major products obtained ***ul*-3.20R** and ***ul*-3.20S** were consistent with an open transition state (**Figure 3.9**, left, (*S*)-sulfinylimine only). However, the glyceraldehyde stereogenic centre was found responsible for the difference in stereoselectivity observed (96:4 *vs* 88:12). The Cornforth-Evans or polar Felkin-Anh models of stereoselection both predict that the (*S*)-configured α-stereocentre of the glyceraldimines induces *Si*-face attack (**Figure 3.9**, right). According to the open transition state, the (*S*)-configured sulfinylimine also directs the nucleophilic attack on the *Si*-face leading to a matched stereoinduction and a 96:4 *dr* observed for the (S,S_S) combination found in **3.19S**. In contrast, the (S,R_S) combination found in **3.19R** resulted in a mismatched stereoinduction and a decreased 88:12 *dr*. Such double diastereodifferentiation had been reported by Ellman when adding a benzylzinc reagent to the same sulfinylimines **3.19R** and **3.19S**,[92] and has also been described by us for the corresponding Reformatsky reaction with ethyl bromodifluoroacetate (*cf* section **3.5.2** below).[95]

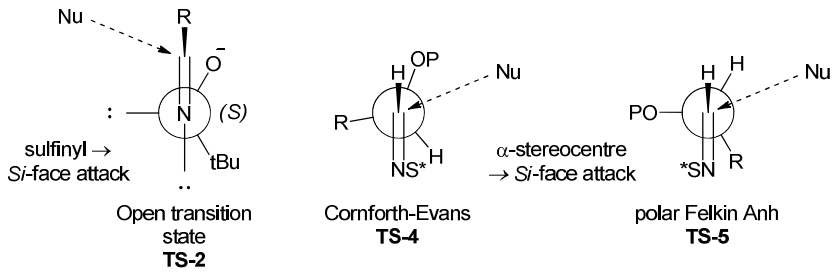


Figure 3.9: Explanation for the diastereoselectivity of the addition reactions

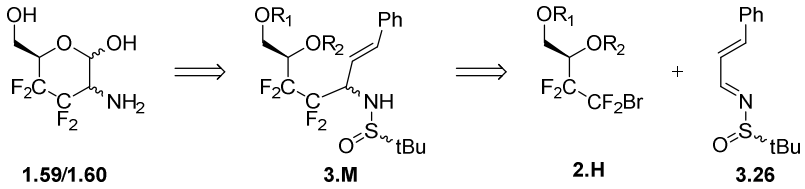
3.4 Synthesis of 3,3,4,4-tetrafluoro-2-aminosugars

3.4.1 Synthesis of 2-amino-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose 1.59

Given the high structural similarity between the aminosugars **1.59**/**1.60** and their non aminated counterparts **1.55** and **1.56**, the retrosynthesis designed followed the same strategy,

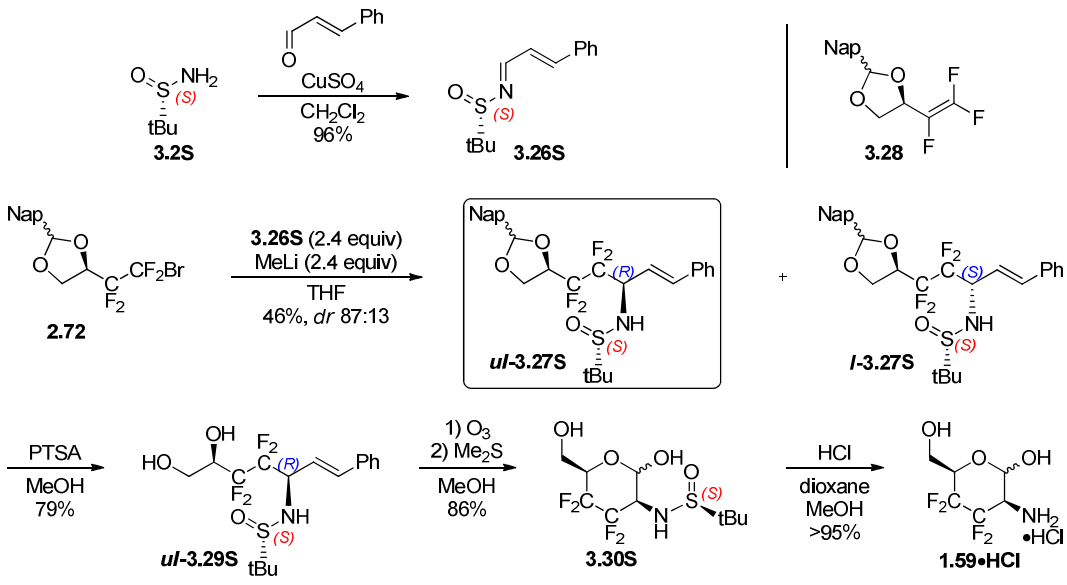
now using *N-tert*-butanesulfinylimine **3.26** (**Scheme 3.11**) as substrate. In contrast to the unselective synthesis of **1.55** and **1.56**, addition to each enantiomer of the *N-tert*-butanesulfinylimine **3.26** was expected to result in either tetrafluorinated mannosamine **1.59** or glucosamine **1.60** with high diastereoselectivity.

Scheme 3.11: Retrosynthetic route involving *N-tert*-butanesulfinylimine **3.C**



First, the condensation of cinnamaldehyde and (*S*)-*tert*-butanesulfinamide **3.2S** was performed using copper (II) sulphate and afforded the desired *N-tert*-butanesulfinylimine **3.26S** in 96% (**Scheme 3.12**).[80] Following Konno's conditions, 2.4 equiv of the latter was then mixed with 700 mg of the bromide **2.72** and 2.4 equiv of MeLi was added dropwise (*ca* 10 min). The addition resulted in the formation of the two major diastereoisomers ***ul*-3.27S** and the two minor ones ***l*-3.27S** in a 47:41:8:4 ratio as estimated by fitting the relevant peaks in the crude ^{19}F NMR. After column chromatography, the 8% of one minor diastereoisomer could be separated (not isolated) from the three other isomers leading to a 95:5 mixture of the desired products ***ul*-3.27S** and the remaining minor diastereoisomer ***l*-3.27S**, isolated together in 49% yield.

Scheme 3.12: Syntheses of *N-tert*-butanesulfinylimine **3.26S** and tetrafluorinated mannosamine **1.59·HCl**

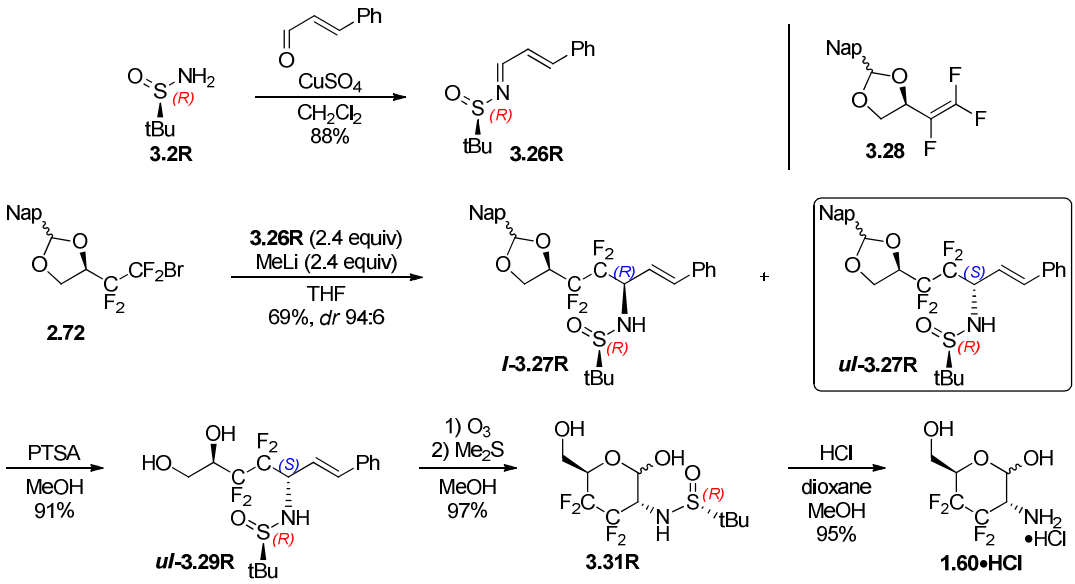


The sulfinylimine proved less reactive than cinnamaldehyde as the crude ^{19}F NMR also revealed the presence of the by-product **3.28** resulting from β-fluoride elimination following the lithiation. The integration of the related peaks unveiled an addition/elimination ratio of 3.5:1 perhaps explaining the medium yield obtained after purification. It should be noted that **3.28** had not been observed when performing the reaction with cinnamaldehyde. To avoid elimination, MeLi was added *via* a syringe pump over 30 min in a second attempt starting from 300 mg of **2.72**. This proved successful as the ratio **3.27S**/**3.28** increased to 5.3:1 for a similar addition products ratio of 44:43:9:4. Although less elimination by-product was formed, a 95:5 mixture comparable to that described above was obtained in only 46% after column chromatography. Unfortunately, the residual 5% of minor diastereoisomer could not be easily separated from the two major ones even by HPLC. The major isomers eluted as two very close peaks, with the minor isomer being part of the tail of the second peak. Eventually, by taking and analysing several small fractions, 27% of pure ***ul*-3.27S** could be isolated, a low yield that obviously resulted from the numerous HPLCs needed. Nonetheless, the naphthylmethylidene acetal was then removed with PTSA in MeOH affording the diol ***ul*-3.29S** in 79% yield as a single diastereoisomer and subsequent ozonolysis gave the *N*-protected mannosamine derivative **3.30S** in 86% yield. It is noteworthy that part of the 95:5 mixture described above was subjected to deprotection but the minor isomer was not separable at the stage of **3.29S**. After ozonolysis of the obtained mixture to give **3.30S**, which purification proved cumbersome. Separation by HPLC unexpectedly resulted in two frractions (1:1 integration ratio). However, whereas the first fraction was shown to be pure mannosamine analogue **3.30S** (^{1}H NMR analysis), the second fraction consisted of mannosamine **3.30S** but contaminated with 5% of glucosamine analogue that originated from the minor diastereoisomer. It was suspected that HPLC separated the mannosamine anomers (which subsequently equilibrated upon collection). Using the pure sample **3.30S**, the chiral auxiliary was removed under dry acidic conditions yielding directly the tetrafluorinated mannosamine as the hydrochloride salt **1.59·HCl**. The salt could not be precipitated in Et_2O so it was dissolved in water and washed twice with Et_2O to remove the by-product methyl *tert*-butanesulfinate and afford pure **1.59·HCl** almost quantitatively. The auxiliary removal carried out on the mixture led to an inseparable mixture of mannosamine and glucosamine compounds.

3.4.2 Synthesis of 2-amino-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranose 1.60

The synthetic route to **1.60** was identical except that the enantiomeric sulfinylimine **3.26R** was now required (**Scheme 3.13**). The latter was synthesised in 88% yield using the same procedure as above and was then engaged in the coupling reaction with 500 mg of bromide **2.72**. First, MeLi was added *via* syringe pump over 30 min and this led to a 4:4:45:47 mixture of the minor and major addition products ***l*-3.27R** and ***ul*-3.27R** respectively. This time, one minor diastereoisomer could be separated (not isolated) by column chromatography while the second required the use of HPLC and could be isolated together with a small amount of one major isomer. Thus, both major diastereoisomers ***ul*-3.27R** were obtained as a pure mixture in 50% yield. The medium yield was explained again by the formation of the elimination by-product **3.28** which was found in a 1:4.2 ratio compared to all the addition products ***l*-** and ***ul*-3.27R** according to the crude ^{19}F NMR. The MeLi addition time was therefore increased to 1 h which resulted in a decreased **3.28**/**3.27R** ratio of 1:8.8. The addition products were obtained in a 3:3:46:48 ratio which afforded, after careful separation, the major acetal diastereoisomer mixture ***ul*-3.27R** in an improved 69% yield. The naphthylmethylidene group was then removed giving the diol ***ul*-3.29R** as a single diastereoisomer in 91% yield and ozonolysis followed by auxiliary removal afforded almost quantitatively the 2-aminoglucose derivative as the hydrochloride salt **1.60·HCl**. This aminosugar could be nicely precipitated from Et_2O almost exclusively as the α-anomer; unfortunately no crystals suitable for X-ray could be acquired. The anomeric equilibrium in CD_3OD consisted of a 54:46 α/β mixture

Scheme 3.13: Syntheses of *N-tert*-butanesulfinylimine **3.26R** and tetrafluorinated glucosamine **1.60·HCl**



3.4.3 Configuration analysis and possible transition states

No crystal structures could be obtained for the 2-aminosugar derivatives and their intermediates so the configuration at C-2 had to be deduced by ^{13}C NMR analysis of the pyranose derivatives similar as shown above. Indeed, as shown in Figure 3.10, both anomers of **3.30S** exhibited a doublet of doublets for C-2 with $^{2}J_{C2-F}$ values of around 30 and 17 Hz indicating a chair conformation and the presence of an axial electronegative substituent at this carbon. This allowed the attribution of the manno configuration for **3.30S**. A similar NMR analysis could be performed for the deprotected 2-aminomannose **1.59·HCl** with $^{2}J_{C2-F}$ values of 33/30 and 19 Hz (**Figure 3.11**).

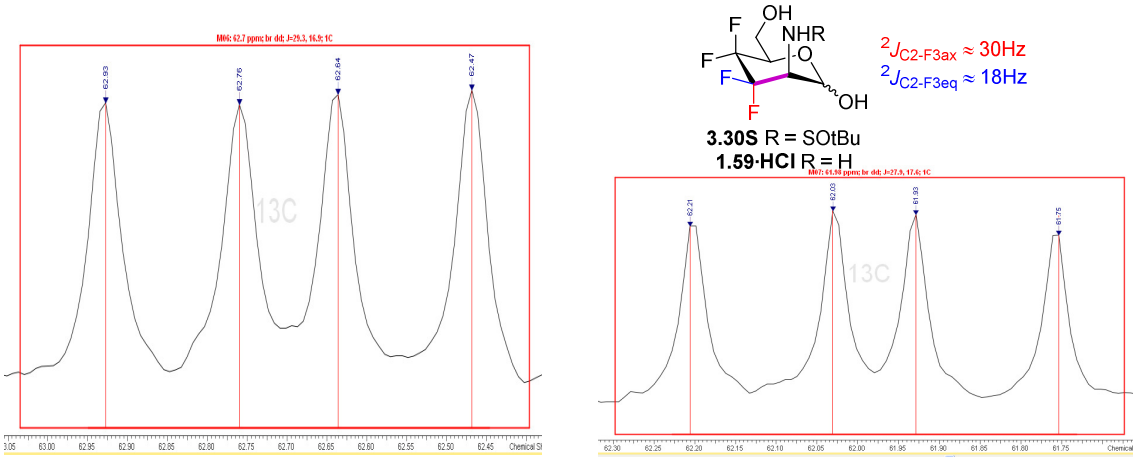


Figure 3.10: Detail of the ^{13}C NMR spectrum of **3.30S** centred on C-2, β anomer (left) and α anomer (right)

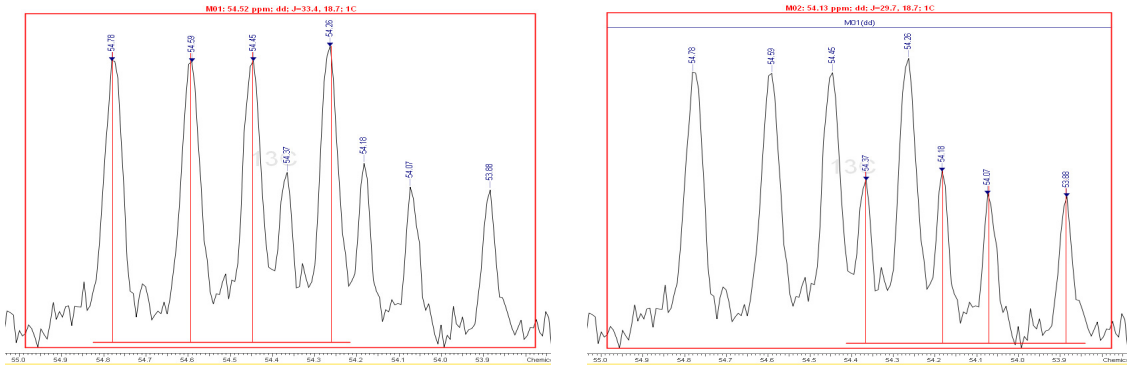


Figure 3.11: Detail of the ^{13}C NMR spectrum of **1.59·HCl** centred on C-2, β anomer (left) and α anomer (right)

Conversely, both anomers of **3.31R** showed a triplet with $^{2}J_{C2-F}$ values of around 17 Hz indicating again a chair conformation but this time with an equatorial electronegative substituent at C-2 (**Figure 3.12**). Similarly, a triplet with $^{2}J_{C2-F}$ values of around 18 Hz was

observed for the predominant α anomer of **1.60·HCl** (**Figure 3.13**). Consequently, the gluco configuration could be assigned to both **3.31R** and unprotected **1.60·HCl**.

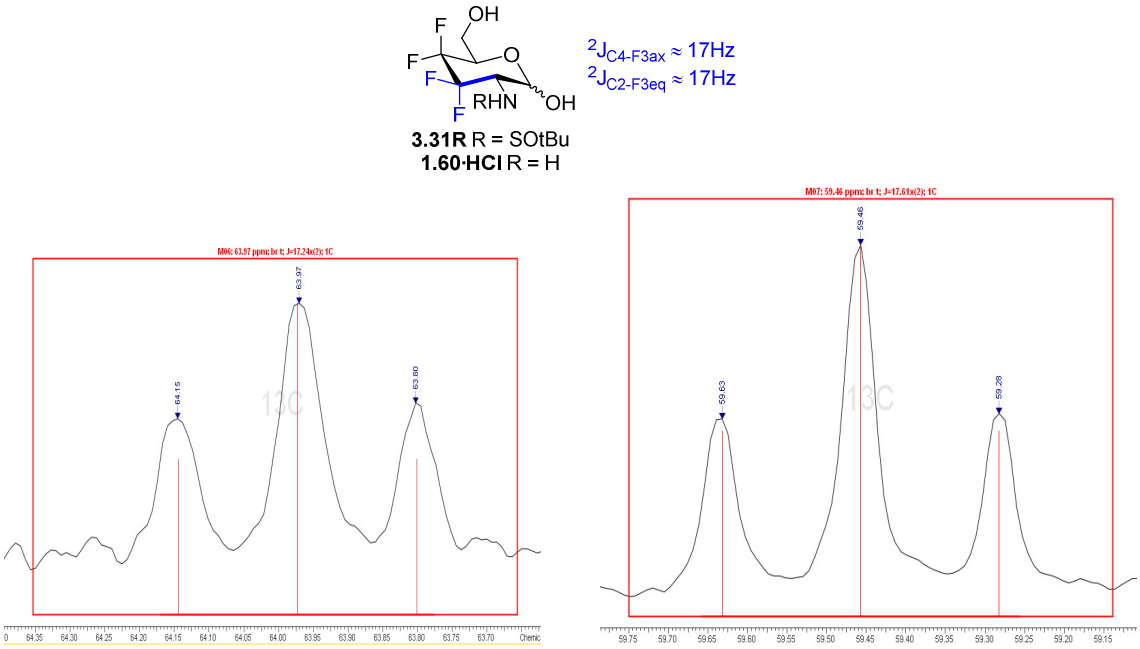


Figure 3.12: Detail of the ^{13}C NMR spectrum of **3.31R** centred on C-2, β anomer (left) and α anomer (right)

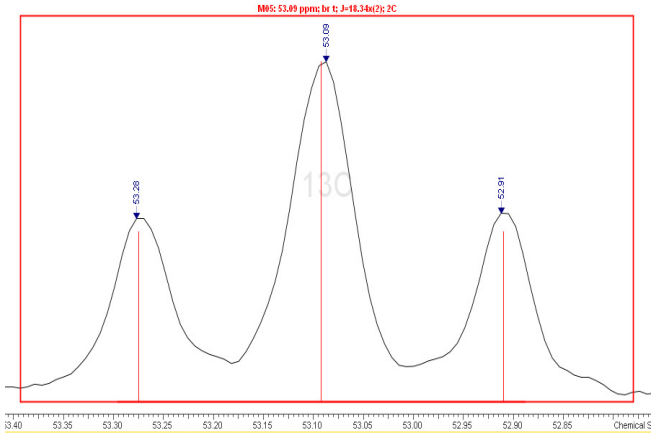


Figure 3.13: Detail of the ^{13}C NMR spectrum of **1.60·HCl** centred on C-2, α anomer

The deduced configurations for the ring structures implied that the addition of lithiated **2.72** to the (*S*)-sulfinylimine **3.26S** resulted in the newly formed stereocentre for the major diastereoisomers ***ul*-3.27S** to be *R* configured. On the contrary, the (*R*)-sulfinylimine **3.26R** led mainly to the *S* configured addition products ***ul*-3.27R** as confirmed by the X-ray structure obtained for ***ul*-3.29R** after acetal hydrolysis (see **Figure 3.14**).

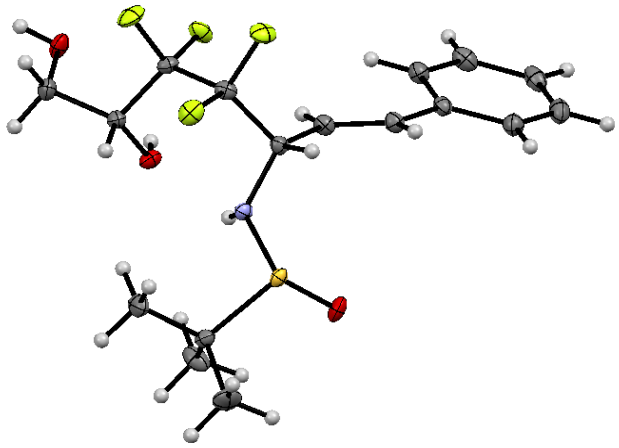


Figure 3.14: X-ray crystallographic analysis of ***ul*-3.29R**

Both results were in agreement with a stereoinduction which resulted from the sulfinyl groups according to the open transition states depicted in **Figure 3.15**.

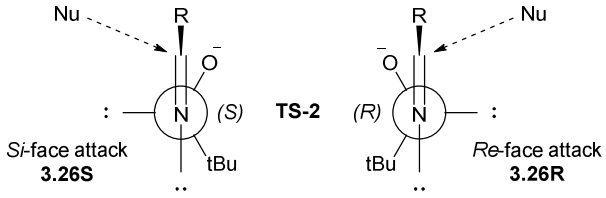


Figure 3.15: Open transition state for the addition to (*S*) and (*R*)-sulfinylimines

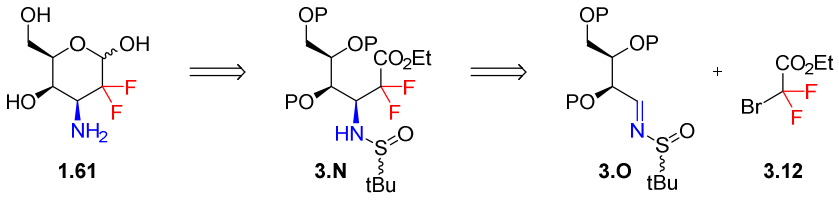
Although both imines exhibited an achiral phenylethenyl substituent, a difference of diastereoselectivity (87:13 *vs* 94:6) was observed during the coupling reaction. This must have been the result of a slight double diastereodifferentiation effect exerted by the chiral ether centre of the reagent.

3.5 Synthesis of 3-amino-2,2-difluoro-D-*lyxo*-hexopyranose 1.61

3.5.1 From the target molecule 1.61 to a new methodology

It was envisioned that **1.61** could be obtained by functional group interconversion of the ester **3.N** resulting from a Reformatsky type addition of ethyl bromodifluoroacetate (EBDFA, **3.12**) to threose derived chiral imine **3.O** (**Scheme 3.14**).

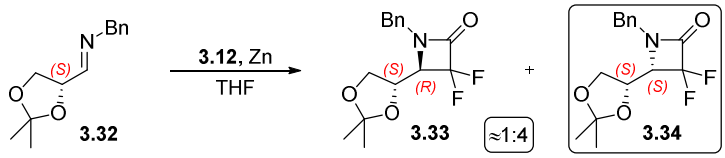
Scheme 3.14: Proposed retrosynthesis of the aminodifluorogalactose **1.61**



Although nucleophilic addition to sulfinylimines possessing a chiral α-oxygenated centre has proven a popular method to access β-aminoalcohols diastereoselectively, no example of Reformatsky type reactions involving EBDFA (**3.12**) or ethyl bromoacetate with such sulfinylimines could be found when browsing the literature.

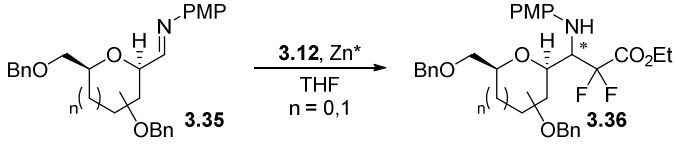
In 1988, Kobayashi *et al.* studied the addition of **3.12** to the achiral benzyl imine **3.32** derived from glyceraldehyde acetonide and reported a *dr* of ≈4:1 in favour of the *syn* β-lactam **3.34** (**Scheme 3.15**).[96] Similar results were obtained four years later by Baldwin *et al.* when reproducing the work.[97]

Scheme 3.15: Reformatsky type addition to glyceraldehyde acetonide derived imine **3.32**



In 2005, Dondoni et al. published the synthesis of fluorinated aminoesters **3.36** obtained as a single diastereoisomer by adding **3.12** to imines derived from per-*O*-benzylated pentofuranose or hexopyranose. However, the yields obtained were low around 30% (**Scheme 3.16**).[98]

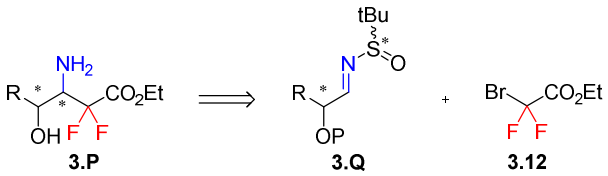
Scheme 3.16: Reformatsky type addition to *C*-glycosyl derived imine **3.35**



We therefore became interested in developing a methodology for the synthesis of the motif **3.P** *via* a Reformatsky reaction with *N-tert*-butanesulfinylimines **3.Q**. The adducts **3.P** will be

versatile intermediates for the synthesis of complex α,α-difluoro-β-amino acids and of 2,2-difluoro-3-amino carbohydrate analogues such as **1.61**.

Scheme 3.17: Retrosynthetic route to **3.P** *via* a Reformatsky reaction with sulfinylimine **3.Q**

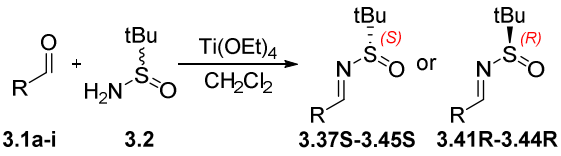


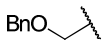
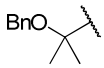
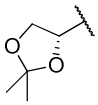
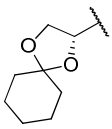
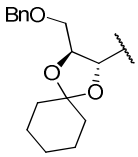
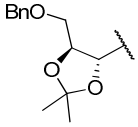
As mentioned above (*cf* section **3.3.3**), addition of various organometallic derivatives to α-chiral sulfinylimines resulted in a double diastereoselection where the stereoinduction by the sulfinyl auxiliary usually dominates that of the α-stereocentre.[92,95] In order to investigate this double diastereodifferentiation, both *R* and *S* sulfinyl auxiliaries were systematically used with all the chiral aldehydes studied.

3.5.2 Honda-Reformatsky Reaction with Ethyl Bromodifluoroacetate and α-Oxygenated Sulfinylimines

The sulfinylimines **3.37**-**3.45** were synthesised from the corresponding aldehydes in good yields mainly using the modified $Ti(OEt)_4$ procedure described above for **3.19R** and **3.19S** (**Table 3.1**).[81,99]

Table 3.1: Synthesis of the *N-tert*-butanesulfinylimines[a]



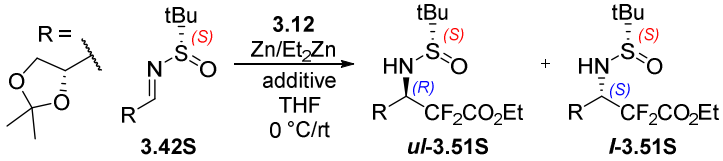
entry	aldehyde	R	product	yield[b] (%)
1	**3.1a**	Et	**3.37S**	72
2	**3.1b**	$C_{11}H_{23}$	**3.38S**	87
3[c]	**3.1c**		**3.39S**	88
4	**3.1d**		**3.40S**	79
5[d]	**3.1e**		**3.41S**	82
6[d]			**3.41R**	71
7	**3.1f**		**3.42S**	86
8			**3.42R**	86
9	**3.1g**		**3.43S**	89
10			**3.43R**	88
11[d]	**3.1h**		**3.44S**	83
12[d]			**3.44R**	85
13[d]	**3.1i**		**3.45S**	54

[a] The suffix *R* or *S* in the numbering refers to the absolute configuration of the sulfinylimine auxiliary. The aldehydes **2.20** and **1.75** are numbered **3.1c** and **3.1f** respectively for the ease of reading. [b] Isolated yield. [c] $CuSO_4$ instead of $Ti(OEt)_4$. [d] Enantiomers were synthesised.

The aldehydes were commercially available (**3.1a**-**b**) or synthesised according to known procedures from the literature (**3.1c**-**g**, **3.1i**).[91,100-102] Only the D-threose derivative **3.1h** was a novel compound and was therefore synthesised by oxidation of the corresponding alcohol of which the synthesis of the enantiomer had been previously published.[103]

First, a short optimisation of the Reformatsky reaction was conducted by trying different conditions found in the literature (**Table 3.2**). For this purpose, the imine **3.42S** was chosen as model substrate and the products **3.51S** were obtained. Indium has been reported by Poisson *et al.* to induce Reformatsky reactions with **3.12** but no reaction occurred in our case even after several hours at 60 °C (entry 1).[104] The most common zinc was then tried following the procedure described by Staas and co-workers.[89] Around three equivalents of the Reformatsky reagent was preformed in THF at 30 °C then cooled to rt and added dropwise to a solution of **3.42S** in THF. The reaction was left stirring overnight and afforded the desired products ***ul*-3.51S** and ***l*-3.51S** in 46% yield and a 72:28 diastereoisomeric ratio (entry 2). As a significant quantity of homocoupling product diethyl 2,2,3,3-tetrafluorosuccinate could be observed in the crude ^{19}F NMR (singlet at δ = –120.6 ppm), meaning that part of the preformed Reformatsky reagent reacted with the excess of starting bromide **3.12**, the stoichiometry was slightly increased which led to a promising 61% yield and 85:15 dr (entry 3). The use of zinc preactivated with dilute HCl and CH_2Cl_2 as co-solvent further improved the yield to 78% but the dr decreased to 75:25 (entry 4). Similar results were obtained with Et_2O and toluene as co-solvent (not shown). Zn activation by DMSO and TMSCl[105] resulted in the formation of a negligible amount of products (entry 5). The reaction was attempted following the Honda-Reformatsky conditions which employ Et_2Zn together with the Wilkinson's catalyst $RhCl(PPh_3)_3$ acting as a promoter for the insertion of the zinc into the C—Br bond. Remarkably, the first attempt conducted at 0 °C resulted in complete diastereoselectivity for ***ul*-3.51S** which was obtained in 45% yield (entry 6). The starting amounts of Et_2Zn and bromide **3.12** were slightly increased which improved the yield to 61% while the selectivity was maintained (entry 7).The Wilkinson's catalyst was substituted for $NiCl_2(PPh_3)_2$ which was reported to be more efficient[106] but this led to a complete loss of reactivity (entry 8). The ethyl groups of Et_2Zn are quite nucleophilic and can potentially add directly to an electrophile. The substitution for less nucleophilic Me_2Zn which is believed to prevent such addition was attempted but it resulted similarly in no reaction (entry 9).

Table 3.2: Optimisation of the reaction[a]

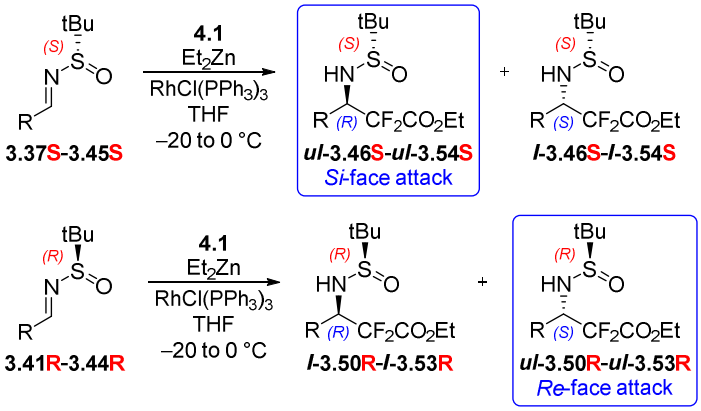


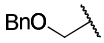
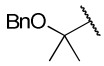
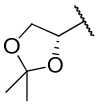
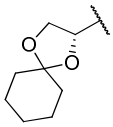
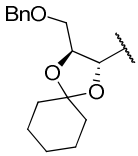
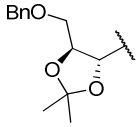
entry	**3.12** (equiv)	metal (equiv)	additive (mol%)	dr[b] (*ul*:*l*)	yield (%)[c]
1	2	In (2)	-	-	NR
2	4	Zn (3)	-	72:28	46
3	5	Zn (4)	-	85:15	61
4	5	Zn[d] (4)	-[e]	75:25	78
5	5	Zn[f] (4)	-	-	<5
6	1.5	Et_2Zn (1.5)	$RhCl(PPh_3)_3$ (3)	>95:5	45
7	3	Et_2Zn (2)	$RhCl(PPh_3)_3$ (3)	>95:5	61
8	1.5	Et_2Zn (1.5)	$NiCl_2(PPh_3)_2$ (5)	-	NR
9	1.1	Me_2Zn (3)	$RhCl(PPh_3)_3$ (3)	-	NR

[a] The prefix l (like) indicates that the sulfinyl group and the newly formed amine stereocenter have the same absolute configuration (and otherwise for ul (unlike)). [b] Determined by 19F NMR (crude reaction mixture) [c] Isolated yield. [d] Dilute aq HCl activation. [e] DCM was used as co-solvent. [f] DMSO/TMSCl activation.

The best Honda-Reformatsky conditions (**Table 3.2**, entry 7) were then applied to the range of sulfinylimines synthesised. First, the reaction with the imines **3.37S** and **3.38S** which did not possess an α-oxygenated substituent was not diastereoselective (**Table 3.3**, entries 1 and 2). It should be noted that the age of the Et_2Zn, the rate of its addition as well as the use of different batches of Wilkinson's catalyst resulted in slight variations of diastereoselectivity (53:47 to 60:40) but always in favour of the same diastereoisomer. This absence of selectivity was unexpected given that Staas[89] and Soloshonok[88] obtained dr up to 86:14 with similar aliphatic sulfinylimines by using zinc metal in refluxing THF. Remarkably, the presence of an α-benzyloxy substituent in **3.39S**, even achiral, restored the diastereoselectivity of the reaction and afforded the products **3.48S** in 46% yield and a 88:12 dr (entry 3). Interestingly, no reaction occurred with the sulfinylimine **3.40S** presumably due to steric hindrance (entry 4). The first imine with a chiral substituent was derived from benzyl protected (*R*)-lactaldehyde. The combination with the (S)-configured chiral auxiliary (**3.41S**, entry 5) resulted in an enhanced dr of 96:4 compared to imine **3.39S**. In contrast, the combination with the enantiomeric auxiliary (**3.41R**, entry 6) led to an almost complete loss of diastereoselectivity evidencing a double diastereoselection effect. As shown above, the (*S*)-sulfinylimine derived from (*R*)-glyceraldehyde **3.42S** afforded uniquely ***ul*-3.51S** in 62% yield (entry 7) while **3.42R** offered an 88:12 mixture of diastereoisomers in favour of ***ul*-3.51R** (entry 8) also suggesting a double diastereodifferentiation effect. Similar results were obtained with the other imines derived from glyceraldehyde (**3.43**) and threose (**3.44** and **3.45S**) for which the matched cases ((*S*)-configured auxiliary) proceeded with total diastereoselectivity (entries 9, 11 and 13). The mismatched cases still resulted in medium to good selectivities (entries 10 and 12).

Table 3.3: Scope of the reaction

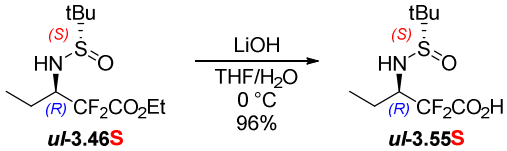


entry	R	imine	major product	yield[a] (%)	d.r. (*ul*:*l*)
1	Et	**3.37S**	***ul*-3.46S**	64	53:47
2	$C_{11}H_{23}$	**3.38S**	***ul*-3.47S**	58	53:47
3		**3.39S**	***ul*-3.48S**	46	88:12
4		**3.40S**	-	NR	-
5[b]		**3.41S**	***ul*-3.50S**	57	94:6
6[b]		**3.41R**	***ul*-3.50R**	46	54:46
7		**3.42S**	***ul*-3.51S**	62	>95:5
8		**3.42R**	***ul*-3.51R**	59	88:12
9		**3.43S**	***ul*-3.52S**	52	>95:5
10		**3.43R**	***ul*-3.52R**	56	81:19
11[b]		**3.44S**	***ul*-3.53S**	62 (67)	>95:5
12[b]		**3.44R**	***ul*-3.53R**	48	60:40
13[b]		**3.45S**	***ul*-3.54S**	≈70	>95:5

[a] Isolated yield. [b] Enantiomers were synthesised, shown as is to facilitate stereochemical analysis.

Both major diastereoisomers ***ul*-3.51S** and ***ul*-3.51R** could be recrystallised and analysed by X-ray. The ester ***ul*-3.46S** had first to be hydrolysed to the acid (**Scheme 3.18**) of which crystals suitable for X-ray could be obtained. All three crystal structures undoubtedly revealed the *ul*-relative configuration (**Figure 3.16**). Since the (*S*)- and (*R*)-sulfinylimines **3.42S** and **3.42R**, both derived from (*R*)-glyceraldehyde but with either enantiomer of the chiral auxiliary, resulted in a new amine stereocentre with an opposite absolute configuration, it is clear that the diastereoinduction operated by the sulfinyl group overrode that of the chiral α-stereocentre. Accordingly, the *ul*-configuration was attributed to all major diastereoisomers obtained.

Scheme 3.18: Hydrolysis of the ester ***ul*-3.46S**



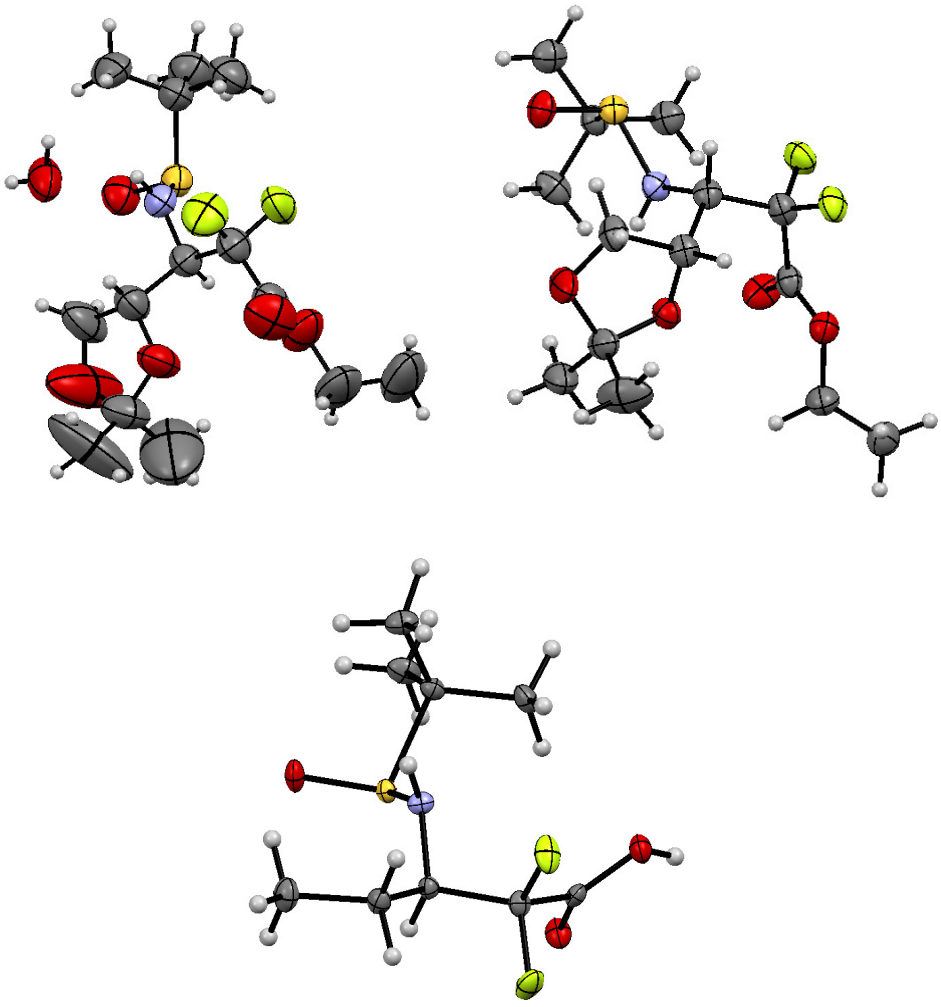


Figure 3.16: X-ray crystallographic analysis of ***ul*-3.51S** (top left), ***ul*-3.51R** (top right) and ***ul*-3.55S** (bottom).

Interestingly, the relative configuration obtained for ***ul*-3.51S** was the opposite of that reported by both Staas and Soloshonok for similar aliphatic sulfinylimines when using Zn metal in THF at rt or reflux. The Honda-Reformatsky conditions we used were obviously not comparable and resulted in a very low dr that precluded drawing conclusions. However, Ellman *et al.* determined the same stereoinduction for the addition in THF of various benzylzinc reagents to sulfinylimines derived from both aliphatic aldehydes and (*R*)-glyceraldehyde acetonide, including the match/mismatch effect already mentioned in **3.3.3**.[92]

As explained in section **3.3.3**, the *S* configured α-alkoxy group in **3.42S** induces a *Si*-face attack according to both Cornforth-Evans (**TS-4**) and polar Felkin-Anh (**TS-5**) models (**Figure 3.17**).[107] On the contrary, the cyclic Cram model (**TS-6**) involving the chelation of both the imine nitrogen and the α-oxygen predicts a *Re*-face attack.

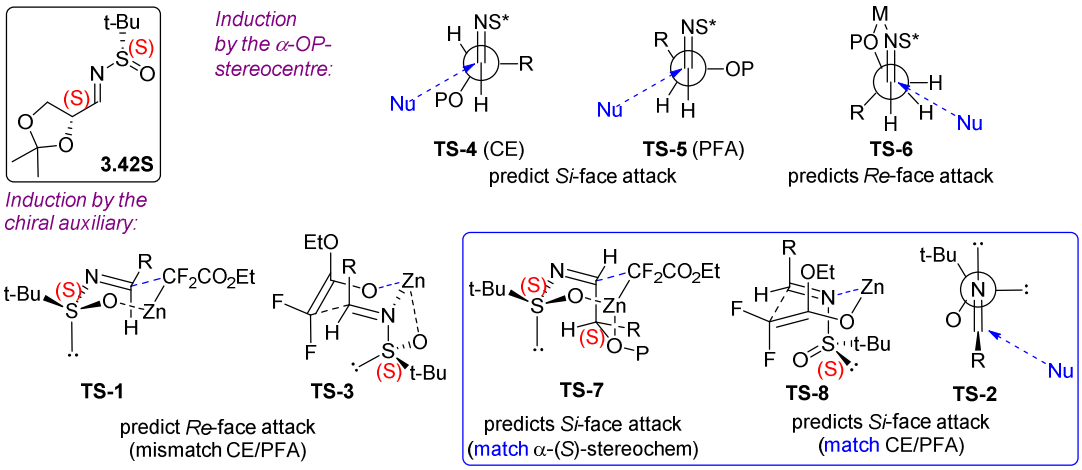


Figure 3.17: Models to explain the stereoinduction/double diastereodifferentiation

As shown in **3.2.2**, Ellman and Davis proposed the two cyclic transition states **TS-1** and **TS-3** to explain the stereoselectivity of Reformatsky reactions of **3.12** with our results which must have originated from a *Si*-face attack. The open transition state (**TS-2**) proposed by Davis predicts the right facial selectivity and has been used by Ellman and co-workers to justify the stereochemical outcome of the aforementioned addition of benzylzinc reagents to various sulfinylimines including **3.42S**. However, **TS-2** is usually invoked in the case of non-chelating metals such as lithium or when coordinating additives or solvents are used. In fact, the benzylzinc reagents used by Ellman were formed using Knochel conditions which involved the use of Mg, $ZnCl_2$ and LiCl in THF. This large excess of coordinating species present during the

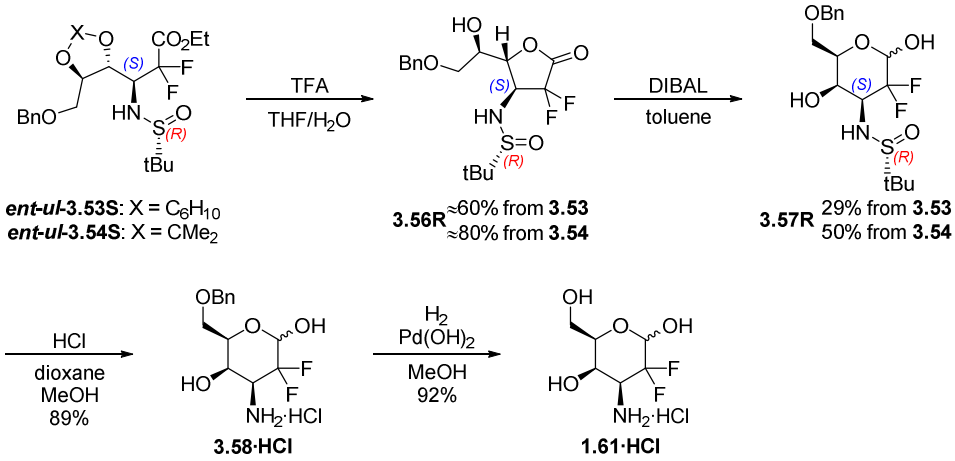
reaction might indeed have disrupted any chelated transition state resulting in a stereocontrol via **TS-2**. Although the solvent used in our study was also THF, the much higher diastereoselectivities obtained for the α-alkoxy sulfinylimines suggested rather a chelated transition state involving the α-oxygenated substituent. Barrow *et al.* published the first report on addition of organometallic reagents to α-alkoxy *N*-*tert*-butanesulfinyl aldimines.[108] The stereochemistry of the newly formed amine was indeed opposite to that predicted by **TS-1** usually invoked for Grignard reagent additions to sulfinylimines. They therefore proposed **TS-7** which relies on a rapid imine isomerisation to the less stable *Z*-isomer thereby allowing a coordination of the α-alkoxy substituent in the pseudo-axial position to the metal. This model predicts the correct *Si*-face attack as well as the double diastereodifferentiation which now occurs from the avoidance of a steric clash with the sulfinyl group rather than from a matched induction with **TS-4**/**TS-5**. Finally, the model **TS-8** depicted by Marek *et al.* for the addition of allylzinc reagent to aryl sulfinylimines also predicts the correct stereochemical outcome.[109] It only differs from **TS-3** in that the oxygen of the sulfinyl group does not coordinate to the metal but points antiperiplanar to the C=N bond instead, resulting in opposite facial selectivities. However, the additional ethoxy group in the case of a Reformatsky reaction could disfavour **TS-8**.

In conclusion, the Barrow transition state seems to explain best both the diastereoselectivity and the match/mismatch effect of the Honda-Reformatsky reaction of **3.12** to α-oxygenated sulfinylimines. The α-chelation is obviously not possible for the imines **3.37S** and **3.38S** which resulted in an unselective process most likely driven by more than one transition state among those presented above.

3.5.3 Completion of the synthesis of 1.61

With the enantiomers ***ent-ul*-3.53S** and ***ent-ul*-3.54S** in hand, the synthesis of **1.61** could be achieved *via* the lactone **3.56R** (**Scheme 3.19**).

Scheme 3.19: Synthesis of **1.61·HCl** from the sulfinylaminoesters



Diol deprotection of ***ent-ul*-3.52S** followed by spontaneous cyclisation into the more stable γ-lactone proved troublesome as the use of concentrated HCl, PTSA or Dowex® in MeOH/H_2O mixtures all resulted in either degradation or recovery of the starting material. However, when treated with a 10:5:1 mixture of TFA/THF/H_2O,[110] the lactone was cleanly formed without loss of the sulfinyl auxiliary although the complete removal of the cyclohexanone byproduct and the TFA appeared very difficult. Column chromatography resulted in a medium yield of around 60% of **3.56R** and the apparition of extra peaks in the ^{1}H and ^{19}F NMR spectra, suggesting degradation occurred over silica. The crude mixture was left for several days under high vacuum and although the amount of TFA decreased, it also led to the apparition of impurities evidencing the instability of the lactone over time. Since the lactone could not be purified, the isopropylidene protected sulfinylaminoester ***ent-ul*-3.54S** was synthesised as its deprotection would form volatile acetone instead of cyclohexanone. Surprisingly, if the acetonide of compounds ***ul*-3.20R** and ***ul*-3.20S** could be readily hydrolysed with PTSA in MeOH (*cf* **3.3**), these same conditions left ***ent-ul*-3.54S** unreacted and so did the use of HCl. The TFA/THF/H_2O mixture was then attempted and led cleanly to the lactone in shorter reaction times. The maximum of TFA was removed under high vacuum and **3.56R**, obtained in an estimated 80% yield, was subjected to reduction.

The reduction was performed in toluene at –70 °C using 2 or 2.5 equivalents of DIBAL depending on the amount of remaining TFA. This afforded the two desired anomers **3.57R** and the overreduction by-product (not shown) which were not easily separable. HPLC using hexane/iPrOH as eluent completed the separation where a hexane/acetone mixture had failed. This resulted in the protected aminosugar **3.57R** to be isolated in 29% yield from ***ent-ul*-3.53S** and 50% yield from ***ent-ul*-3.54S**.

The sulfinyl auxiliary had to be removed before conducting the benzyl group hydrogenolysis as the latter never proceeded starting from **3.57R**. Nonetheless, the common acidic conditions afforded **3.58·HCl** as the hydrochloride salt which could be nicely precipitated as a 90:10 α/β anomeric mixture. The salt could then be directly submitted to hydrogenolysis using Pearlman's catalyst in MeOH which, after filtration over Celite® and precipitation, offered the desired 2,2-difluoro-3-amino-D-galactose derivative **1.61·HCl** also as a 90:10 anomeric mixture.

3.5.4 Configuration analysis

Although a crystal structure could not be obtained for **1.61·HCl** and its intermediates, a similar ^{13}C NMR analysis was conducted as for the tetrafluorosugars and aminosugars. Both α and β anomers exhibited a triplet for C-3 with a coupling constant of around 19 Hz to both axial and equatorial fluorine (**Figure 3.18**). This suggests that C-3 bears an equatorial electronegative substituent as in D-galactose. This is also in agreement with the aminosugar being in the pyranose form in solution in CD_3OD, hypothesis that was further confirmed by a HMBC analysis which showed a cross-peak between H-1 and C-5 as well as between H-5 and C-1.

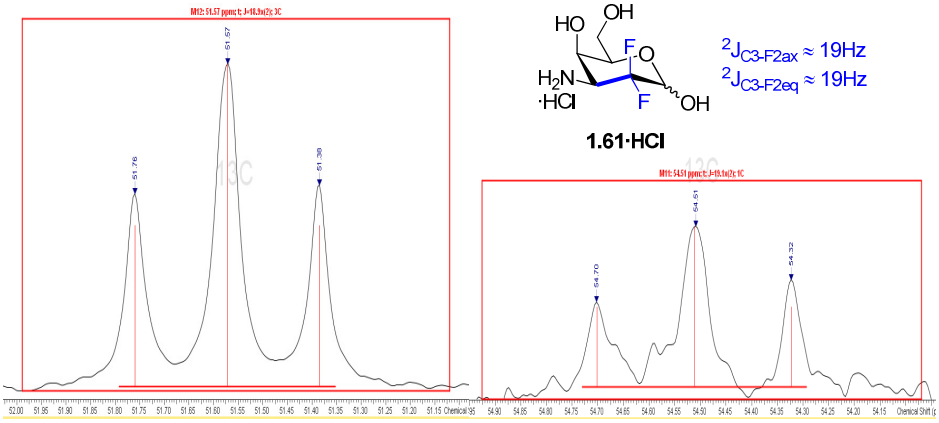


Figure 3.18: Detail of the ^{13}C NMR spectrum of **1.61·HCl** centred on C-3, α anomer (left) and β anomer (right)

3.6 Summary

Ellman's *N-tert*-butanesulfinylimines proved a very powerful tool to access the desired tetra and difluoro aminosugars.

The addition of lithiated bromotetrafluorobutene proceeded with excellent diastereoselectivities *via* an open transition state and in most cases, the major isomers were separable from the minor ones leading to the desired amines in medium to good yields. The acid labile sulfinyl groups resisted to the acetal hydrolysis conditions (PTSA, MeOH) and to ozonolysis providing the *N*-protected tetrafluoroaminosugars in very good yields. The sulfinyl groups were then readily removed affording the hydrochloride salts which could be precipitated in the case of the glucose derivatives. Otherwise, the aminosugar was purified by extraction of the by-products with Et_2O from an aqueous solution resulting in a sufficient level of purity.

The Reformatsky addition of ethyl bromodifluoroacetate to various sulfinylimines derived from aliphatic aldehydes possessing an α-alkoxy substituent proceeded with medium to good yields. With chiral aldehydes, a double diastereodifferentiation was evidenced as the matched cases resulted in complete diastereoselectivity while the mismatched ones provided medium to good dr's. The stereochemical outcomes suggested that the addition followed a Barrow transition state which invokes a chelation of the α-oxygenated substituent. Finally, transformation and deprotection of the sulfinylaminoesters derived from threose afforded the 2,2-difluoro-3-amino-D-galactose derivative **1.61** in satisfactory yield.

Chapter 4: Conclusions

4.1 3,3,4,4-Tetrafluorinated carbohydrates

In the first chapter, the syntheses of enantiopure 2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hexopyranose **1.54**, 3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose **1.55** and 3,4-dideoxy-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranose **1.56** were presented (**Figure 4.1**). In light of the concept of "Polar Hydrophobicity", these fluorinated carbohydrates are expected to exhibit enhanced affinity for their cognate protein receptors.

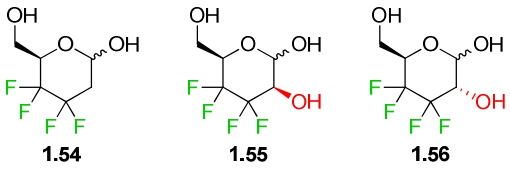


Figure 4.1: 3,3,4,4-tetrafluorinated carbohydrate analogues

First, the enantiopure starting material benzyl and naphthylmethyl protected bromotetrafluorobutanediol **1.66** and **2.2** were prepared on large scale following known procedures developed within the group. The enantiopure tetrafluorinated hexose **1.54** was synthesised using the sodium dithionite induced radical coupling to ethyl vinyl ether published by former group members. Minor modifications of the protocol resulted in **1.54** to be obtained in a slightly improved yield.

The same radical methodology was then applied to the synthesis of tetrafluorinated mannose **1.55** and glucose **1.56** by using a protected enediol in order to introduce the alcohol at position 2. However, no reaction occurred with alkoxysilyloxyalkenes while the use of dimethyldioxole only afforded the desired products in low yields. Nonetheless, the mannose and glucose acetonide derivatives obtained were separable by HPLC and further deprotection afforded **1.55** and **1.56** in three steps and an 8% overall yield per sugar.

Consequently, a second approach was envisioned which involved a MeLi mediated cyclisation onto a methyl ester. Such cyclisation had not been reported before and proceeded in very good yields to offer the alkyl 2-hexulosides. The diastereoselectivity of the ketone reduction step depended on the orientation of the anomeric substituent therefore providing the β-mannosides and the α-glucosides as the major components of the mixture obtained. It

should be noted that the use of other reducing agents than sodium borohydride was unsuccessful. The separation and hydrolysis of the anomeric substituent proved much troublesome than expected. Only the glucose derivative could be isolated in pure form after debenzylation of the 6-OH whereas the mannose analogue remained contaminated with 5% of the glucose analogue. Regarding the hydrolysis, satisfactory yields could only be reached with the assistance of a neighbouring acetyl group at position 2. This approach necessitated six steps (plus three for the synthesis of methyl ethoxybromoacetate) which afforded **1.56** in approximately 15% overall yield.

Finally, a third route inspired by Konno's intermolecular addition of lithiated bromotetrafluorobutene to electrophiles was developed. A mixture of **1.55** and **1.56** was readily obtained on multigram scale in four steps for a 51% overall yield (25% per sugar). However, the separation of the two carbohydrates analogues required another four protection/deprotection steps including a β-selective naphthylmethylation of the anomeric position. Unfortunately, this process was responsible for a decrease of the overall yield of each sugar to 14%.

In my opinion, the first approach probably deserves more optimisation as the radical coupling with dimethyldioxole provides the carbohydrate directly separable in one single step. Perhaps, the use of a different initiator and/or different reaction conditions could result in this approach to be competitive with or even better than the two others. Although good yields were finally reached for the hydrolysis, the second route will always suffer from the difficult separation. Additionally, some reactions have already shown reduced yields when scaling up above the gram scale. As explained in section **2.3.5**, although long of eight steps, the third approach emerged as the best because of the practicality of most reactions and the fact that multigram scale synthesis could be performed. Furthermore, the overall yield for the separation could potentially be improved by conducting a more thorough optimisation of solvents, temperature, etc.

4.2 Tetra and Difluorinated Aminosugars

The introduction of a polyfluorinated moiety adjacent to an alcohol results in the loss of its hydrogen bond accepting capacity. In an effort to restore the latter, four tetrafluoro and one difluoro aminosugars (**Figure 4.2**, **1.57**-**1.61**) were synthesised as direct analogues of previously reported fluorinated carbohydrates (**1.23**-**1.25**, **1.55** and **1.56**). Their synthesis relied on *N*-*tert*-butanesulfinylimines which involve the use of Ellman's auxiliary.

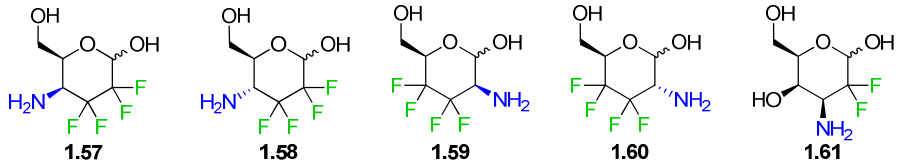


Figure 4.2: 2,2,3,3- and 3,3,4,4-tetrafluoroaminosugars and 2,2-difluoro-3-amino-D-galactose

The tetrafluoroaminosugars **1.57**-**1.60** were obtained by addition of lithiated tetrafluorinated substrates to each *R* and *S* epimer of two different sulfinylimines. The major products were formed in medium to good yields with high diastereoselectivity, and were separable form the minor products in most cases. The addition reactions were stereochemically governed by the sulfinyl auxiliary and proceeded *via* an open transition state. A slight double diastereodifferentiation was observed when the sulfinylimine possessed a chiral α-alkoxy substituent. Subsequent diol deprotection, ozonolysis and auxiliary removal provided the desired aminosugars in very good yields as their hydrochloride salts.

The difluoroaminosugar **1.61** was synthesised *via* a Honda-Reformatsky addition of ethyl bromodifluoroacetate to a sulfinylimine derived from d-threose. Beforehand, the reaction was optimised and performed on a range of aliphatic sulfinylimines. The reaction required an α-oxygenated substituent to proceed with high diastereoselectivity. When this substituent was chiral, a strong double diastereoselection was evidenced leading to a complete selectivity for the matched cases and a low to very good stereoinduction for the mismatched cases. These results were in agreement with a Barrow transition state. The galactose analogue **1.61** was finally obtained in four steps from the sulfinylaminoester in good yield.

Chapter 5: Experimental

5.1 General conditions

All air/ moisture sensitive reactions were carried out under an inert atmosphere (Ar), in oven dried glassware. CH_2Cl_2 (from CaH_2), THF (from Na and benzophenone) and MeCN (from CaH_2) were distilled prior to use, and where appropriate, other reagents and solvents were purified by standard techniques. TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F_{254} merck indicator; visualised under UV light (254 nm) and/or by staining with $KMnO_4$ (10% aq.). Flash column chromatography was performed with Sigma Aldrich 60 silica gel (40-63 nm).

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded in $CDCl_3$, DMSO or MeOD solutions using Bruker, AV300 (300, 75 and 282 MHz respectively) and AV400 (400, 101 and 376 MHz respectively) spectrometers. ^{19}F NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in δ units using $CHCl_3$ as an internal standard. Coupling constants (*J*) were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), dddd (doublet of doublets of doublets of doublets) dt (doublet of triplets), t (triplet), q (quartet), qd (quartet of doublets), qt (quartet of triplets), br. s (broad singlet), and m (multiplet).

Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected on a PerkinElmer Spectrum one FT6IR fitted with an ATR accessory using neat samples (solids and liquids). The abbreviations s (strong), m (medium), w (weak) and br (followed by either s, m or w to indicate the strength of a broad peak) are used when reporting the spectra.

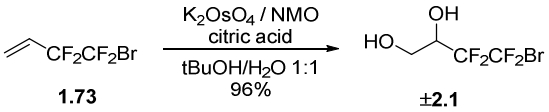
Electrospray mass spectra were obtained using a Waters 2700 sample manager ESI, samples were ran in HPLC methanol or MeCN, labelled *m/z* (abundance percentage) $[M+X]^{-/+}$. HRMS were obtained using a Bruker APEX III FT-ICR-MS.

Optical rotations were collected on an Optical Activity POLAAR 2001 at 589 nm with samples in MeOH, EtOH, $CHCl_3$.

5.2 Preparation of starting materials

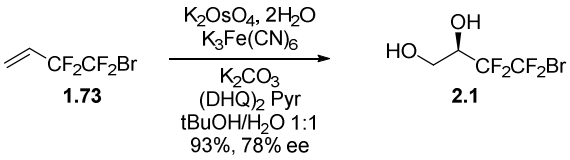
5.2.1 (2*R*)-4-Bromo-3,3,4,4-tetrafluorobutane-1,2-diol (2.1)

5.2.1.1 Racemic diol



1.73 (10 g, 48.3 mmol), K_2OsO_4 (17.8 mg, 48.3 µmol), and NMO (7.18 g, 53.1 mmol) were added to citric acid previously dissolved in *t*BuOH/H_2O 1:1 (50 mL). The reaction mixture was stirred at rt for 48 h, concentrated, acidified with aqueous HCl 1M (60 mL) and extracted with Et_2O (2×50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated in *vacuo*. The desired diol **2.1** was obtained as a yellowish oil (11.2 g, 96%) and was used without any further purification.

5.2.1.2 Enantioenriched diol

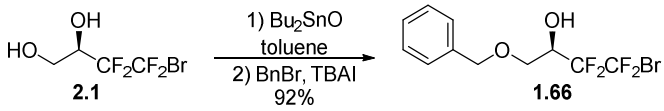


$K_3Fe(CN)_6$ (57.3 g, 174 mmol, 3 equiv.), K_2CO_3 (24.0 g, 174 mmol, 3 equiv), K_2OsO_4 (427 mg, 1.16 mmol, 0.02 equiv) and $(DHQ)_2$ Pyr (1.02 g, 1.16 mmol, 0.02 equiv) were dissolved in *t*BuOH/H_2O 1:1 (580 mL). The reaction mixture was stirred until dissolution was complete and cooled down to 0 °C. **1.73** (12.0 g, 58.0 mmol, 1 equiv) was added and the reaction mixture was stirred at 4 °C for 10 days. Na_2SO_3 (87 g) was added and the reaction mixture was allowed to warm up to rt with vigorous stirring over 2 h and then diluted with H_2O (54 mL) and Et_2O (230 mL). The aqueous phase was extracted with Et_2O (2×230 mL). The combined organic phases were washed with HCl 2M (2×54 mL) and brine (54 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The product was purified by distillation under reduced pressure (76 °C, 1 mbar) using a short path condenser to yield the desired diol (13.0 g, 93%, 78% ee)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36–4.22 (1H, m, C*H*OH), 3.96–3.91 (2H, m, CH_2OH), 2.68 (2H, br. s., 2 x OH) ppm. **^{13}C NMR** (75MHz, $CDCl_3$) δ ppm 117.1 (tt, *J* = 312.5, 39.5Hz, *C*F_2Br), 114.4 (ddt, *J* = 262.0, 257.8, 31.0 Hz, *C*F_2), 69.4 (dd, *J* = 27.4, 22.1 Hz, *C*HOH), 60.4 (*C*H_2); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –63.28 (1F, dd, *J* = 180.5, 8.6 Hz, C*F*FBr), –64.56 – –63.71 (1F, m, CF*F*Br), –

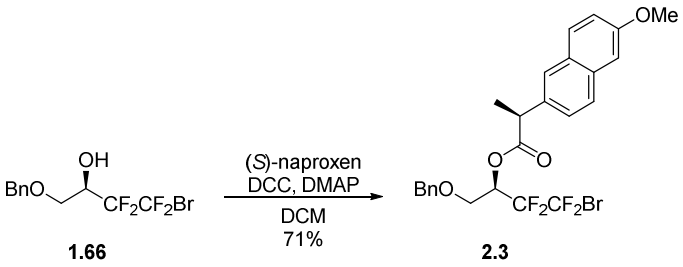
117.08 – –115.25 (1F, m, C*F*FCF$_2$), –123.75 – –122.53 (1F, m, CF*F*CF$_2$). The spectral data matched with the literature.[48]

5.2.2 (2*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-ol (1.66)



To **2.1** (10 g, 41.5 mmol, 1 equiv) in dry toluene (150 mL) was added Bu_2SnO (12.4 g, 49.8 mmol, 1.2 equiv). The reaction mixture was heated at reflux (100–110 °C) using a Dean-Stark condenser for 6 h. Benzyl bromide (5.92 mL, 49.8 mmol, 1.2 equiv) and TBAI (3.84 g, 10.4 mmol, 0.25 equiv) were added and the reaction mixture was stirred at reflux for 16 h, cooled down to rt and diluted with Et_2O (175 mL). The reaction mixture was then washed with aqueous KF 10% w/v (2×50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained product was purified by flash chromatography to yield **1.66** (12.6 g, 92%) as an orange solid. $\mathbf{R_f}$ 0.22 (petroleum ether 40-60 °C/Et_2O 80:20); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.45–7.29 (5H, m, 5×H_{Ar}), 4.62 (2H, s, CH_2Ph), 4.46–4.28 (1H, m, C<u>H</u>OH), 3.86–3.70 (2H, m, C<u>H</u>$_2$O), 2.90 (1H, d, *J*=6.6 Hz, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.0 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (CH_{Ar}), 73.8 (<u>C</u>H$_2$Ph), 68.4 (dd, *J* = 27.8, 22.0 Hz, <u>C</u>HOH), 67.4 (CH<u>C</u>H$_2$O); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –62.91 (1F, m, C<u>F</u>FBr), –64.06 (1F, m, CF<u>F</u>Br), –115.41 (1F, m, C<u>F</u>FCF$_2$Br), –123.92 (1F, m, CF<u>F</u>CF$_2$Br). The spectral data matched with the literature.[48]

5.2.3 (*R*)-1-Benzyloxymethyl-3-bromo-2,2,3,3-tetrafluoropropyl (*S*)-2-(6-methoxynaphtalen-2yl)-propanoate (2.3)

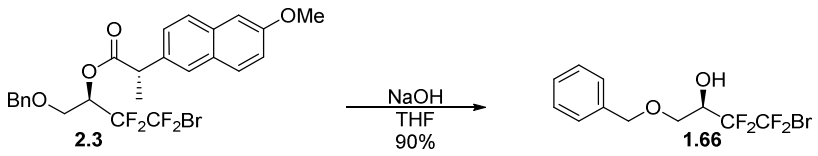


To a stirring solution of **1.66** (10.8 g, 32.6 mmol) in dry DCM (150 mL) was added DCC (7.40 g, 35.9 mmol, 1.1 equiv) and DMAP (398 mg, 3.26 mmol, 0.1 equiv). The reaction mixture was stirred at rt until complete dissolution was obtained, (*S*)–naproxen (8.27 g, 35.9 mmol, 1.1 equiv) was added and the reaction mixture stirred for 18 h. The white precipitate was removed

by filtration and washed with DCM (20 mL). The resultant filtrate was reduced *in vacuo* to tield a crude suspension which was purified by column chromatography on silica gel (petroleum ether 40-60 °C/acetone 85:15) to yield a white solid as a mixture of diastereoisomers. The desired major diastereoisomer **2.3** was then recrystalised from hexane as a white solid (12.5 g, 71%).

Mp 68–70 °C (hexane); **[α]$_D$** +26.6 (c 1, $CHCl_3$, 27 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.73–7.63 (3H, m, 3×H_{Ar}), 7.42 (1H, dd, *J* = 8.5, 1.3 Hz, H_{Ar}), 7.26–7.10 (5H, m, 5×H_{Ar}), 7.01 (2H, d, *J* = 7.2 Hz, 2×H_{Ar}), 5.86 (1H, dtd, *J* = 16.4, 7.6, 3.0 Hz, C<u>H</u>CF_2), 4.33 (1H, d, *J* = 12.0 Hz, C<u>H</u>HPh), 4.24 (1H, d, *J* = 12.0 Hz, CH<u>H</u>Ph), 4.00–3.91 (4H, m, C<u>H</u>CH_3 and O$C\underline{H}_3$), 3.81–3.74 (1H, m, C<u>H</u>HOBn), 3.62 (1H, dd, *J* = 11.1, 7.8 Hz, CH<u>H</u>OBn), 1.64 (3H, d, *J* = 7.2 Hz, CHC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 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}), 128.3 (2×CH_{Ar}), 127.6 (CH_{Ar}), 127.3 (CH_{Ar}), 127.2 (CH_{Ar}), 126.2 (CH_{Ar}), 126.1 (CH_{Ar}), 119.0 (CH_{Ar}), 116.7 (tt, *J* = 313.2, 39.5 Hz, <u>C</u>F_2), 113.4 (tt, *J* = 259.8, 32.2 Hz, CF_2), 105.6 (CH_{Ar}), 73.2 (CH_2Ph), 67.8 (dd, *J* = 29.3, 22.0 Hz, <u>C</u>HCF_2), 66.5 (CHOBn), 55.3 (CH<u>C</u>H$_3$), 45.1 (<u>C</u>CH_3), 18.5 (OCH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –64.1 (2F, s, CF_2Br), –114.0 (1F, d, *J* = 275.1 Hz, CHC<u>F</u>F), –119.5 (1F, dd, *J* = 275.1, 17.2 Hz, CHCF<u>F</u>). The spectral data matched with the literature.[48]

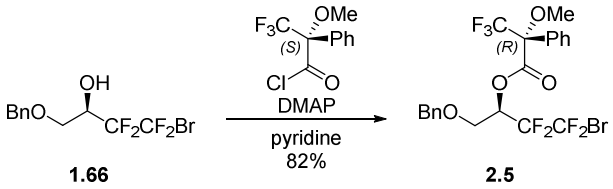
5.2.4 (2*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-ol (1.66)



To the ester **2.3** (9.25 g, 17.0 mmol, 1 equiv) in dry THF (110 mL) was added NaOH (7.5 g, 187 mmol, 11 equiv) and the reaction mixture was stirred at reflux for 3 h. Volatiles were removed and residue was dissolved in sat. aq. $NaHCO_3$ and extracted with Et_2O. The etheral extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a colorless oil. Purification by column chromatography (petroleum ether 40-60 °C/Et_2O 80:20) yielded 5.08 g (15.3 mmol, 90%) of the desired alcohol **1.66** as a colourless oil. **R_f** 0.21 (Petroleum ether 40-60 °C/Et_2O 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.43–7.30 (5H, m, H_{Ar}), 4.66–4.58 (2H, m, C<u>H</u>$_2$Ph), 4.43–4.31 (1H, m, C<u>H</u>OH), 3.83–3.72 (2H, m, CHC<u>H</u>$_2$O), 2.91 (1H, d, *J* = 6.69 Hz, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.0 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (CH_{Ar}), 73.8 (<u>C</u>H_2Ph), 68.4 (dd, *J* = 27.8, 22.0 Hz, <u>C</u>HOH), 67.4 (CH<u>C</u>H_2O); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –

63.0 (1F, m, *J* = 180.5 Hz, CFFBr),–63.9 (1F, d, *J* = 180.5 Hz, CFFBr),–115.4 (1F, d, *J* = 270.8 Hz, CHCFF),–123.9 (1F, ddd, *J* = 270.8, 21.5, 8.6 Hz, CHCFF). The spectral data matched with literature.[48]

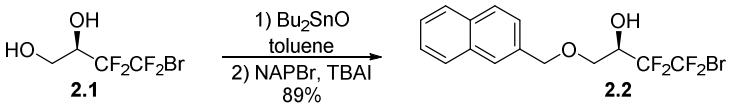
5.2.5 (*R*)-1-Benzyloxymethyl-3-bromo-2,2,3,3-tetrafluoropropyl (*R*)-α -trifluoromethyl-α-methoxy-phenylacetate (2.5)



To the alcohol **1.66** (25 mg, 0.076 mmol) in pyridine (0.5 mL) was added DMAP (1.8 mg, 0.015 mmol, 0.2 equiv) and (*S*)-α-methoxyl-α-(trifluoromethyl)phenylacetyl chloride (0.028 mL, 0.15 mmol, 2 equiv). The reaction mixture was stirred at rt for 7 d then water (0.5 mL) and Et_2O (5 mL) were added, the phases were separated and the organic phase washed with 2M HCl (4×3 mL), sat aq $NaHCO_3$ (2×3 mL) and dried over $MgSO_4$. The solvents were reduced *in vacuo* to yield colourless oil. Purification by column chromatography (petroleum ether 40-60 °C/Et_2O 90:10) afforded 34 mg (0.062 mmol, 82%) of the pure Mosher's ester **2.5**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.47 (m, 2H, H_{Ar}), 7.43 – 7.18 (m, 8H, H_{Ar}), 6.04 (tdd, *J*=11.0, 8.7, 2.7 Hz, 1H, CF_2CH), 4.49 (d, *J*=11.9 Hz, 1H, CHHPh), 4.44 (d, *J*=11.9 Hz, 1H, CHHPh), 3.85 (dd, *J*=11.0, 2.7 Hz, 1H, CHHOBn), 3.70 (dd, *J*=11.0, 8.7 Hz, 1H, CHHOBn), 3.53 (s, 3H, OCH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –64.3 (s, 2F, CF_2Br), –72.1 (s, 3F, CF_3), –115.5 (br d, *J*=8.6 Hz, 1F, CHCFF), –116.1 (dd, *J*=275.1, 12.9 Hz, 1F, CHCFF) ppm.[111]

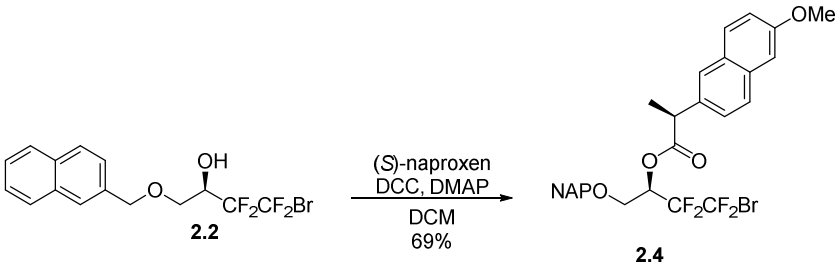
5.2.6 (2*R*)-1-(2-Naphthylmethyl)-4-bromo-3,3,4,4-tetrafluorobutane-1,2-diol (2.2)



To **2.1** (13.8 g, 57.3 mmol, 1 equiv) in dry toluene (200 mL) was added Bu_2SnO (17.1 g, 68.7 mmol, 1.2 equiv) and the reaction mixture was heated at reflux (100–110 °C) using a Dean-Stark condenser for 18 h. The reaction mixture was cooled to rt then 2-(bromomethyl)-naphthalene (15.2 g, 68.7 mmol, 1.2 equiv) and TBAI (5.29 g, 14.3 mmol, 0.25 equiv) were added and the reaction mixture was stirred at reflux for 24 h, cooled to rt and diluted with

Et_2O (300 mL). The resultant mixture was then washed with aqueous KF 10% w/v (2×150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained product was purified by flash chromatography (petroleum ether 40-60 °C/Et_2O 85:15 to 75:25) to yield **2.2** (18.7 g, 49.1 mmol, 86%) as a pale yellow solid. **R*f*** 0.27 (petroleum ether 40-60 °C/Et_2O 80:20). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93–7.75 (m, 4H, H_{Ar}), 7.58–7.42 (m, 3H, H_{Ar}), 4.78 (s, 2H, C$\underline{H_2}$Nap), 4.48–4.31 (m, 1H, C$\underline{H}$OH), 3.88–3.76 (m, 2H, CHC$\underline{H_2}$O), 2.94 (d, $^3J_{HH}$=6.8 Hz, 1H, O$\underline{H}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4 ($C_{q,Ar}$), 133.1 ($C_{q,Ar}$), 133.2 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 127.7 (CH_{Ar}), 127.9 (CH_{Ar}), 126.8 (CH_{Ar}), 126.2 (CH_{Ar}), 126.3 (CH_{Ar}), 125.5 (CH_{Ar}), 73.9 (C$\underline{H_2}$Nap), 68.5 (dd, $^2J_{CF}$=28.7, 23.2 Hz, C$\underline{H}$OH), 67.5 (CH$\underline{C}H_2$O) ppm. ^{19}F NMR (282MHz, $CDCl_3$) δ –62.99 (dd, $^2J_{FF}$=179.5, $^3J_{FF}$=7.5 Hz, 1F, C$\underline{F}$FBr), –63.92 (dd, $^2J_{FF}$=179.5, *J*=4.3 Hz, 1F, CF$\underline{F}$Br), –115.37 (d, $^2J_{FF}$=269.7 Hz, 1F, C$\underline{F}$FCF$_2$Br), –123.86 (ddd, $^2J_{FF}$=269.7, $^3J_{HF}$=18.3, $^3J_{FF}$=7.5 Hz, 1F, CF$\underline{F}$CF$_2$Br) ppm. The spectral data matched with the literature.[48]

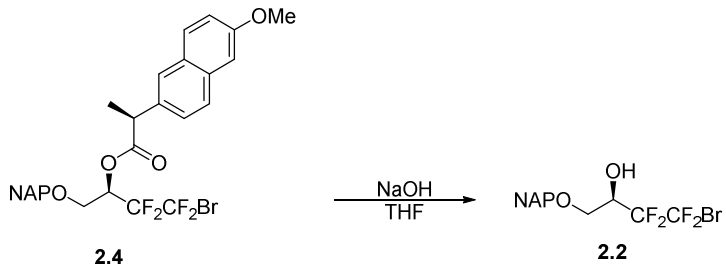
5.2.7 (*R*)-1-((2-Naphthylmethoxy)-methyl)-3-bromo-2,2,3,3-tetrafluoropropyl (*S*)-2-(6-methoxynaphtalen-2yl)-propanoate (2.4)



To a stirring solution of **2.2** (18.7 g, 49.1 mmol) in dry CH_2Cl_2 (150 mL) was added DCC (11.1 g, 54.0 mmol, 1.1 equiv) and DMAP (599 mg, 4.91 mmol, 0.1 equiv). The reaction mixture was stirred at rt until complete dissolution was obtained, (*S*)–naproxen (12.4 g, 54.0 mmol, 1.1 equiv) was added and the reaction mixture stirred at rt for 18.5 h. The white precipitate was removed by filtration and washed with CH_2Cl_2 (3 × 30 mL). The resultant filtrate was reduced *in vacuo* to yield a crude suspension which was purified by column chromatography on silica gel (petroleum ether 40-60 °C/acetone 90:10) to yield a white solid as a mixture of diastereoisomers. The desired major diastereoisomer **2.4** was then recrystallised from hexane as a white solid (20.1 g, 33.9 mmol, 69%). **R*f*** 0.25 (petroleum ether 40-60 °C/acetone 90:10). **^{1}H NMR** (300MHz, $CDCl_3$) δ 7.82–7.73 (m, 1H, CH_{Ar}), 7.71–7.64 (m, 2H, CH_{Ar}), 7.64–7.56 (m, 3H, CH_{Ar}), 7.53–7.36 (m, 4H, CH_{Ar}), 7.15–7.00 (m, 3H, CH_{Ar}), 5.90 (dddd appears as dtd, $^3J_{HF}$=16.3, $^3J_{HF}$=7.7, $^3J_{HH}$=7.7, $^3J_{HH}$=3.2 Hz, 1H, C$\underline{H}$O), 4.46 (d, $^2J_{HH}$=12.1 Hz, 1H, C$\underline{H}$HNap), 4.36 (d, $^2J_{HH}$=12.1 Hz, 1H, C$\underline{H}$HNap), 3.96 (q, $^3J_{HH}$=7.1 Hz, 1H, C$\underline{H}$CH$_3$), 3.90 (s, 3H, OC$\underline{H_3}$), 3.81 (ddd, $^2J_{HH}$=11.1,

$^{3}J_{HH}$=3.2, *J*=1.9 Hz, 1H, CHC<u>H</u>HO), 3.65 (dd, $^{2}J_{HH}$=11.1, $^{3}J_{HH}$=7.7 Hz, 1H, CHCH<u>H</u>O), 1.63 (d, $^{3}J_{HH}$=7.1 Hz, 3H, CHC<u>H$_3$</u>) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -64.1 (s, 2F, C<u>F$_2$</u>Br), –114.0 (d, $^{2}J_{FF}$=275.1 Hz, 1F, C<u>F</u>FCF$_2$Br), –119.4 (dd, $^{2}J_{FF}$=275.1, $^{3}J_{HF}$=16.3 Hz, 1F, CF<u>F</u>CF$_2$Br) ppm. The spectral data matched with the literature.[48]

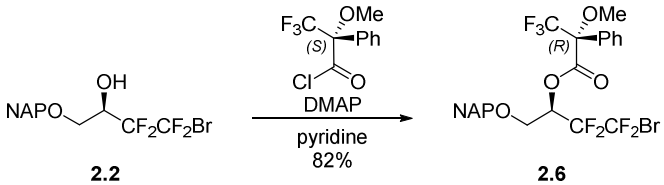
5.2.8 (2*R*)-1-(2-Naphthylmethyl)-4-bromo-3,3,4,4-tetrafluorobutane-1,2-diol (2.2)



2.4 **2.2**

To the ester **2.4** (20.1 g, 33.9 mmol, 1 equiv) in THF (200 mL) was added ground NaOH (14.9 g, 373 mmol, 11 equiv) and the reaction mixture was stirred at reflux for 1h. The solvents were reduced *in vacuo* to yield a crude residue which was taken up in sat. aq. $NaHCO_3$ (500 mL) and extracted with Et_2O (3×500 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (petroleum ether 40-60 °C/Et_2O 80:20 to 70:30) afforded the desired enantiopure alcohol **2.2** (12.6 g, 33.0 mmol, 97%) as a white solid. The spectral data matched with the literature.[48]

5.2.9 (*R*)-1-((2-Naphthylmethoxy)-methyl)-3-bromo-2,2,3,3-tetrafluoropropyl (*R*)-α-trifluoromethyl-α-methoxyphenylacetate (2.6)



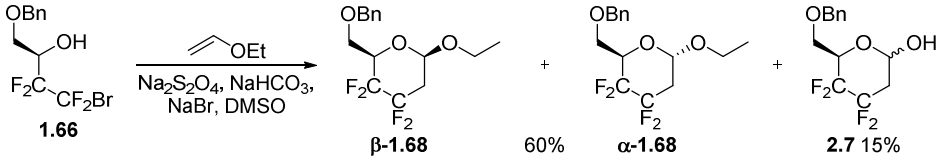
2.2 **2.6**

To the alcohol **2.2** (25 mg, 0.066 mmol) in pyridine-*d*5 (0.6 mL) was added DMAP (3.2 mg, 0.026 mmol, 0.4 equiv) and (*S*)-α-methoxyl-α-(trifluoromethyl)phenylacetyl chloride (0.025 mL, 0.13 mmol, 2 equiv). The reaction mixture was stirred at rt for 7 d then water (0.5 mL) and Et_2O (5 mL) were added, the phases were separated and the organic phase washed with 2M HCl (4×3 mL), sat aq $NaHCO_3$ (2×3 mL) and dried over $MgSO_4$. The solvents were reduced *in vacuo* to yield 39 mg (0.066 mmol, 99%) of the pure Mosher's ester **2.6** as a colourless oil. **^{1}H**

NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.76 (m, 3H, H_{Ar}), 7.68 (br s, 1H, H_{Ar}), 7.63 – 7.46 (m, 4H, H_{Ar}), 7.39 – 7.22 (m, 5H, H_{Ar}), 6.07 (tdd, *J*=11.3, 8.8, 2.9 Hz, 1H, $CF_2C\underline{H}O$), 4.66 (d, *J*=12.1 Hz, 1H, $C\underline{H}HNap$), 4.59 (d, *J*=12.1 Hz, 1H, $CH\underline{H}Nap$), 3.89 (dd, *J*=11.3, 2.9 Hz, 1H, $C\underline{H}HONAP$), 3.74 (dd, *J*=11.3, 8.8 Hz, 1H, $CH\underline{H}ONAP$), 3.53 (d, *J*=0.7 Hz, 3H, $OC\underline{H}_3$) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –64.3 (s, 2F, $C\underline{F}_2Br$), –72.1 (br s, 3F, $C\underline{F}_3$), –115.0 (dd, *J*=275.1, 10.7 Hz, 1F, $C\underline{F}FCF_2Br$), –116.1 (dd, *J*=275.1, 10.7 Hz, 1F, $CF\underline{F}CF_2Br$) ppm.

5.3 Radical addition/cyclisation for 1.54

5.3.1 Ethyl 6-*O*-benzyl-2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hexopyranoside (1.68)



Ethyl vinyl ether (1.5 mL, 15.1 mmol, 10 equiv) was added at rt to a stirred solution of the alcohol **1.66** (500 mg, 1.51 mmol, 1 equiv) in anhydrous DMSO (6 mL) in a sealed tube under N_2. $Na_2S_2O_4$ (390 mg, 2.27 mmol, 1.5 equiv), NaBr (234 mg, 2.27 mmol, 1.5 equiv) and $NaHCO_3$ (190 mg, 2.27 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 45 °C for 16 h. Water (25 mL) was added and the resultant mixture was extracted with Et_2O (4×50 mL). After addition of brine (25 mL), the aqueous phase was extracted with Et_2O (50 mL and 2×100 mL). The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated to give a pale yellow oil. Column chromatography (petroleum ether 40-60 °C/Et_2O 80:20 to 60:40) gave 291 mg (0.903 mmol, 60%) of the desired ethyl hexosides **α-1.68** and **β-1.68** as a 3:1 mixture and a colorless oil and 67 mg (0.228 mmol, 15%) of the hexose **2.7** as a white solid.

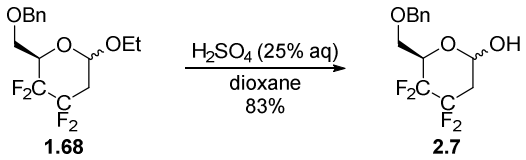
Data for β-1.68: R_f 0.70 (petroleum ether 40-60 °C/Et_2O 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.40–7.28 (5H, m, H_{Ar}), 4.75 (1H, d, *J* = 9.6 Hz, $C\underline{H}OEt$), 4.65 (1H, d, *J* = 12.1 Hz, $C\underline{H}HPh$), 4.59 (1H, d, *J* = 12.1 Hz, $CH\underline{H}Ph$), 4.05–3.88 (3H, m, $C\underline{H}HOBn$, $CF_2C\underline{H}$, $CH_3C\underline{H}H$) 3.76 (1H, dd, *J* = 11.3, 7.6 Hz, $CH\underline{H}OBn$), 3.61 (1H, dq, *J*=9.4, 7.1 Hz, $CH_3CH\underline{H}$), 2.57–2.40 (1H, m, $CF_2C\underline{H}H$), 2.38–2.17 (1H, m, $CF_2CH\underline{H}$), 1.26 (3H, t, *J* = 7.1 Hz, $C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.6 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 97.9 (d, *J* = 13.2 Hz, $\underline{C}HOEt$), 73.8 ($\underline{C}H_2Ph$), 72.6 (dd, *J* = 26.3, 23.4 Hz, $CF_2\underline{C}H$), 66.4 (CH_2OBn), 65.5 ($\underline{C}H_2CH_3$), 38.9 (t, *J* = 20.5 Hz, $CF_2\underline{C}H_2$), 15.0 ($\underline{C}H_3$); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –113.6 (1F, ddqd, *J* = 259.5, 36.2, 12.9, 3.4 Hz, $C\underline{F}FCH_2$), –120.1 (1F, dddd, *J* = 259.5, 19.8, 9.5, 5.2 Hz, $CF\underline{F}CH_2$), –132.6 (1F, m, *J* = 257.8 Hz, $CHC\underline{F}F$), –

140.2 (1F, dddd, *J* = 257.8, 13.8, 9.5, 4.3 Hz, CHCF<u>F</u>). The spectral data matched with literature.

Data for α-1.68: R_f 0.58 (petroleum ether 40-60 °C/Et_2O 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.40–7.28 (5H, m, H_{Ar}), 5.07 (1H, t, *J* = 3.66 Hz, C<u>H</u>OEt), 4.65 (1H, d, *J* = 12.1 Hz, C<u>H</u>HPh), 4.59 (1H, d, *J* = 12.1 Hz, CH<u>H</u>Ph), 4.42–4.30 (1H, m), 3.84–3.71 (2H, m), 3.53 (1H, dq, *J* = 9.7, 7.2 Hz, CH_3CHH), 2.57–2.40 (1H, m, CF_2C<u>H</u>H), 1.25 (3H, t, *J* = 7.1 Hz, C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.7 ($C_{q,Ar}$), 128.4 (CH_{Ar}), 127.8 (CH_{Ar}), 127.5 (CH_{Ar}), 95.2 (d, *J* = 13.2 Hz, <u>C</u>HOEt), 73.6 (<u>C</u>H_2Ph), 67.9 (dd, *J* = 26.3, 22.0 Hz, <u>C</u>HCF_2), 66.0 (<u>C</u>H_2OBn), 63.8 (<u>C</u>H_2CH_3), 37.1 (t, *J* = 20.9 Hz, CF_2<u>C</u>H_2), 14.8 (<u>C</u>H_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –110.6 (1F, ddq, *J* = 255.2, 33.6, 12.9 Hz, C<u>F</u>FCH_2), –118.9 (1F, m, *J* = 255.2 Hz, CF<u>F</u>CH_2), –133.5 (1F, m, *J* = 256.9 Hz, CHC<u>F</u>F), –137.9 (1F, m, *J* = 256.9 Hz, CHCF<u>F</u>).

HRMS (MS^+) for $C_{15}H_{18}F_4NaO_3$ $(M + Na)^+$ calcd 345.1084, found 345.1091.

5.3.2 6-*O*-Benzyl-2,3,4-trideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hexopyranose (2.7)



1.68 **2.7**

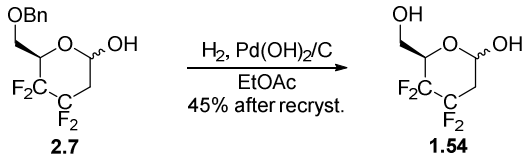
To a stirred solution of the acetal **1.68** (250 mg, 0.776 mmol) in dioxane (4 mL) was added the H_2SO_4 solution (25% v/v aq, 4 mL). The reaction mixture was stirred at reflux for 4 h, cooled to rt and extracted with EtOAc (3×30 mL). The organic extracts were then dried over Na_2SO_4, filtered and concentrated. Column chromatography (petroleum ether 40-60 °C/Et_2O 80:20 to 60:40) gave 190 mg (0.646 mmol, 83%) of the desired hemiacetal **2.7** as a mixture of anomers and a white solid. **Rf** 0.23 (petroleum ether 40-60 °C/Et_2O 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.42–7.29 (10H, m, H_{Ar}), 5.46 (1H, q, *J* = 3.8 Hz, H-1α), 4.98 (1H, d, *J* = 9.3 Hz, H-1β), 4.66–4.52 (1H, m, H-5α or H-5β), 4.63 (1H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.61 (1H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.58 (1H, d, *J* = 12.0 Hz, CH<u>H</u>Ph), 4.57 (1H, d, *J* = 11.9 Hz, CH<u>H</u>Ph), 3.98 (1H, ddddd, *J* = 23.5, 7.8, 3.9, 2.5, 1.5 Hz, H-5α or H-5β), 3.88 (2H, dddd, *J* = 10.9, 4.3, 2.5, 1.5 Hz, H-6α and H-6β), 3.82 (1H, br. s., OHβ), 3.76 (2H, ddd, *J* = 10.7, 7.8, 2.8 Hz, H-6'α and H-6'β), 3.40–3.35 (1H, m, OHα), 2.54–2.25 (3H, m, 2×H-2α and H-2β), 2.20 (1H, dtq, *J* = 35.7, 9.7, 4.3 Hz, H-2β); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.2 ($C_{q,Ar}$), 137.2 ($C_{q,Ar}$), 128.5 (4×CH_{Ar}), 128.1 (2×CH_{Ar}), 128.0 (4×CH_{Ar}), 92.7 (d, *J* = 11.7 Hz, C-1β), 90.3 (d, *J* = 11.7 Hz, C-1α), 74.0 (<u>C</u>H_2Ph), 73.8 (<u>C</u>H_2Ph), 72.3 (dd, *J* = 27.8, 22.0 Hz, C-5α or C-5β), 67.8 (dd, *J* = 26.3, 22.0 Hz, C-5α or C-5β), 66.1 (C-6α or C-6β), 66.0

(C-6α or C-6β), 39.4 (t, *J* = 20.5 Hz, C-2β), 36.9 (t, *J* = 20.5 Hz, C-2α); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –110.28 (1F, ddqd, *J* = 256.9, 33.6, 12.9, 2.6 Hz), –113.83 (1F, ddqd, *J* = 259.5, 35.0, 13.8, 3.4 Hz), –118.95 (1F, m, *J* = 256.9 Hz), –120.31 (1F, m, *J* = 259.5 Hz), –132.44 (1F, ddddd, *J* = 257.8, 24.1, 16.4, 13.8, 3.4 Hz), –133.83 (1F, ddddd, *J* = 256.9, 24.1, 15.5, 12.9, 2.6 Hz), –137.96 (1F, m, *J* = 256.9 Hz), –140.58 (1F, m, *J* = 257.8 Hz); **{^{1}H} ^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –110.28 (1F, dt, *J* = 256.9, 12.9 Hz), –113.83 (1F, dt, *J* = 259.5, 13.8 Hz), –118.95 (1F, ddd, *J* = 256.9, 15.5, 8.6 Hz), –120.31 (1F, ddd, *J* = 259.5, 16.4, 9.5 Hz), –132.44 (1F, ddd, *J* = 257.8, 16.4, 13.8 Hz), –133.83 (1F, ddd, *J* = 256.9, 15.5, 12.9 Hz), –137.96 (1F, ddd, *J* = 256.9, 12.9, 8.6 Hz), –140.58 (1F, ddd, *J* = 257.8, 13.8, 9.5 Hz). **HRMS** (MS^+) for $C_{13}H_{14}F_4NaO_3$ $(M + Na)^+$ calcd 317.0771, found 317.0766.

5.3.3 General procedure for debenzylation

The benzyl protected compound (1 equiv) was dissolved in dry EtOAc under N_2 at rt. $Pd(OH)_2/C$ (0.1–0.2 equiv) was added and H_2 was bubbled through the solution for 20 min. The reaction mixture was stirred under H_2 for 2.5 h then filtered through Celite® and concentrated.

5.3.4 2,3,4-Trideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hexopyranose (1.54)



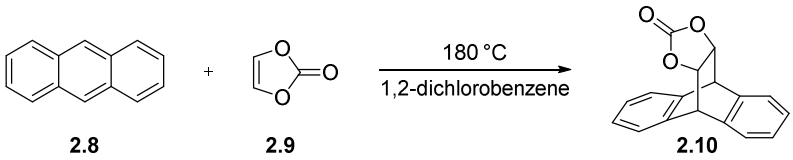
2.7 **1.54**

1.54 was obtained from **2.7** (225 mg, 0.765 mmol) following the procedure described above using 0.1 equiv of $Pd(OH)_2/C$. Recrystallisation from hexane/Et_2O/DCM afforded 70 mg (0.34 mmol, 45%) of the desired unprotected hexose **1.54** as a 0.75:1 α/β mixture of anomers and white crystals. **^{1}H NMR** (400 MHz, Acetone-*d*6) δ ppm 6.42 (1H, dd, *J* = 6.5, 1.6 Hz, OH-1β), 5.96–5.89 (1H, m, OH-1α), 5.55–5.47 (1H, m, H-1α), 5.13–5.05 (1H, m, H-1β), 4.47–4.33 (1H, m, H-5α), 4.09 (1H, t, *J* = 6.1 Hz, OH-6β), 4.00–3.81 (4H, m, H-5β, H-6β, H-6α and OH-6α), 3.80–3.67 (2H, m, H-6α and H-6β), 2.61 (1H, ttd, *J* = 13.0, 5.0, 2.1 Hz, H-2β), 2.52–2.28 (2H, m, H-2α), 2.18 (1H, dtq, *J* = 36.8, 9.1, 4.3 Hz, H-2β); **^{13}C NMR** (101 MHz, Acetone-*d*6) δ ppm 93.6 (d, *J* = 13.2 Hz, C-1β), 90.8 (d, *J* = 13.2 Hz, C-1α), 74.5 (dd, *J* = 26.3, 22.0 Hz, C-5β), 69.9 (dd, *J* = 24.9, 22.0 Hz, C-5α), 59.3–59.0 (m, C-6α and C-6β), 40.8 (t, *J* = 19.8 Hz, C-2β), 38.3 (t, *J* = 20.3 Hz, C-2α) and 4×CF_2 not seen. **^{19}F NMR** (282 MHz, Acetone-*d*6) δ ppm–110.6 (1F, ddq, *J* = 253.5, 34.5, 12.9 Hz, Fα),–114.4 (1F, ddqd, *J* = 256.9, 36.2, 13.8, 3.4 Hz, Fβ),–119.0 (1F, m, *J* = 253.4 Hz,

Fα),–120.5 (1F, m, *J* = 256.9 Hz, Fβ),–133.5 (1F, dddtd, *J* = 256.9, 16.4, 13.8, 11.2, 3.4 Hz, Fβ),–134.9 (1F, ddqd, *J* = 256.0, 14.7, 12.9, 2.6 Hz, Fα),–139.0 (1F, m, *J* = 256.0 Hz, Fα),–141.9 (1F, dddd, *J* = 256.9, 13.8, 8.6, 4.3 Hz, Fβ); **{^{1}H}^{19}F NMR** (282 MHz, Acetone-*d*6) δ –110.6 (1F, dt, *J* = 253.5, 12.9 Hz, Fα),–114.4 (1F, dt, *J* = 256.9, 13.8 Hz, Fβ),–119.0 (1F, ddd, *J* = 253.5, 14.7, 7.8 Hz, Fα),–120.5 (1F, ddd, *J* = 256.9, 16.4, 8.6 Hz, Fβ),–133.5 (1F, ddd, *J* = 256.9, 16.4, 13.8 Hz, Fβ),–134.9 (1F, ddd, *J* = 256.0, 14.7, 12.9 Hz, Fα),–139.1 (1F, ddd, *J* = 256.0, 12.9, 7.8 Hz, Fα),–141.9 (1F, ddd, *J* = 256.9, 13.8, 8.6 Hz, Fβ) ppm; **HRMS** (MS^+) for $C_6H_8F_4NaO_3$ $(M + Na)^+$ calcd 227.0302, found 227.0299.

5.4 Radical addition/cyclisation for 1.55/1.56

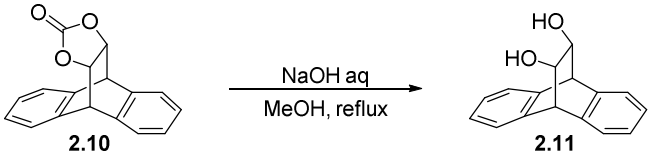
5.4.1 9,10,11,15-Tetrahydro-9,10-[4,5]epidioxoloanthracen-13-one (2.10)



2.8 + **2.9** → **2.10**

To anthracene (20 g, 112 mmol) in a 250 mL round-bottom flask was added vinylene carbonate (9.64 g, 112 mmol) and 1,2-dichlorobenzene (40 mL). The reaction mixture was heated at reflux (180 °C) for 1.5 days and then cooled down to rt. Hexane (200 mL) was added and the reaction mixture was stirred for 30 min and then filtered. The solid residue was washed with hexane until no colour persisted in the organic solvent to give **2.10** (27.9 g, 106 mmol, 95%) as a brownish solid which was used without any further purification. **^{1}H NMR** (300 MHz, CDCl3) δ 7.44–7.34 (4H, m, H_{Ar}), 7.31–7.20 (4H, m, H_{Ar}), 4.95–4.84 (2H, m, C*H*O), 4.76–4.66 (2H, m, C*H*CHO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.05 (*C*=O), 137.68, 136.22, 127.77, 127.65, 126.58, 125.62, 76.22 (C*C*HO), 47.70 (*C*HCHO). The spectral data matched with the literature.[61]

5.4.2 9,10-Dihydro-9,10-ethanoanthracene-11,12-diol (2.11)

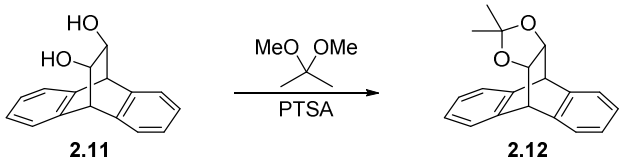


2.10 → **2.11**

To **2.10** (27.9 g, 106 mmol) in a 1 L round-bottomed flask was added methanol (400 mL) and NaOH (3.3M, aq, 70 mL). The reaction mixture was heated at reflux overnight, cooled down to

rt, acidified with 2N aq. HCl (150 mL) and filtered. The solid was washed twice with acidified water. The desired diol **2.11** was obtained as a yellowish solid (23.7 g, 99.5 mmol, 94%) which was used without any further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.43–7.29 (4H, m, H_{Ar}), 7.26–7.13 (4H, m, H_{Ar}), 4.46–4.38 (2H, m, C*H*OH), 4.10–4.00 (2H, m, C*H*CHOH), 2.38–2.29 (2H, m, OH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 139.9, 138.6, 126.7, 126.6, 126.5, 124.7, 68.1 (C*C*HO), 51.3 (*C*HCHO). The spectral data matched with the literature.[61]

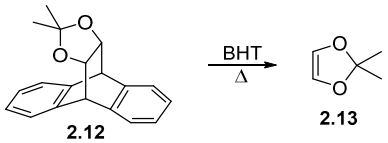
5.4.3 13,13-Dimethyl-9,10,11,15-tetrahydro-9,10-[4,5]epidioxoloanthracene (2.12)



2.11 **2.12**

To **2.11** (14.7 g, 61.7 mmol) was added 2,2-dimethoxypropane (61.0 mL, 494 mmol, 8 equiv) and PTSA (586 mg, 3.08 mmol, 0.05 equiv) and the reaction mixture was stirred at rt for 24 h. The reaction mixture was then diluted with dichloromethane (500 mL), washed with 5% aq. $NaHCO_3$ (2×80 mL) followed by water (100 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The obtained product was recrystalized from hexane to yield the desired ketal **2.12** (15.3 g, 55.0 mmol, 89%). **R_f** 0.44 (PE 40-60 °C/ Et_2O 80:20); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.39–7.29 (4H, m, H_{Ar}), 7.23–7.11 (4H, m, H_{Ar}), 4.56–4.52 (2H, m, C*H*O), 4.51–4.46 (2H, m, C*H*CHO), 1.23 (3H, s, CH_3), 0.68 (3H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 140.0, 139.2, 126.7, 126.1, 126.0, 125.3, 112.2 ($(CH_3)_2C$), 78.4 (*C*HO), 49.4 (*C*HCHO), 25.7 (*C*H_3), 25.4 (*C*H_3). The spectral data matched with the literature.[61]

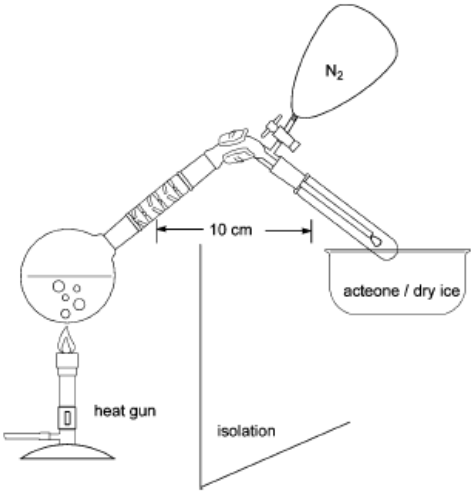
5.4.4 2,2-Dimethyl-1,3-dioxole (2.13)



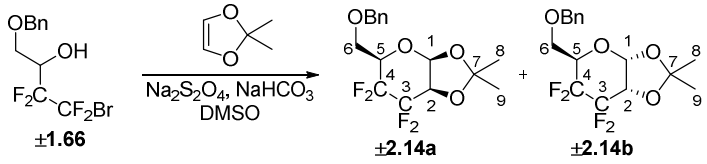
2.12 **2.13**

The whole apparatus (see picture below) was flame-dried under vacuum and filled with N_2. The starting material (11.9 g, 42.8 mmol of **2.12** and a few crystals of BHT) was added under a N_2 stream. The Vigreux column was wrapped with coton in aluminium foil. The RDA reaction was carried out under N_2 protection and the temperature of the collecting tube was adjusted to –50 °C with acetone/dryice. (Dioxole **2.13** is a volatile liquid, solidifying at –70 °C.) After the

solid was melted with a heat gun and the temperature was increased to about 600 °C, the RDA reaction started, indicated by vigorous boiling. The heating was kept until no product is distilled anymore. The dioxole **2.13** (3.16 g, 31.6 mmol, 74%) was obtained as a colorless oil, was used without any further purification and was kept in the freezer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 6.19 (2H, s, C*H*), 1.53 (6H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 126.6 (*C*H), 114.1 (CCH_3), 24.8 (CH_3). The spectral data matched with the literature.[62]



5.4.5 6-*O*-Benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-1,2-*O*,*O*-isopropylidene-*threo*-hexopyranose (±2.14a) and *erythro*-hexopyranose (±2.14b)

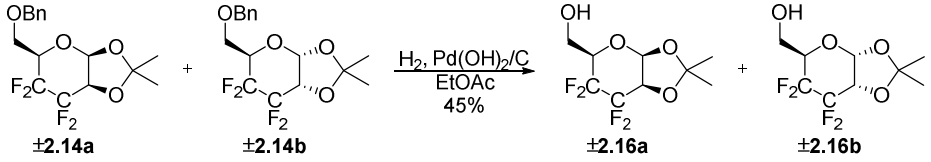


In a sealed tube, **±1.66** (500 mg, 1.51 mmol, 1 equiv) was dissolved in DMSO (4 mL) under N_2. Dimethyldioxole (151 mg, 1.51 mmol, 5 equiv) was added, then $Na_2S_2O_4$ (390 mg, 2.27 mmol, 1.5 equiv), NaBr (234 mg, 2.27 mmol, 1.5 equiv) and $NaHCO_3$ (190 mg, 2.27 mmol, 1.5 equiv) simultaneously and the reaction mixture was stirred at 35 °C for 19 h. Brine (25 mL) and water (10 mL) were added and the reaction mixture was extracted with Et_2O (5×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The obtained product was purified by flash chromatography to give a mixture of the two diastereoisomers **±2.14a** and **±2.14b** (115 mg, 0.328 mmol, 22%) as colourless oil. Analytical samples of the pure diastereoisomers **±2.14a** and **±2.14b** were obtained by HPLC.

Data for **±2.14a**: $\mathbf{R_f}$ 0.58 (PET 40-60 °C/ Et_2O 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.38–7.28 (5H, m, H_{Ar}), 5.45–5.42 (1H, m, H–1), 4.66 (1H, d, *J* = 12.0 Hz, C<u>H</u>HPh), 4.59 (1H, d, *J* = 12.0 Hz, CH<u>H</u>Ph), 4.36 (1H, dddd, *J* = 10.1, 5.6, 3.3, 2.3 Hz, H–2), 3.99 (1H, ddddd, *J* = 22.9, 6.9, 4.0, 2.9, 1.6 Hz, H–5), 3.91 (1H, ddd, *J* = 11.0, 2.9, 1.4 Hz, H–6a), 3.73 (1H, dd, *J* = 10.9, 7.1 Hz, H–6b), 1.62 (3H, s, H–8 or H–9), 1.45 (3H, s, H–8 or H–9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.4 (C–7), 128.5 (2C, C_{Ar}), 127.9 (C_{Ar}), 127.8 (2C, C_{Ar}), 115.2 ($C_{q,\ Ar}$), 96.9 (d, *J* = 5.9 Hz, C–1), 77.9 (dd, *J* = 39.5, 17.6 Hz, C–2 or C–5), 73.8 (*C*H_2Ph), 71.1 (dd, *J* = 26.0, 23.0 Hz, C–2 or C–5), 66.1 (C–6), 27.6 (C–8 or C–9), 26.1 (C–8 or C–9); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm -115.02 (1F, ddtd, *J* = 282.8, 13.8, 10.3, 10.3, 3.4 Hz, F–3), -129.85 (1F, dddd, *J* = 282.8, 16.4, 10.3, 1.7 Hz, F–3), -131.12 (1F, dddd, *J* = 261.2, 22.4, 16.4, 11.2 Hz, F–4), -135.91 (1F, dddd, *J* = 262.1, 13.8, 9.5, 5.3 Hz, F–4); **{^{1}H} ^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm -115.02 (1F, ddd, *J* = 281.9, 13.8, 10.3 Hz, F–3), -129.85 (1F, ddd, *J* = 282.8, 16.4, 10.3 Hz, F–3), -131.13 (1F, ddd, *J* = 262.1, 16.4, 11.2 Hz, F–4), -135.91 (1F, ddd, *J* = 262.1, 13.8, 9.5 Hz, F–4); **MS** (ESI) *m/z* 414 $(M + CH_3CN + Na)^+$; **HRMS** calculated for $C_{16}H_{18}F_4NaO_4$ 373.1033, found 373.1038 (1.3 ppm error).

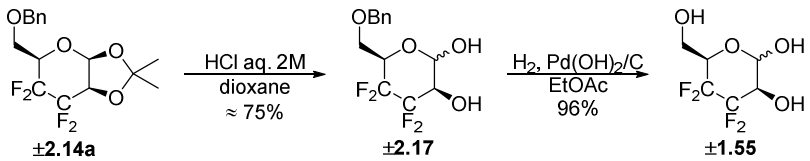
Data for **±2.14b**: $\mathbf{R_f}$ 0.52 (PET 40-60 °C/ Et_2O 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.40–7.28 (5H, m, H_{Ar}), 5.73 (1H, d, *J* = 5.1 Hz, H–1), 4.65 (1H, d, *J* = 12.3 Hz, C<u>H</u>HPh), 4.59 (1H, d, *J* = 12.1 Hz, CH<u>H</u>Ph), 4.49 (1H, dddd, *J* = 13.0, 6.5, 5.4, 1.5 Hz, H–2), 4.42 (1H, dtd, *J* = 20.0, 7.7, 4.5 Hz, H–5), 3.85 (1H, dd, *J* = 11.1, 4.2 Hz, H–6a), 3.71 (1H, ddd, *J*=10.9, 7.1, 0.9 Hz, H–6b), 1.65 (3H, s, H–8 or H–9), 1.41 (3H, s, H–8 or H–9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.5 (C–7), 128.5 (2C, C_{Ar}), 127.9 (C_{Ar}), 127.8 (2C, C_{Ar}), 112.3 (C_{Ar}), 97.3 (d, *J* = 5.9 Hz, C–1), 73.6 (*C*H_2Ph), 73.4 (dd, *J* = 35.1, 20.5 Hz, C–2 or C–5), 71.0 (dd, *J* = 30.7, 23.4 Hz, C–2 or C–5), 65.8 (d, *J* = 8.8 Hz, C–6), 25.6 (C–8 or C–9), 25.5 (C–8 or C–9); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm–113.79 (1F, ddd, *J* = 259.5, 7.8, 4.3 Hz, F–4), -117.17 (1F, ddd, *J* = 275.0, 6.0, 2.6 Hz, F–3), -126.01 (1F, dtd, *J* = 275.9, 6.0, 6.0, 4.3 Hz, F–3), -133.07 (1F, ddtd, *J* = 260.4, 20.0, 5.2, 5.2, 2.6 Hz, F–4); **{^{1}H} ^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm -113.80 (1F, dd, *J* = 259.5, 4.3 Hz, F–4), -117.17 (1F, dd, *J* = 275.9, 2.6 Hz, F–3), -126.01 (1F, ddd, *J* = 275.9, 6.0, 4.3 Hz, F–3), -133.08 (1F, ddd, *J* = 260.4, 6.0, 2.6 Hz, F–4); **MS** (ESI) *m/z* 414 $(M + CH_3CN + Na)^+$; **HRMS** (MS^+) for $C_{16}H_{18}F_4NaO_4$ $(M + Na)^+$ calcd 373.1033, found 373.1035 (0.5 ppm error).

5.4.6 3,4-Dideoxy-3,3,4,4-tetrafluoro-1,2-*O*,*O*-isopropylidene-*threo*-hexopyranose (±22a) and *erythro*-hexopyranose (±22b)



Starting from a mixture of **±2.14a** and **±2.14b** (45 mg, 0.128 mmol) following the debenzylation procedure described above using 0.1 equiv of $Pd(OH)_2/C$ gave 15 mg (0.058 mmol, 45%) of the desired products **±2.16a** and **±2.16b** as a 1.1:1 mixture of diastereoisomers and a colourless oil. $\mathbf{R}_f$ 0.39 (petroleum ether 40-60 °C/Acetone 70:30); **IR** (neat, cm^{-1}) 3398 (w br), 2292 (w), 1388 (m), 1096 (s), 1048 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 5.74 (1H, d, *J* = 5.1 Hz, H-1g), 5.46 (1H, s, H-1m), 4.51 (1H, qdd, *J* = 6.4, 5.0, 1.6 Hz, H-2g), 4.38 (1H, dddd, *J* = 10.2, 5.5, 3.2, 2.3 Hz, H-2m), 4.29 (1H, dtd, *J* = 20.2, 7.8, 4.0 Hz, H-5g), 4.02–3.84 (5H, m, H-5m, H-6m, H-6m', H-6g and H-6g'), 1.65 (3H, s, CH_3g), 1.62 (3H, s, CH_3m), 1.46 (3H, s, CH_3m), 1.41 (3H, s, CH_3g); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 115.3 ($\underline{C}(CH_3)_2$g or $\underline{C}(CH_3)_2$m), 112.4 ($\underline{C}(CH_3)_2$g or $\underline{C}(CH_3)_2$m), 97.3 (d, *J* = 5.9 Hz, C-1g), 97.1 (d, *J* = 5.9 Hz, C-1m), 78.0 (dd, *J* = 39.5, 16.1 Hz, C-2m), 73.4 (dd, *J* = 35.1, 19.0 Hz, C-2g), 72.2 (dd, *J* = 30.7, 23.4 Hz, C-5g), 71.7 (dd, *J* = 29.3, 22.0 Hz, C-5m), 58.9 (d, *J* = 10.2 Hz, C-6g or C-6m), 58.6 (C-6g or C-6m), 27.6 (CH_3m), 26.0 (CH_3m), 25.5 (CH_3g), 25.4 (CH_3g); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –113.4 (1F, dd, *J* = 257.9, 8.6 Hz, Fg), –115.2 (1F, dtd, *J* = 283.7, 11.0, 8.6 Hz, Fm), –117.5 (1F, d, *J* = 279.4 Hz, Fg), –126.5 (1F, d, *J* = 279.4 Hz, Fg), –131.6 – –129.5 (2F, m, 2×Fm), –133.1 (1F, dd, *J* = 257.9, 17.2 Hz, Fg), –137.2 – –136.0 (1F, m, Fm); **{^{1}H} ^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –113.4 (1F, d, *J* = 257.9 Hz, Fg), –115.2 (1F, dt, *J* = 283.7, 11.0 Hz, Fm), –117.5 (1F, d, *J* = 279.4 Hz, Fg), –126.5 (1F, d, *J* = 279.4 Hz, Fg), –131.6 – –129.4 (2F, m, 2×Fm), –133.1 (1F, d, *J* = 257.9 Hz, Fg), –137.3 – –136.0 (1F, m, Fm); **MS** (ESI) *m/z* 261 $(M + H)^+$; **HRMS** (MS^+) for $C_9H_{12}F_4NaO_4$ $(M + Na)^+$ calcd 283.0564, found 283.0566 (0.8 ppm error).

5.4.7 3,4-Dideoxy-3,3,4,4-tetrafluoro-*threo*-hexopyranose (±1.55)

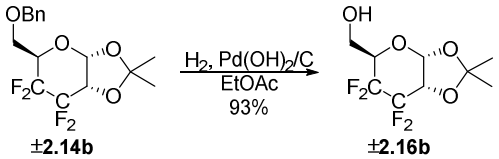


A 5% aq. HCl solution (1.4 mL, 1.92 mmol, 4 equiv) was added to a solution of **±2.14a** (162 mg, 0.462 mmol, 1 equiv) in dioxane (2 mL) at rt. The reaction mixture was stirred at rt for 6 h then

heated at 60 °C overnight. To bring the reaction to completion, 0.6 mL of a 4M HCl was added (overall concentration: 2.2M) and the resultant mixture was heated at reflux for 3 h then neutralized with $NaHCO_3$ and concentrated. The residue was extracted with EtOAc (3×25 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/Acetone 75:25) to give 114 mg (≈ 75%) of the desired product **±2.17** along with some inseparable impurities which was used without any further purification.

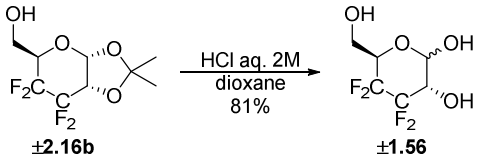
±1.55 was obtained from **±2.17** (100 mg, 0.322 mmol) following the procedure described above using 0.2 equiv of $Pd(OH)_2/C$. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/Acetone 60:40) to give 68 mg (0.309 mmol, 96%) of the desired product **±1.55** as a 1:0.6 α/β mixture of anomers and a white solid. $\mathbf{R_f}$ 0.31 (petroleum ether 40-60 °C/Acetone 60:40); **IR** (neat, cm^{-1}) 3370 (m, br), 2953 (w), 1195 (m), 1154 (s), 1068 (s); **^{1}H NMR** (400 MHz, acetone-*d*6) δ ppm 6.11 (1H, dd, *J* = 4.6, 2.3 Hz, OH-1α, disappears after D_2O-exchange), 5.96 (1H, d, *J* = 9.5 Hz, OH-1β, disappears after D_2O-exchange), 5.28 (1H, t, *J* = 4.6 Hz, H-1α, simplifies to d, *J* = 5.7 Hz after D_2O-exchange), 5.18 (2H, d, *J* = 5.8 Hz, OH-2α and OH-2β, disappears after D_2O-exchange), 5.07–5.00 (1H, m, H-1β), 4.44–4.31 (1H, m, H-5α), 4.15–4.00 (3H, m, H-2α, H-2β and OH-6β, simplifies after D_2O-exchange), 3.98 (1H, t, *J* = 5.8 Hz, OH-6α, disappears after D_2O-exchange), 3.94–3.82 (1H, m, H-5β, H-6α and H-6β), 3.81–3.71 (2H, m, H-6α' and H-6β'); **^{13}C NMR** (101 MHz, acetone-*d*6) δ ppm 95.6 (d, *J* = 5.9 Hz, C-1α), 94.3 (d, *J* = 7.3 Hz, C-1β), 74.9 (dd, *J* = 27.8, 22.0 Hz, C-5β), 72.2 (dd, *J* = 27.8, 19.0 Hz, C-2α), 72.1 (dd, *J* = 30.7, 17.6 Hz, C-2β), 70.6 (dd, *J* = 27.8, 20.5 Hz, C-5α), 59.2 (dd, *J* = 5.9, 2.9 Hz, C-6α or C-6β), 59.0 (dd, *J* = 5.9, 2.9 Hz, C-6α or C-6β); **^{19}F NMR** (282 MHz, Acetone-*d*6) δ ppm –118.2 (1F, d, *J* = 266.5 Hz, α), –120.2 (1F, d, *J* = 266.5 Hz, β), –131.9 – –129.1 (5F, m, 3×α and 2×β), –134.1 (1F, d, *J* = 259.5 Hz, β); **{^{1}H} ^{19}F NMR** (282 MHz, Acetone-*d*6) δ ppm –118.2 (1F, d, *J* = 266.5 Hz, α), –120.2 (1F, dt, *J* = 266.5, 12.9 Hz, β), –131.9 – –129.1 (5F, m, 3×α and 2×β), –134.1 (1F, dt, *J* = 262.2, 12.9 Hz, β); **MS** (ESI) *m/z* 284 (M + Na + MeCN)$^+$, **HRMS** (MS^+) for $C_6H_8F_4NaO_4$ $(M + Na)^+$ calcd 243.0251, found 243.0248.

5.4.8 3,4-Dideoxy-3,3,4,4-tetrafluoro-1,2-*O*,*O*-isopropylidene-*erythro*-hexopyranose (±2.16b)



±2.16b was obtained from **±2.14b** (134 mg, 0.383 mmol) following the debenzylation procedure described above using 0.2 equiv of $Pd(OH)_2/C$ to give 93 mg (0.36 mmol, 93%) of the desired product **±2.16b** as a colorless oil. $\mathbf{R_f}$ 0.31 (petroleum ether 40-60 °C/Acetone 70:30); IR (neat cm^{-1}) 3390 (w, br), 2995 (w), 1123 (s), 1094 (s), 1021 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 5.74 (1H, d, *J* = 5.1 Hz, H-1), 4.51 (1H, qdd, *J* = 6.4, 5.0, 1.6 Hz, H-2),), 4.29 (1H, dtd, *J* = 20.2, 7.8, 4.0 Hz, H-5), 4.02–3.84 (2H, m, H-6 and H-6'), 1.65 (3H, s, CH_3), 1.41 (3H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 112.4 ($\underline{C}(CH_3)_2$), 97.3 (d, *J* = 5.9 Hz, C-1), 73.4 (dd, *J* = 35.1, 19.0 Hz, C-2), 72.2 (dd, *J* = 30.7, 23.4 Hz, C-5), 58.9 (d, *J* = 10.2 Hz, C-6), 25.5 (CH_3), 25.4 (CH_3) and 2×CF_2 invisible; **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –113.4 (1F, dd, *J* = 257.9, 8.6 Hz), –117.5 (1F, d, *J* = 279.4 Hz), –126.5 (1F, d, *J* = 279.4 Hz), –133.1 (1F, dd, *J* = 257.9, 17.2 Hz), ; **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –113.4 (1F, d, *J* = 257.9 Hz), –117.5 (1F, d, *J* = 279.4 Hz), –126.5 (1F, d, *J* = 279.4 Hz), –133.1 (1F, d, *J* = 257.9 Hz); **MS** (ESI) *m/z* 261 $(M + H)^+$; **HRMS** (MS^+) for $C_9H_{12}F_4NaO_4$ $(M + Na)^+$ calcd 283.0564, found 283.0559.

5.4.9 3,4-Dideoxy-3,3,4,4-tetrafluoro-*erythro*-hexopyranose (±1.56)

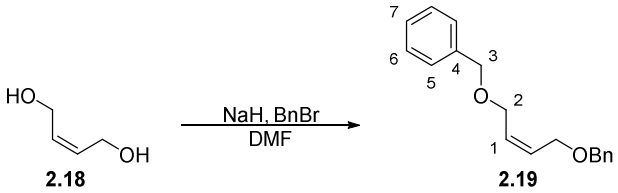


±2.16b **±1.56**

A 2M aq. HCl solution (1.0 mL, 2.0 mmol, 6 equiv) was added to a solution of **±2.16b** (89 mg, 0.34 mmol, 1 equiv) in dioxane (1 mL) at rt. The reaction mixture was heated at 80 °C for 2.5 h then neutralized with $NaHCO_3$ and concentrated. The residue was diluted with water (5 mL) then extracted with EtOAc (3×15 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/Acetone 60:40) to give 61 mg (0.28 mmol, 81%) of the desired product **±1.56** as a 1.0.55 α/β mixture and a white solid. $\mathbf{R_f}$ 0.32 (petroleum ether 40-60 °C/Acetone 60:40); **IR** (neat cm^{-1}) 3347 (m, br), 2955 (w), 1167 (m), 1099 (s), 1031 (s); **^{1}H NMR** (400 MHz, Acetone-*d6*) δ ppm 6.54 (1H, d, *J* = 6.8 Hz, OH-1β, disappears after D_2O-exchange), 6.38 (1H, d, *J* = 4.8 Hz, OH-1α, disappears after D_2O-exchange), 5.49 (1H, d, *J* = 6.3 Hz, OH-2β, disappears after D_2O-exchange), 5.37 (1H, dt, *J* = 4.8, 4.3 Hz, H-1α, simplifies to t, *J* = 4.3 Hz after D_2O-exchange), 4.80 (1H, dd, *J* = 7.7, 6.8 Hz, H-1β, simplifies to d, *J* = 7.7 Hz after D_2O-exchange), 4.62 (1H, d, *J* = 10.4 Hz, OH-2α, disappears after D_2O-exchange), 4.42–4.30 (1H, m, H-5α), 4.15 (1H, dd, *J* = 6.6, 5.8 Hz, OH-6β, disappears after D_2O-exchange), 4.06 (1H, dd, *J* = 6.6, 5.8 Hz, OH-6α, disappears after D_2O-exchange), 4.02–3.82

(4H, m, H-2α, H-5β, H-6α, H-6β), 3.80–3.65 (3H, m, H-2β, H-6α', H-6β'); **^{13}C NMR** (101 MHz, Acetone-*d*6) δ ppm 96.7 (d, *J* = 10.2 Hz, C-1β), 92.7 (d, *J* = 8.8 Hz, C-1α), 74.2 (dd, *J* = 26.3, 22.0 Hz, C-5β), 73.0 (t, *J* = 17.6 Hz, C-2β), 69.6 (t, *J* = 19.0 Hz, C-2α), 69.3 (t, *J* = 23.4 Hz, C-5α), 59.2–58.9 (m, C-6α and C-6β); **^{19}F NMR** (282 MHz, Acetone-*d*6) δ ppm –126.7 (1F, dd, *J* = 253.6, 21.5 Hz, Fβ), –132.6 – –130.6 (3F, m, 2×Fα and Fβ), –132.5 (1F, m, *J* = 262.2 Hz, Fβ), –133.2 (1F, ddd, *J* = 257.9, 17.2, 8.6 Hz, Fα), –133.5 (1F, m, *J* = 262.2 Hz, Fβ), –135.0 (1F, m, *J* = 257.9 Hz, Fα); **{^{1}H}^{19}F NMR** (282 MHz, Acetone-*d*6) δ ppm –126.7 (1F, d, *J* = 253.6 Hz, Fβ), –132.6 – –130.6 (3F, m, 2×Fα and Fβ), –132.5 (1F, dd, *J* = 262.2, 12.9 Hz, Fβ), –133.2 (1F, m, *J* = 253.6 Hz, Fα), –133.5 (1F, dt, *J* = 262.2, 8.6 Hz, Fβ), –135.0 (1F, m, *J* = 257.9 Hz, Fα); **MS** (ESI) *m/z* 284 (M + Na + MeCN)$^{+}$, **HRMS** (MS^{+}) for $C_6H_8F_4NaO_4$ (M + Na)$^{+}$ calcd 243.0251, found 243.0248.

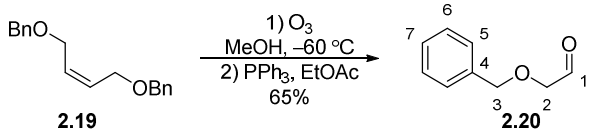
5.4.10 (*Z*)-1,4-Dibenzyloxybut-2-ene (2.19)



2.18 **2.19**

To a suspension of NaH (60% mineral oil, 12.3 g, 308 mmol, 2.7 equiv) in DMF (250 mL), a solution of **2.18** (9.3 mL, 113 mmol, 1 equiv) in DMF (50 mL) was added at 0 °C. After the mixture was stirred at rt for 1 h 30, BnBr (35.3 mL, 297 mmol, 2.6 equiv) was added dropwise at 0 °C. The reaction mixture was stirred overnight at rt then quenched with sat. aq. NH_4Cl (50 mL), diluted with Et_2O (500 mL) and washed with water (250 mL) and brine (250 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The impurities were distilled 130 °C under a reduced pressure of 0.7 mbar leaving the pure desired product **2.19** along with some mineral oil. The distillate was then columned to recover 2.91 g (10.8 mmol, 9.6%) of desired product which had been distillated with the impurities. **R_f** 0.21 PE/EtOAc 95:5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.36–7.24 (10H, m, H_{Ar}), 5.80–5.76 (2H, m, H–1), 4.48 (4H, s, H–3), 4.05 (4H, d, *J* = 4.0 Hz, H–2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 138.1 (C–4), 129.5, 128.4 (C–5 or C–6), 127.8 (C–5 or C–6), 127.6, 72.2 (C–3), 65.7 (C–2). The data matched with the literature.[64]

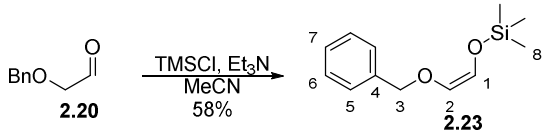
5.4.11 Benzyloxyacetaldehyde (2.20)



2.19 **2.20**

Dibenzyloxybutene **2.19** (2.00 g, 7.45 mmol, 1 equiv) was dissolved in MeOH (30 mL) and the solution was cooled to -60 °C. Ozone was introduced until the starting material disappeared (40 min) and then excess ozone was removed by bubbling O_2 (20 min). A solution of PPh_3 (2.34 g, 8.94 mmol, 1.2 equiv) in EtOAc (10 mL) was added dropwise at -60 °C to the reaction mixture which was stirred for 2 h. The mixture was then allowed to warm to rt and was concentrated in vacuo to give a pale yellow oil. Distillation at 68–70 °C for 0.2 mbar gave the desired product **2.20** along with a small amount of unknown impurities (1.45 g, 9.6 mmol, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.74 (1H, s, *H*C=O), 7.40–7.30 (5H, m, H_{Ar}), 4.65 (2H, s, CH_2Ph), 4.12 (2H, s, CH_2CHO); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 200.4 (*C*-1), 136.8 (C-4), 128.6 (C-5 or C-6), 128.2 (C-7), 128.0 (C-5 or C-6), 75.3 (C-2), 73.7 (C-3). The data matched with the literature.[65]

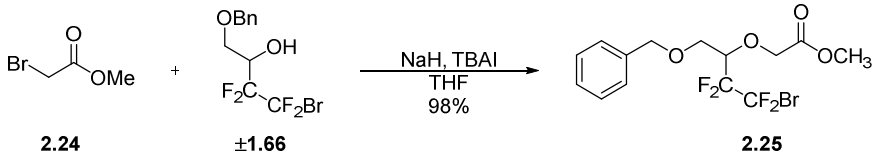
5.4.12 (*Z*)-(2-(Benzyloxy)vinyloxy)trimethylsilane (2.23)



TMSCl (2.1 mL, 16.7 mmol, 1.26 equiv) was added to a cold (0 °C) solution of benzyloxyacetaldehyde **2.20** in MeCN (16 mL) followed by addition of Et_3N (2.5 mL, 17.7 mmol, 1.33 equiv). The reaction mixture was warmed to 80 °C and additional Et_3N (1.9 mL, 13.3 mmol, 1 equiv) was added. After 2h, the reaction mixture was brought to rt and volatiles were removed. The residue was extracted with pentane (40 mL) containing 2% of Et_3N. The pentane extract was washed with water, sat. Aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. The resultant oil was distilled to yield 1.72 g (7.74 mmol, 58%) of the desired silyl enol ether **2.23** as a colorless oil. The *Z*/*E* ratio was found to be 90:10. **Bp** (0.07 mbar): 78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41–7.28 (5H, m, H_{Ar}), 6.39 (2H, s, H-1*E* and H-2*E*), 5.49 (1H, d, *J* = 3.4 Hz, H-2*Z*), 5.45 (1H, d, *J* = 3.4 Hz, H-1*Z*), 4.82 (2H, s, H-3*Z*), 4.67–4.64 (1H, m, H-3*E*), 0.21 (9H, s, H-8*Z*), 0.16 (1H, s, H-8*E*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.6 (C-4*Z*), 137.4 (C-4*E*), 130.9 (C-2*Z*), 128.5 (C-2*E*), 128.4 (C-1*E*), 128.4 (C-5*Z*), 127.9 (C-7*E*), 127.8 (C-6*Z*), 127.8 (C-5*E*), 127.6 (C-7*Z* and C-6*E*), 122.5 (C-1*Z*), 73.9 (C-3*Z*), 73.5 (C-3*E*), -0.4 (C-8*Z*), -0.7 (C-8*E*). The spectral data matched with the literature.[66]

5.5 Anionic cyclisation

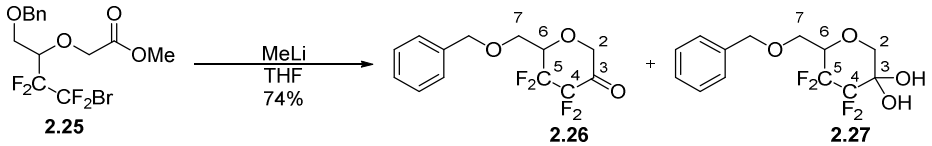
5.5.1 Methyl 2-(1-benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-2-yloxy)acetate (2.25)



2.24 **±1.66** **2.25**

To a suspension of NaH (60% mineral oil, 193 mg, 4.83 mmol, 1.6 equiv) in THF (5 mL) was added a solution of the alcohol **±1.66** (1.00 g, 3.02 mmol, 1 equiv) in THF (2.5 mL) at 0 °C. After the reaction mixture was stirred for 1 h at rt, methyl bromoacetate **2.24** (0.572 mL, 6.04 mmol, 2 equiv) was added dropwise at 0 °C followed by TBAI (335mg, 0.906 mmol, 0.3 equiv). The resultant mixture was stirred at rt overnight then quenched with sat. aq. NH_4Cl (5 mL), diluted with Et_2O (50 mL) and washed with water (25 mL) and brine (25 mL). The etheral layer was dried over Na_2SO_4, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/Et_2O 80:20) to give 1.19 g (2.95 mmol, 98%) of the desired ester **2.25**. $\mathbf{R_f}$ 0.30 (petroleum ether 40-60 °C/Et_2O 80:20); **IR** (neat cm^{-1}) 2955 (w), 1760 (m), 1217 (m), 1147 (s), 1100 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41–7.28 (5H, m, H_{Ar}), 4.59 (1H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.55 (1H, d, *J* = 11.9 Hz, CH<u>H</u>Ph), 4.41 (1H, d, *J* = 16.1 Hz, C<u>H</u>HCO_2Me), 4.34 (1H, d, *J* = 16.2 Hz, CH<u>H</u>CO_2Me), 4.30 (1H, dtd, *J* = 15.8, 7.2, 2.8 Hz, C<u>H</u>CF_2), 3.93–3.83 (2H, m, CHC<u>H</u>$_2$O), 3.72 (3H, s, C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 169.5 (C=O), 137.3 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 77.8 (dd, *J* = 27.8, 23.4 Hz, <u>C</u>HCF_2), 73.8 (<u>C</u>H_2Ph), 69.3 (<u>C</u>H_2CO_2Me), 68.8 (CH<u>C</u>H_2O), 51.9 (<u>C</u>H_3) and 2×CF_2 invisible; **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –62.7 (1F, dd, *J* = 180.5, 8.6 Hz, C<u>F</u>FBr), –63.5 (1F, d, *J* = 180.5 Hz, CF<u>F</u>Br), –112.8 (1F, d, *J* = 275.1 Hz, C<u>F</u>FCF_2Br), –120.6 (1F, ddd, *J* = 275.1, 17.2, 8.6 Hz, CF<u>F</u>CF_2Br); **MS** (ESI) *m/z* 425 and 427 $(M + Na)^+$ 1:1 ratio. **HRMS** (MS^+) for $C_{14}H_{15}F_4NaO_4$ $(M + Na)^+$ calcd 424.9982, found 424.9993.

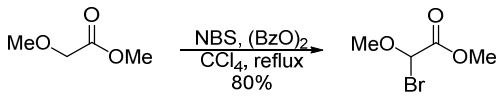
5.5.2 6-Benzyloxymethyl-4,4,5,5-tetrafluorodihydropyran-3-one (2.26) and 6-benzyloxymethyl-4,4,5,5-tetrafluorodihydropyran-3,3-diol (2.27)



2.25 **2.26** **2.27**

A solution of the ester **2.25** in DCM was filtered through $MgSO_4$ while drying with N_2 then dried under high vacuum overnight. The ester **2.25** (450 mg, 1.12 mmol, 1 equiv) was dissolved in dry THF (10 mL) then cooled to –78 °C. MeLi (1.6M in Et_2O, 0.70 mL, 1.12 mmol, 1 equiv) was added at –78 °C dropwise and the reaction mixture stirred at–78 °C for 4–5 h. The reaction was quenched at –78 °C by adding sat. aq. NH_4Cl (5 mL) then allowed to warm up to rt. The resultant mixture was diluted with water (5 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/Et_2O 80:20 to 40:60) to give 236 mg (0.761 mmol, 68%) of a 1:10 mixture of the desired hexulose derivative **2.26** and its hydrate **2.27**. $\mathbf{R}_f$ 0.25 (petroleum ether 40-60 °C/Et_2O 40:60); **IR** (neat cm^{-1}) 3376 (w, br), 2929 (w), 1285 (m), 1124 (s), 1092 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.29 (10H, m, H_{Ar}), 4.64 (1H, d, *J* = 11.9 Hz, C<u>H</u>HPh, hydrate), 4.69–4.57 (2H, m, C<u>H$_2$</u>Ph ketone), 4.57 (1H, d, *J* = 12.0 Hz, CH<u>H</u>Ph, hydrate), 4.43 (1H, ddd, *J* = 15.4, 3.3, 1.0 Hz, C<u>H</u>HC=O), 4.32 (1H, ddd, *J* = 15.5, 3.9, 0.9 Hz, CH<u>H</u>C=O), 4.24 (1H, ddtt, *J* = 22.2, 7.5, 2.6, 1.2 Hz, C<u>H</u>CF_2 ketone), 3.99–3.76 (5H, m, C<u>H</u>CF_2, C<u>H</u>HOBn, C<u>H</u>$HC(OH)_2$, hydrate and C<u>H$_2$</u>OBn ketone), 3.75 (1H, dd, *J* = 11.2, 7.6 Hz, CH<u>H</u>OBn, hydrate), 3.65 (1H, ddd, *J* = 12.6, 3.4, 1.1 Hz, CH<u>H</u>C<u>(</u>$OH)_2$, hydrate) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.0 ($C_{q,Ar}$ hydrate, 137.0 ($C_{q,Ar}$), 128.6 (2 × CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar} hydrate), 128.0 (CH_{Ar} hydrate), 127.9 (CH_{Ar}), 91.6 (dd, *J* = 23.4, 20.5 Hz, <u>C</u>$(OH)_2$), 77.1 (t, *J* = 23.4 Hz, CF_2<u>C</u>H hydrate), 74.1 (<u>C</u>H_2Ph), 73.9 (<u>C</u>H_2Ph hydrate), 71.4 (<u>C</u>H_2C=O), 71.2 (d, *J* = 2.9 Hz, <u>C</u>$H_2C(OH)_2$), 66.0 (br. s., <u>C</u>H_2OBn ketone and hydrate); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –117.3 (1F, dd, *J* = 279.4, 12.9 Hz), –124.3 (1F, d, *J* = 257.9 Hz, hydrate), –126.5 (1F, dt, *J* = 262.2, 12.9 Hz), –129.3 (1F, dt, *J* = 262.2, 15.0 Hz, hydrate), –130.5 (1F, d, *J* = 262.2 Hz, hydrate), –133.5 (1F, ddd, *J* = 262.2, 21.5, 12.9 Hz), –144.3 (1F, dt, *J* = 279.4, 12.9 Hz), –150.5 (1F, d, *J* = 257.9 Hz, hydrate); **MS** (ESI) for **2.27** *m/z* 311 $(M + H)^+$, **HRMS** (MS^+) for $C_{13}H_{14}F_4NaO_4$ $(M + Na)^+$ calcd 333.0720, found 333.0714.

5.5.3 Methyl bromomethoxyacetate (2.33)

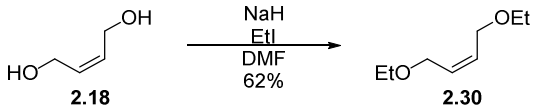


2.31 **2.33**

A mixture of the ester **2.31** (5.0 mL, 50.5 mmol, 1 equiv), *N*-bromosuccinimide (8.99 g, 50.5 mmol, 1 equiv) and dibenzoyl peroxide (25 mg, 0.103 mmol, 0.2 mol %) in CCl_4 (25 mL) was refluxed for overbight. The reaction mixture was then filtered, the residue was washed with petroleum ether 40-60 °C/Et_2O and filtrate was concentrated to give a crude brown oil. The

obtained crude was then distilled under reduced pressure (38–40 °C, 0.1–0.2 mbar) to give 7.38 g (40.3 mmol, 80%) of the desired ester **2.33**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 6.03 (1H, s, C<u>H</u>BrOMe), 3.87 (3H, s, OC<u>H</u>$_3$), 3.60 (3H, s, COOC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 165.8 (C=O), 83.1 (<u>C</u>H), 58.7 (O<u>C</u>H$_3$), 53.3 (<u>C</u>OOCH$_3$). The spectral data matched with the literature.[112]

5.5.4 (Z)-1,4-diethoxybut-2-ene (2.30)

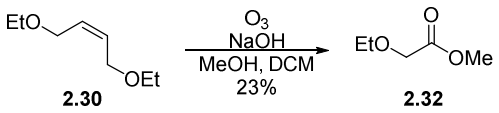


2.18 **2.30**

To a suspension of NaH (60% in mineral oil, 11.8 g, 298 mmol, 2.6 equiv) in DMF (200 mL), a solution of *cis*-but-2-ene-1,4-diol **2.18** (9.3 mL, 114 mmol, 1 equiv) in DMF (50 mL) was added at 0 °C. After the mixture was stirred at rt for 1.5 h, ethyl iodide (28 mL, 352 mmol, 3.1 equiv) was added dropwise to the mixture at 0 °C. The reaction mixture was stirred at rt overnight then quenched with sat aq NH_4Cl (50 mL), diluted with Et_2O (500 mL), and washed with water (250 mL) and brine (250 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. Distillation afforded the desired product along with some DMF. The distilled product was dissolved in Et_2O (100 mL) and washed with water (2×50 mL) to give 10.2 g (70.7 mmol, 62%) of the desired product **2.30**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddd, *J* = 4.7, 3.7, 0.9 Hz, 2H, C<u>H</u>CH$_2$), 4.10–4.01 (m, 4H, CHC<u>H</u>$_2$), 3.49 (q, *J* = 7.0 Hz, 4H, OCH$_2$), 1.22 (t, *J* = 7.0 Hz, 6H, C<u>H</u>$_3$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 129.4 (<u>C</u>HCH$_2$), 66.2 (CH_2), 65.7 (CH_2), 15.2 (CH_3) ppm.

5.5.5 Methyl ethoxyacetate (2.32)



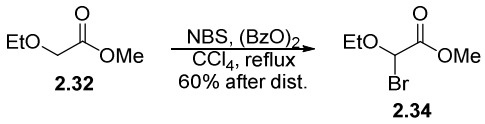
2.30 **2.32**

A solution of 4 g (27.8 mmol) of 1,4-diethoxybut-2-ene **2.30** in 180 mL of CH_2Cl_2 and 50 mL of 2.5M methanolic NaOH was stirred at –78 °C as ozone was passed through the solution. After 7 h, the initially yellow reaction mixture acquired the blue characteristic colour of ozone and a yellow precipitate had formed. The reaction mixture was diluted with ether (180 mL) and water (120 mL), allowed to warm to room temperature, and extracted with ether (200 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Crude product was purified by column

chromatography (petroleum ether 40-60 °C/Et_2O 85:15) to afford 1.52 g (12.8 mmol, 23%) of pure **2.32** as a pale yellow oil. The spectral date matched with the literature.[113]

R_f 0.19 (petroleum ether 40-60 °C/Et_2O 85:15); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.09 (s, 2H, C$\underline{H_2}$C=O), 3.76 (s, 3H, OC$\underline{H_3}$), 3.60 (q, *J* = 7.1 Hz, 2H, OC$\underline{H_2}$), 1.26 (t, *J* = 7.0 Hz, 3H, $CH_2C\underline{H_3}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.9 (C=O), 68.0 (O$\underline{C}H_3$), 67.2 ($\underline{C}H_2$C=O), 51.8 (O$\underline{C}H_2$), 14.9 ($\underline{C}H_3$) ppm.

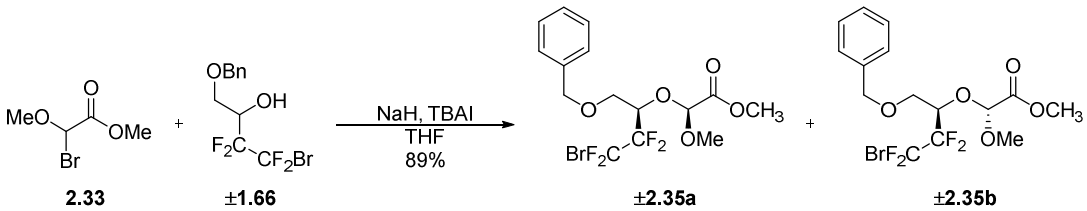
5.5.6 Methyl bromoethoxyacetate (2.34)



A mixture of the ester **2.32** (1.91 g, 16.2 mmol, 1 equiv), *N*-bromosuccinimide (3.02 g, 17.0 mmol, 1.05 equiv) and dibenzoyl peroxide (8 mg, 0.032 mmol, 0.2 mol %) in CCl_4 was refluxed for 2h. The reaction mixture was then filtered, the residue was washed with PE/Et_2O and filtrate was concentrated to give 3.07 g of a crude brown oil. The crude product was distilled under reduced pressure (15 mbar, 90-94 °C) to give 1.90 g (9.66 mmol, 60%) of the product **2.34** as a pale yellow oil along side a small amount of impurities.

Bp: 90-94 °C, 15 mbar. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.12 (s, 1H, C$\underline{H}$), 4.03 (dq, *J* = 9.6, 7.1 Hz, 1H, C$\underline{H}$HCH$_3$), 3.88 (s, 3H, OC$\underline{H_3}$), 3.66 (dq, *J* = 9.6, 7.1 Hz, 1H, CH$\underline{H}$CH$_3$), 1.36 (t, *J* = 7.1 Hz, 3H, C$\underline{H_3}$) ppm.

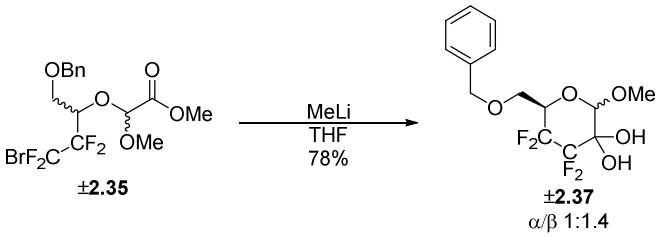
5.5.7 Methyl 2-(1-benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-2-yloxy)-2-methoxyacetate (±2.35a) and (±2.35b)



To a suspension of NaH (60% mineral oil, 97 mg, 2.42 mmol, 1.6 equiv) in THF (3 mL) was added a solution of the alcohol **±1.66** (500 mg, 1.51 mmol, 1 equiv) in THF (1.5 mL) at 0 °C. After the reaction mixture was stirred for 1 h at rt, methyl bromomethoxyacetate **2.33** (553 mg, 3.02 mmol, 2 equiv) was added dropwise at 0 °C followed by TBAI (167mg, 0.453 mmol, 0.3 equiv). The resultant mixture was stirred at rt overnight then quenched with sat. aq. NH_4Cl

(2.5 mL), diluted with Et_2O (25 mL) and washed with water (10 mL) and brine (10 mL). The etheral layer was dried over Na_2SO_4, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/Et_2O 80:20) to give 581 mg (1.34 mmol, 89%) of the desired esters **±2.35a** and **±2.35b** as a 1:0.8 mixture of diastereoisomers and a colorless liquid. $\mathbf{R_f}$ 0.21 (petroleum ether 40-60 °C/Et_2O 80:20); **IR** (neat cm^{-1}) 2951 (w), 1756 (m), 1205 (m), 1127 (s), 1094 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41–7.28 (5H, m, H_{Ar}), 5.19 (1H, s, C<u>H</u>CO_2Me, minor isomer), 5.10 (1H, s, C<u>H</u>CO_2Me, major isomer), 4.63–4.48 (6H, m, 2×C<u>H</u>$_2$Ph and 2×C<u>H</u>CF_2), 3.89–3.75 (4H, m, 2×CHC<u>H</u>$_2$O), 3.77 (3H, s, OC<u>H</u>$_3$, major isomer), 3.71 (3H, s, OC<u>H</u>$_3$, minor isomer), 3.47 (3H, s, OC<u>H</u>$_3$, minor isomer), 3.46 (3H, s, OC<u>H</u>$_3$, major isomer); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 166.7 (C=O), 166.4 (C=O), 137.1 ($C_{q,Ar}$), 137.2 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 99.6 (<u>C</u>HCO_2Me), 99.5 (<u>C</u>HCO_2Me), 74.6 (t, *J* = 24.9 Hz, <u>C</u>HCF_2), 74.3 (dd, *J* = 26.3, 23.4 Hz, <u>C</u>HCF_2), 73.7 (<u>C</u>H_2Ph), 73.6 (<u>C</u>H_2Ph), 68.8 (CH<u>C</u>H_2O), 68.5 (CH<u>C</u>H_2O), 55.0 (O<u>C</u>H_3), 54.7 (O<u>C</u>H_3), 52.4 (O<u>C</u>H_3), 52.3 (O<u>C</u>H_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –62.4 (1F, m, *J* = 180.5 Hz, C<u>F</u>FBr, minor isomer), –62.9 (1F, m, *J* = 180.5 Hz, C<u>F</u>FBr, major isomer), –63.4 (1F, m, *J* = 180.5 Hz, CF<u>F</u>Br, minor isomer), –63.5 (1F, d, *J* = 180.5 Hz, CF<u>F</u>Br, major isomer), –113.4 (1F, m, *J* = 275.1 Hz, CHC<u>F</u>F, minor isomer), –114.3 (1F, dd, *J* = 275.1, 8.6 Hz, CHC<u>F</u>F, major isomer), –116.4 (1F, dd, *J* = 275.1, 8.6 Hz, CHCF<u>F</u>, major isomer), –117.7 (1F, dt, *J* = 275.1, 10.8 Hz, CHCF<u>F</u>, minor isomer). **MS** (EI) *m*/*z* (%) 329 and 331 ((M – MeOCHCO_2Me$^{\bullet}$)$^+$, 4), 251 and 253 (6), 103 (MeOCHCO_2Me$^+$, 9), 91 ($C_7H_7^+$, 100). **HRMS** (MS+) for $C_{15}H_{17}{}^{79}BrF_4NaO_5$ $(M + Na)^+$ calcd 455.0088, found 455.0081.

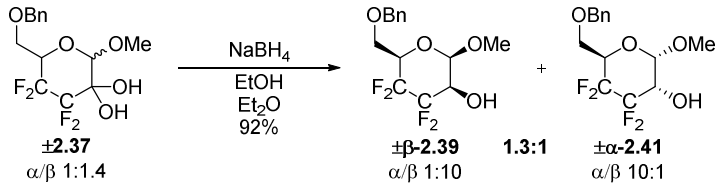
5.5.8 Methyl 6-O-benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-*glycero*-hex-2-ulopyranoside (±2.37)



A solution of the ester **±2.35** in DCM was filtered through $MgSO_4$ while drying with N_2 then dried under high vacuum overnight. The ester **±2.35** (484 mg, 1.12 mmol, 1 equiv) was dissolved in dry THF (10 mL) then cooled to –78 °C. MeLi (1.6M in Et_2O, 0.70 mL, 1.12 mmol, 1 equiv) was added at –78 °C dropwise and the reaction mixture stirred at –78 °C for 5 h. The reaction was quenched at –78 °C by adding sat. aq. NH_4Cl (5 mL) then allowed to warm up to rt. The resultant mixture was diluted with water (5 mL) and extracted with EtOAc (3×15 mL).

The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/acetone 80:20 to 70:30) to give 282 mg (0.878 mmol, 78%, 1.4:1 anomeric mixture) of the desired hexulose **±2.37**. $\mathbf{R_f}$ 0.25 (petroleum ether 40-60 °C/acetone 70:30); **IR** (neat cm^{-1}) 3396 (w, br), 2943 (w), 1288 (m), 1105 (s), 1025 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41–7.28 (1H, m, H_{Ar}), 4.70 (1H, d, *J* = 5.4 Hz, C<u>H</u>OMe minor anomer), 4.65 (2H, d, *J* = 12.0 Hz, 2×C<u>H</u>HPh), 4.63–4.57 (2H, m, 2×CH<u>H</u>Ph), 4.55 (1H, d, *J* = 2.9 Hz, C<u>H</u>OMe major anomer), 4.38–4.26 (1H, m, C<u>H</u>CF_2 minor anomer), 4.10–3.98 (1H, m, C<u>H</u>CF_2, major anomer), 3.97–3.89 (2H, m, 2×C<u>H</u>HOBn), 3.78 (2H, dd, *J* = 11.1, 7.6 Hz, 2×CH<u>H</u>OBn), 3.68 (3H, s, major anomer), 3.53 (3H, s, minor anomer); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.5 ($C_{q,Ar}$), 137.3 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 100.9 (<u>C</u>HOMe, minor anomer), 99.9 (d, *J* = 4.4 Hz, <u>C</u>HOMe, major anomer), 73.9 (<u>C</u>H_2Ph), 73.8 (<u>C</u>H_2Ph), 72.7 (t, *J* = 24.9 Hz, <u>C</u>HCF_2, major anomer), 68.0 (t, *J* = 24.5 Hz, <u>C</u>HCF_2, minor anomer), 66.0 (br. s., <u>C</u>H_2OBn), 65.8 (br. s., <u>C</u>H_2OBn), 57.8 (O<u>C</u>H_3, major anomer), 56.3 (O<u>C</u>H_3, minor anomer); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –122.8 (1F, d, *J* = 266.5 Hz, major anomer), –123.0 (1F, d, *J* = 266.5 Hz, minor anomer), –132.0 – –128.6 (4F, m), –145.2 (1F, d, *J* = 266.5 Hz, minor anomer), –147.5 (1F, dt, *J* = 266.5, 12.9 Hz, major anomer). **HRMS** (MS+) for $C_{14}H_{16}F_4NaO_5$ $(M + Na)^+$ calcd 363.0826, found 363.0831.

5.5.9 Methyl 6-*O*-benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-β-*threo*-hexopyranoside (±β-2.39) and α-*erythro*-hexopyranoside (±α-2.41)



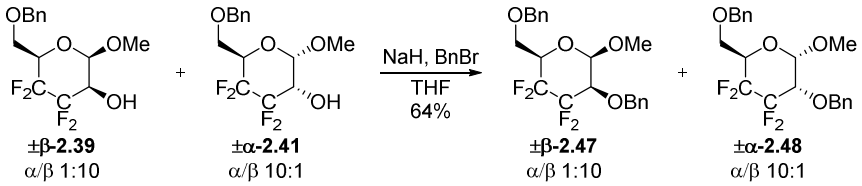
To a solution of hydrate (500 mg, 1.47 mmol, 1 equiv) in dry Et_2O (10 mL) was added $NaBH_4$ (2.2 equiv) and 10 drops of EtOH. The reaction mixture was stirred at rt for 7 h after which some starting material could still be observed by TLC. 1 equiv of $NaBH_4$ was added and the resultant mixture was stirred overnight then quenched with water (20 mL) and extracted with Et_2O (3×40 mL). Organic extracts were dried over $MgSO_4$, filtered and concentrated to give 440 mg (1.36 mmol, 92%) of a 1.3:1 mixture of **±2.39** and **±2.41** as a colourless oil which was used without any further purification.

Data for mixture: **IR** (neat cm^{-1}) 3415 (w, br), 2939 (w), 1197 (m), 1102 (s), 1027 (s); **MS** (EI) m/z (%) 324 ($M^{+\bullet}$, 2), 305 (3), 292 $(M - MeOH)^{+\bullet}$, 2), 291 (3), 107 (14), 105 (14), 91 ($C_7H_7^+$,100).

Data for **±β-2.39**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41–7.29 (5H, m, H_{Ar}), 4.71 (1H, dt, *J* = 3.7, 1.3 Hz, H-1), 4.65 (1H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.60 (1H, dd, *J* = 11.9, 1.9 Hz, CH<u>H</u>Ph), 4.17–4.09 (1H, m, H-2), 4.09–3.97 (1 H, m, H-5), 3.94 (1H, dd, *J* = 11.1, 3.0 Hz, H-6a), 3.82 (1H, dd, *J* = 11.0, 7.5 Hz, H-6b), 3.63 (3H, s, OC<u>H</u>$_3$), 2.66 (1H, d, *J* = 5.3 Hz, OH-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.5 ($C_{q,Ar}$), 128.5 (2C, CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (2C, CH_{Ar}), 99.5 (d, *J* = 8.8 Hz, C-1), 73.7 (<u>C</u>H$_2$Ph), 70.6 (dd, *J* = 31.0, 20.0 Hz, C-2), 68.6 (t, *J* = 19.8 Hz, C-5), 66.2 (C-6), 57.3 (O<u>C</u>H$_3$), 2×CF_2 not visible; **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –121.5 (1F, d, *J* = 275.1 Hz), –129.9 (1F, d, *J* = 262.2 Hz), –131.4 – –133.1 (2F, m). **HRMS** (MS+) for $C_{14}H_{16}F_4NaO_4$ $(M + Na)^+$ calcd 347.0877, found 347.0882.

Data for **±α-2.41**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41–7.29 (5H, m, H_{Ar}), 4.92 (1H, t, *J*=4.2 Hz, H-1), 4.65 (1H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.60 (1H, dd, *J* = 11.9, 1.9 Hz, CH<u>H</u>Ph), 4.34–4.23 (1H, m, H-5), 4.09–3.97 (1H, m, H-2), 3.90 (1H, ddd, *J* = 11.1, 2.7, 0.6 Hz, H-6a), 3.75 (1H, dd, *J* = 11.1, 7.5 Hz, H-6b), 3.51 (3H, s, OC<u>H</u>$_3$), 2.72 (1H, d, *J* = 11.9 Hz, OH-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.4 ($C_{q,Ar}$), 128.5 (2C, CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (2C, CH_{Ar}), 98.0 (d, *J* = 8.8 Hz, C-1), 73.8 (<u>C</u>H$_2$Ph), 73.2 (dd, *J* = 27.8, 23.0 Hz, C-2), 67.5 (t, *J* = 24.2 Hz, C-5), 65.7 (C-6), 56.3 (O<u>C</u>H$_3$), 2×CF_2 not visible; **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –128.1 (1F, dd, *J* = 254.0, 21.5 Hz), –133.1 – –131.4 (3F, m). **HRMS** (MS+) for $C_{14}H_{16}F_4NaO_4$ $(M + Na)^+$ calcd 347.0877, found 347.0879.

5.5.10 Methyl 2,6-di-*O*-benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-β-*threo*-hexopyranoside (±β-2.47) and α-*erythro*-hexopyranoside (±α-2.48)

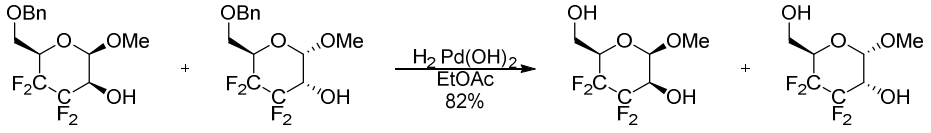


A stirred solution of a mixture of methyl mannoside and glucoside (250 mg, 0.771 mmol) in THF (5 mL) was cooled to 0 °C. NaH (60% in mineral oil, 37 mg, 0.925 mmol) was added and stirring continued at 0 °C for 1 h. BnBr (0.11 mL, 0.925 mmol) was added and stirring continued at 0 °C to rt for 22 h. NH_4Cl (sat aq, 2.5 mL) was added and the resultant mixture stirred at rt for 30 min. Extraction was carried out into Et_2O (3×5 mL). The combined organic phase was washed with brine (7.5 mL), dried over $MgSO_4$, filtered and concentrated. Crude product was

purified by column chromatography (petroleum ether 40-60 °C/acetone 85:15) to give 206 mg (0.497 mmol, 64%) of a 1:1.2 mixture of ±**β-2.47** and ±**α-2.48**.

R_f 0.26 (petroleum ether 40-60 °C/acetone 85:15); **IR** (neat cm^{-1}) 3032 (w), 2935 (w), 1201 (m), 1110 (s), 1038 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.44–7.25 (20H, m, H_{Ar}), 4.96 (1H, d, *J* = 12.3 Hz, C<u>H</u>HPh), 4.87 (2H, s, C<u>H</u><u>H</u>Ph), 4.72–4.53 (7H, m, 2×H-1, 2×C<u>H</u><u>H</u>Ph, CH<u>H</u>Ph), 4.38–4.22 (1H, m, H-5), 4.07–3.65 (7H, m, 4×H–6, 2×H–2, H–5), 3.60 (3H, s, C<u>H</u>$_3$), 3.45 (3H, s, C<u>H</u>$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.6 ($C_{q,Ar}$), 137.4 ($C_{q,Ar}$), 136.7 ($C_{q,Ar}$), 136.5 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.8 (CH_{Ar}), 127.6 (CH_{Ar}), 127.4 (CH_{Ar}), 117.0 – 109.3 (m, 4 × CF_2), 100.8 (d, *J*=8.1 Hz, C-1), 97.7 (d, *J*=9.5 Hz, C-1), 75.8 (dd, *J*=28.2, 18.7 Hz), 75.0 (d, *J*=2.2 Hz, <u>C</u>H_2Ph), 74.4 (d, *J*=2.2 Hz, <u>C</u>H_2Ph), 73.9 – 73.4 (m), 73.8 (<u>C</u>H_2Ph), 73.6 (<u>C</u>H_2Ph), 67.1 (ddd, *J*=25.7, 22.0, 1.5 Hz), 66.4 (dd, *J*=4.4, 2.9 Hz, C-6), 65.7 – 65.6 (C-6), 57.5 (O<u>C</u>H_3), 56.2 (O<u>C</u>H_3) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –118.7 (1F, m, *J* = 275.1 Hz, threo), –125.7 (1F, ddt, *J* = 253.6, 21.5, 8.6 Hz, erythro), –129.6 (1F, m, *J* = 253.6 Hz), –130.8 (1F, m, *J* = 266.5 Hz), –131.0 (1F, m, *J* = 262.2 Hz), –131.7 (1F, m, *J* = 262.2 Hz), –133.2 (1F, m, *J* = 262.2 Hz), –131.8 (1F, m, *J* = 257.9 Hz). **HRMS** (MS+) for $C_{21}H_{22}F_4NaO_4$ $(M + Na)^+$ calcd 437.1346, found 437.1354.

5.5.11 Methyl 3,4-dideoxy-3,3,4,4-tetrafluoro-β-*threo*-hexopyranoside (±β-2.55) and α-*erythro*-hexopyranoside (±α-2.57)



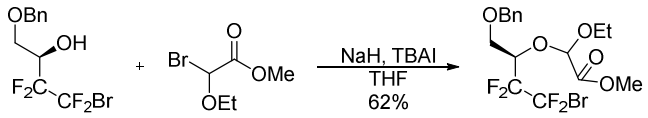
To a stirred solution of hexoses **±2.39** and **±2.41** (250 mg, 0.77 mmol, 1 equiv) in EtOAc (6 mL) under N_2 was added $Pd(OH)_2$ (0.1 equiv) at rt and the reaction mixture was stirred under H_2 for 2.5 h. The reaction mixture was filtered through Celite® and concentrated. Crude material was purified by column chromatography (petroleum ether 40-60 °C/acetone 85:15 to 70:30) to afford 148 mg (0.63 mmol, 82%). Further purification by HPLC (petroleum ether 40-60 °C/acetone 70:30) gave 62 mg of pure **±β-2.55** and 66 mg of impure **±α-2.57**.

Data for **±β-2.55**: **R_f** 0.27 (petroleum ether 40-60 °C/acetone 70:30); **IR** (neat cm^{-1}) 3195 (br w), 2946 (w), 1453 (m), 1068 (s), 1017 (s); **^{1}H NMR** (400 MHz, Acetone-*d*6) δ ppm 4.83 (1H, d, *J* = 5.6 Hz, OH-2, disappears upon D_2O-exchange), 4.77 (1H, dt, *J* = 4.2, 1.5 Hz, H–1), 4.29 (1H, dd, *J* = 6.7, 5.4 Hz, OH–6, disappears upon D_2O-exchange), 4.17–4.08 (1H, m, H–2), 3.98–3.77 (3H,

m, H–5, H–6a and H–6b), 3.55 (3H, s, OC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, Acetone-*d*6) δ ppm 101.1 (d, *J* = 8.8 Hz, C–1), 75.2 (dd, *J* = 26.3, 22.0 Hz, C–5), 71.4 (dd, *J* = 29.3, 19.0 Hz, C–2), 59.3–59.0 (m, C–6), 57.3 (O<u>C</u>H$_3$); **^{19}F NMR** (282 MHz, Acetone-*d*6) δ ppm –120.33 (1F, d, *J* = 267.2 Hz), –129.53 (1F, m, *J* = 262.1 Hz), –131.82 (1F, d, *J* = 267.2 Hz), –132.46 (1F, d, *J* = 262.1 Hz). **MS** (EI) m/z (%) 234 ($M^{+\bullet}$, 2), 203 (M – MeO$^{\bullet}$)$^+$, 21), 183 (M – MeO$^{\bullet}$ – HF)$^+$, 50), 182 (M – MeOH – HF)$^{+\bullet}$, 26), 154 (M – MeOH – HF – CO)$^{+\bullet}$, 46), 61 ($C_2H_5O_2^+$, 100). **HRMS** (MS+) for $C_7H_{10}F_4NaO_4$ (M + Na)$^+$ calcd 257.0407, found 257.0407.

Data for **±α-2.57**: **R$_f$** 0.32 (petroleum ether 40-60 °C/acetone 70:30); **IR** (neat cm^{-1}) 3393 (br w), 3026 (w), 2973 (w), 1208 (m), 1101 (s), 1066 (s); **^{1}H NMR** (400 MHz, Acetone-*d*6) δ ppm 4.93 (1H, t, *J* = 4.3 Hz, H-1), 4.90 (1H, d, *J* = 9.7 Hz, OH-2, disappears upon D_2O-exchange), 4.29 (1H, t, *J* = 6.1 Hz, OH-6, disappears upon D_2O-exchange), 4.17–3.97 (2H, m, H-2 + H-5), 3.96–3.87 (1H, m, H-6a, simplifies to dd, *J* = 11.9, 3.0 Hz after D_2O-exchange), 3.83–3.72 (1H, m, H-6b, simplifies to dd, *J* = 12.0, 7.3 Hz after D_2O-exchange), 3.44 (3H, s, OC<u>H</u>$_3$); **^{13}C NMR** (101 MHz, Acetone-*d*6) δ ppm 99.6 (d, *J* = 10.2 Hz, C-1), 69.7 (t, *J* = 23.4 Hz, C-2 or C-5), 69.6 (t, *J* = 18.5 Hz, C-2 or C-5), 58.7 (C-6), 56.4 (O<u>C</u>H$_3$); **^{19}F NMR** (282 MHz, Acetone-*d*6) δ ppm –126.9 (1F, m, *J* = 253.6 Hz), –131.7 (1F, d, *J* = 253.6 Hz), –132.2 (1F, m, *J* = 262.2 Hz), –133.56 (1F, m, *J* = 262.2 Hz). **MS** (EI) m/z (%) 234 ($M^{+\bullet}$, 1), 203 (M – MeO$^{\bullet}$)$^+$, 11), 183 (M – MeO$^{\bullet}$ – HF)$^+$, 14), 182 (M – MeOH – HF)$^{+\bullet}$, 9), 154 (M – MeOH – HF – CO)$^{+\bullet}$, 23), 61 ($C_2H_5O_2^+$, 100). **HRMS** (MS+) for $C_7H_{10}F_4NaO_4$ (M + Na)$^+$ calcd 257.0407, found 257.0401.

5.5.12 Methyl 2-((2*R*)-1-benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-2-yloxy)-2-ethoxyacetate (2.36)

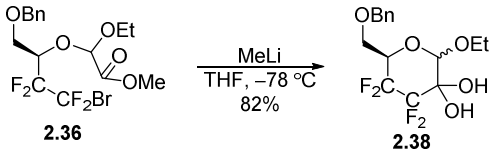


To a suspension of NaH (60% mineral oil, 387 mg, 9.67 mmol, 1.6 equiv) in THF (12.5 mL) was added a solution of the alcohol **1.66** (2.00 g, 6.04 mmol, 1 equiv) in THF (7.5 mL) at 0 °C. After the reaction mixture was stirred for 1 h at rt, methyl bromomethoxyacetate **2.34** (2.14 g, 10.9 mmol, 1.8 equiv) was added dropwise at 0 °C followed by TBAI (669 mg, 1.81 mmol, 0.3 equiv). The resultant mixture was stirred at rt for 16 h then quenched with sat. aq. NH_4Cl (10 mL), diluted with Et_2O (100 mL) and washed with water (35 mL) and brine (35 mL). The etheral layer was dried over Na_2SO_4, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/Et_2O 87:13 to 80:20) to give 1.67 g (3.73

mmol, 62%) of the desired ester **2.36** as a 1.2:1 mixture of diastereoisomers and a colourless liquid.

R_f 0.29 (petroleum ether 40-60 °C/Et_2O 80:20); **IR** (neat cm^{-1}) 2978 (w), 1742 (m), 1215 (m), 1081 (s), 1017 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.40–7.28 (10H, m, H_{Ar} both isomers), 5.22 (1H, s, C<u>H</u>OEt, one isomer), 5.13 (1H, s, C<u>H</u>OEt one isomer), 4.61–4.49 (6H, m, C<u>H$_2$</u>Ph, C<u>H</u>CF_2 both isomers), 3.90–3.64 (8H, m, CHC<u>H$_2$</u>, C<u>H$_2$</u>CH_3 both isomers), 3.76 (3H, s, OC<u>H$_3$</u> one isomer), 3.70 (3H, s, OC<u>H$_3$</u> one isomer), 1.23 (3H, t, *J* = 7.1 Hz, CH_2C<u>H$_3$</u> one isomer), 1.17 (3H, t, *J* = 7.0 Hz, OC<u>H$_3$</u> one isomer); **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 167.0 (C=O), 166.7 (C=O), 137.2 ($C_{Ar,q}$), 137.2 ($C_{Ar,q}$), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.6 (CH_{Ar}), 98.8 (<u>C</u>HOEt), 98.8 (<u>C</u>HOEt), 74.4 (t, *J* = 24.9 Hz, <u>C</u>HCF_2), 74.0 (dd, *J* = 26.3, 23.4 Hz, <u>C</u>HCF_2), 73.7 (<u>C</u>H_2Ph), 73.6 (<u>C</u>H_2Ph), 68.8 (CH<u>C</u>H_2), 68.5 (CH<u>C</u>H_2), 63.6 (<u>C</u>H_2CH_3), 63.3 (<u>C</u>H_2CH_3), 52.3 (OCH_3), 52.2 (OCH_3), 14.8 (CH_2<u>C</u>H_3), 14.8 (CH_2<u>C</u>H_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –62.4 (1F, dd, *J* = 180.5, 8.6 Hz, C<u>F</u>FBr, one isomer), –62.9 – –63.9 (3F, m, C<u>F</u>FBr, one isomer, CF<u>F</u>Br, both isomers), –113.5 (1F, ddd, *J* = 275.1, 12.9, 8.6 Hz, C<u>F</u>FCF_2), –114.4 (1F, dd, *J* = 275.1, 8.6 Hz, C<u>F</u>FCF_2), –116.3 (1F, dd, *J* = 275.1, 8.6 Hz, CF<u>F</u>CF_2), –117.8 (1F, ddd, *J* = 275.1, 12.9, 8.6 Hz, CF<u>F</u>CF_2). **HRMS** (MS+) for $C_{16}H_{19}{}^{79}BrF_4NaO_5$ $(M + Na)^+$ calcd 469.0244, found 469.0252.

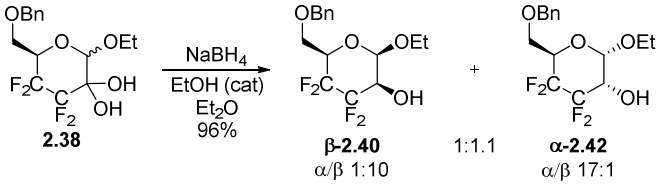
5.5.13 Ethyl 6-O-benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-D-*glycero*-hex-2-ulopyranoside (2.38)



A solution of the ester **2.36** in DCM was filtered through $MgSO_4$ while drying with N_2 then dried under high vacuum overnight. The reactant (1.35 g, 3.02 mmol, 1 equiv) was dissolved in dry THF (25 mL) then cooled to –78 °C. MeLi (1.6M in Et_2O, 1.89 mL, 3.02 mmol, 1 equiv) was added at –78 °C dropwise and the reaction mixture stirred at –78 °C for 5 h. The reaction was quenched at –78 °C by adding sat. aq. NH_4Cl (10 mL) then allowed to warm up to rt. The resultant mixture was diluted with water (10 mL) and extracted with EtOAc (3×35 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The obtained crude was then subjected to column chromatography (petroleum ether 40-60 °C/acetone 80:20 to 70:30) to give 0.814 g (2.30 mmol, 76%) of the desired hydrated hexulose **2.38** as a 1.1:1 α/β mixture and a colourless oil.

R_f 0.25 (petroleum ether 40-60 °C/acetone 70:30); **IR** (neat cm^{-1}) 3420 (w, br), 2934 (w), 1289 (m), 1101 (s), 1023 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.43–7.28 (m, 10H, H_{Ar}), 4.81 (d, *J* = 5.4 Hz, 1H, H–1, one isomer), 4.66–4.62 (m, H–1, 1H, one isomer), 4.65 (d, *J* = 12.2 Hz, 2H, C<u>H</u>HPh, both isomers), 4.59 (d, *J* = 12.1 Hz, 2H, CH<u>H</u>Ph, both isomers), 4.44–4.27 (m, H–5, 1H, one isomer), 4.13–3.59 (m, 9H, H–5, one isomer, 2 × H-6 and 2 × $C\underline{H}_2CH_3$, both isomers), 3.46 (br. s., 1H, OH), 3.21 (br. s., 1H, OH), 1.32 (m, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$, one isomer), 1.30 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$, one isomer); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 137.5 ($C_{Ar,q}$), 137.3 ($C_{Ar,q}$), 128.5 (CH_{Ar}), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (CH_{Ar}), 99.7 (C–1), 98.8 (C–1), 91.6 (dd, *J* = 23.4, 20.5 Hz, C–2), 91.1 (dd, *J* = 23.4, 20.5 Hz, C-2), 73.9 ($\underline{C}H_2Ph$), 73.7 ($\underline{C}H_2Ph$), 72.6 (t, *J* = 24.9 Hz, C–5), 68.1 (t, *J* = 24.9 Hz, C–5), 66.5 ($\underline{C}H_2CH_3$), 66.1 (C–6), 65.8 (C–6), 65.0 ($\underline{C}H_2CH_3$), 14.9 ($CH_2\underline{C}H_3$), 14.7 ($CH_2\underline{C}H_3$); **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –123.0 (d, *J* = 266.5 Hz, 1F), –122.8 (d, *J* = 266.5 Hz, 1F), –129.2 (m, *J* = 257.9 Hz, 1F), –130.3 (dt, *J* = 262.2, 15.0 Hz, 1F), –130.5 (m, *J* = 257.9 Hz, 1F), –131.4 (m, *J* = 262.2 Hz, 1F), –145.1 (d, *J* = 266.5 Hz, 1F), –147.3 (ddd, *J* = 266.5, 12.9, 8.6 Hz, 1F). **HRMS** (MS+) for $C_{15}H_{18}F_4NaO_5$ $(M + Na)^+$ calcd 377.0983, found 377.0980.

5.5.14 Ethyl 6-*O*-benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-β-D-*threo*-hexopyranoside (β-2.40) and α-D-*erythro*-hexopyranoside (α-2.42)



To a solution of hydrate (814 mg, 2.30 mmol, 1 equiv) in dry Et_2O (12.5 mL) was added $NaBH_4$ (350 mg, 9.19 mmol, 4 equiv) and 10 drops of EtOH. The reaction mixture was stirred at rt for 4.5 h then quenched with water (20 mL) and extracted with Et_2O (3×60 mL). Organic extracts were dried over $MgSO_4$, filtered and concentrated to give 747 mg (2.21 mmol, 96%) of a 1:1.1 mixture of **2.40** and **2.42** as a colourless oil.

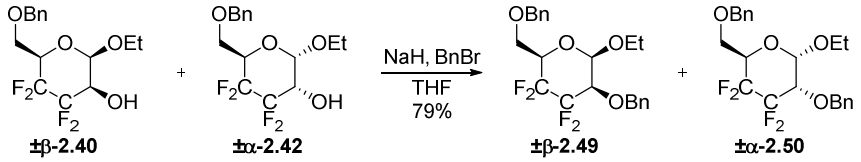
IR (neat cm^{-1}) 3445 (w, br), 2933 (w), 1293 (m), 1099 (s), 1029 (s).

Unambiguous resonances for **β-2.40**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H, HAr), 4.81 – 4.78 (m, 1H, H-1), 4.64 (d, *J*=12.1 Hz, 1H, C<u>H</u>HPh), 4.58 (d, *J*=12.1 Hz, 1H, CH<u>H</u>Ph), 2.54 (dd, *J*=5.2, 1.1 Hz, 1H, OH-2), 1.29 (t, *J*=7.0 Hz, 3H, $OCH_2C\underline{H}_3$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.5 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 98.2 (d, *J*=8.8 Hz, C-1), 73.8 ($\underline{C}H_2Ph$), 73.5 – 72.9 (m, C-5), 70.9 (dd, *J*=32.2, 19.0 Hz, C-2), 66.3 (C-6), 65.9 ($O\underline{C}H_2CH_3$), 14.9 ($OCH_2\underline{C}H_3$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –121.3 (d, *J*=275.1 Hz, 1F), –129.2 – –130.4 (m, *J*=266.5, 1F) ppm. **MS** (ESI+) m/z 361 $(M + Na)^+$. **HRMS** (MS+) for $C_{15}H_{18}F_4NaO_4$ $(M + Na)^+$ calcd 361.1033, found 361.1037.

Data for **α-2.42**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41–7.28 (5H, m, H_{Ar}), 5.03 (1H, t, *J* = 4.2 Hz, H–1), 4.64 (1 H, d, *J* = 12.0 Hz, C<u>H</u>HPh), 4.59 (1H, d, *J* = 12.0 Hz, CH<u>H</u>Ph), 4.38–4.26 (1H, m, H–5), 4.09–3.95 (1H, m, H–2), 3.93–3.87 (1H, m, H–6a), 3.88 (1H, dq, *J* = 9.9, 7.1 Hz, C<u>H</u>HCH$_3$), 3.74 (1 H, dd, *J* = 11.1, 7.3 Hz, H–6b), 3.62 (1H, dq, *J* = 9.9, 7.1 Hz, CH<u>H</u>CH$_3$), 2.68 (1H, d, *J* = 11.7 Hz, OH), 1.29 (3H, t, *J* = 7.1 Hz, C<u>H$_3$</u>); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.5 ($C_{Ar,q}$), 128.5 (CH_{Ar}), 127.8 (CH_{Ar}), 127.5 (CH_{Ar}), 96.8 (d, *J* = 10.2 Hz, C–1), 73.7 (<u>C</u>H$_2$Ph), 68.5 (t, *J* = 19.8 Hz, C–2), 67.5 (t, *J* = 23.4 Hz, C–5), 65.7 (C–6), 65.1 (<u>C</u>H$_2$CH$_3$), 14.8 (CH$_2$<u>C</u>H$_3$) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –128.0 (ddd, *J* = 253.6, 21.5, 8.6 Hz, 1F), –131.9 (d, *J* = 253.6 Hz, 1F), –131.7 – –133.0 (m, 1F), –132.7 – –133.9 (m, 1F) ppm. **MS** (ESI+) m/z 361 $(M + Na)^+$. **HRMS** (MS+) for $C_{15}H_{18}F_4NaO_4$ $(M + Na)^+$ calcd 361.1033, found 361.1039.

5.5.15 Ethyl 2,6-*O*,*O*-dibenzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-β-*threo*-hexopyranoside (±β-2.49) and α-*erythro*-hexopyranoside (±α-2.50)

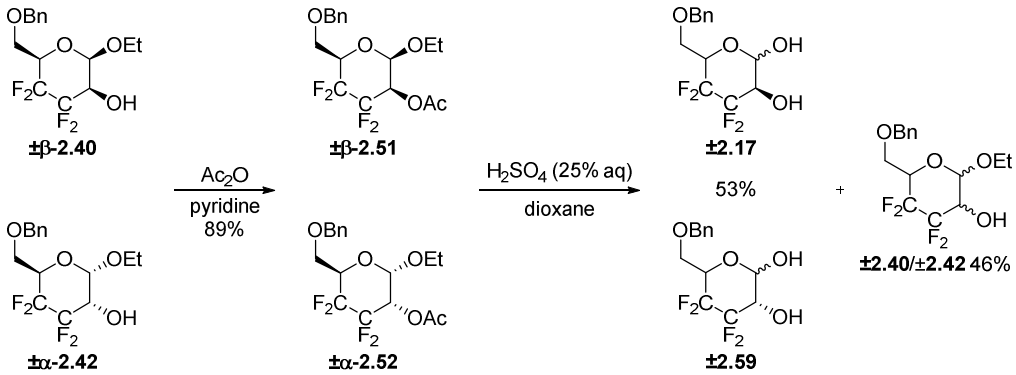


A stirred solution of a mixture of ethyl mannoside and glucoside **±2.40** and **±2.42** (123 mg, 0.364 mmol, 1 equiv) in THF (2.5 mL) was cooled to 0 °C. NaH (60% in mineral oil, 29 mg, 0.727 mmol, 2 equiv) was added and stirring continued at 0 °C for 1 h. BnBr (65 µL, 0.545 mmol, 1.5 equiv) was added and stirring continued at 0 °C to rt for 22 h. NH_4Cl (sat aq, 2.5 mL) was added and the resultant mixture stirred at rt for 30 min. Extraction was carried out into Et_2O (3×5 mL). The combined organic phase was washed with brine (5 mL), dried over MgSO4, filtered and concentrated. Crude product was purified by column chromatography (petroleum ether 40-60 °C/acetone 85:15) to give 123 mg (0.287 mmol, 79%) of a 1:1.4 mixture of **±2.49** and **±2.50**.

R$_f$ 0.29 (petroleum ether 40-60 °C/acetone 85:15); **IR** (neat cm^{-1}) 3034 (w), 2931 (w), 1377 (w), 1107 (s), 1039 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.44–7.25 (20H, m), 4.96 (1H, d, *J* = 12.4 Hz, C<u>H</u>HPh), 4.89 (2H, s, C<u>HH</u>Ph), 4.77 (1H, t, *J* = 4.0 Hz, H–1), 4.73–4.69 (1H, m, H–1), 4.66 (1H, d, *J* = 12.4 Hz, CH<u>H</u>Ph), 4.65 (1H, d, *J* = 11.8 Hz, C<u>H</u>HPh), 4.61 (1H, d, *J* = 12.1 Hz, C<u>H</u>HPh), 4.58

(1H, d, *J* = 11.8 Hz, CH<u>H</u>Ph), 4.56 (1H, d, *J* = 12.1 Hz, CH<u>H</u>Ph), 4.35 (1H, dd, *J* = 22.9, 6.8 Hz, H–5), 4.05 (1H, dq, *J* = 9.3, 7.1 Hz, C<u>H</u>HCH$_3$), 3.77 (1H, dq, *J* = 10.0, 7.1 Hz, CH<u>H</u>Ph), 4.05–3.73 (6H, m, 2×H–2, H–5, 3×H–6), 3.69 (1H, dd, *J* = 11.1, 7.4 Hz, H–6), 3.60 (1H, dq, *J* = 9.3, 7.1 Hz, CH<u>H</u>CH$_3$), 3.57 (1H, dq, *J* = 10.0, 7.0 Hz, CH<u>H</u>CH$_3$), 1.29 (3H, t, *J* = 7.1 Hz, CH$_3$), 1.29 (3H, t, *J* = 7.0 Hz, CH$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ ppm 137.7 (C$_{Ar,q}$), 137.5 (C$_{Ar,q}$), 136.7 (C$_{Ar,q}$), 136.8 (C$_{Ar,q}$), 128.6 (CH$_{Ar}$), 128.5 (CH$_{Ar}$), 128.4 (CH$_{Ar}$), 128.4 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 128.0 (CH$_{Ar}$), 127.8 (CH$_{Ar}$), 127.8 (CH$_{Ar}$), 127.6 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 99.6 (d, *J* = 8.8 Hz, C–1), 96.4 (d, *J* = 10.2 Hz, C–1), 75.9 (dd, *J* = 29.3, 19.0 Hz, C–2 or C–5), 74.9 (<u>C</u>H$_2$Ph), 74.4 (<u>C</u>H$_2$Ph), 73.4 (dd, *J* = 27.8, 22.0 Hz, C–2 or C–5), 73.6 (<u>C</u>H$_2$Ph), 73.9 (<u>C</u>H$_2$Ph), 73.8 (t, *J* = 17.6 Hz), 67.2 (t, *J* = 24.9 Hz, C–5), 66.5 (C–6), 66.0 (C–6), 65.8 (<u>C</u>H$_2$CH$_3$), 64.7 (<u>C</u>H$_2$CH$_3$), 14.8 (<u>C</u>H$_3$), 15.0 (<u>C</u>H$_3$); **^{19}F NMR** (282 MHz, CDCl$_3$) δ ppm –118.5 (1F, d, *J* = 275.1 Hz, threo), –125.7 (1F, ddt, *J* = 253.6, 21.5, 8.6 Hz, erythro), –129.9 (1F, m, *J* = 253.6 Hz), -130.8 (1F, m, *J* = 266.5 Hz), –131.7 (1F, m, *J* = 262.2 Hz), –132.2 (1F, m, *J* = 266.5 Hz), –133.0 (1F, m, *J* = 257.9 Hz), –133.8 (1F, m, *J*=266.5 Hz). **MS** (EI) *m*/*z* (%) 337 ((M – C$_7$H$_7^{\bullet}$)$^+$, 4), 201 (13), 91 (100). **HRMS** (MS+) for C$_{22}$H$_{24}$F$_4$NaO$_4$ (M + Na)$^+$ calcd 451.1503, found 451.1512.

5.5.16 6-*O*-Benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-*threo*-hexopyranose (±2.17) and *erythro*-hexopyranose (±2.59)



To a solution of hexose (200 mg, 0.591 mmol, 1 equiv) in pyridine at 0 °C was added Ac$_2$O (2.4 equiv). The resultant mixture was stirred at rt for 5 h then quenched with EtOH (1 mL) at 0 °C. Volatiles were evaporated and then azeotroped with toluene and CHCl$_3$ to afford 201 mg (0.528 mmol, 89%) of the desired acetates ±**2.51** and ±**2.52**.

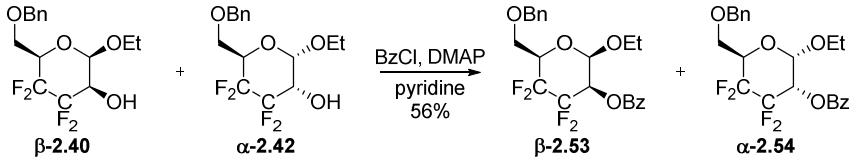
R$_f$ 0.24 (petroleum ether 40-60 °C/Et$_2$O 70:30); **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.42 – 7.28 (m, 10H, H$_{Ar}$), 5.57 – 5.48 (m, 1H, H-2), 5.25 – 5.10 (m, 2H, H–1, H–2), 4.83 (m, *J*=3.8 Hz, 1H, H–1), 4.68–4.55 (m, 4H, 2 × C<u>H</u>$_2$Ph), 4.47 – 4.32 (m, 1H, H–5), 4.10–3.53 (m, 9H, H–5, 2 × H–6a, 2 × H–6b, 2 × C<u>H</u>$_2$CH$_3$), 2.22 (s, 3H, OCOC<u>H</u>$_3$), 2.20 (s, 3H, OCOC<u>H</u>$_3$), 1.27 (t, *J*=7.0 Hz, 3H, CH$_2$C<u>H</u>$_3$),

1.25 (t, *J*=6.7 Hz, 3H, $CH_2C\underline{H}_3$) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ –119.9 (m, *J*=275.1 Hz, 1F), –124.2 – –125.4 (m, 1F), –130.0 – –131.2 (m, 1F), –131.2 – –133.9 (m, 4F), –134.2 – –135.5 (m, 1F) ppm.

The acetates **±2.51**/**±2.52** (100 mg, 0.263 mmol) obtained above were dissolved in dioxane and the 25% aq. H_2SO_4 solution was added. The reaction mixture was then stirred at 100 °C for 4.5 h before cooling to rt. The reaction mixture was diluted with water (1 mL) then extracted with EtOAc (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Crude product was purified by column chromatography (petroleum ether 40-60 °C/acetone 85:15 to 75:25) to give 41 mg (0.139 mmol, 53%) of a 2.1:1 mixture of **±2.17** and **±2.59** and 43 mg (0.121 mmol, 46%) of a mixture of **±2.40** and **±2.42**.

Data for **±2.17** and **±2.59**: **R_f** 0.25 (petroleum ether 40-60 °C/acetone 70:30); **IR** (neat cm^{-1}) 3484 (w), 3278 (w), 2924 (w), 1096 (s), 1038 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 20 H, H_{Ar}), 5.33 (br t, *J*=4.1 Hz, 1H, H-$1_{\alpha\text{-Glc}}$), 5.28 (br d, *J*=4.9 Hz, 1H, H-$1_{\alpha\text{-Man}}$), 4.89 (br s, 1H, H-$1_{\beta\text{-Man}}$), 4.76 (br d, *J*=8.1 Hz, 1H, H-$1_{\beta\text{-Glc}}$), 4.64 – 4.51 (m, 10H, 4 × CH_2Ph + 2 × H-5), 4.06–3.62 (m, 14H, 4×H–2 + 4×H–6 + 4×H–6' + 2×H–5) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 136.7 ($C_{q,Ar}$), 136.6 ($C_{q,Ar}$), 136.8 ($C_{q,Ar}$), 136.7 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 94.9 (d, *J* = 8.8 Hz, C–$1_{\beta\text{-Glc}}$), 94.3 (d, *J* = 4.4 Hz, C–$1_{\alpha\text{-Man}}$), 93.0 (d, *J* = 7.3 Hz, C–$1_{\beta\text{-Man}}$), 91.3 (d, *J* = 8.8 Hz, C–$1_{\alpha\text{-Glc}}$), 74.0 (2 × $\underline{C}H_2$Ph), 73.9 (2 × $\underline{C}H_2$Ph), 72.3 (dd, *J* = 29.3, 23.4 Hz, C–$5_{\beta\text{-Man}}$), 70.9 (dd, *J* = 32.2, 17.6 Hz, C–$2_{\beta\text{-Man}}$), 70.7 (dd, *J* = 29.3, 19.0 Hz, C–2 or C–5), 68.4 (t, *J* = 19.0 Hz, C–2 or C–5), 67.8 (dd, *J* = 27.8, 23.4 Hz, C–2 or C–5), 67.0 (t, *J* = 24.9 Hz, C–2 or C–5), 65.9 – 65.6 (m, 4 × C–6), 2 × C-2 or C-5 and 8 × CF_2 not visible; **^{19}F NMR** (282 MHz, $CDCl_3$) δ ppm –118.8 (m, *J*=270.8 Hz, 1F, α-Man), –121.1 (br d, *J*=270.8 Hz, 1F, β-Man), –127.7 (dd, *J* = 257.9, 21.5 Hz, 1F, α-Glc), –129.2 (m, *J* = 262.2 Hz, 1F, α-Man), –129.6 (m, *J* = 266.5 Hz, 1F, β-Man), –131.0 – –133.6 (m, 9F, 2 × α-Man + 1 × β-Man + 3 × α-Glc + 3 × β-Glc), –134.3 (m, *J* = 266.5 Hz, 1F, β-Man), –134.7 (ddd, *J* = 262.2, 17.2, 8.6 Hz, 1F, β-Glc). **HRMS** (MS+) for $C_{13}H_{14}F_4NaO_4$ $(M + Na)^+$ calcd 333.0720, found 333.0727.

5.5.17 Ethyl 2-*O*-benzoyl-6-*O*-benzyl-3,4-dideoxy-3,3,4,4-tetrafluoro-β-D-*threo*-hexopyranoside (β-2.53) and α-D-*erythro*-hexopyranoside (α-2.54)



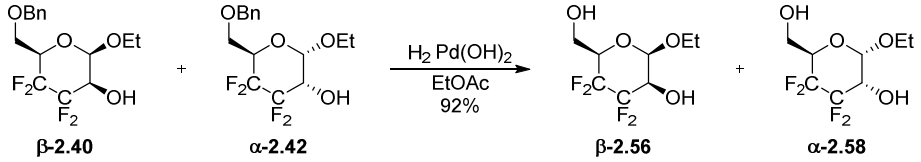
To a solution of hexose (250 mg, 0.739 mmo, 1 equiv) in pyridine (6 mL) at 0 °C was added BzCl (172 µL, 1.48 mmol, 2 equiv) and DMAP (9 mg, 0.074 mmol, 0.1 equiv). The resultant mixture was stirred at rt for 1.5 h then quenched with EtOH (0.1 mL). Volatiles were evaporated and residue was taken into Et_2O (30 mL) then washed with sat aq $NaHCO_3$ (10 mL), 1M HCl (10 mL) and brine (10 mL). Etheral layer was dried over $MgSO_4$, filtered, evaporated then azeotroped with toluene and $CHCl_3$. Crude product was purified by column chromatography (petroleum ether 40-60 °C/Et_2O 90:10 to 80:20) to give 96 mg of a 12.5:1 **α-2.53**/**α-2.54** mixture and 88 mg of pure **β-2.53**.

Data for **α-2.54**: $\mathbf{R_f}$ 0.5 (petroleum ether 40-60 °C/Et_2O 80:20); **IR** (neat cm^{-1}) 2934 (w), 1732 (s), 1263 (s), 1089 (s), 1027 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.18–8.10 (m, 2H, $H_{Ar,OBz}$), 7.64 (tt, *J* = 7.5, 1.2 Hz, 1H,$H_{Ar,OBz}$), 7.50 (t, *J* = 7.8 Hz, 2H, $H_{Ar,OBz}$), 7.43–7.28 (m, 5H, $H_{Ar,OBn}$), 5.47–5.28 (m, 2H, H–1 + H–2), 4.67 (d, *J* = 12.2 Hz, 1H, C<u>H</u>HPh), 4.61 (d, *J* = 12.2 Hz, 1H, CH<u>H</u>Ph), 4.56–4.39 (m, 1H, H–5), 3.95 (dd, *J* = 11.0, 2.4 Hz, 1H, H–6a), 3.83 (dq, *J* = 10.1, 7.0 Hz, 1H, C<u>H</u>HCH$_3$), 3.79 (dd, *J* = 11.0, 7.3 Hz, 1H, H–6b), 3.59 (dq, *J* = 10.1, 7.0 Hz, 1H, CH<u>H</u>CH$_3$), 1.23 (t, *J* = 7.0 Hz, 3H, C<u>H$_3$</u>) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.0 (C=O), 137.5 ($C_{q,Ar}$), 133.9 ($C_{q,Ar}$), 130.1 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 127.8 (CH_{Ar}), 127.5 (CH_{Ar}), 116.1 – 109.6 (2 × CF_2), 95.3 (d, *J*=8.1 Hz, C-1), 73.6 (<u>C</u>H$_2$Ph), 68.8 – 68.3 (C-2 or C-5), 67.5 (ddd, *J*=25.7, 22.4, 1.8 Hz, C-2 or C-5), 65.8 – 65.6 (C-6), 65.0 (O<u>C</u>H$_2$CH$_3$), 14.8 (OCH$_2$<u>C</u>H$_3$) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –124.8 (m, *J* = 253.6 Hz, 1F), –130.2 (m, *J* = 253.6 Hz, 1F), –132.0 (m, *J* = 262.2 Hz, 1F), –133.3 (m, *J* = 262.2 Hz, 1F) ppm. **MS** (EI) *m*/*z* (%) 442 ($M^{+\bullet}$, 1), 105 ($PhCO^{+\bullet}$,94), 91 ($C_7H_7^+$, 100). **HRMS** (MS+) for $C_{22}H_{22}F_4NaO_5$ $(M + Na)^+$ calcd 465.1296, found 465.1292.

Data for **β-2.53**: $\mathbf{R_f}$ 0.3 (petroleum ether 40-60 °C/Et_2O 80:20); **IR** (neat cm^{-1}) 2889 (w), 1738 (s), 1261 (s), 1109 (s), 1064 (s), 728 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14–8.07 (m, 2H, $H_{Ar,OBz}$), 7.65–7.57 (m, 1H, $H_{Ar,OBz}$), 7.52–7.43 (m, 2H, $H_{Ar,OBz}$), 7.43–7.29 (m, 5H, $H_{Ar,OBn}$), 5.81–5.72 (m, 1H,H–2), 4.93 (dt, *J* = 4.3, 1.6 Hz, 1H, H–1), 4.69 (d, *J* = 11.9 Hz, 1H, C<u>H</u>HPh), 4.62 (d, *J* = 11.9 Hz, 1H, CH<u>H</u>Ph), 4.18–3.85 (m, H–5, H–6a, H–6b, 4H, C<u>H</u>HCH$_3$), 3.68 (dq, *J* = 9.5, 7.0 Hz, 1H, CH<u>H</u>CH$_3$), 1.20 (t, *J* = 7.0 Hz, 3H,CH$_2$C<u>H$_3$</u>) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7 (C=O), 137.5

($C_{q,Ar}$), 133.6 ($C_{q,Ar}$), 130.2 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 128.7 (CH_{Ar}), 128.4 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 115.1 – 108.8 (2 × $\underline{C}F_2$), 97.7 (d, *J*=8.1 Hz, C-1), 73.8 ($\underline{C}H_2Ph$), 73.1 (ddd, *J*=27.1, 22.0, 1.5 Hz, C-5), 69.3 (ddd, *J*=34.2, 19.4, 1.5 Hz, C-2), 66.3 (dd, *J*=4.8, 2.6 Hz, C-6), 66.0 ($O\underline{C}H_2CH_3$), 14.8 ($OCH_2\underline{C}H_3$) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –120.0 (d, *J* = 275.1 Hz, 1F), –130.7– –132.7 (m, 2F), –134.8 (d, *J* = 266.5 Hz, 1F) ppm. **MS** (EI) *m/z* (%) 442 ($M^{+\bullet}$, 1), 105 ($PhCO^{+\bullet}$,81), 91 ($C_7H_7^+$, 100). **HRMS** (MS+) for $C_{22}H_{22}F_4NaO_5$ $(M + Na)^+$ calcd 465.1296, found 465.1289.

5.5.18 Ethyl 3,4-dideoxy-3,3,4,4-tetrafluoro-β-D-*threo*-hexopyranoside (β-2.56) and α-D-*erythro*-hexopyranoside (α-2.58)



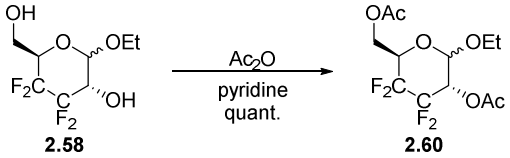
To a stirred solution of hexoses **β-2.40** and **α-2.42** (490 mg, 1.45 mmol, 1 equiv) in EtOAc (6 mL) under N_2 was added $Pd(OH)_2$ (0.2 equiv) at rt and the reaction mixture was stirred under H_2 for 2.5 h. The reaction mixture was filtered through Celite® and concentrated. Crude material was purified by column chromatography (petroleum ether 40-60 °C/Et_2O 45:55 to 0:100) to afford 329 mg (1.363 mmol, 92%).

Data for **β-2.56**: $\mathbf{R}_f$ 0.19 (petroleum ether 40-60 °C/Et_2O 30:70); **IR** (neat cm^{-1}) 3385 (br, w), 2922 (w), 1383 (m), 1098 (s), 1030 (s); **^{1}H NMR** (300 MHz, Acetone-*d*6) δ 5.06 (t, *J* = 4.2 Hz, 1H, H–1), 4.72 (d, *J* = 10.4 Hz, 1H, OH), 4.26–3.70 (m, 6H, H–2, H–5, H–6a, H–6b, $C\underline{H}HCH_3$, OH), 3.59 (dq, *J* = 9.8, 7.1 Hz, 1H, $CH\underline{H}CH_3$), 1.22 (t, *J* = 7.1 Hz, 3H, $C\underline{H}_3$) ppm. **^{13}C NMR** (101 MHz, Acetone-*d*6) δ 98.3 (d, *J* = 10.0 Hz, C–1), 69.8 (t, *J* = 23.2 Hz, C–2 or C–5), 69.6 (t, *J* = 19.9 Hz, C–2 or C–5), 65.4 ($\underline{C}H_2CH_3$), 58.8 (C–6), 15.2 ($\underline{C}H_3$); **^{19}F NMR** (282 MHz, Acetone-*d*6) δ –120.3 (d, *J*=266.5 Hz, 1F), –129.8 (m, *J*=262.2 Hz, 1F), –131.7 (m, *J*=266.5 Hz, 1F), –132.5 (m, *J*=262.2 Hz, 1F) ppm. **MS** (EI) *m/z* (%) 217 $(M - MeO^{\bullet})^+$, 25), 203 $(M - EtO^{\bullet})^+$, 6), 183 $(M - MeO^{\bullet} - HF)^+$, 11), 182 $(M - MeOH - HF)^{+\bullet}$, 15), 154 $(M - MeOH - HF - CO)^{+\bullet}$, 58), 75 ($C_3H_7O_2^+$, 83), 47 ($EtOH_2^+$, 100); **HRMS** (MS+) for $C_8H_{12}F_4NaO_4$ $(M + Na)^+$ calcd 271.0564, found 271.0562.

Data for **α-2.58**: $\mathbf{R}_f$ 0.30 (petroleum ether 40-60 °C/Et_2O 30:70); **IR** (neat cm^{-1}) 3473 (w), 2947 (w), 1227 (m), 1100 (s), 1014 (s); **^{1}H NMR** (400 MHz, Acetone-*d*6) δ ppm 4.88 (1H, dt, *J* = 4.1, 1.5 Hz, H–1), 4.70 (1H, d, *J* = 5.5 Hz, OH), 4.20–4.06 (2H, m, H–2 or H–5, H–6a), 4.04–3.76 (4H, m, H–2 or H–5, H–6b, $C\underline{H}HCH_3$, OH), 3.69 (1H, dq, *J* = 9.7, 7.1 Hz, $CH\underline{H}CH_3$), 1.19 (3H, t, *J* = 7.1 Hz, CH_3); **^{13}C NMR** (101 MHz, Acetone-*d*6) δ ppm 99.8 (d, *J* = 8.8 Hz, C–1), 75.3 (dd, *J* = 27.1, 22.6 Hz, C–2 or C–5), 71.7 (dd, *J* = 29.9, 18.8 Hz, C–2 or C–5), 65.9 ($\underline{C}H_2CH_3$), 59.3 (C–6), 15.3

($\underline{C}H_3$); **^{19}F NMR** (282 MHz, Acetone-*d*6) δ –126.8 (m, *J* = 253.6 Hz, 1F), –131.5 (m, *J* = 253.6 Hz, 1F), –132.1 (m, *J* = 257.9 Hz, 1F), –133.4 (m, *J* = 257.9 Hz, 1F) ppm. **MS** (EI) *m*/*z* (%) 248 ($M^{+\bullet}$, 2), 217 $(M - MeO^{\bullet})^+$, 10), 203 $(M - EtO^{\bullet})^+$, 1), 183 $(M - MeO^{\bullet} - HF)^+$, 31), 182 $(M - MeOH - HF)^{+\bullet}$, 13), 154 $(M - MeOH - HF - CO)^{+\bullet}$, 37), 75 ($C_3H_7O_2^+$, 100); **HRMS** (MS+) for $C_8H_{12}F_4NaO_4$ $(M + Na)^+$ calcd 271.0564, found 271.0564.

5.5.19 Ethyl 2,6-*O*,*O*-diacetyl-3,4-dideoxy-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranoside (2.60)

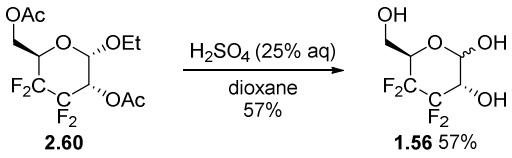


2.58 **2.60**

To a solution of hexose **2.58** (125 mg, 0.504 mmol, 1 equiv) in pyridine (4 mL) at 0 °C was added Ac_2O (190 µL, 2.02 mmol, 4 equiv). The resultant mixture was stirred at rt for 5 h then quenched with EtOH (1 mL) at 0 °C. Volatiles were evaporated and then azeotroped with toluene and $CHCl_3$ to give 167 mg (0.503 mmol, 100%) of the desired product **2.60** as a 20:1 α/β mixture and a white solid.

Data for α anomer: **IR** (neat cm^{-1}) 2980 (w), 1751 (s), 1372 (m), 1220 (s), 1030 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.24–5.09 (m, 2H, H–1, H–2), 4.53–4.29 (m, 3H, H–5, H–6a, H–6b), 3.77 (dq, *J* = 10.2, 7.1 Hz, 1H, $C\underline{H}HCH_3$), 3.62 (dq, *J* = 10.2, 7.1 Hz, 1H, $CH\underline{H}CH_3$), 2.22 (s, 3H,$C\underline{H_3}CO$), 2.11 (s, 3H, $C\underline{H_3}CO$), 1.27 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H_3}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3 (C=O), 169.4 (C=O), 95.2 (dd, *J*=8.4, 1.5 Hz, C-1), 67.9 (ddd, *J*=19.8, 16.1, 1.5 Hz, C-2 or C-5), 66.0 (ddd, *J*=25.7, 22.0, 2.2 Hz, C-2 or C-5), 65.2 ($O\underline{C}H_2CH_3$), 59.5 (dd, *J*=3.7, 2.2 Hz, C-6), 20.6 ($\underline{C}H_3CO$), 20.4 ($\underline{C}H_3CO$), 14.8 ($OCH_2\underline{C}H_3$) ppm (2 × CF_2 not visible). **^{19}F NMR** (282 MHz, $CDCl_3$) δ –124.9 (m, *J*=253.6 Hz, 1F), –130.6 (m, *J*=253.6 Hz, 1F), –132.2 (dt, *J*=262.2, 12.9 Hz, 1F), –133.4 (m, *J*=262.2 Hz, 1F) ppm. **MS** (EI) *m*/*z* (%) 289 $(M - MeCO^{\bullet})^+$, 2), 287 $(M - EtO^{\bullet})^+$, 3), 272 $(M - AcOH)^{+\bullet}$, 4), 215 $(M - EtOAc - CH_2O)^{+\bullet}$, 39), 43 ($CH_3CO^+$, 100); **HRMS** (MS+) for $C_{12}H_{16}F_4NaO_6$ $(M + Na)^+$ calcd 355.0775, found 355.0771.

5.5.20 3,4-Dideoxy-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranose (1.56)

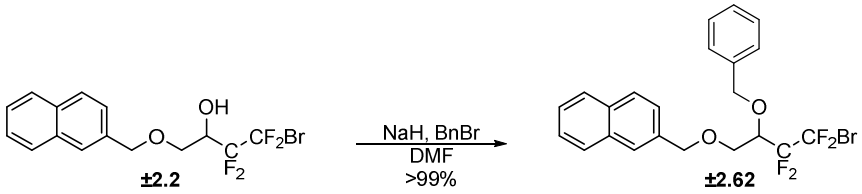


2.60 **1.56** 57%

To a stirred solution of hexose **2.60** (167 mg, 0.503 mmol, 1 equiv) in dioxane (2.5 mL) was added H_2SO_4 solution (25% v/v, 2.5 mL). The reaction mixture was then stirred at 100 °C for 17 h before cooling to rt. The reaction mixture was neutralised with $NaHCO_3$, diluted with water (1 mL) then extracted with EtOAc (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography (petroleum ether 40-60 °C/acetone 65:35) to give 63 mg (0.286 mmol, 57%) of the desired product **1.56** as a 1:1.8 α/β mixture. Spectroscopic and physical data are the same as above (*cf* section **5.4.9**).

5.6 Intermolecular addition approach

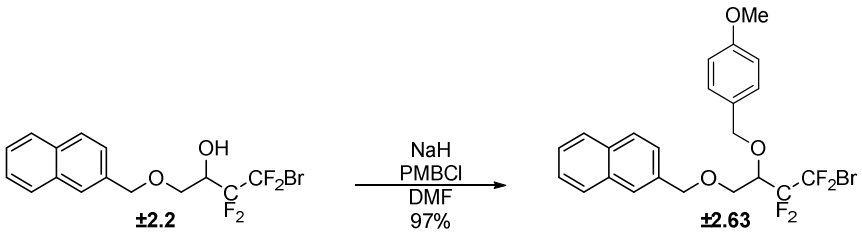
5.6.1 1-(2-Naphthylmethoxy)-2-benzyloxy-4-bromo-3,3,4,4-tetrafluorobutane (±2.62)



To a solution of alcohol **±2.2** (2.0g, 5.25 mmol, 1 equiv) in DMF (1 mL/mmol) was added NaH (60% in mineral oil, 252 mg, 6.30 mmol, 1.2 equiv) at 0 °C. The mixture was stirred for 15 min then BnBr was added and the resultant mixture was stirred at rt for 1.5 h then quenched with Et_3N (0.2 mL) and sat aq NH_4Cl (10 mL). The reaction mixture was then extracted with Et_2O (20 + 2 × 10 mL) and combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated to afford a brownish oil. Purification by column chromatography (petroleum ether 40-60 °C/Et_2O 95:5) afforded 2.47 g (5.25 mmol, 100%) of **±2.62** as a pale yellow oil. $\mathbf{R_f}$ 0.19 (petroleum ether 40-60 °C/Et_2O 95:5). **IR** (neat cm^{-1}) 3059 (w), 2873 (w), 1125 (s), 1096 (s), 736 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 – 7.74 (m, 4H, H_{Ar}), 7.56 – 7.42 (m, 3H, H_{Ar}), 7.42 – 7.28 (m, 5H, H_{Ar}), 4.85 (d, *J*=11.1 Hz, 1H, C<u>H</u>HAr), 4.79 (d, *J*=11.1 Hz, 1H, CH<u>H</u>Ar), 4.74 (s, 2H, C<u>H</u>$_2$Ar), 4.31 (dtd, *J*=15.5, 7.6, 2.8 Hz, 1H, CF_2C<u>H</u>), 3.94 (dt, *J*=10.5, 2.0 Hz, 1H, C<u>H</u>HONAP), 3.83 (dd, *J*=10.5, 7.3 Hz, 1H, CH<u>H</u>ONAP) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.9 ($C_{q,Ar}$), 135.0 ($C_{q,Ar}$), 133.3 ($C_{q,Ar}$), 133.1 ($C_{q,Ar}$), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 126.2 (CH_{Ar}), 126.5 (CH_{Ar}), 126.0 (CH_{Ar}), 125.5 (CH_{Ar}), 121.0 – 111.4 (2 × CF_2), 77.1 – 76.4 (<u>C</u>HCF_2), 74.7 (<u>C</u>H$_2$Ar), 73.8 (<u>C</u>H$_2$Ar), 69.0 (<u>C</u>H$_2$OAr) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –63.2 (d, *J*=178.4 Hz, 1F, C<u>F</u>FBr), –62.4 (dd, *J*=178.4, 6.4 Hz, 1F, CF<u>F</u>Br),

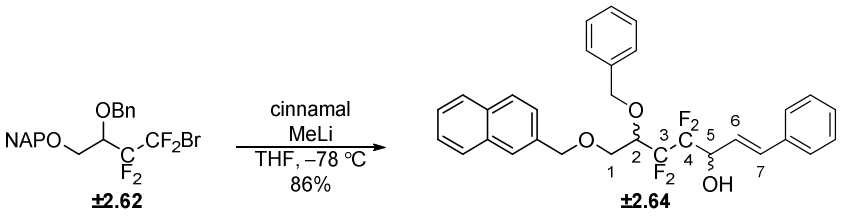
–112.4 (d, *J*=272.9 Hz, 1F, CHCFF), –120.4 (ddd, *J*=272.9, 17.2, 6.4 Hz, 1F, CHCFF) ppm. **MS** (EI) *m/z* (%) 470 and 472 ($M^{+\bullet}$, 1), 379 and 381 (M – $PhCH_2^{\bullet})^+$, 5), 329 and 331 (M – $NAPCH_2^{\bullet})^+$, 7), 141 (NAP^+, 100), 91 ($PhCH_2^+$, 43); **HRMS** (MS+) for $C_{22}H_{19}{}^{79}BrF_4NaO_2$ $(M + Na)^+$ calcd 493.0397, found 493.0389.

5.6.2 1-(2-Naphthylmethoxy)-2-(4-methoxy-benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutane (±2.63)



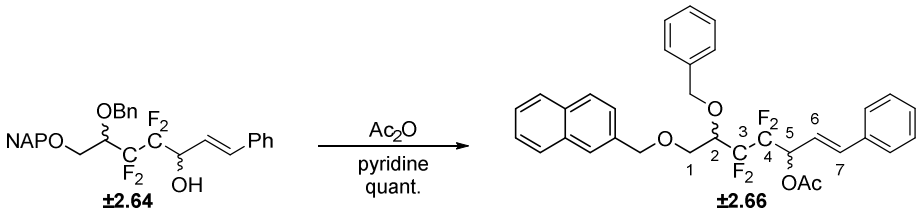
To a solution of alcohol **±2.2** (2.0g, 5.25 mmol, 1.0 equiv) in DMF (1 mL/mmol) was added NaH (60% in mineral oil, 252 mg, 6.30 mmol, 1.2 equiv) at 0 °C. The mixture was stirred for 15 min then PMBCl was added and the resultant mixture was stirred at rt for 2 h then quenched with Et_3N (0.2 mL) and sat aq NH_4Cl (10 mL). The reaction mixture was then extracted with Et_2O (20 + 2 × 10 mL) and combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated to afford a brownish oil. Purification by column chromatography (petroleum ether 40-60 °C/Et_2O 95:5) afforded 2.55 g (5.09 mmol, 97%) of **±2.63** as a pale yellow oil. $\mathbf{R_f}$ 0.21 (petroleum ether 40-60 °C/Et_2O 90:10). **IR** (neat cm^{-1}) 3055 (w), 2933 (w), 1512 (s), 1247 (s), 1096 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 – 7.76 (m, 4H, $H_{Ar,NAP}$), 7.55 – 7.43 (m, 3H, $H_{Ar,NAP}$), 7.31 – 7.24 (m, 1H, $H_{Ar,PMB}$), 6.89 – 6.82 (m, 2H, $H_{Ar,PMB}$), 4.79 – 4.69 (m, 4H, 2 × CH_2Ar), 4.28 (dtd, *J*=15.5, 7.6, 3.0 Hz, 1H, $CHCF_2$), 3.95 – 3.88 (m, 1H, CHHONAP), 3.85 – 3.76 (m, 1H, CHHONAP), 3.79 (s, 3H, OCH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5 ($C_{q,Ar}$), 135.0 ($C_{q,Ar}$), 133.2 ($C_{q,Ar}$), 133.0 ($C_{q,Ar}$), 129.9 (CH_{Ar}), 128.9 (CH_{Ar}), 128.2 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 126.4 (CH_{Ar}), 126.2 (CH_{Ar}), 126.0 (CH_{Ar}), 125.5 (CH_{Ar}), 113.7 (CH_{Ar}), 117.4 (tt, *J*=313.5, 39.3 Hz, CF_2), 114.5 (ddt, *J*=263.4, 257.5, 30.8 Hz, CF_2), 76.2 (dd, *J*=27.1, 22.0 Hz, $CHCF_2$), 74.3 (CH_2Ar), 73.7 (CH_2Ar), 69.0 – 68.9 (CH_2ONAP), 55.1 (OCH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –62.3 (dd, *J*=178.6, 8.7 Hz, 1F, CFFBr), –62.9 (dd, *J*=178.6, 4.4 Hz, 1F, CFFBr), –111.8 – –112.7 (m, *J*=273.1, 1F, CHCFF), –120.2 (ddd, *J*=273.1, 15.6, 7.8 Hz, 1F, CHCFF) ppm. **MS** (EI) *m/z* (%) 379 and 381 ((M – $PMB^{\bullet})^+$, 13), 329 and 331 ((M – $NAP^{\bullet})^+$, 35), 141 (NAP^+, 100), 121 (PMB^+, 97); **HRMS** (MS+) for $C_{23}H_{21}{}^{79}BrF_4NaO_3$ $(M + Na)^+$ calcd 523.0502, found 523.0509.

5.6.3 2-Benzyloxy-3,3,4,4-tetrafluoro-1-(2-naphthylmethoxy)-7-phenylhept-6-en-5-ol (±2.64)



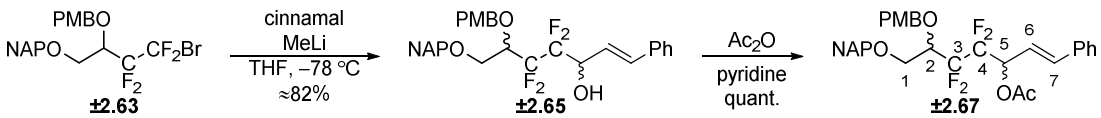
To a solution of bromide **±2.62** (251 mg, 0.533 mmol, 1 equiv) in THF at –78 °C was added cinnamaldehyde (0.161 mL, 1.28 mmol, 2.4 equiv). After 10 min, MeLi (1.5 M in Et2O, 0.85 mL, 1.28 mmol, 2.4 equiv) was added dropwise and the reaction mixture was stirred for 2 h. The reaction was quenched with saturated NH_4Cl aq. (mL) and extracted with Et_2O (3 × mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether 40-60 °C/Et_2O, 70:30 to 50:50) afforded 240 mg (0.458 mmol, 86%) of **±2.64** as a pale yellow oil. $\mathbf{R_f}$ 0.24/0.13 (petroleum ether 40-60 °C/Et_2O 70:30). **IR** (neat cm^{-1}) 3410 (br, w), 3058 (w), 2924 (s), 1101 (s), 748 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.77 (m, 8H, H_{Ar}), 7.55 – 7.45 (m, 6H, H_{Ar}), 7.43 – 7.24 (m, 20H, H_{Ar}), 6.76 (d, *J*=15.9 Hz, 1H, H-7), 6.64 (dd, *J*=16.1, 1.3 Hz, 1H, H-7), 6.26 (br d, *J*=15.9 Hz, H-6), 6.24 (br d, *J*=16.1 Hz, H-6), 4.95 (d, *J*=11.0 Hz, 1H, C<u>H</u>HPh), 4.92 (d, *J*=11.0 Hz, 1H, C<u>H</u>HPh), 4.86 (d, *J*=11.0 Hz, 1H, CH<u>H</u>Ph), 4.81 (d, *J*=11.0 Hz, 1H, CH<u>H</u>Ph), 4.76 (s, 4H, 2 × C<u>H$_2$</u>NAP), 4.78 – 4.65 (m, 2H, 2 × H-5), 4.35 – 4.23 (m, 2H, 2 × H-2), 4.01 – 3.86 (m, 4H, 2 × C<u>H$_2$</u>ONAP), 3.65 (d, *J*=4.4 Hz, 1H, OH), 3.28 (d, *J*=7.8 Hz, 1H, OH) ppm. **^{13}C NMR** (101MHz, $CDCl_3$) δ 136.4, 136.3, 136.0, 135.9, 135.1, 135.0, 135.0, 134.2, 133.2, 133.1, 128.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 127.8, 127.7, 126.8, 126.5, 126.5, 126.2, 126.2, 126.0, 126.0, 125.6, 125.6, 122.3 – 122.1 (m, C-6), 121.4 – 121.3 (m, C-6), 78.8 – 78.1 (m, 2 × C-2), 75.6, 75.5, 73.8, 71.7 (t, *J*=26.4 Hz, C-5), 70.3 (dd, *J*=27.9, 22.7 Hz, C-5), 69.3 – 69.0 (m, 2 × C-1) ppm (2 × CF_2 not visible). **^{19}F NMR** (282 MHz, $CDCl_3$) δ –115.4 (d, *J*=283.7 Hz, 1F), –118.3 – –116.7 (m, 1F), –117.6 (d, *J*=275.1 Hz, 1F), –119.9 (br d, *J*=270.8 Hz, 1F), –120.3 (d, *J*=283.7 Hz, 1F), –121.1 (d, *J*=275.1 Hz, 1F), –125.4 (br dd, *J*=275.1, 12.9 Hz, 1F), –128.1 (br dd, *J*=270.8, 19.3 Hz, 1F) ppm. **HRMS** (MS+) for $C_{31}H_{28}F_4NaO_3$ $(M + Na)^+$ calcd 547.1867, found 547.1877.

5.6.4 5-Acetoxy-2-benzyloxy-3,3,4,4-tetrafluoro-1-(2-naphthylmethoxy)-7-phenylhept-6-ene (±2.66)



To a solution of alcohol **±2.64** (439 mg, 0.837 mmol, 1 equiv) in pyridine (8 mL) was added Ac_2O (0.158 mL, 1.67 mmol, 2 equiv). The resultant mixture was stirred at rt overnight then quenched with EtOH (2 mL). Volatiles were evaporated and then azeotroped with toluene and $CHCl_3$ to afford 472 mg (0.833 mmol, quant.) of **±2.66** as a colourless oil. **IR** (neat cm^{-1}) 3059 (w), 2874 (w), 1750 (s), 1217 (s), 1101 (s); **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 8H, $H_{Ar,NAP}$), 7.55 – 7.28 (m, 26H, H_{Ar}), 6.71 (d, *J*=15.4 Hz, 1H, H-7), 6.73 (d, *J*=15.4 Hz, 1H, H-7), 6.23 – 6.06 (m, 4H, 2 × H-5, 2 × H-6), 4.93 – 4.81 (m, 4H, 2 × C$\underline{H}_2$Bn), 4.75 (s, 4H, 2 × C$\underline{H}_2$NAP), 4.31 – 4.20 (m, 2H, 2 × C-2), 4.00 – 3.93 (m, 2 × H-1_a), 3.90 – 3.82 (m, 2 × H-1_b), 2.16 (s, 3H, OAc), 2.14 (s, 3H, OAc) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9 (C=O), 169.0 (C=O), 137.9, 137.9, 137.1, 135.4, 135.4, 135.0, 135.2, 135.1, 133.2, 133.0, 128.7, 128.6, 128.6, 128.6, 128.6, 128.4, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.7, 126.9, 126.8, 126.4, 126.4, 126.1, 126.1, 125.9, 125.9, 125.6, 118.4 – 118.2, 77.7 (t, *J*=24.2 Hz, C-2), 74.9 (C$\underline{H}_2$Ar), 74.6 (C$\underline{H}_2$Ar), 73.7 (C$\underline{H}_2$Ar), 73.7 (C$\underline{H}_2$Ar), 71.1 (dd, *J*=27.9, 23.5 Hz, C-5), 70.9 (dd, *J*=25.7, 24.2 Hz, C-5), 69.2 – 68.9 (2 × C-1), 20.7 (2 × C$\underline{H}_3$) ppm (2 × CF_2 not visible). **^{19}F NMR** (376 MHz, $CDCl_3$) δ –117.3 (m, *J*=282.6 Hz, 1F), –117.4 (dd, *J*=282.6, 8.7 Hz, 1F), –120.0 (ddd, *J*=275.7, 11.3, 6.1 Hz, 1F), –120.2 (dd, *J*=275.7, 12.1 Hz, 1F), –120.6 (dd, *J*=282.6, 13.9 Hz, 1F), –121.0 (dd, *J*=275.7, 10.4 Hz, 1F),–121.2 (ddd, *J*=275.7, 12.1, 5.2 Hz, 1F), –121.9 (ddd, *J*=282.6, 15.6, 5.2 Hz, 1F) ppm. **HRMS** (MS+) for $C_{33}H_{30}F_4NaO_4$ $(M + Na)^+$ calcd 589.1972, found 589.1982.

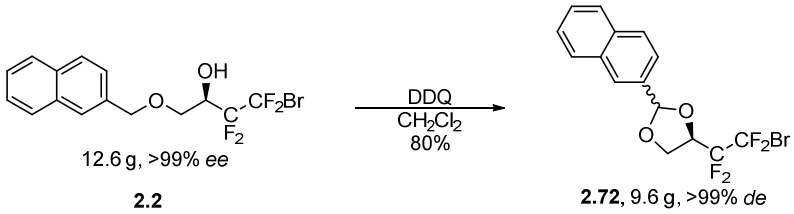
5.6.5 5-Acetoxy-3,3,4,4-tetrafluoro-2-(4-methoxybenzyloxy)-1-(2-naphthylmethoxy)-7-phenylhept-6-ene (±2.67)



To a solution of bromide **±2.63** (990 mg, 1.98 mmol, 1 equiv) in THF at –78 °C was added cinnamaldehyde (0.597 mL, 4.74 mmol, 2.4 equiv). After 10 min, MeLi (1.5 M in Et2O, 3.16 mL, 4.74 mmol, 2.4 equiv) was added dropwise and the reaction mixture was stirred for 2 h. The

reaction was quenched with saturated NH_4Cl aq. (15 mL) and extracted with Et_2O (3 × 45 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether 40-60 °C/Et_2O, 70:30 to 50:50) afforded 1.38 g of a 1:1.3 mixture of the desired product **±2.65** and methyl cinnamyl alcohol. To 683 mg of the mixture obtained above (equivalent to 505 mg (0.911 mmol, 1 equiv) of the coupling product) in pyridine (8 mL) was added Ac_2O (0.430 mL, 4.55 mmol, 5 equiv). The resultant mixture was stirred at rt overnight then quenched with EtOH (2 mL). Volatiles were evaporated and then azeotroped with toluene and $CHCl_3$. Purification by column chromatography (petroleum ether 40-60 °C/Et_2O, 80:20) afforded 522 mg (0.875 mmol, 96%) of **±2.67** as a colourless oil. $\mathbf{R_f}$ 0.21 (petroleum ether 40-60 °C/Et_2O 80:20). **IR** (neat cm^{-1}) 3059 (w), 2935 (w), 1749 (s), 1513 (s), 1218 (s), 1101 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.77 (m, 8H, H_{Ar}), 7.54 – 7.44 (m, 6H, H_{Ar}), 7.41 – 7.25 (s, 14H, H_{Ar}), 6.90 – 6.83 (m, 4H, H_{Ar}), 6.70 (dd, *J*=15.4, 7.8 Hz, 2H, 2 × H-7), 6.21 – 6.07 (m, 4H, 2 × H-6, 2 × H-5), 4.81 (d, *J*=10.8 Hz, 1H, C<u>H</u>HAr), 4.78 – 4.69 (m, 7H, C<u>H$_2$</u>Ar), 4.27 – 4.16 (m, 2H, 2 × H-2), 3.98 – 3.89 (m, 2H, 2 × H-1a), 3.87 – 3.77 (m, 2H, 2 × H-1b), 3.80 (s, 3H, OC<u>H$_3$</u>), 3.79 (s, 3H, OC<u>H$_3$</u>), 2.15 (s, 3H, OAc), 2.13 (s, 3H, OAc) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0 (C=O), 168.9 (C=O), 159.5 ($C_{q,Ar}$), 159.4 ($C_{q,Ar}$), 137.9 (C-7), 137.8 (C-7), 135.5 ($C_{q,Ar}$), 135.4 ($C_{q,Ar}$), 135.2 ($C_{q,Ar}$), 135.2 ($C_{q,Ar}$), 133.2 ($C_{q,Ar}$), 133.0 ($C_{q,Ar}$), 130.1 (CH_{Ar}), 130.0 (CH_{Ar}), 129.2 ($C_{q,Ar}$), 129.2 ($C_{q,Ar}$), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 128.2 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 126.9 (CH_{Ar}), 126.4 (CH_{Ar}), 126.4 (CH_{Ar}), 126.1 (CH_{Ar}), 126.1 (CH_{Ar}), 125.9 (CH_{Ar}), 125.6 (CH_{Ar}), 118.4 (C-6), 118.3 (C-6), 113.8 (CH_{Ar}), 77.5 – 76.9 (C-2), 76.6 (dd, *J*=27.1, 22.6 Hz, C-2) 74.5 (<u>C</u>H$_2$Ar), 74.2 (<u>C</u>H$_2$Ar), 73.7 (<u>C</u>H$_2$Ar), 73.7 (<u>C</u>H$_2$Ar), 71.1 (dd, *J*=27.9, 23.5 Hz, C-5), 71.3 – 70.7 (C-5), 69.3 – 69.1 (C-1), 69.1 – 69.0 (C-1), 55.2 (O<u>C</u>H$_3$), 55.2 (O<u>C</u>H$_3$), 20.8 (2 × CO<u>C</u>H$_3$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –116.8 – –117.9 (m, 2F), –119.8 – –121.5 (m, 5F), –121.9 (ddd, *J*=282.6, 15.6, 5.2 Hz, 1F) ppm. **HRMS** (MS+) for $C_{34}H_{32}F_4NaO_5$ $(M + Na)^+$ calcd 619.2078, found 619.2089.

5.6.6 (4*R*)-1-Bromo-1,1,2,2-tetrafluoro-3,4-(2-naphthylmethylidenedioxy)-butane (2.72)



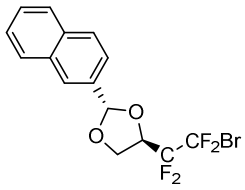
12.6 g, >99% *ee*

2.2

2.72, 9.6 g, >99% *de*

To a mixture of primarily NAP protected alcohol **2.2** (12.00 g, 31.5 mmol, 1 equiv) and dried powdered MS 4Å (26 g) in dry CH_2Cl_2 (300 mL) was added DDQ (9.29 g, 40.9 mmol, 1.3 equiv) at 0 °C under Ar atmosphere. The mixture was stirred for 5h at rt, quenched with aqueous ascorbate buffer (L-ascorbic acid (0.7 g), citric acid monohydrate (1.2 g), and NaOH (0.92 g) in water (100 mL), 300 mL), and then filtered through Celite®. The filter cake is rinsed with $CHCl_3$ (300 mL) and layers are partitioned. The aqueous layer was extracted with $CHCl_3$ (300 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ aq (300 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether 40-60 °C/Et_2O 80:20) afforded a mixture of enantiopure diastereoisomers **2.72** (9.57 g, 25.2 mmol, 80%) as a pale yellow solid.

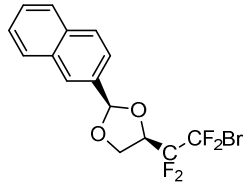
*5.6.6.1 **Trans-2.72***



R_f 0.59 (petroleum ether 40-60 °C/Et_2O 80:20). **IR** (neat cm^{-1}) 3060 (w), 2903 (w), 1125 (s), 1088 (s), 897 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99–7.95 (m, 1H, H_{Ar}), 7.94–7.83 (m, 3H, H_{Ar}), 7.59 (dd, *J*=8.5, 1.6 Hz, 1H, H_{Ar}), 7.56–7.50 (m, 2H, H_{Ar}), 6.16 (s, 1H, C<u>H</u>OO), 4.83 (dddd, $^3J_{HF}$=17.4, $^3J_{HH}$=7.2, $^3J_{HF}$=6.8, $^3J_{HH}$=6.6 Hz, 1H, C<u>H</u>CF$_2$), 4.49 (dd, $^2J_{HH}$=9.2, $^3J_{HH}$=7.2 Hz, 1H, C<u>H</u>HCHO), 4.34 (dd, $^2J_{HH}$=9.2, $^3J_{HH}$=6.6 Hz, 1H, CH<u>H</u>CHO) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.1 ($C_{q,Ar}$), 133.2 ($C_{q,Ar}$), 132.8 ($C_{q,Ar}$), 128.3 (CH_{Ar}), 128.5 (CH_{Ar}), 127.8 (CH_{Ar}), 126.4 (CH_{Ar}), 126.6 (CH_{Ar}), 126.8 (CH_{Ar}), 123.5 (CH_{Ar}), 116.8 (tt, $^1J_{CF}$=311.8, $^2J_{CF}$=39.5 Hz, <u>C</u>F$_2$), 114.2 (ddt, $^1J_{CF}$=262.0, $^1J_{CF}$=256.1, $^2J_{CF}$=32.2 Hz, <u>C</u>F$_2$), 106.0 (<u>C</u>HOO), 72.3 (dd, $^2J_{CF}$=30.7, $^2J_{CF}$=20.5 Hz, <u>C</u>HCF2), 65.3 (<u>C</u>H$_2$CHO) ppm. **^{19}F NMR** (282MHz, $CDCl_3$): δ –63.8 (dd, $^2J_{FF}$=182.7, $^3J_{FF}$=7.5 Hz, 1F, C<u>F</u>FBr), –64.9 (dd, $^2J_{FF}$=182.7, $^3J_{FF}$=5.9 Hz, 1F, CF<u>F</u>Br), –118.0 (dt, $^2J_{FF}$=271.3 , *J*=5.9 Hz, 1F, CHOC<u>F</u>F), –123.1 ppm (ddd, $^2J_{FF}$=271.3, $^3J_{HF}$=17.2, $^3J_{FF}$=7.5 Hz, 1F, CHOCF<u>F</u>) ppm. **MS** (EI) *m/z* (%)

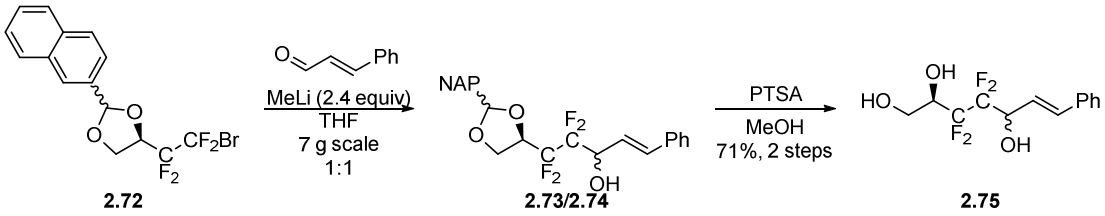
378 and 380 ($M^{+\bullet}$, 9), 377 and 379 ($(M - H^{\bullet})^+$, 5), 299 ($(M - Br^{\bullet})^+$, 5), 155 ($NAPCO^+$, 30), 128 ($NAP^{+\bullet}$, 100); **HRMS** (MS+) for $C_{15}H_{12}{}^{79}BrF_4O_2$ $(M + H)^+$ calcd 378.9960, found 378.9955.

*5.6.6.2 **Cis-2.72***



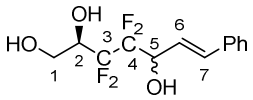
R_f 0.41 (petroleum ether 40-60 °C/Et_2O 80:20). **IR** (neat cm^{-1}) 3060 (w), 2906 (w), 1151 (s), 1076 (s), 818 (s); **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.96 (s, 1H, H_{Ar}), 7.93–7.83 (m, 3H, H_{Ar}), 7.64 (dd, *J*=8.5, 1.2 Hz, 1H, H_{Ar}), 7.57–7.48 (m, 2H, H_{Ar}), 6.02 (s, 1H, C<u>H</u>OO), 4.85–4.72 (m, 1H, C<u>H</u>CF_2), 4.60 (dd, $^2J_{HH}$=9.5, $^3J_{HH}$=2.3 Hz, 1H, C<u>H</u>HCHO), 4.27 ppm (dd, $^2J_{HH}$=9.5, $^3J_{HH}$=7.7 Hz, 1H, CH<u>H</u>CHO) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.2 ($C_{q,Ar}$), 132.7 ($C_{q,Ar}$), 132.8 ($C_{q,Ar}$), 128.4 (CH_{Ar}), 128.5 (CH_{Ar}), 127.8 (CH_{Ar}), 127.2 (CH_{Ar}), 126.8 (CH_{Ar}), 126.3 (CH_{Ar}), 123.7 (CH_{Ar}), 116.9 (ddt, $^1J_{CF}$=314.7, $^1J_{CF}$=311.8, $^2J_{CF}$=39.5 Hz, <u>C</u>F_2), 113.5 (ddt, $^1J_{CF}$=264.9, $^1J_{CF}$=253.2, $^2J_{CF}$=30.7 Hz, <u>C</u>F_2), 106.4 (<u>C</u>HOO), 72.6 (dd, $^2J_{CF}$=33.7, $^2J_{CF}$=22.0 Hz), 65.8 (<u>C</u>H_2CHO) ppm. **^{19}F NMR** (282MHz, $CDCl_3$): δ –63.2 (dd, $^2J_{FF}$=181.1, *J*=8.1 Hz, 1F, C<u>F</u>FBr), –64.2 (dd, $^2J_{FF}$=181.1, *J*=4.8 Hz, 1F, CF<u>F</u>Br), –115.3 (dt, $^2J_{FF}$=269.0, *J*=5.0 Hz, 1F, CHOC<u>F</u>F), –126.1 ppm (ddd, $^2J_{FF}$=269.0, *J*=18.1, *J*=8.3 Hz, 1F, CHOCF<u>F</u>) ppm. **MS** (EI) *m/z* (%) 378 and 380 ($M^{+\bullet}$, 11), 377 and 379 ($(M - H^{\bullet})^+$, 7), 299 ($(M - Br^{\bullet})^+$, 6), 155 ($NAPCO^+$, 37), 128 ($NAP^{+\bullet}$, 100); **HRMS** (MS+) for $C_{15}H_{12}{}^{79}BrF_4O_2$ $(M + H)^+$ calcd 378.9951, found 378.9943.

5.6.7 (2*R*)-3,3,4,4-Tetrafluoro-7-phenylhept-6-ene-1,2,5-triol (2.75)



To a solution of bromide **2.72** (7.00 g, 18.5 mmol, 1 equiv) in THF (75 mL) was added cinnamaldehyde (5.58 mL, 44.3 mmol, 2.4 equiv) then cooled to –78 °C. After 10 min, MeLi (1.5 M in Et_2O, 27.7 mL, 44.3 mmol, 2.4 equiv) was added dropwise and the reaction mixture was stirred for 2.5 h. The reaction was quenched with saturated NH_4Cl aq. (100 mL) and extracted with Et_2O (3 × 300 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* and used without further purification. To a solution of crude acetal (m_{th}:

7.98 g, 18.5 mmol, 1 equiv) in MeOH (200 mL) was added PTSA (318 mg, 1.85 mmol, 0.1 equiv) and the resultant mixture was stirred at rt for 5 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (100 mL), diluted with water (200 mL) and extracted with EtOAc (4 × 250 mL). The combined organic layers were reduced *in vacuo* to 500 mL, washed with brine (150 mL), dried (Na_2SO_4), filtered and concentrated to offer 14.3 g of crude material. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 75:25 to 50:50) afforded 3.88 g (13.2 mmol, 71% over two steps) of pure triol **2.75** as a 1:1 mixture of diastereoisomers and white solid.

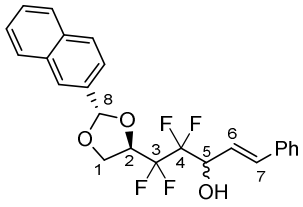


R_f 0.26 (petroleum ether 40-60 °C/acetone 65:35). **IR** (neat cm^{-1}) 3365 (br, m), 1257 (m), 1099 (s), 968 (m); **^{1}H NMR** (400MHz, Acetone-*d*6): δ 7.49 (d, *J*=7.6 Hz, 4H, H_{Ar}), 7.40–7.32 (m, 4H, H_{Ar}), 7.32–7.24 (m, 2H, H_{Ar}), 6.88 (d, $^3J_{HH}$=15.9 Hz, 2H, H-7, both dia), 6.39 (dd, $^3J_{HH}$=15.9, $^3J_{HH}$=6.0 Hz, 1H, H-6, dia 1), 6.37 (dd, $^3J_{HH}$=15.9, $^3J_{HH}$=5.9 Hz, 1H, H-6, dia 2), 5.43 (d, $^3J_{HH}$=6.2 Hz, 2H, OH-5, both dia), 5.23 (d, $^3J_{HH}$=6.2 Hz, 1H, OH-2, dia 1), 5.17 (d, $^3J_{HH}$=6.4 Hz, 1H, OH-2, dia 2), 4.94–4.80 (m, 2H, H-5, both dia), 4.35–4.19 (m, 2H, H-2, both dia), 4.14–3.97 (m, 2H, OH-1, both dia), 3.95–3.83 (m, 2H, H-6a, both dia), 3.80–3.67 (m, 2H, H-6b, both dia) ppm. **^{13}C NMR** (101 MHz, Acetone-*d*6) δ 137.4 ($C_{q,\,Ar}$), 135.2 (C-7, dia 1), 135.1 (C-7, dia 2), 129.6 (CH_{Ar}), 129.0 (CH_{Ar}), 127.6 (CH_{Ar}), 124.1 (C-6), 121.1–114.6 (4×CF_2), 72.3 (dd, $^2J_{CF}$=25.7, 23.5 Hz, C-2 or C-5), 71.9 (dd, $^2J_{CF}$=26.4, 24.9 Hz, , C-2 or C-5), 71.9 (t, $^2J_{CF}$=24.3 Hz, , C-2 or C-5), 71.7 (dd, $^2J_{CF}$=27.9, 23.5 Hz, , C-2 or C-5), 61.3 (C-1) ppm. **^{19}F NMR** (376 MHz, Acetone-*d*6) δ –119.4 (app. dt, *J*=271.5, 6.5 Hz, 1F), –119.9 (app. dtd, *J*=270.5, 6.6, 6.6, 1.4 Hz, 1F), –120.5 (app. dt, *J*=274.9, 6.9 Hz, 1F), –121.0 (app. dt, *J*=273.6, 6.8 Hz, 1F), –123.9 (ddd, *J*=274.9, 16.4, 6.6 Hz, 1F), –124.9 (app. ddd, *J*=273.6, 17.5, 6.2 Hz, 1F), –125.5 (ddd, *J*=271.5, 15.9, 6.6 Hz, 1F), –126.1 (app. ddd, *J*=270.5, 16.7, 5.8 Hz, 1F) ppm. **{^{1}H}^{19}F NMR** (376 MHz, Acetone-*d*6) δ –119.4 (dd, *J*=271.5, 5.9 Hz, 1F), –119.9 (ddd, *J*=270.5, 6.5, 2.2 Hz, 1F), –120.5 (dd, *J*=274.9, 5.9 Hz, 1F), –121.0 (ddd, *J*=273.6, 6.1, 2.2 Hz, 1F), –123.9 (dd, *J*=274.9, 6.6 Hz, 1F), –124.9 (ddd, *J*=273.6, 6.5, 2.7 Hz, 1F), –125.5 (dd, *J*=271.5, 6.6 Hz, 1F), –126.1 (ddd, *J*=270.5, 6.1, 2.7 Hz, 1F) ppm. **HRMS** (MS+) for $C_{13}H_{14}F_4NaO_2$ $(M + Na)^+$ calcd 317.0771, found 317.0771.

5.6.7.1 (2R)-3,3,4,4-Tetrafluoro-1,2-(2-naphthylmethylidenedioxy)-7-phenylhept-6-ene-5-ol

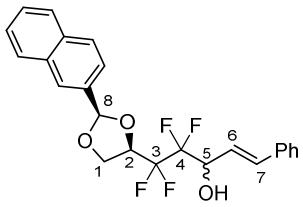
Analytical samples of the coupling product obtained above was purified by column chromatography (petroleum ether 40–60 °C/Et_2O 70:30)

*5.6.7.2 Trans acetal diastereoisomer (**2.73**)*



The diastereoisomer **2.73** was obtained with the by-product **2.68** as 1:2.2 mixture. $\mathbf{R_f}$ 0.29/0.19 (petroleum ether 40-60 °C/Et_2O 70:30). **IR** (neat cm^{-1}) 3444 (w), 3022 (w), 2906 (w), 1126 (s), 1095 (s), 1066 (s); **^{1}H NMR** (300MHz, $CDCl_3$) δ 7.97 – 7.81 (m, 4H, H_{Ar}), 7.67 – 7.49 (m, 4H, H_{Ar}), 7.47 – 7.21 (m, 16 H, H_{Ar}), 6.84 (d, *J* = 15.7 Hz, 1H, H-7, dia 1), 6.80 (dd, *J* = 16.0, 1.0 Hz, 1H, H-7, dia 2), 6.40 – 6.25 (m, 2H, H-6, both dia), 6.11 (s, 1H, H-8, dia 1), 6.13 (s, 1H, H-8, dia 2), 4.97 – 4.75 (m, 4H, H-2 and H-5, both dia), 4.56 – 4.44 (m, 2H, H-1a, both dia), 4.35 (dd, *J* = 9.2, 6.7 Hz, 1H, H-1b, dia 1), 4.34 (dd, *J* = 9.1, 7.0 Hz, 1H, H-1b, dia 2), 3.19 (d, *J* = 5.4 Hz, 1H, OH, dia 2), 3.08 (d, *J* = 7.5 Hz, 1H, OH, dia 1) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –119.0 (d, *J*=270.8 Hz, 1F, dia 2), –122.8 (dd, *J*=275.1, 8.6 Hz, 1F, dia 1), –123.9 – –125.4 (m, 4F, 2 × dia 1, 2 × dia2), –126.7 – –128.0 (m, 2F, dia 1, dia 2) ppm. **HRMS** (MS+) for $C_{24}H_{20}F_4NaO_3$ $(M + Na)^+$ calcd 455.1241, found 455.1241.

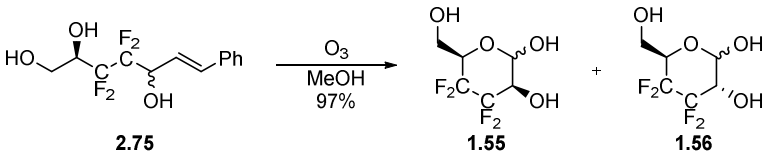
*5.6.7.3 Cis acetal diastereoisomer (**2.74**)*



$\mathbf{R_f}$ 0.21 (toluene/Et_2O 95:5). **^{1}H NMR** (300MHz, $CDCl_3$) δ 8.01 – 7.77 (m, 8H, H_{Ar}), 7.70 – 7.40 (m, 8H, H_{Ar}), 7.40 – 7.21 (m, 8H, H_{Ar}), 6.86 – 6.56 (dd, *J* = 15.6, 1.2 Hz, 1H, H-7, dia 1), 6.67 (dd, *J* = 15.6, 1.3 Hz, 1H, H-7, dia 2), 6.29 – 6.15 (m, 2H, H-6 both dia), 6.05 (s, 2H, H-8, both dia), 4.87 – 4.59 (m, 6H, H1a, H-2 and H-5, both dia), 4.34 – 4.24 (m, 2H, H-1b, both dia), 2.91 (d, *J* = 5.2 Hz, 1H, OH, dia 2), 2.79 (d, *J* = 7.5 Hz, 1H, OH, dia 1) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –118.3 (m,

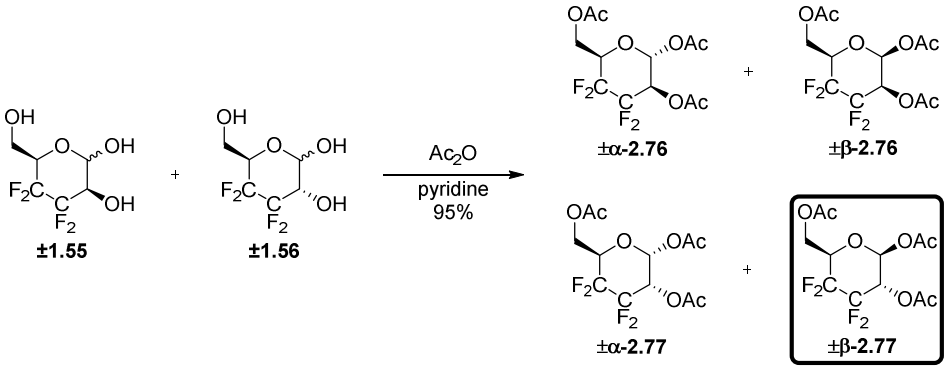
J=275.1 Hz, 1F), –121.3 (d, *J*=275.1 Hz, 1F), –122.0 (d, *J*=275.1 Hz, 1F), –122.4 (d, *J*=275.1 Hz, 1F), –126.1 – –128.8 (m, 4F) ppm.

5.6.8 3,4-Dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose (1.55) and D-*erythro*-hexopyranose (1.56)



Ozone was bubbled through a solution of triol **2.75** (2.50 g, 8.50 mmol) in MeOH (75 mL) until a light blue colour was obtained (20 min). O_2 was bubbled through to remove excess ozone (10 min) and then, Me_2S (6.24 mL, 85.0 mmol, 10 equiv) was added and the reaction mixture was allowed to warm to rt and concentrated to offer 2.58 g of crude material. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 60:40) afforded 1.67 g (7.59 mmol, 89%) of a pure 1:1 mixture of **1.55** (α/β 65:35) and **1.56** (68:32) as a colourless syrup which solidified into an off-white solid on standing. Spectroscopic and physical data are the same as above (*cf* sections **5.4.7** and **5.4.9**).

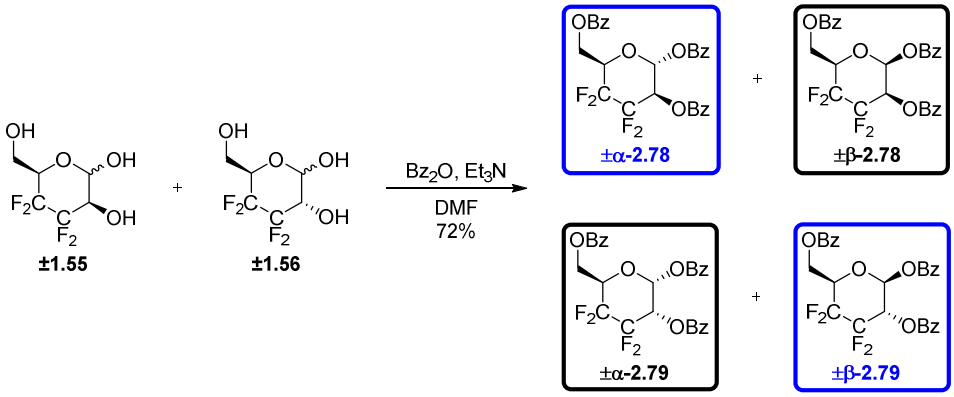
5.6.9 1,2,6-Tri-*O*-acetyl-3,4-dideoxy-3,3,4,4-tetrafluoro-*threo*-hexopyranose (±2.76) and *erythro*-hexopyranose (±2.77)



To a solution of Man and Glc (1.20 g, 5.45 mmol, 1 equiv) in pyridine (12 mL) was added Ac_2O (1.86 mL, 19.6 mmol, 3.6 equiv). The resultant mixture was stirred at rt 17 h then quenched with EtOH (10 mL). Volatiles were evaporated and then azeotroped with toluene and $CHCl_3$ to afford 1.79 g (5.18 mmol, 95%) of **2.76** and **2.77** as a colourless oil. Repeated column chromatography (CHCl3/EtOAc 96:4) afforded 486 mg (1.40 mmol, 26%) of pure **±2.77** as a 4:96 α/β mixture.

Data for **±β-2.77**: R_f 0.52 ($CHCl_3$/EtOAc 90:10). **IR** (neat cm^{-1}) 2973 (w), 1770 (m), 1750 (m), 1199 (s), 1056 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.83 (d, *J*=8.4 Hz, 1H, H-1), 5.42 (ddt, *J*=20.8, 8.6, 4.3 Hz, 1H, H-2), 4.48 (dd, *J*=12.2, 3.1 Hz, 1H, H-6_a), 4.33 (dd, *J*=12.2, 7.1 Hz, 1H, H-6_b), 4.19 (dddd, *J*=21.6, 7.1, 4.3, 3.1 Hz, 1H, H-5), 2.19 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.11 (s, 3H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –127.3 – –128.7 (m, 1F), –131.3 – –132.5 (m, 1F), –131.7 – –132.9 (m, 1F), –134.8 (ddd, *J*=263.3, 14.0, 8.6 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 369 $(M+Na)^+$. **HRMS** (MS+) for $C_{12}H_{14}F_4NaO_7$ $(M + Na)^+$ calcd 369.0568, found 369.0575.

5.6.10 1,2,6-Tri-*O*-benzoyl-3,4-dideoxy-3,3,4,4-tetrafluoro-*threo*-hexopyranose (±2.78) and *erythro*-hexopyranose (±2.79)

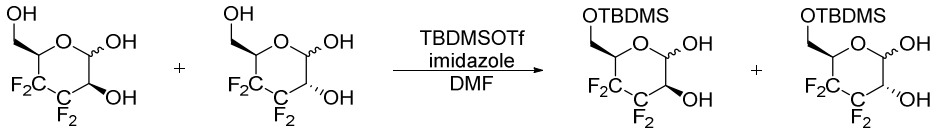


A 1:1 mixture of hexoses (75 mg, 0.341 mmol, 1 equiv) was dissolved in DMF (3.4 mL), Et_3N (0.57 mL, 4.09 mmol, 12 equiv) was added followed by addition of Bz_2O (462 mg, 2.04 mmo, 6 equiv), and the mixture was stirred at rt for 15 h. Excess of MeOH was added and the mixture was stirred 1 h at rt. After concentration, a solution of the residue in CH_2Cl_2 was washed with sat. aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered, concentrated, and the crude mixture was chromatographed (hexane/$CHCl_3$ 40:60), to give 68 mg (0.127 mmol, 37%) of a 1:2 **±α-2.78**/**±β-2.79** mixture and 62 mg (0.117 mmol, 34%) of a 1:2 **±α-2.79**/**±β-2.78** mixture.

Data for **±α-2.78** and **±β-2.79**: R_f 0.19 (hexane/$CHCl_3$ 40:60). **IR** (neat cm^{-1}) 2975 (w), 1730 (s), 1247 (s), 1067 (s), 707 (s); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 – 7.93 (m, 6H, H_{Ar}), 7.70 – 7.36 (m, 9H, H_{Ar}), 6.55 (d, *J*=5.1 Hz, 1H, H-1, α-Man), 6.28 (d, *J*=8.8 Hz, 1H, H-1, β-Glc), 5.94 (ddt, *J*=20.7, 8.5, 3.9 Hz, 1H, H-2, β-Glc), 5.81 – 5.73 (m, 1H, H-2, α-Man), 4.88 – 4.59 (m, 5H, H-5 and 2 × H-6, α-Man, 2 × H-6, β-Glc), 4.52 (ddt, *J*=21.4, 6.8, 3.6 Hz, 1H, H-5, β-Glc) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –118.3 (dq, *J*=276.2, 8.6 Hz, 1F, α-Man), –127.9 (m, *J*=259.0 Hz, 1F, β-Glc), –130.5 – –132.6 (m, 4F, 2 × α-Man, 2 × β-Glc), –133.3 (m, *J*=265.4 Hz, 1F, α-Man), –134.4 (ddd, *J*=263.3, 14.0, 8.6 Hz, 1F, β-Glc) ppm. **HRMS** (MS+) for $C_{27}H_{20}F_4NaO_7$ $(M + Na)^+$ calcd 555.1037, found 555.1045.

Data for **±α-2.79** and **±β-2.78**: **R*f*** 0.10 (hexane/$CHCl_3$ 40:60). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.21 – 7.85 (m, 6H, H_{Ar}), 7.72 – 7.30 (m, 9H, H_{Ar}), 6.81 (t, *J*=4.1 Hz, 1H, H-1, α-Glc), 6.45 – 6.39 (m, 1H, H-1, β-Man), 6.02 – 5.93 (m, 1H, H-2, β-Man), 5.89 – 5.75 (m, 1H, H-2, α-Glc), 4.91 – 4.61 (m, 5H, H-5 and 2 × H-6, α-Glc, 2 × H-6, β-Man), 4.61 – 4.45 (m, 1H, β-Man) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –120.2 (d, *J*=276.2 Hz, 1F, β-Man), –125.4 (ddt, *J*=255.7, 21.2, 10.3 Hz, 1F, α-Glc), –130.0 – –132.3 (m, 4F, 2 × α-Glc, 2 × β-Man), –132.5 – –134.0 (m, 2F, α-Glc, β-Man) ppm.

5.6.11 6-*O*-*tert*-Butyldimethylsilyl-3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose (2.90) and D-*erythro*-hexopyranose (2.91)

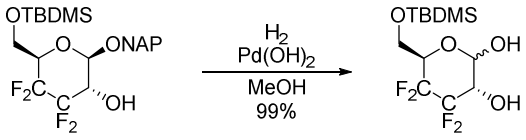


To a solution of sugars **1.55**/**1.56** (450 mg, 2.04 mmol, 1 equiv) in dry DMF (6.75 mL) was added imidazole (181 mg, 2.66 mmol, 1.3 equiv) and TBDMSOTf (0.563 mL, 2.45 mmol, 1.2 equiv) at 0 °C. The resultant mixture was stirred at rt for 2.5 h, diluted with brine (20 mL) and water (5 mL), extracted with EtOAc (4 × 50 mL), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (compound loaded as $CHCl_3$ solution, eluted with petroleum ether 40–60 °C/Et_2O, 60:40) afforded 654 mg (1.96 mmol, 96%) of a pure 1:1 mixture of **2.90** (α/β 44:56) and **2.91** (51:49) as a colourless gummy solid. Another experiment starting from 880 mg (4.00 mmol) afforded 1.030 g (3.08 mmol, 77%).

R_f 0.26 (petroleum ether 40–60 °C/Et_2O, 60:40). **IR** (neat cm^{-1}) 3386 (w), 2932 (w), 1099 (s), 1034 (s), 834 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.43 (q, *J*=3.9 Hz, 1H, H-1, α-Glc), 5.35 - 5.40 (m, 1H, H-1, α-Man), 5.30 (br. s., 1H, OH-1, β-Glc), 5.03 (br. s., 1H, H-1, β-Man), 4.86 (br. d, *J*=7.8 Hz, 1H, β-Glc), 4.71 (br. d, *J*=8.3 Hz, 1H, OH-1, β-Man), 4.55 (d, *J*=3.1 Hz, 1H, OH-1, α-Glc), 4.47 – 4.28 (m, 2H, H-5, α-Glc, H-5, α-Man), 4.31 (br. s, 1H, OH-1, α-Man), 4.14 – 3.95 (m, 7H, H-2, H-6_a, α-Glc, H-6_a, β-Glc, H-2, H-6_a, α-Man, H-2, H-6_a, β-Man), 3.95 – 3.79 (m, 7H, H-6_b, α-Glc, H-2, H-5, H-6_b, β-Glc, H-6_b, α-Man, H-5, H-6_b, β-Man), 3.34 (br. s., 1H, OH-2, β-Man), 3.08 (br d, *J*=10.7 Hz, 1H, OH-2, α-Glc), 2.97 (br. s., 1H, OH-2, α-Man), 0.92 (s, 9H, $CH_{3,tBu}$), 0.92 (s, 9H, $CH_{3,tBu}$), 0.91 (s, 18H, $CH_{3,tBu}$), 0.12 (s, 6H, CH_3), 0.12 (s, 6H, CH_3), 0.11 (s, 12H, CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 94.9 (d, *J*=9.5 Hz, C-1, β-Glc), 94.3 (d, *J*=5.9 Hz, C-1, α-Man), 92.9 (d, *J*=7.3 Hz, C-1, β-Man), 91.3 (d, *J*=8.8 Hz, C-1, α-Glc), 74.2 (dd, *J*=26.4, 22.0 Hz, C-5, β-Man), 73.8 (dd, *J*=25.7, 22.0 Hz, C-5, β-Glc), 71.6 (t, *J*=17.6 Hz, C-2, β-Glc), 71.1 (dd, *J*=32.3, 19.1 Hz, C-2, β-Man), 70.9 (dd, *J*=30.1, 19.1 Hz, C-2, α Man), 69.8 (dd, *J*=27.1, 22.0 Hz, C-5, α-Man), 68.9 (t,

J=23.9 Hz, C-5, α-Glc), 68.4 (t, *J*=19.1 Hz, C-2, α-Glc), 59.9 – 59.5 (m, C-6, all isomers), 25.8 ($CH_{3,tBu}$), 25.8 ($CH_{3,tBu}$), 25.8 ($CH_{3,tBu}$), 18.5 ($C_{q,tBu}$), 18.4 ($C_{q,tBu}$), 18.3 ($C_{q,tBu}$), –5.5 (CH_3), –5.5 (CH_3), –5.6 (CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm –118.9 (m, $^2J_{FF}$=273.5 Hz, 1F, α-Man), –121.3 (m, $^2J_{FF}$=274.8 Hz, 1F, β-Man), –127.9 (dd, $^2J_{FF}$=255.8, 20.8 Hz, 1F, α-Glc), –129.5 (dddd, $^2J_{FF}$=265.3, 23.8, 15.4, 7.8 Hz, 1F, α-Man), –130.0 (dddd, $^2J_{FF}$=267.5, 24.1, 16.0, 8.9 Hz, 1F, β-Man), –132.5 – –131.4 (m, 6F, 2 × α-Man, β-Man, α-Glc, 2 × β-Glc), –133.3 (app. t, *J*=12.1 Hz, 2F, α-Glc), –134.4 – –133.5 (m, 1F, β-Glc), –134.7 – –133.8 (m, 1F, β-Man), –134.8 (ddd, $^2J_{FF}$=262.1, 13.7, 8.5 Hz, 1F, β-Glc). **HRMS** (MS+) for $C_{12}H_{22}F_4NaO_4Si$ $(M + Na)^+$ calcd 357.1116, found 357.1109.

5.6.12 6-*O*-*tert*-Butyldimethylsilyl-3,4-dideoxy-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranose (2.91)



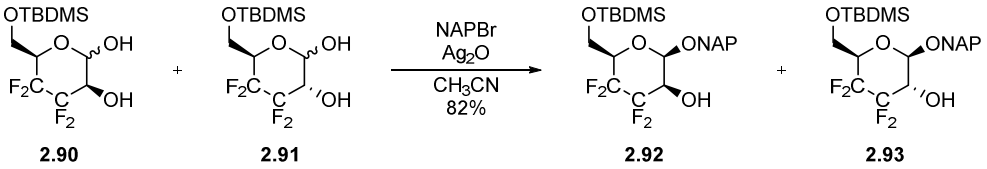
2.93 **2.91**

To a solution of **2.93** (36 mg, 0.076 mmol, 1 equiv) in MeOH (1 mL) was added $Pd(OH)_2$/C (20%, 11 mg, 0.165 mmol, 0.2 equiv) and H_2 was bubbled through the solution via a needle for 10 min. The reaction mixture was left stirring at rt under H_2 for 16 h then filtered over a pad of Celite® and concentrated *in vacuo*. Purification by column chromatography (petroleum ether 40–60 °C/Et_2O, 60:40) afforded 25 mg (0.075 mmol, 99%) of **2.91** as 70:30 α/β mixture ($CDCl_3$) and a white solid.

R_f 0.26 (petroleum ether 40–60 °C/Et_2O, 60:40). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.43 (q, *J*=4.3 Hz, 1H, H-1α), 4.90 – 4.83 (m, 1H, H-1β), 4.62 (d, $^3J_{HH}$=4.7 Hz, 1H, OH-1β), 4.42 – 4.27 (m, 1H, H-5α), 4.31 (d, $^3J_{HH}$=3.9 Hz, 1H, OH-1α), 4.12 – 3.94 (m, 2H, H-2α, H-6_aβ), 4.04 (dd, $^2J_{HH}$=11.4, $^3J_{HH}$=3.0 Hz, 1H, H-6_aα), 3.93 – 3.79 (m, 3H, H-2β, H-5β, H-6_bβ), 3.87 (dd, $^2J_{HH}$=11.4, $^3J_{HH}$=7.5 Hz, 1H, H-6_bα), 3.30 (d, $^3J_{HH}$=4.5 Hz, 1H, OH-2β), 2.81 (d, $^3J_{HH}$=11.4 Hz, 1H, OH-2α), 0.92 (s, 9H, $CH_{3,tBu}$α), 0.91 (s, 9H, $CH_{3,tBu}$β), 0.12 (s, 6H, CH_3α), 0.11 (s, 6H, CH_3β) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 116.1 – 110.1 (2 × CF_2, α + β), 95.0 (d, $^3J_{CF}$=8.8 Hz, C-1β), 91.4 (d, $^3J_{CF}$=8.8 Hz, C-1α), 73.9 (dd, $^2J_{CF}$=26.4, 22.0 Hz, C-2β or C-5β), 71.9 (td, $^2J_{CF}$=18.5, *J*=2.2 Hz, C-2β or C-5β), 69.0 (t, $^2J_{CF}$=23.5 Hz, C-5α), 68.5 (t, $^2J_{CF}$=19.4 Hz, C-2α), 59.8 – 59.6 (C-6, α + β), 25.82 ($CH_{3,tBu}$α), 25.79 ($CH_{3,tBu}$β), 18.44 ($C_{q,tBu}$α), 18.37 ($C_{q,tBu}$β), -5.4 (2 × CH_3, α + β), -5.46 (CH_3,α), -5.5 (CH_3,β) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –127.9 (dd, $^2J_{FF}$=255.8, 20.8 Hz, 1F, α), –132.5 – –131.4 (m, 3F, α, 2 ×

β), –133.3 (app. t, *J*=12.1 Hz, 2F, α), –133.5 – –134.3 (m, *J*=257.5 Hz, 1F, β), –134.4 – –135.2 (m, *J*=261.8 Hz, 1F, β) ppm.

5.6.13 2-Naphthylmethyl 6-*O*-*tert*-butyldimethylsilyl-3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose (2.92) and D-*erythro*-hexopyranoside (2.93)



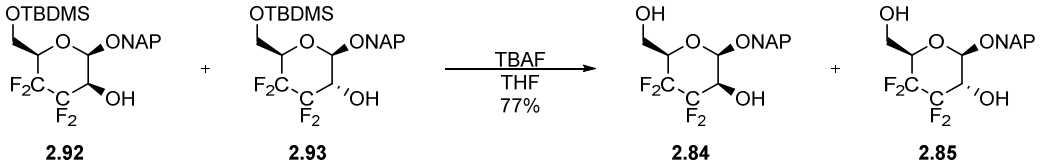
To a solution of **2.90/2.91** (950 mg, 2.84 mmol, 1 equiv) in CH_3CN (17.5 mL) was added NAPBr (1.26 g, 5.68 mmol, 2 equiv) and Ag_2O (1.65 g, 7.10 mmol, 2.5 equiv). The reaction mixture was stirred at rt for 2 h then filtered through Celite® and concentrated. Purification by column chromatography (petroleum ether 40–60 °C/Et_2O, 90:10 to 70:30) afforded 1.11 g (2.34 mmol, 82%) of a mixture of **2.92** and **2.93** alongside some 2-O-NAP isomers as a white solid. Analytical samples of pure **2.93** and of a pure mixture of **2.92** and **2.93** could be obtained.

Data for **2.93**: $\mathbf{R_f}$ 0.44 (petroleum ether 40-60 °C/Et_2O 70:30). **IR** (neat cm^{-1}) 3442 (br, w), 3056 (w), 2930 (w), 1256 (m), 1102 (s), 1033 (s); **^{1}H NMR** (400MHz ,$CDCl_3$) δ 7.91 – 7.80 (m, 4H, H_{Ar}), 7.56 – 7.46 (m, 3H, H_{Ar}), 5.12 (d, $^2J_{HH}$=11.6 Hz, 1H, H-7_a), 4.85 (d, $^2J_{HH}$=11.6 Hz, 1H, H-7_b), 4.65 (br d, $^3J_{HH}$=7.9 Hz, 1H, H-1), 4.11 – 4.05 (m, 1H, H-6_a), 4.03 – 3.81 (m, 3H, H-2, H-5, H-6_b), 2.57 (d, $^3J_{HH}$=4.5 Hz, 1H, OH-2), 0.96 (s, 9H, tBu), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.4 ($C_{q,Ar}$), 133.2 ($C_{q,Ar}$), 133.2 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (CH_{Ar}), 126.3 (CH_{Ar}), 126.4 (CH_{Ar}), 125.9 (CH_{Ar}), 116.8 – 110.3 (m, 2 × CF_2), 99.4 (d, $^4J_{CF}$=9.2 Hz, C-1), 73.9 (dd, $^2J_{CF}$=24.9, 22.7 Hz, C-5), 71.4 ($\underline{C}H_2$Nap), 71.6 – 70.9 (C-2), 59.5 (d, *J*=2.9 Hz, C-6), 25.8 ($CH_{3,tBu}$), 18.3 ($C_{q,tBu}$), -5.3 (CH_3), -5.5 (CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –132.3 – –131.3 (m, 2F, 2 × C$\underline{F}$F), –134.3 – –133.4 (m, 1F, CF$\underline{F}$), –135.4 – –134.5 (m, 1F, CF$\underline{F}$) ppm. **HRMS** (MS+) for $C_{23}H_{30}F_4NaO_4Si$ $(M + Na)^+$ calcd 497.1742, found 497.1755.

Data for **2.92**: $\mathbf{R_f}$ 0.33 (petroleum ether 40-60 °C/Et_2O 70:30). Unambiguous resonances: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 4H, CH_{Ar}), 7.57 – 7.46 (m, 3H, CH_{Ar}), 5.13 (d, $^2J_{HH}$=11.8 Hz, 1H, H-7_a), 4.83 – 4.79 (m, 1H, H-1), 4.90 (d, $^2J_{HH}$=11.8 Hz, 1H, H-7_b), 2.68 (d, $^3J_{HH}$=5.3 Hz, 1H, OH-2), 0.98 (s, 9H, $CH_{3,tBu}$), 0.18 (s, 3H, CH_3), 0.16 (s, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.0 ($C_{q,Ar}$), 133.2 ($C_{q,Ar}$), 133.3 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (2C, CH_{Ar}), 126.4 (2C, CH_{Ar}), 126.0 (CH_{Ar}), 96.4 (d, $^3J_{CF}$=8.1 Hz), 74.6 (dd, $^2J_{CF}$=26.4, 23.5 Hz, C-5), 71.0 (dd, $^2J_{CF}$=30.8, 19.8 Hz, C-2), 70.8 (C-7), 59.8 – 59.6 (C-6), 25.8 ($CH_{3,tBu}$), 18.3 ($C_{q,tBu}$), -5.3 (CH_3), -5.4 (CH_3) ppm

(2 × $\underline{C}F_2$ not visible). **^{19}F NMR** (376 MHz, $CDCl_3$) δ –120.8 (br. d, $^2J_{FF}$=273.1 Hz, 1F, F-3_{ax}), –129.9 (dddd, $^2J_{FF}$=266.2, *J*=22.5, 16.5, 8.7 Hz, 1F, F-3_{eq}), –132.0 – –133.6 (m, 2F, 2 × F-4) ppm.

5.6.14 2-Naphthylmethyl 3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose (2.84) and D-*erythro*-hexopyranoside (2.85)



2.92 **2.93** **2.84** **2.85**

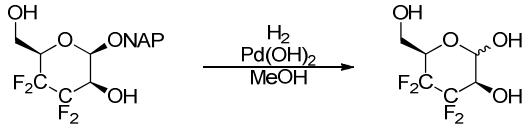
To the mixture of **2.92** and **2.93** (1.11 g, 2.34 mmol, 1 equiv), in THF (20 mL) at 0 °C was added TBAF (1 M in THF, 2.45 mL, 2.45 mmol, 1.05 equiv) and the resulting mixture was stirred at 0 °C for 1 h then concentrated. Purification by column chromatography ($CHCl_3$/Et_2O, 80:20, crude was loaded with pure $CHCl_3$) afforded 325 mg (0.902 mmol, 38%) of pure **2.84** and 327 mg (0.908 mmol, 39%) of **2.85** together with a small amount of unknown impurities.

Data for **2.85**: $\mathbf{R_f}$ 0.44 ($CHCl_3$/Et_2O 70:30). **IR** (neat cm^{-1}) 3398 (br, w), 3239 (br, w), 3060 (w), 2952 (w), 1290 (m), 1098 (s), 1023 (s); **^{1}H NMR** (400 MHz, Acetone-*d*6) δ 7.96 – 7.83 (m, 4H, H_{Ar}), 7.58 – 7.46 (m, 3H, H_{Ar}), 5.72 (d, $^3J_{HH}$=6.4 Hz, 1H, OH-2), 5.15 (d, $^2J_{HH}$=12.0 Hz, 1H, H-7_a), 4.92 (d, $^2J_{HH}$=12.0 Hz, 1H, H-7_b), 4.82 (d, $^3J_{HH}$=8.0 Hz, 1H, H-1), 4.30 (dd, $^3J_{HH}$=6.9, 5.7 Hz, 1H, OH-6), 4.06 – 3.81 (m, 4H, H-2, H-5, 2 × H-6) ppm. **^{13}C NMR** (101 MHz, Acetone-*d*6) δ 135.9 ($C_{q,Ar}$), 134.3 ($C_{q,Ar}$), 134.1 ($C_{q,Ar}$), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 127.6 (CH_{Ar}), 127.1 (CH_{Ar}), 127.0 (CH_{Ar}), 126.9 (CH_{Ar}), 101.4 (d, *J*=10.3 Hz, C-1), 74.3 (dd, $^2J_{CF}$=25.7, 22.0 Hz, C-5), 72.0 (t, *J*=17.6 Hz, C-2), 71.9 (C-7), 59.0 (dd, *J*=4.4, 1.5 Hz, C-6) ppm. **^{19}F NMR** (376 MHz, Acetone-*d*6) δ –130.8 (app. dddd, $^2J_{FF}$=255.8, $^3J_{HF}$=20.9, $^3J_{FF}$=13.9, 10.4, 1F), –131.3 – –132.3 (m, *J*=260.1 Hz, 1F), –133.2 (dddd, $^2J_{FF}$=255.8, $^3J_{FF}$=15.6, 8.7, $^3J_{HF}$=6.9 Hz, 1F), –135.0 (ddd, $^2J_{FF}$=260.1, *J*=13.9, 8.7 Hz, 1F) ppm. **MS** (EI) *m*/*z* (%) 360 ($M^{+\bullet}$, 2), 141 (NAP^+, 100); **HRMS** (MS+) for $C_{17}H_{16}F_4O_4$ $(M + Na)^+$ calcd 383.0877, found 383.0884.

Data for **2.84**: $\mathbf{R_f}$ 0.26 ($CHCl_3$/Et_2O 70:30). **IR** (neat cm^{-1}) 3444 (br, w), 3205 (br, w), 2925 (w), 1206 (m), 1113 (s), 1029 (s); **^{1}H NMR** (400 MHz, Acetone-*d*6) δ 8.00 – 7.81 (m, 4H, CH_{Ar}), 7.60 – 7.46 (m, 3H, CH_{Ar}), 5.16 (d, $^2J_{HH}$=12.0 Hz, 1H, H-7_a), 5.06 – 5.01 (m, 1H, H-1), 4.97 (d, ^3J=5.0 Hz, 1H, OH-2), 4.94 (d, $^2J_{HH}$=12.0 Hz, 1H, H-7_b), 4.34 – 4.21 (m, 2H, H-2, OH-6), 4.04 – 3.86 (m, 3H, H-5, 2 × H-6) ppm. **^{13}C NMR** (101 MHz, Acetone-*d*6) δ 135.8 ($C_{q,Ar}$), 134.3 ($C_{q,Ar}$), 134.1 ($C_{q,Ar}$), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 127.8 (CH_{Ar}), 127.2 (CH_{Ar}), 127.0 (CH_{Ar}), 127.0 (CH_{Ar}), 117.3 – 111.3 (2 × CF_2), 99.3 (d, *J*=8.4 Hz, C-1), 75.5 (dd, $^2J_{CF}$=27.7, 22.6 Hz, C-5), 71.7 (C-7), 72.1

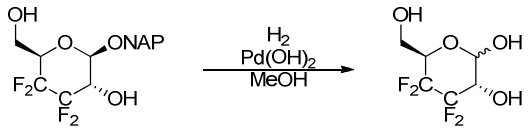
– 71.4 (C-2), 59.4 – 59.2 (C-6) ppm. **^{19}F NMR** (376 MHz, Acetone-*d*6) δ –120.1 (br. d, $^{2}J_{FF}$=266.2 Hz, 1F), –128.9 – –129.9 (m, 1F), –131.3 – –133.1 (m, 2F) ppm. **MS** (EI) *m*/*z* (%) 360 ($M^{+\bullet}$, 4), 141 (NAP^{+}, 100); **HRMS** (MS+) for $C_{17}H_{16}F_4O_4$ $(M + Na)^{+}$ calcd 383.0877, found 383.0878.

5.6.15 3,4-Dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose (1.55)



To a solution of **2.84** (330 mg, 0.916 mmol, 1 equiv) in MeOH (10 mL) was added $Pd(OH)_2$/C (20%, 129 mg, 0.183 mmol, 0.2 equiv) and H_2 was bubbled through the solution via a needle for 10 min. The reaction mixture was left stirring at rt under H_2 for 17 h then filtered over a pad of Celite® and concentrated *in vacuo*. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 65:35 to 60:40) afforded 178 mg (0.809 mmol, 88%) of **1.55** as 63:37 α/β mixture (acetone-*d*6) and a white solid. Spectroscopic and physical data are the same as above (*cf* section **5.4.7**).

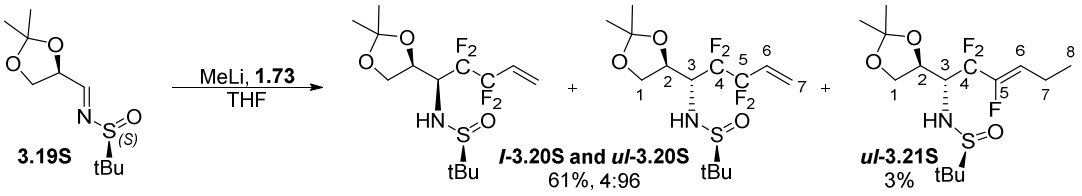
5.6.16 3,4-Dideoxy-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranose (1.56)



To a solution of **2.85** (297 mg, 0.824 mmol, 1 equiv) in MeOH (18 mL) was added $Pd(OH)_2$/C (20%, 116 mg, 0.165 mmol, 0.2 equiv) and H_2 was bubbled through the solution via a needle for 10 min. The reaction mixture was left stirring at rt under H_2 for 16 h then filtered over a pad of Celite® and concentrated *in vacuo*. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 65:35 to 60:40) afforded 156 mg (0.709 mmol, 86%) of **1.56** as 36:64 α/β mixture (acetone-*d*6) and a white solid. Spectroscopic and physical data are the same as above (*cf* section **5.4.9**).

5.7 2,2,3,3-Tetrafluoro-4-aminosugars

5.7.1 (2*S*,3*S*,S_S)-1,2-Isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene (*l*-3.20S) and (2*S*,3*R*,S_S)-1,2-isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene (*ul*-3.20S)



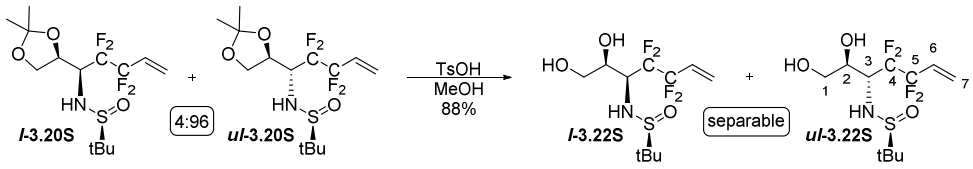
To a solution of sulfinylimine **3.19S** (2.5 g, 10.7 mmol, 1.2 equiv) in THF (40 mL) at –78 °C was added bromotetrafluorobutene **1.73** (1.14 mL, 8.93 mmol, 1.0 equiv). After 10 min, MeLi (1.6 M in Et_2O, 13.4 mL, 21.4 mmol, 2.4 equiv) was added dropwise over 30 min and the reaction mixture was stirred for another 1.5 h. The reaction was quenched with saturated NH_4Cl aq. (25 mL), diluted with H_2O (15 mL) and extracted with Et_2O (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude mixture of diastereoisomers (*dr* 97:3). Purification via column chromatography (petroleum ether/EtOAc 60:40 to 50:50) afforded 1.96 g (5.43 mmol, 61%) of a mixture of diastereoisomers ***l*-3.20S**/***ul*-3.20S** along with 0.098 g (0.27 mmol, 3%) of ***ul*-3.21S** as an off-white solid. $\mathbf{R_f}$ 0.23 (petroleum ether 40-60 °C/EtOAc 60:40). **IR** (neat) 3219 (w, br), 2985 (m), 1371 (m), 1112 (s), 1056 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.14–5.80 (m, 4H, H-7_{trans}+H-6, major and minor), 5.71 (d, $^3J_{HH}$=10.6 Hz, 1H, H-7_{cis}, major), 5.70 (d, $^3J_{HH}$=10.9 Hz, 1H, H-7_{cis}, minor), 4.61–4.54 (m, 2H, H-2, major and minor), 4.20–4.08 (m, 1H, H-3, major), 4.08–3.99 (m, 3H, H-1_{a+b}, major and H-1_a, minor), 3.95 (d, $^3J_{HH}$=10.2 Hz, 1H, NH, minor), 3.78 (dd, $^2J_{HH}$=8.2, $^3J_{HH}$=6.1 Hz, 1H, H-1_b, minor), 3.82–3.70 (m, 1H, H-3, minor), 3.68 (d, $^3J_{HH}$=5.4 Hz, 1H, NH, major), 1.55 (s, 3H, $CH_{3,iPr}$, major), 1.45 (s, 3H, $CH_{3,iPr}$, minor), 1.32 (s, 6H, $CH_{3,iPr}$, major and minor), 1.24 (s, 9H, $CH_{3,tBu}$, minor), 1.22 (s, 9H, $CH_{3,tBu}$, major) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 126.4 (t, $^2J_{CF}$=24.2 Hz, C-6, minor), 126.0 (t, $^2J_{CF}$=24.2 Hz, C-6, major), 124.5 (t, $^3J_{CF}$=9.5 Hz, C-7, major), 124.3 (t, $^3J_{CF}$=9.5 Hz, C-7, minor), 115.9 (tt, $^1J_{CF}$=256.1, $^2J_{CF}$=36.6 Hz, CF_2, major), 115.5 (tt, $^1J_{CF}$=248.8, $^2J_{CF}$=35.1 Hz, CF_2, major), 110.1 ($C_{q,iPr}$, minor), 109.7 ($C_{q,iPr}$, major), 72.7 (C-2, minor), 72.6 (C-2, major), 66.5 (C-1, minor), 64.6 (d, $^4J_{CF}$=4.4 Hz, C-1, major), 58.4 (t, $^2J_{CF}$=23.4 Hz, C-3, minor), 57.8 (t, $^2J_{CF}$=21.3 Hz, C-3, major), 57.6 ($C_{q,tBu}$, minor), 56.7 ($C_{q,tBu}$, major), 26.2 ($CH_{3,iPr}$, minor), 25.8 ($CH_{3,iPr}$, major), 24.34 ($CH_{3,iPr}$, major), 24.25 ($CH_{3,iPr}$, minor), 22.5 ($CH_{3,tBu}$, minor), 22.3 ($CH_{3,tBu}$, major) ppm (2 × CF_2, minor not visible). **^{19}F NMR** (282 MHz, $CDCl_3$) δ –109.8 (dd, $^2J_{FF}$=279.2, *J*=8.6 Hz, 1F, minor),

–111.8 – –112.8 (m, 1F, major), –112.4 – –113.5 (m, 1F, major), –113.1 – –114.2 (m, 1F, major), –118. 7 (ddd, $^2J_{FF}$=279.4, *J*=17.2, $^3J_{FF}$=4.4 Hz, 1F, minor), –120.1 (app. ddt, $^2J_{FF}$=281.5, *J*=16.1, 7.5 Hz, 1F, major) ppm (2 × F, minor overlap with major). **MS** (ESI+) (*m/z*) 425 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{14}H_{23}F_4NNaO_3S$ $(M + Na)^+$ calcd 384.1227, found 384.1233.

5.7.1.1 (2S,3R,S$_S$,Z)-1,2-Isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5-trifluorooct-5-ene (ul-3.21S)

Selected data for the MeLi S_N2' byproduct: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.47 (dt, $^3J_{HF,trans}$=36.5, $^3J_{HH}$=7.6 Hz, 1H, H-6), 2.28–2.15 (m, 2H, H-7), 1.03 (t, $^3J_{HH}$=7.5 Hz, 3H, H-8) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.8 (d, $^4J_{CF}$=4.4 Hz, C-7), 13.1 (s, C-8) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –108.1 (dddt, $^2J_{FF}$=265.0, $^3J_{FF}$=14.8, *J*=10.8, 2.2 Hz, 1F, F-4), –110.8 (app. dt, $^2J_{FF}$=265.0, *J*=13.3 Hz, 1F, F-4'), –132.0 – –132.2 (m, 1F, F-5) ppm. **MS** (ESI+) (*m/z*) 358 $(M+H)^+$. **HRMS** (MS+) for $C_{15}H_{27}F_3NO_3S$ $(M + H)^+$ calcd 358.1658, found 358.1663. The C-3 stereochemistry is assumed.

5.7.2 (2*S*,3*R*,*S*$_S$)- 3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene-1,2-diol (*ul*-3.22S)



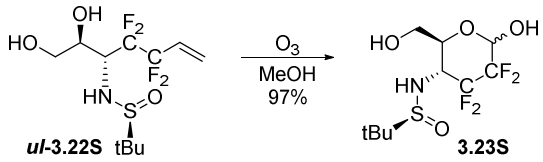
The 4:96 mixture of ***l*-3.20S**/***ul*-3.20S** (2.06 g, 5.70 mmol, 1 equiv) was dissolved in MeOH (60 mL). PTSA (196 mg, 1.14 mmol, 0.2 equiv) was added, and the solution stirred for 23 h, and then quenched with sat. aq. $NaHCO_3$ (30 mL). H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 120 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification via column chromatography (petroleum ether/acetone 70:30 to 50:50) afforded 1.607 g (5.00 mmol, 88%) of the pure major diasteroisomer ***ul*-3.22S** as a yellow syrup. **R_f** 0.51 (petroleum ether 40-60 °C/acetone 60:40). **$[\alpha]_D$** +68.3 (c 0.204, $CHCl_3$, 25 °C). **IR** (neat) 3362 (m, br), 3243 (m, br), 2962 (w), 1102 (s), 1068 (s), 1039 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.12–5.83 (m, 2H, H-6+H-7_{trans}), 5.73 (d, $^3J_{HH}$=10.6 Hz, 1H, H-7_{cis}), 5.57 (d, $^3J_{HH}$=9.5 Hz, 1H, NH), 4.83 (d, $^3J_{HH}$=10.3 Hz, 1H, OH-2), 4.21–4.07 (m, 1H, H-3), 4.07–3.91 (m, 3H, H-1_{a+b}, H-2), 3.48–3.35 (m, 1H, OH-1), 1.27 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 126.3 (t, $^2J_{CF}$=24.4 Hz, C-6), 124.3 (t, $^3J_{CF}$=9.5 Hz, C-7), 66.1 (C-2), 65.0 (C-1), 62.8 (t, $^2J_{CF}$=22.6 Hz, C-3), 56.7 ($C_{q,tBu}$), 22.6 ($CH_{3,tBu}$) ppm (2 × CF_2 not visible). **^{19}F NMR** (376 MHz, $CDCl_3$) δ –112.7 (dd, $^2J_{FF}$=264.0, J_{HF}=11.3 Hz, 1F), –113.9 (dd, $^2J_{FF}$=264.0,

J_{HF}=11.3 Hz, 1F), –118.9 (dd, $^2J_{FF}$=277.4, J_{HF}=13.0 Hz, 1F), –119.7 (dd, $^2J_{FF}$=277.4, J_{HF}=15.6 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 385 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{11}H_{19}F_4NNaO_3S$ $(M + Na)^+$ calcd 344.0914, found 344.0915.

5.7.2.1 (2S,3S,S_S)-3-(tert-Butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene-1,2-diol (l-3.22S)

A sample was purified by HPLC to obtain the minor isomer ***l*-3.22S** in pure form (hexane/acetone 70:30). $\mathbf{R_f}$ 0.31 (petroleum ether 40-60 °C/acetone 60:40). $\mathbf{[\alpha]_D}$ –0.87 (c 0.289, $CHCl_3$, 25 °C). **IR** (neat) 3368 (m), 3280 (m), 1107 (s), 1053 (s), 1036 (s) cm^{-1}. **^{1}H NMR** (400MHz, $CDCl_3$) δ 6.13–5.98 (m, 1H, H-6), 5.94–5.87 (m, 1H, H-7_{trans}), 5.74 (d, $^3J_{HH}$=10.9 Hz, 1H, H-7_{cis}), 4.36 (d, $^3J_{HH}$=9.0 Hz, 1H, NH), 4.28 (qd, *J*=5.8, 2.9 Hz, 1H, H-2), 4.08–3.96 (m, 1H, H-3), 3.71 (dd, $^2J_{HH}$=11.6, $^3J_{HH}$=6.0 Hz, 1H, H-1_a), 3.65 (dd, $^2J_{HH}$=11.6, $^3J_{HH}$=6.4 Hz, 1H, H-1_b), 3.13 (d, $^3J_{HH}$=5.3 Hz, 1H, OH-2), 3.02 (t, $^3J_{HH}$=6.6 Hz, 1H, OH-1), 1.26 ppm (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 126.3 (t, $^2J_{CF}$=24.5 Hz, C-6), 124.4 (t, $^3J_{CF}$=9.5 Hz, C-7), 116.7 (tt, $^1J_{CF}$=256.1, $^2J_{CF}$=35.5 Hz, CF_2), 115.8 (tt, $^1J_{CF}$=249.6, $^2J_{CF}$=35.9 Hz, CF_2), 68.6 (C-2), 63.1 (C-1), 57.7 ($C_{q,tBu}$), 54.7 (t, $^2J_{CF}$=22.7 Hz, C-3), 22.4 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –110.4 (dd, $^1J_{FF}$=279.4, *J*=10.7 Hz, 1F, C<u>F</u>F), –112.7 (d, *J*=11.8 Hz, 2F, CF_2), –117.0 (dd, $^1J_{FF}$=279.4, *J*=16.1 Hz, 1F, CF<u>F</u>) ppm. **MS** (ESI+) (*m/z*) 385 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{11}H_{19}F_4NNaO_3S$ $(M + Na)^+$ calcd 344.0914, found 344.0910.

5.7.3 (S_S)-4-(tert-Butylsulfinylamino)-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-*erythro*-hexopyranose (3.23S)

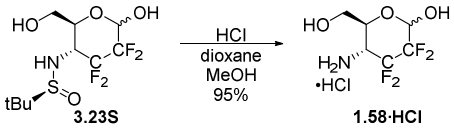


***ul*-3.22S** **3.23S**

Ozone was bubbled through a solution of ***ul*-3.22S** (1.60 g, 4.98 mmol) in MeOH (50 mL) until TLC showed complete consumption of the starting material (15 min). O_2 was bubbled through to remove excess ozone (10 min) and then, Me_2S (1.83 mL, 24.9 mmol, 5 equiv) was added and the reaction mixture was allowed to warm to rt and concentrated to afford 1.56 g (4.83 mmol, 97%) of the pure aminosugar derivative **3.23S**, which solidified as the pure β–anomer. At equilibrium in CD_3OD, a 60:40 α/β mixture of anomers is obtained. $\mathbf{R_f}$ 0.23 (petroleum ether 40-60 °C/acetone 60:40). $\mathbf{[\alpha]_D}$ +97.6 (c 0.469, CH_3OH, 26 °C, at anomeric equilibrium). **IR** (neat) 3245 (m), 2985 (w), 1303 (m), 1151 (m), 1037 (s) cm^{-1}. **^{1}H NMR** (400 MHz, CD_3OD) δ 5.23 (dd,

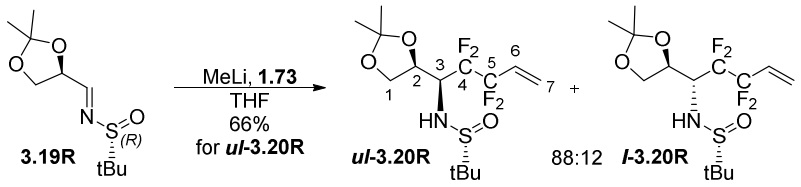
$^{3}J_{HF}$=7.8, 5.5 Hz, 1H, H-1α), 4.90 (dd, $^{3}J_{HF}$=15.5, J_{HF}=2.9 Hz, 1H, H-1β), 4.29–4.18 (m, 1H, H-5α), 3.98–3.76 (m, 6H, H-4α, H-4β, 2 × H-6α, 2 × H-6β), 3.76–3.69 (m, 1H, H-5β), 1.26 (s, 18H, $CH_{3,tBu}$,α+ $CH_{3,tBu}$,β) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 92.9 (ddd, $^{2}J_{CF}$=26.4, $^{2}J_{CF}$=19.4, $^{3}J_{CF}$=2.6 Hz, C-1β), 92.8 (dd, $^{2}J_{CF}$=36.6, $^{2}J_{CF}$=26.3 Hz, C-1α), 75.2 (d, J_{CF}=2.9 Hz, C-5β), 70.6 (d, J_{CF}=4.4 Hz, C-5α), 61.4 (C-6β), 61.3 (C-6α), 59.2 (t, $^{2}J_{CF}$=18.7 Hz, C-4β), 59.0 (t, $^{2}J_{CF}$=17.6 Hz, C-4α), 58.6 (2×$C_{q,tBu}$), 23.2 ($CH_{3,tBu}$,α), 23.2 ($CH_{3,tBu}$,β) ppm (2 × CF_2, α + β not visible). **^{19}F NMR** (376 MHz, CD_3OD) δ –121.3 – –122.3 (m, 1F, Fα), –125.2 (dddd, $^{2}J_{FF}$=258.4, J=21.7, 15.6, 6.9 Hz, 1F, Fα), –125.9 – –126.8 (m, 1F, Fα), –128.2 (dt, $^{2}J_{FF}$=259.2, J=16.5 Hz, 1F, Fβ), –129.1 (dq, $^{2}J_{FF}$=259.2, J=10.4 Hz, 1F, Fβ), –135.8 (ddd, $^{2}J_{FF}$=265.3, J=15.2, 11.7 Hz, 1F, Fα), –138.5 (dt, $^{2}J_{FF}$=257.5, 12.6 Hz, 1F, Fβ), –140.8 – –141.7 (m, 1F, Fβ) ppm. **MS** (ESI+) (*m/z*) 387 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{10}H_{17}F_4NNaO_4S$ $(M + Na)^+$ calcd 346.0707, found 346.0706.

5.7.4 4-Amino-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-*erythro*-hexopyranose hydrochloride (1.58·HCl)



A solution of **3.23S** (700 mg, 2.17 mmol, 1 equiv) in MeOH (1.65 mL) and 4M HCl in dioxane (1.1 mL, 4.33 mmol, 2 equiv) was stirred at rt for 1 h then evaporated *in vacuo* to near dryness. Et_2O (10 mL) was added in order to precipitate the hydrochloride salt and the supernatant was removed. The solid was washed once more with Et_2O (10 mL) then dried under vacuum to yield 525 mg (2.05 mmol, 95%) of the **1.58·HCl** as a white solid consisting only of α-anomer. At equilibrium in CD_3OD, a 75:25 α/β mixture of anomers is obtained. **$[\alpha]_D$** +52.7 (c 0.430, CH_3OH, 26 °C, at anomeric equilibrium). **IR** (neat) 3343 (m, br), 2888 (m, br), 1153 (s), 1111 (s), 1059 (s) cm^{-1}. Data for the α anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 5.33 (dd, J_{HF}=7.3, 4.3 Hz, 1H, H-1), 4.38 (dt, J=10.3, 3.5 Hz, 1H, H-5), 4.07–3.93 (m, 1H, H-4), 3.85 (dd, $^{2}J_{HH}$=12.5, $^{3}J_{HH}$=4.3 Hz, 1H, H-6_a), 3.80 (dd, $^{2}J_{HH}$=12.5, $^{3}J_{HH}$=3.7 Hz, 1H, H-6_b) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 117.9–108.8 (2 × CF_2), 92.6 (dd, $^{2}J_{CF}$=35.6, 26.0 Hz, C-1), 67.9 (d, J_{CF}=2.2 Hz, C-5), 61.7 (C-6), 52.5 (t, $^{2}J_{CF}$=19.1 Hz, C-4) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –121.4 – –122.5 (m, 1F), –124.0 – –125.8 (m, 2F), –137.1 (dt, $^{2}J_{FF}$=267.6, J=12.4 Hz, 1F) ppm. Unambiguous resonances for the β anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 5.06 (d, J_{HF}=14.3 Hz, 1H, H-1). **^{13}C NMR** (101 MHz, CD_3OD) δ 72.4 (s, C-5), 61.8 (s, C-6). **^{19}F NMR** (376 MHz, CD_3OD) δ –127.8 (t, J=12.1 Hz, 2F), –139.6 (dt, $^{2}J_{FF}$=260.1, J=11.3 Hz, 1F), –140.8 (dd, $^{2}J_{FF}$=260.1, J=13.9 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 261 $(M+H+MeCN)^+$. **HRMS** (MS+) for $C_6H_{10}F_4NO_3$ $(M + H)^+$ calcd 220.0591, found 220.0590.

5.7.5 (2*S*,3*S*,R_S)-1,2-Isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene (*ul*-3.20R)



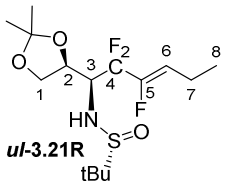
To a solution of sulfinylimine **3.19R** (0.52 g, 2.23 mmol, 1.2 equiv) in THF at –78 °C was added bromotetrafluorobutene **1.73** (0.236 mL, 1.86 mmol, 1.0 equiv). After 10 min, MeLi (1.6 M in Et_2O, 2.8 mL, 4.46 mmol, 2.4 equiv) was added over 45 min and the reaction mixture was stirred for another 1.5 h. The reaction was quenched with saturated NH_4Cl aq. (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude mixture of diastereoisomers ***ul*-3.20R** and ***l*-3.20R** (*dr* 88:12). Purification via column chromatography (petroleum ether/EtOAc 75:25) afforded 442 mg (1.22 mmol, 66%) of pure ***ul*-3.20R** as a white solid. $\mathbf{R_f}$ 0.29 (petroleum Ether 40-60 °C/EtOAc 70:30). $\mathbf{[\alpha]_D}$ –77.6 (c 0.502, $CHCl_3$, 19 °C). **IR** (neat) 3347 (w), 2982 (w), 1189 (m), 1109 (s), 1073 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.98 (ddd, $^3J_{HF}$=22.6, $^3J_{HH,trans}$=17.3, $^3J_{HH,cis}$=10.9 Hz, 1H, H-6), 5.90–5.81 (m, 1H, H-7_{trans}), 5.69 (d, $^3J_{HH,cis}$=10.9 Hz, 1H, H-7_{cis}), 4.54 (t, *J*=6.9 Hz, 1H, H-2), 4.31 (d, *J*=7.3 Hz, 1H, NH), 4.17 (app. t, *J*=8.2 Hz, 1H, H-1_a), 4.07 (dd, $^2J_{HH}$=8.5, $^3J_{HH}$=6.7 Hz, 1H, H-1_b), 3.82 (td, *J*=12.9, 7.6 Hz, 1H, H-3), 1.46 (s, 3H, $CH_{3,iPr}$), 1.37 (s, 3H, $CH_{3,iPr}$), 1.25 ppm (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 126.5 (t, $^2J_{CF}$=24.2 Hz, C-6), 124.0 (t, $^3J_{CF}$=9.5 Hz, C-7), 115.7 (tt, $^1J_{CF}$=256.1, $^2J_{CF}$=35.1 Hz, CF_2), 115.5 (tt, $^1J_{CF}$=250.3, $^2J_{CF}$=35.1 Hz, CF_2), 110.2 ($C_{q,iPr}$), 71.3 (C-5), 66.2 (C-1), 56.7 ($C_{q,tBu}$), 56.1 (t, $^2J_{CF}$=23.4 Hz, C-3), 26.2 ($CH_{3,iPr}$), 25.3 ($CH_{3,iPr}$), 22.6 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –112.3 (dd, $^2J_{FF}$=265.3, *J*=11.3 Hz, 1F), –113.1 (dd, $^2J_{FF}$=265.3, *J*=11.3 Hz, 1F), –117.2 (dd, $^2J_{FF}$=277.4, *J*=13.9 Hz, 1F), –118.3 (ddd, $^2J_{FF}$=277.4, *J*=12.1, 3.5 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 425 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{14}H_{23}F_4NNaO_3S$ $(M + Na)^+$ calcd 384.1227, found 384.1230.

*5.7.5.1 (2*S*,3*R*,R_S)-1,2-Isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene (**l-3.20R**)*

The minor isomer could be isolated along with the MeLi S_N2' byproduct and some unknown impurity (53 mg, 76:9:15 ratio). Selected characterization data: $\mathbf{R_f}$ 0.17 (petroleum ether 40-60 °C/EtOAc 70:30). **^{1}H NMR** (400MHz, $CDCl_3$) δ 6.14–5.98 (m, 1H, H-6), 5.93–5.85 (m, $^3J_{HH,trans}$=17.5 Hz, 1H, H-7_{trans}), 5.73 (d, $^3J_{HH,cis}$=10.9 Hz, 1H, H-7_{cis}), 4.50–4.43 (m, 1H, H-2), 4.24–4.12 (m, 1H, H-3), 3.98 (app. t, *J*=7.5 Hz, 1H, H-1_a), 3.79 (app. t, *J*=7.8 Hz, 1H, H-1_b), 3.73 (d,

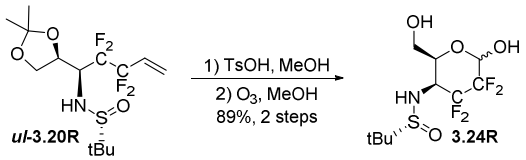
$^{3}J_{HH}$=7.6 Hz, 1H, NH), 1.40 (s, 3H, $CH_{3,iPr}$), 1.32 (s, 3H, $CH_{3,iPr}$), 1.24 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 125.9 (t, $^{2}J_{CF}$=24.2 Hz, C-6), 124.9 (t, $^{3}J_{CF}$=9.5 Hz, C-7), 115.7 (tt, $^{1}J_{CF}$=256.4, $^{2}J_{CF}$=35.6 Hz, CF_2), 115.6 (tt, $^{1}J_{CF}$=249.4, $^{2}J_{CF}$=33.7 Hz, CF_2), 109.0 ($C_{q,iPr}$), 73.3 (C-2), 64.8 (C-1), 57.5 (t, $^{2}J_{CF}$=23.1 Hz, C-3), 57.0 ($C_{q,tBu}$), 26.0 ($CH_{3,iPr}$), 24.6 ($CH_{3,iPr}$), 22.5 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –111.3 (m, $^{2}J_{FF}$=264.9 Hz, 1F), –113.3 (ddt, $^{2}J_{FF}$=264.9, *J*=12.1, 6.5 Hz, 1F), –114.6 (ddt, $^{2}J_{FF}$=278.5, *J*=12.6, 5.6 Hz, 1F), –117.4 (ddt, $^{2}J_{FF}$=278.5, *J*=14.5, 6.1 Hz, 1F) ppm.

*5.7.5.2 (2S,3S,R$_s$,Z)-1,2-Isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5-trifluorooct-5-ene (***ul-*3.21R*)**



Selected data for the MeLi S_N2' byproduct: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.42 (dt, $^{3}J_{HF,trans}$=35.9, $^{3}J_{HH}$=7.6 Hz, 1H, H-6), 2.28–2.15 (m, 2H, H-7), 1.05 (t, $^{3}J_{HH}$=7.5 Hz, 3H, H-8) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 16.7 (d, $^{4}J_{CF}$=4.0 Hz, C-7), 13.0 (C-8) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –107.2 (app. dt, $^{2}J_{FF}$=264.4, *J*=13.9 Hz, 1F, F-4), –112.8 (app. dt, $^{2}J_{FF}$=264.4, *J*=13.9 Hz, 1F, F-4'), –130.8 (app. dt, $^{3}J_{HF,trans}$=35.5, *J*=14.7 Hz, 1F, F-3) ppm. The stereochemistry at C-3 is presumed.

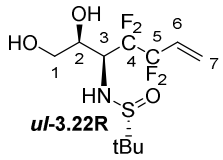
5.7.6 (*R*$_s$)-4-(tert-Butylsulfinylamino)-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-*threo*-hexopyranose (3.24R)



A mixture of sulfinamine ***ul*-3.20R** (435 mg, 1.20 mmol, 1 equiv) and PTSA (41 mg, 0.24 mmol, 0.2 equiv) in MeOH (10 mL) was stirred for 13.5 h then quenched with sat. aq. $NaHCO_3$ (3 mL). H_2O (12 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), filtered and concentrated to afford 383 mg of the crude product ***ul*-3.22R**. The latter was dissolved in MeOH (15 mL) and ozone was bubbled through the solution until blue colour appeared (15 min). O_2 was bubbled through to remove excess ozone (10 min) and then, Me_2S (0.44 mL, 6.0 mmol, 5 equiv) was added and the reaction mixture was allowed to warm to rt and concentrated. Purification via column chromatography (petroleum ether/acetone 70:30 to 60:40) afforded 348 mg (1.01 mmol, 89%) of the pure aminosugar derivative **3.24R,** as a white solid enriched in β-anomer. At equilibrium in both acetone-d_6 and CD_3OD, a 50:50 α/β mixture of anomers was obtained. **R_f** 0.19 (petroleum ether 40-60 °C/acetone 60:40). **$[\alpha]_D$** +20.0 (c 0.627, CH_3OH, 26 °C, at anomeric equilibrium). **IR** (neat) 3487 (w), 3287 (m), 2975 (w), 1041 (s), 1005 (s) cm^{-1}. **^{1}H NMR** (400 MHz,

acetone-d_6) δ 5.36 (dd, *J*=9.3, 6.4 Hz, 1H, H-1α), 5.11 (ddd, *J*=14.7, 3.9, 0.7 Hz, 1H, H-1β), 4.61–4.53 (m, 1H, H-5α), 4.51–4.41 (m, 2H, NHα, NHβ), 4.35–4.16 (m, 2H, 2×OH-6), 4.16–4.03 (m, 3H, H-4α, H-4β, H-5β), 3.82–3.64 (m, 4H, 2 × H-6α, 2 × H-6β), 1.26 (s, 9H, tBu,β), 1.25 (s, 9H, tBu,α) ppm. **^{13}C NMR** (101 MHz, acetone-d_6) δ 93.2 (ddd, $^2J_{CF}$=27.1, 19.8, $^3J_{CF}$=3.7 Hz, C-1β), 92.7 (dd, $^2J_{CF}$=36.6, 26.3 Hz, C-1α), 73.6 (d, $^3J_{CF}$=4.4 Hz, C-5β), 68.4 (d, $^3J_{CF}$=2.9 Hz, C-5α), 60.5 (C-6α), 60.2 (C-6β), 59.8 (dd, $^2J_{CF}$=30.7, 19.0 Hz, C-4α), 59.5 (dd, $^2J_{CF}$=29.3, 17.6 Hz, C-4β), 57.4 ($C_{q,tBu}$,β), 57.4 ($C_{q,tBu}$,α), 22.8 (6×$CH_{3,tBu}$,α+β) ppm (2×CF_2, α + β not visible). **^{19}F NMR** (376 MHz, CD_3OD) δ –116.6 (ddtd, $^2J_{FF}$=260.5, *J*=15.2, 9.1, 2.2 Hz, Fα), –118.2 (m, $^2J_{FF}$=261.8 Hz, Fβ), –119.1 (dddd, $^2J_{FF}$=269.6, *J*=19.5, 9.5, 9.1 Hz, Fα), –126.3 (m, $^2J_{FF}$=260.5 Hz, Fα), –128.9 (m, $^2J_{FF}$=261.8 Hz, Fβ), –134.6 (dddd, $^2J_{FF}$=269.6, *J*=16.0, 11.3, 5.2 Hz, Fα), –137.4 (m, $^2J_{FF}$=263.1 Hz, Fβ), –138.5 (dddd, $^2J_{FF}$=263.1, *J*=17.8, 14.3, 6.9 Hz, Fβ) ppm. **MS** (ESI+) (*m/z*) 387 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{10}H_{17}F_4NNaO_4S$ $(M + Na)^+$ calcd 346.0707, found 346.0713.

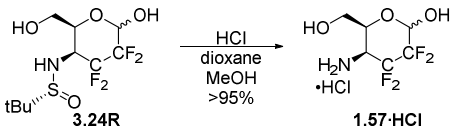
*5.7.6.1 (2S,3S,R$_S$)-3-(tert-Butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene-1,2-diol (***ul-*3.22R*)**



***ul*-3.22R**

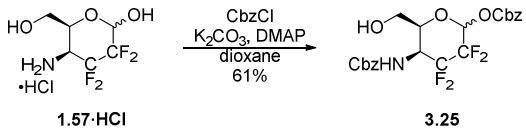
Analytical sample of the pure diol was obtained by column chromatography (petroleum ether 40-60 °C/acetone 70:30). **R_f** 0.25 (petroleum ether 40-60 °C/acetone 60:40). **$[\alpha]_D$** –44.8 (c 0.532, $CHCl_3$, 21 °C). **IR** (neat) 3299 (m), 2963 (w), 1237 (m), 1116 (s), 1028 (s) cm^{-1}. **^{1}H NMR** (400 MHz, CD_3OD) δ ppm 6.19– 6.03 (m, 1H, H-6), 5.87 (dt, $^3J_{HH,trans}$=17.3, $^4J_{HF}$=2.3 Hz, 1H, H-7_{trans}), 5.77 (d, $^3J_{HH,cis}$=11.1 Hz, 1H, H-7_{cis}), 4.15 (dd, $^3J_{HH}$=8.5, 5.9 Hz, 1H, H-2), 4.03 (t, $^3J_{HF}$=13.6 Hz, 1H, H-3), 3.62 (dd, $^2J_{HH}$=10.9, $^3J_{HH}$=8.5 Hz, 1H, H-1_a), 3.54 (dd, $^2J_{HH}$=10.9, $^3J_{HH}$=5.9 Hz, 1H, H-1_b), 1.26 (s, 9H). **^{13}C NMR** (101 MHz, CD_3OD) δ 128.5 (t, $^2J_{CF}$=24.2 Hz, C-6), 124.8 (t, $^3J_{CF}$=9.5 Hz, C-7), 118.1 (tt, $^1J_{CF}$=255.4, $^2J_{CF}$=33.7 Hz, CF_2), 117.2 (tt, $^1J_{CF}$=248.8, $^2J_{CF}$=34.4 Hz, CF_2), 68.4 (C-2), 63.2 (C-1), 58.6 (t, $^2J_{CF}$=22.7 Hz, C-3), 58.3 ($C_{q,tBu}$), 23.1 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (282 MHz, CD_3OD) δ –112.8 (dd, $^2J_{FF}$=265.7, 11.8 Hz, 1F), –113.8 (dd, $^2J_{FF}$=265.7, 10.7 Hz, 1F), –117.2 (dd, $^2J_{FF}$=274.0, 14.0 Hz, 1F), –119.3 (dd, $^2J_{FF}$=274.0, 12.9 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 385 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{11}H_{19}F_4NNaO_3S$ $(M + Na)^+$ calcd 344.0914, found 344.0909.

5.7.7 4-Amino-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-*threo*-hexopyranose hydrochloride (1.57·HCl)



A solution of sulfinamide **3.24R** (190 mg, 0.588 mmol, 1 equiv) in MeOH (1.2 mL) and 4M HCl in dioxane (0.60 mL, 2.35 mmol, 4 equiv) was stirred at rt for 0.5 h then evaporated *in vacuo*. The residue was coevaporated with MeOH (10 × 20 mL) then diluted in H_2O (15 mL), washed with Et_2O (2 × 5 mL) and concentrated to afford 153 mg of the amine hydrochloride **1.57·HCl** along with less than 3% of impurities as a colourless oil. Anomeric ratio at equilibrium in CD_3OD: 54:46 α/β. Approximated yield >95%. **IR** (neat) 3210 (m, br), 2886 (m), 1526 (m), 1109 (s), 1029 (s) cm^{-1}. **^{1}H NMR** (400MHz, CD_3OD) δ 5.39 (dd, *J*=8.5, 7.1 Hz, 1H, H-1α), 5.12 (dd, *J*=15.0, 3.1 Hz, 1H, H-1β), 4.66–4.57 (m, 1H, H-5α), 4.34–4.20 (m, 2H, H-4α, H-4β), 4.19–4.10 (m, 1H, H-5β), 3.96–3.71 (m, 4H, 2 × H-6α, 2 × H-6β) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 117.5–108.7 (2 × CF_2, α+β), 93.5 (ddd, $^2J_{CF}$=26.4, 19.0, $^3J_{CF}$=3.4 Hz, C-1β), 92.9 (dd, $^2J_{CF}$=36.7, 24.9 Hz, C-1α), 72.0 (d, J_{CF}=4.4 Hz, C-5β), 66.7 (d, J_{CF}=3.7 Hz, C-5α), 60.9 (C-6α), 60.7 (C-6β), 54.3 (dd, $^2J_{CF}$=33.4, 19.4 Hz, C-4α), 53.9 (dd, $^2J_{CF}$=32.6, 19.4 Hz, C-4β) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –116.9 (app. ddt, $^2J_{FF}$=274.0, *J*=15.9, 9.2, Hz, Fα), –118.1 – –118.9 (m, Fβ), –119.5 (ddt, $^2J_{FF}$=273.8, $^3J_{FF}$=17.5, $^3J_{FF}$=8.7, J_{HF}=8.7 Hz, Fα), –125.3 – –126.3 (m, Fα), –127.8 – –128.7 (m, Fβ), –136.0 (dddd, $^2J_{FF}$=273.8, $^3J_{FF}$=16.2, $^3J_{FF}$=10.3, J_{HF}=4.2 Hz, Fα), –137.9 (app. dtd, $^2J_{FF}$=267.5, *J*=15.4, 6.6 Hz, Fβ), –139.2 (m, $^2J_{FF}$=267.5 Hz, Fβ) ppm. **{^{1}H} ^{19}F NMR** (376 MHz, CD_3OD) δ –116.8 (ddd, $^2J_{FF}$=274.0, $^3J_{FF}$=16.1, $^3J_{FF}$=8.6 Hz, Fα), –118.5 (ddd, $^2J_{FF}$=275.0, $^3J_{FF}$=13.4, $^3J_{FF}$=6.4 Hz, Fβ), –119.4 (ddd, $^2J_{FF}$=273.9, $^3J_{FF}$=17.3, $^3J_{FF}$=8.5 Hz, Fα), –125.8 (ddd, $^2J_{FF}$=274.0, $^3J_{FF}$=17.3, $^3J_{FF}$=10.3 Hz, Fα), –128.3 (ddd, $^2J_{FF}$=275.2, $^3J_{FF}$=15.6, $^3J_{FF}$=10.5 Hz, Fβ), –136.0 (ddd, $^2J_{FF}$=273.8, $^3J_{FF}$=16.1, $^3J_{FF}$=10.3 Hz, Fα), –138.3 – –137.5 (m, Fβ), –139.2 (ddd, $^2J_{FF}$=267.5, $^3J_{FF}$=13.4, $^3J_{FF}$=10.5 Hz, Fβ) ppm. **MS** (ESI+) (*m/z*) 220 $(M+H)^+$. **HRMS** (MS+) for $C_6H_{10}F_4NO_3$ $(M + H)^+$ calcd 220.0591, found 220.0596.

5.7.8 4-Amino-1,4-*O*,*N*-dicarboxybenzyl-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-*threo*-hexopyranose hydrochloride (3.25)



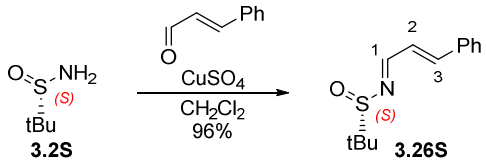
To the amine hydrochloride **1.57·HCl** (122 mg, 0.477 mmol, 1 equiv) in dry dioxane (3 mL) was added K_2CO_3 (198 mg, 1.43 mmol, 3 equiv), benzylchloroformate (0.341 mL, 2.39 mmol, 5

equiv) and DMAP (5.8 mg, 0.048 mmol, 0.1 equiv) and the resultant mixture was stirred at rt for 4 h. Brine was added and the aqueous phase was extracted with EtOAc. The combined organic layers were dried, filtered and concentrated. Column chromatography (petroleum ether 40-60 °C/acetone 80:20 to 70:30) afforded 141 mg (0.289 mmol, 61%) of the product **3.25** as a 1:1 anomeric mixture.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.33 (m, 10H), 6.14 (dd, *J*=8.7, 5.7 Hz, 1H, H-1α), 5.80 (dd, *J*=15.3, 3.5 Hz, 1H, H-1β), 5.33 – 5.11 (m, 6H, 2 × CH_2Ph, 2 × NH), 4.67 – 4.56 (m, 2H, 2 × H-4), 4.45 (br t, *J*=6.0 Hz, 1H, H-5), 4.13 – 4.05 (m, 1H, H-5), 3.82 – 3.53 (m, 4H, 2 × H-6_a, 2 × H-6_b), 2.82 – 2.72 (m, 2H, 2 × OH-6) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9 (C=O), 156.8 (C=O), 152.6 (C=O), 135.3, 134.0, 133.8, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 128.2, 92.8 – 91.5 (m, 2C, 2 × C-1), 74.4 (d, *J*=3.7 Hz, C-5), 71.3 (CH_2Ph), 71.1 (CH_2Ph), 71.1 (d, *J*=4.4 Hz, C-5), 68.1 (2 × CH_2Ph), 59.7 (C-6), 59.6 (C-6), 52.8 (dd, *J*=31.9, 18.0 Hz, C-2) ppm (1 × C-2 not visible). **^{19}F NMR** (376 MHz, $CDCl_3$) δ –117.0 – –119.1 (m, 4F), –127.6 – –128.7 (m, 1F), –129.5 (dt, *J*=267.7, 12.1 Hz, 1F), –134.0 – –135.0 (m, 1F), –137.3 (dt, *J*=266.9, 10.3 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 488 $(M+H)^+$. **HRMS** (MS+) for $C_{22}H_{21}F_4NNaO_7$ $(M + Na)^+$ calcd 510.1146, found 510.1156.

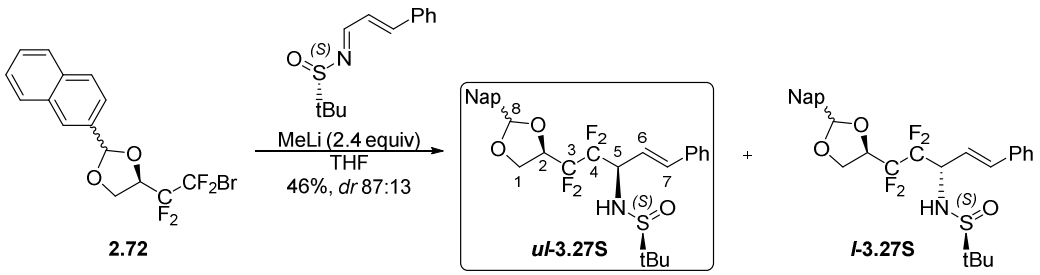
5.8 3,3,4,4-Tetrafluoro-2-aminosugars

5.8.1 (*S*)-N-[(E)-3-phenylprop-2-enylidene]-*tert*-butanesulfinamide (3.26S)



To cinnamaldehyde (1.05 g, 7.95 mmol) in CH_2Cl_2 (4.0 mL) were added (*S*)-2-methyl-2-propanesulfinamide (1.06 g, 8.74 mmol, 1.1 equiv) and $CuSO_4$ (2.79 g, 17.5 mmol, 2.2 equiv). The resultant mixture was stirred at rt for 22 h then filtered over Celite® to afford the desired crude product. Purification over a short pad of silica eluting with PE/EtOAc 80:20 yielded **3.26S** (1.80 g, 7.63 mmol, 96%) as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, *J*=9.1 Hz, 1H, H-1), 7.58 – 7.51 (m, 2H, H_{Ar}), 7.45 – 7.35 (m, 3H, H_{Ar}), 7.25 (d, *J*=15.9 Hz, 1H, H-3), 7.09 (dd, *J*=15.9, 9.1 Hz, 1H, H-2), 1.25 (s, 9H, 3 × CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8, 146.3, 135.0, 130.2, 128.9, 127.9, 125.6, 57.5, 22.5 ppm. The spectral data matched the literature for **3.56R**.[114]

5.8.2 (2*R*,5*R*,*S*$_S$)-3,3,4,4-Tetrafluoro-1,2-(2-naphthylmethylidenedioxy)-7-phenyl-5-(*tert*-butylsulfinylamino)-hept-6-ene (*ul*-3.27S)



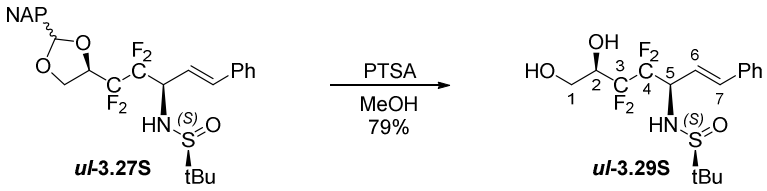
To a solution of bromide **2.72** (300 mg, 0.791 mmol, 1 equiv) and sulfinylimine (0.447 g, 1.90 mmol, 2.4 equiv) in THF (4 mL) at –78 °C was added dropwise MeLi (1.6 M in Et_2O, 1.19 mL, 1.90 mmol, 2.4 equiv) and the reaction mixture was stirred at –78 °C for 2.5 h. The reaction was quenched with saturated NH_4Cl aq. (7 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* (crude *dr* 87:13). Purification by column chromatography (toluene/Et_2O, 80:20) afforded 194 mg (0.362 mmol, 46%) of ***ul*-3.27S**/***l*-3.27S** as 95:5 mixture of diastereoisomers and a white solid. HPLC (toluene/EtOAc) afforded each naphthylmethylidene diastereoisomer of ***ul*-3.27S** pure for a total mass of 114 mg (0.213 mmol, 27%).

Dia 1: $\mathbf{R}_f$ 0.34 (toluene/EtOAc 85:15). $\mathbf{[\alpha]_D}$ +66.2 (c 0.136, $CHCl_3$, 23 °C). **IR** (neat) 3200 (br, w), 2956 (w), 1178 (m), 1088 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.81 (m, 4H, $CH_{Ar,NAP}$), 7.59 – 7.48 (m, 3H, $CH_{Ar,NAP}$), 7.42 – 7.23 (m, 5H, $CH_{Ar,Ph}$), 6.84 (d, $^3J_{HH}$=15.9 Hz, 1H, H-7), 6.29 (dd, $^3J_{HH}$=15.9, 7.7 Hz, 1H, H-6), 6.05 (s, 1H, H-8), 4.82 – 4.65 (m, 2H, H-2, H-5), 4.46 (dd, $^2J_{HH}$=8.9, $^3J_{HH}$=7.4 Hz, 1H, H-1$_a$), 4.28 (dd, $^2J_{HH}$=8.9, $^3J_{HH}$=6.8 Hz, 1H, H-1$_b$), 3.56 (d, $^3J_{HH}$=8.3 Hz, 1H, NH), 1.26 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.6 (C-7), 135.6 ($C_{q,Ar}$), 134.1 ($C_{q,Ar}$), 133.1 ($C_{q,Ar}$), 132.7 ($C_{q,Ar}$), 128.6 (2C, CH_{Ar}), 128.5 (2C, CH_{Ar}), 128.3 (CH_{Ar}), 127.7 (CH_{Ar}), 126.9 (2C, CH_{Ar}), 126.8 (2C, CH_{Ar}), 126.4 (CH_{Ar}), 123.5 (CH_{Ar}), 121.2 (br. s, C-6), 116.5 (tt, $^1J_{CF}$=258.3, $^2J_{CF}$=32.3 Hz, CF_2), 116.4 (tt, $^1J_{CF}$=256.8, $^2J_{CF}$=30.1 Hz, CF_2), 105.8 (C-8), 72.5 (dd, $^2J_{CF}$=28.6, 23.5 Hz, C-2), 65.2 (q, *J*=3.7 Hz, C-1), 60.4 (t, $^2J_{CF}$=23.5 Hz, C-5), 57.0 ($C_{q,tBu}$), 22.4 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –116.5 (dd, $^2J_{FF}$=273.1, *J*=10.4 Hz, 1F), –121.9 – – 123.6 (m, 3F) ppm. **MS** (ESI+) *m/z* 536 $(M + H)^+$. **HRMS** (MS+) for $C_{28}H_{30}F_4NO_3S$ $(M + H)^+$ calcd 536.1877, found 536.1879.

Dia 2: $\mathbf{R}_f$ 0.26 (toluene/EtOAc 85:15). $\mathbf{[\alpha]_D}$ +34.5 (c 0.232, $CHCl_3$, 23 °C). **IR** (neat) 3200 (br, w), 2956 (w), 1178 (m), 1088 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (br. s, 1H, $CH_{Ar,NAP}$), 7.82 (br. d, *J*=8.8 Hz, 2H, $CH_{Ar,NAP}$), 7.76 (d, *J*=8.5 Hz, 1H, $CH_{Ar,NAP}$), 7.58 (dd, *J*=8.5, 1.3 Hz, 1H, $CH_{Ar,NAP}$),

7.56 – 7.44 (m, 2H, $CH_{Ar,NAP}$), 7.30 – 7.16 (m, 5H, $CH_{Ar,Ph}$), 6.64 (d, $^3J_{HH}$=15.9 Hz, 1H, H-7), 6.22 (dd, $^3J_{HH}$=15.9, 7.3 Hz, 1H, H-6), 6.02 (s, 1H, H-8), 4.78 – 4.63 (m, 2H, H-2, H-5), 4.56 (dd, $^2J_{HH}$=9.3, $^3J_{HH}$=3.6 Hz, 1H, H-1_a), 4.25 (dd, $^2J_{HH}$=9.3, $^3J_{HH}$=7.8 Hz, 1H, H-1_b), 3.47 (d, $^3J_{HH}$=8.1 Hz, 1H, NH), 1.25 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.5 (C-7), 135.7 ($C_{q,Ar}$), 134.1 ($C_{q,Ar}$), 132.8 ($C_{q,Ar}$), 132.7 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 128.43 (2C, CH_{Ar}), 128.37 (CH_{Ar}), 128.3 (CH_{Ar}), 127.8 (CH_{Ar}), 127.0 (CH_{Ar}), 126.9 (CH_{Ar}), 126.7 (2C, CH_{Ar}), 126.3 (CH_{Ar}), 123.7 (CH_{Ar}), 121.2 (app. q, *J*=3.3 Hz, C-6), 106.1 (C-8), 72.9 (dd, $^2J_{CF}$=33.0, 21.3 Hz, C-2), 65.6 (app. q, *J*=3.3 Hz, C-1), 60.0 (dd, $^2J_{CF}$=24.2, 22.0 Hz, C-5), 57.0 ($C_{q,tBu}$), 22.4 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –116.1 (dd, $^2J_{FF}$=272.2, *J*=10.4 Hz, 1F), –120.4 (d, $^2J_{FF}$=275.7 Hz, 1F), –122.2 (ddd, $^2J_{FF}$=272.2, *J*=15.6, 5.2 Hz, 1F), –125.6 (dd, $^2J_{FF}$=275.7, *J*=17.3 Hz, 1F) ppm. **MS** (ESI+) *m/z* 536 $(M + H)^+$. **HRMS** (MS+) for $C_{28}H_{30}F_4NO_3S$ $(M + H)^+$ calcd 536.1877, found 536.1881.

5.8.3 (2*R*,5*R*,S_s)-3,3,4,4-Tetrafluoro-7-phenyl-5-(*tert*-butylsulfinylamino)-hept-6-ene-1,2-diol (*ul*-3.29S)

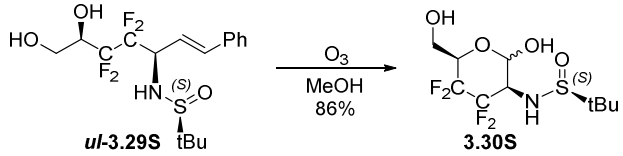


A mixture of sulfinylamine ***ul*-3.27S** (114 mg, 0.213 mmol, 1 equiv) and PTSA (7.3 mg, 0.043 mmol, 0.2 equiv) in CH_2Cl_2/MeOH (1:1, 4 mL) was stirred for 4 h then quenched with sat. aq. $NaHCO_3$ (5 mL). H_2O (5 mL) was added and the mixture was extracted with EtOAc (4 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 70:30 to 60:40) afforded 67 mg (0.17 mmol, 80%) of ***ul*-3.29S** as a white solid.

R_f 0.29 (petroleum ether 40–60 °C/acetone, 60:40). **$[\alpha]_D$** +53.8 (c 0.492, acetone, 22 °C). **IR** (neat) 3344 (br, w), 2943 (w), 1091 (m), 1023 (s) cm^{-1}. **^{1}H NMR** (400 MHz, acetone-*d*6) δ 7.48 – 7.41 (m, 2H, H_{Ar}), 7.35 (br. t, *J*=7.4 Hz, 2H, H_{Ar}), 7.31 – 7.24 (m, 1H, H_{Ar}), 6.90 (d, $^3J_{HH,trans}$=16.0 Hz, 1H, H-7), 6.39 (dd, $^3J_{HH,trans}$=16.0, $^3J_{HH}$=7.4 Hz, 1H, H-6), 5.27 (d, $^3J_{HH}$=6.5 Hz, 1H, OH-2), 4.94 (d, $^3J_{HH}$=8.9 Hz, 1H, NH), 4.81 (dddd, $^3J_{HF}$=15.2, $^3J_{HF}$=11.6, $^3J_{HH}$=8.9, $^3J_{HH}$=7.4 Hz, 1H, H-5), 4.26 – 4.13 (m, 1H, H-2), 4.08 (br. t, $^3J_{HH}$=5.3 Hz, 1H, OH-1), 3.91 – 3.81 (m, 1H, H-1_a), 3.77 – 3.68 (m, 1H, H-1_b), 1.23 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, acetone-*d*6) δ 137.5 ($C_{q,Ar}$), 135.8 (C-7), 129.0 (CH_{Ar}), 129.6 (CH_{Ar}), 127.6 (CH_{Ar}), 124.1 – 123.9 (C-6), 121.2 – 114.9 (2 × CF_2), 71.8 (dd, $^2J_{CF}$=27.1, 22.7 Hz, C-2), 61.9 (t, $^2J_{CF}$=23.8 Hz, C-5), 61.5 – 61.2 (C-1), 57.3 ($C_{q,tBu}$), 23.0 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, acetone-*d*6) δ –116.8 (dd, $^2J_{CF}$=269.0, *J*=11.6 Hz, 1F, F-4_a), –118.4 (br.

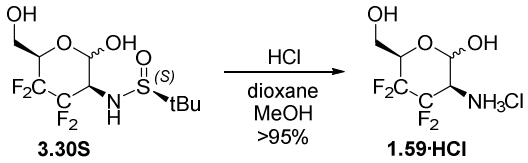
d, $^2J_{CF}$=274.2 Hz, 1F, F-3$_a$), –119.8 (dd, $^2J_{CF}$=269.0, *J*=15.2 Hz, 1F, F-4$_b$), –123.8 (dd, $^2J_{CF}$=274.2, *J*=18.8 Hz, 1F, F-3$_b$) ppm. **MS** (ESI+) *m/z* 398 $(M + H)^+$. **HRMS** (MS+) for $C_{17}H_{24}F_4NO_3S$ (M + H)+ calcd 398.1408, found 398.1414.

5.8.4 (S_s)-2-(*tert*-Butylsulfinylamino)-2,3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose (3.30S)



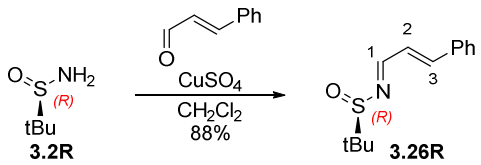
Ozone was bubbled through a solution of alkene ***ul*-3.29S** (67 mg, 0.17 mmol) in MeOH (4 mL) until a light blue colour was obtained (10 min). O_2 was bubbled through to remove excess ozone (10 min) and then, Me_2S (0.062 mL, 0.84 mmol, 5 equiv) was added and the reaction mixture was allowed to warm to rt and concentrated. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 70:30 to 50:50) afforded 47 mg (0.15 mmol, 86%) of **3.30S** as a white solid. **Rf** 0.35 (petroleum ether 40–60 °C/acetone, 60:40). **IR** (neat) 3279 (br, w), 2962 (w), 1105 (m), 1037 (s) cm^{-1}. **^{1}H NMR** (400 MHz, acetone-*d*6) δ 6.44 (br. s, 1H, OH-1α), 6.60 (br. s, 1H, OH-1β), 5.45 (d, *J*=5.0 Hz, 1H, H-1α), 5.21 (br. s, 1H, H-1β), 4.50 – 4.38 (m, 1H, H-5α), 4.38 – 4.11 (m, 5H, H-2β, NHα+β, OH-6α+β), 4.08 – 3.95 (m, 1H, H-5β), 3.95 – 3.86 (m, 3H, H-2α, H-6$_a$α+β), 3.86 – 3.75 (m, 1H, H-6$_b$α+β), 1.25 (s, 9H, $CH_{3,tBu}$β), 1.21 (s, 9H, $CH_{3,tBu}$α) ppm. **^{13}C NMR** (101 MHz, acetone-*d*6) δ 117.3 – 110.7 (m, 2 × CF_2), 95.4 (d, $^3J_{CF}$=4.4 Hz, C-1α), 93.4 (d, $^3J_{CF}$=6.6 Hz, C-1β), 75.3 (t, $^2J_{CF}$=24.6 Hz, C-5β), 70.4 (t, $^2J_{CF}$=23.9 Hz, C-5α), 62.7 (dd, $^2J_{CF}$=29.3, 16.9 Hz, C-2β), 62.0 (dd, $^2J_{CF}$=27.9, 17.6 Hz, C-2α), 59.1 – 58.9 (m, C-6α or β), 58.8 – 58.6 (m, C-6α or β), 57.4 ($C_{q,tBu}$α), 57.3 ($C_{q,tBu}$β), 22.7 ($CH_{3,tBu}$α), 22.6 ($CH_{3,tBu}$β) ppm. **^{19}F NMR** (376 MHz, acetone-*d*6) δ –114.9 (br. d, $^2J_{FF}$=261.3 Hz, 1Fα), –117.2 (br. d, $^2J_{FF}$=262.4 Hz, 1Fβ), –126.4 (app. dtt, $^2J_{FF}$=260.1, *J*=11.8, 6.3 Hz, 1Fα), –127.3 – –128.1 (m, $^2J_{FF}$=261.9 Hz, 1Fβ), –129.8 (dddd, $^2J_{FF}$=265.0, *J*=23.5, 16.9, 8.9 Hz, 1Fβ), –130.3 – –130.5 (m, 2Fα), –133.2 – –132.7 (m, 1Fβ) ppm. **MS** (ESI+) *m/z* 324 $(M + H)^+$. **HRMS** (MS+) for $C_{10}H_{18}F_4NO_4S$ (M + H)+ calcd 324.0887, found 324.0879.

5.8.5 2-Amino-2,3,4-dideoxy-3,3,4,4-tetrafluoro-D-*threo*-hexopyranose hydrochloride (1.59·HCl)



To a solution of **3.30S** (117 mg, 0.362 mmol, 1 equiv) in dry MeOH (0.72 mL) was added dropwise a solution of 4M HCl in dioxane (0.36 mL, 1.45 mmol, 4 equiv) and the reaction was stirred at rt for 0.75 h then evaporated *in vacuo*. The crude was dissolved in H_2O (15 mL), washed twice in Et_2O (5 mL) and evaporated to afford 90 mg (0.352 mmol, 97%) of the aminosugar **1.59·HCl** as the hydrochloride salt. (α/β 26:74, CD_3OD). **^{1}H NMR** (400 MHz, CD_3OD) δ 5.44 (br d, *J*=5.3 Hz, 1H, C-1α), 5.37 (br s, 1H, C-1β), 4.55 – 4.43 (m, 1H, H-5α), 4.24 (dtd, *J*=9.2, 4.5, 1.8 Hz, 1H, H-2β), 4.13 – 4.00 (m, 2H, H-2α and H-5β), 3.99 – 3.91 (m, 2H, H-6_a α and β), 3.86 (dd, *J*=12.1, 6.6 Hz, 1H, H-6_bβ), 3.90 – 3.83 (m, 1H, H-6_bα) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 117.0 – 110.5 (2 × CF_2, α and β), 92.4 (d, *J*=8.1 Hz, C-1β), 92.1 (d, *J*=4.4 Hz, C-1α), 74.6 (dd, *J*=25.3, 21.6 Hz, C-5β), 70.7 (br t, *J*=23.8 Hz, C-5α), 59.0 – 58.8 (C-6β), 58.7 – 58.5 (C-6α), 56.0 (dd, *J*=33.4, 18.7 Hz, C-2β), 55.6 (dd, *J*=29.7, 18.7 Hz, C-2α) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –115.8 (br d, *J*=273.1 Hz, 1Fα), –117.4 – –118.4 (m, *J*=277.4 Hz, 1Fβ), –126.5 – –127.4 (m, *J*=273.1 Hz, 1Fα), –127.7 – –128.7 (m, *J*=277.4 Hz, 1Fβ), –130.4 (dddd, *J*=268.8, 24.3, 15.6, 9.5 Hz, 1Fβ), –130.3 – –131.2 (m, *J*=271.4 Hz, 1Fα), –132.1 (br d, *J*=271.4 Hz, 1Fα), –136.9 (br d, *J*=268.8 Hz, 1Fβ) ppm. **MS** (ESI+) *m/z* 220 $(M + H)^+$. **HRMS** (MS+) for $C_6H_{10}F_4NO_3$ (M + H)+ calcd 220.0591, found 220.0592.

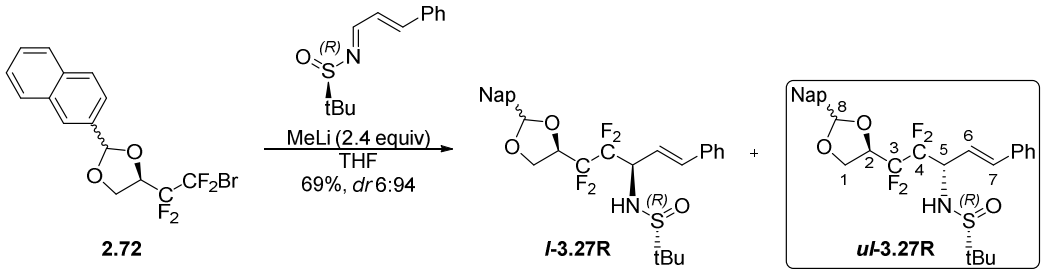
5.8.6 (*R*)-N-[(E)-3-phenylprop-2-enylidene]-*tert*-butanesulfinamide (3.26R)



To cinnamaldehyde (1.05 g, 7.95 mmol) in CH_2Cl_2 (4.0 mL) were added (*S*)-2-methyl-2-propanesulfinamide (1.06 g, 8.74 mmol, 1.1 equiv) and $CuSO_4$ (2.79 g, 17.5 mmol, 2.2 equiv). The resultant mixture was stirred at rt for 22 h then filtered over Celite® to afford the desired crude product. Purification over a short pad of silica eluting with PE/EtOAc 80:20 yielded **3.26S** (1.64 g, 6.96 mmol, 88%) as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, *J*=9.1 Hz, 1H,

H-1), 7.58 – 7.51 (m, 2H, H_{Ar}), 7.45 – 7.37 (m, 3H, H_{Ar}), 7.25 (d, *J*=15.9 Hz, 1H, H-3), 7.09 (dd, *J*=15.9, 9.1 Hz, 1H, H-2), 1.25 (s, 9H, 3 × CH_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8, 146.3, 135.0, 130.2, 128.9, 127.9, 125.6, 57.5, 22.5 ppm. The spectral data matched the literature.[114]

5.8.7 (2*R*,5*S*,*R*$_S$)-3,3,4,4-Tetrafluoro-1,2-(2-naphthylmethylidenedioxy)-7-phenyl-5-(*tert*-butylsulfinylamino)-hept-6-ene (*ul*-3.27R)



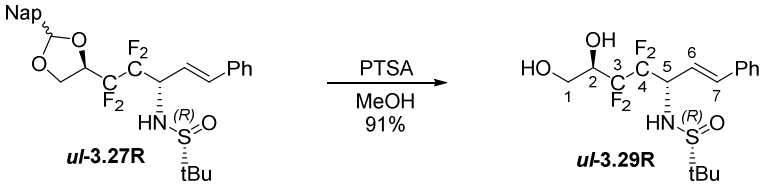
2.72 ***l*-3.27R** ***ul*-3.27R**

To a solution of bromide **2.72** (600 mg, 1.58 mmol, 1 equiv) and sulfinylimine (893 mg, 3.80 mmol, 2.4 equiv) in THF (8 mL) at –78 °C was added MeLi (1.6 M in Et_2O, 2.37 mL, 3.80 mmol, 2.4 equiv) over 1 h and the reaction mixture was stirred at –78 °C for another 2.5 h. The reaction was quenched with saturated NH_4Cl aq. (7 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (toluene/Et_2O, 95:5 to 65:35) afforded 468 mg (0.874 mmol, 55%) of ***ul*-3.27R**. HPLC (toluene/EtOAc, 85:15) of a mixed fraction offered another 95 mg (0.177 mmol, 11%) leading to a total yield of 66%.

Dia 1: R_f 0.33 (toluene/Et_2O, 70:30). **IR** (neat) 3321 (br, w), 3052 (w), 2960 (w), 1177 (m), 1073 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 4H, $CH_{Ar,NAP}$), 7.58 – 7.50 (m, 3H, $CH_{Ar,NAP}$), 7.44 – 7.39 (m, 2H, $CH_{Ar,Ph}$), 7.38 – 7.26 (m, 3H, $CH_{Ar,Ph}$), 6.85 (d, $^3J_{HH}$=15.9 Hz, 1H, H-7), 6.33 (dd, $^3J_{HH}$=15.9, 6.5 Hz, 1H, H-6), 6.06 (s, 1H, H-8), 4.80 – 4.60 (m, 2H, H-2, H-5), 4.50 (dd, $^2J_{HH}$=9.0, $^3J_{HH}$=7.4 Hz, 1H, H-1$_a$), 4.31 (dd, $^2J_{HH}$=9.0, $^3J_{HH}$=7.0 Hz, 1H, H-1$_b$), 3.93 (d, $^3J_{HH}$=9.2 Hz, 1H, NH), 1.23 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8 ($C_{q,Ar}$), 135.7 (C-7), 134.1 ($C_{q,Ar}$), 132.8 ($C_{q,Ar}$), 132.9 ($C_{q,Ar}$), 128.6 (2C, CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 127.8 (CH_{Ar}), 127.0 (2C, CH_{Ar}), 126.84 (CH_{Ar}), 126.79 (CH_{Ar}), 126.4 (CH_{Ar}), 123.4 (CH_{Ar}), 121.5 (br. s, C-6), 119.2 – 113.3 (m, 2 × CF_2), 105.9 (C-8), 72.4 (t, $^2J_{CF}$=26.4 Hz, C-2), 65.4 – 65.2 (m, C-1), 61.0 (t, $^2J_{CF}$=24.9 Hz, C-5), 57.0 ($C_{q,tBu}$), 22.5 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –116.9 (dd, $^2J_{FF}$=274.0, *J*=10.4 Hz, 1F), –119.2 (dd, $^2J_{FF}$=274.0, *J*=13.0 Hz, 1F), –122.8 (app. d, *J*=12.1 Hz, 2F) ppm. **MS** (ESI+) *m/z* 558 $(M + Na)^+$. **HRMS** (MS+) for $C_{23}H_{30}F_4NO_3S$ (M + H)+ calcd 536.1877, found 536.1887.

Dia2: **Rf** 0.23 (toluene/Et_2O, 70:30). **IR** (neat) 3318 (br, w), 3059 (w), 2960 (w), 1178 (m), 1092 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (s, 1H, $CH_{Ar,NAP}$), 7.88 – 7.81 (m, 2H, $CH_{Ar,NAP}$), 7.79 (d, *J*=8.5 Hz, 1H, $CH_{Ar,NAP}$), 7.61 (dd, *J*=8.6, 1.4 Hz, 1H, $CH_{Ar,NAP}$), 7.57 – 7.48 (m, 2H, $CH_{Ar,NAP}$), 7.35 – 7.23 (m, 5H, $CH_{Ar,Ph}$), 6.80 (d, $^3J_{HH}$=15.8 Hz, 1H, H-7), 6.25 (ddd, $^3J_{HH}$=15.8, 7.0, *J*=1.4 Hz, 1H, H-6), 6.03 (s, 1H, H-8), 4.76 – 4.55 (m, 3H, H-2, H-5, H-6_a), 4.25 (dd, $^2J_{HH}$=9.0, $^3J_{HH}$=8.1 Hz, 1H, H-6_b), 3.85 (d, $^3J_{HH}$=9.0 Hz, 1H, NH), 1.24 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8 (C-7), 135.7 ($C_{q,Ar}$), 134.1 ($C_{q,Ar}$), 132.7 ($C_{q,Ar}$), 132.6 ($C_{q,Ar}$), 128.6 (CH_{Ar}), 128.4 (2C, CH_{Ar}), 128.29 (CH_{Ar}), 128.26 (CH_{Ar}), 127.7 (CH_{Ar}), 127.0 (CH_{Ar}), 126.9 (2C, CH_{Ar}), 126.7 (CH_{Ar}), 126.3 (CH_{Ar}), 123.6 (CH_{Ar}), 121.4 (br. s, C-6), 116.2 (tt, $^1J_{CF}$=256.8, $^2J_{CF}$=30.8 Hz, CF_2), 115.6 (ddt, $^1J_{CF}$=261.9, 253.1, $^2J_{CF}$=33.0 Hz, CF_2), 106.0 (C-8), 72.8 (dd, $^2J_{CF}$=33.7, 22.0 Hz, C-2), 65.6 (br. s, C-1), 61.1 (t, $^2J_{CF}$=24.9 Hz, C-5), 56.9 ($C_{q,tBu}$), 22.4 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –117.0 (dd, $^2J_{FF}$=273.1, J_{HF}=12.1 Hz, 1F), –118.0 (dd, $^2J_{FF}$=273.1, J_{HF}=11.3 Hz, 1F), –119.9 (br. d, $^2J_{FF}$=277 Hz, 1F), –124.9 (dd, $^2J_{FF}$=277, J_{HF}=17.8 Hz, 1F) ppm. **MS** (ESI+) *m/z* 558 (M + Na)$^+$. **HRMS** (MS+) for $C_{23}H_{30}F_4NO_3S$ (M + H)+ calcd 536.1877, found 536.1876.

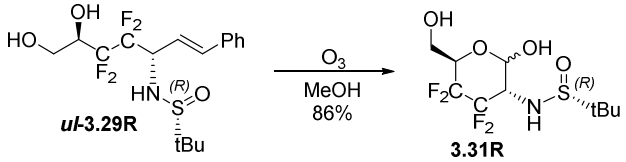
5.8.8 (2*R*,5*S*,R_S)-3,3,4,4-Tetrafluoro-7-phenyl-5-(*tert*-butylsulfinylamino)-hept-6-ene-1,2-diol (*ul*-3.29R)



A mixture of sulfinylamine ***ul*-3.27R** (275 mg, 0.513 mmol, 1 equiv) and PTSA (13 mg, 0.08 mmol, 0.15 equiv) in CH_2Cl_2/MeOH (1:1, 10 mL) was stirred for 19 h then quenched with sat. aq. $NaHCO_3$ (10 mL). H_2O (10 mL) was added and the mixture was extracted with EtOAc (4 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 80:20 to 50:50) afforded 185 mg (0.465 mmol, 91%) of ***ul*-3.29R** as a white solid. **Rf** 0.31 (petroleum ether 40–60 °C/acetone, 60:40). **IR** (neat) 3275 (br, w), 2962 (w), 1172 (m), 1099 (s), 1032 (s) cm^{-1}. **^{1}H NMR** (400MHz ,acetone-*d*6) δ 7.47 – 7.43 (m, 2H, CH_{Ar}), 7.38 – 7.32 (m, 2H, CH_{Ar}), 7.31 – 7.25 (m, 1H, CH_{Ar}), 6.90 (d, $^3J_{HH}$=16.0 Hz, 1H, H-7), 6.39 (dd, $^3J_{HH}$=16.0, 7.6 Hz, 1H-6H), 5.24 (d, $^3J_{HH}$=6.9 Hz, 1H, OH-2), 5.02 (d, $^3J_{HH}$=8.9 Hz, 1H, NH), 4.82 – 4.68 (m, 1H, H-2), 4.25 – 4.13 (m, 1H, H-5), 4.04 (dd, $^3J_{HH}$=6.5, 5.6 Hz, 1H, OH-1), 3.91 – 3.80 (m, 1H, H-1_a), 3.78 – 3.68 (m, 1H, H-1_b), 1.23 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, acetone-*d*6) δ 137.4 ($C_{q,Ar}$), 135.8 (C-7), 129.5 (2C, CH_{Ar}), 129.1 (CH_{Ar}), 127.6 (2C, CH_{Ar}), 123.9 (C-6), 118.1 (ddt, $^1J_{CF}$=259.7, 254.6, $^2J_{CF}$=30.1 Hz, CF_2),

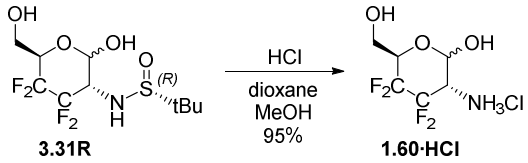
117.7 (tt, $^{1}J_{CF}$=256.8, $^{2}J_{CF}$=29.3 Hz, CF_2), 71.8 (dd, $^{2}J_{CF}$=26.8, 23.1 Hz, C-2), 62.0 (t, $^{2}J_{CF}$=24.2 Hz, C-5), 61.5 – 61.2 (m, C-1), 57.3 ($C_{q,tBu}$), 23.0 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, acetone-*d*6) δ –117.0 (br. d, $^{2}J_{FF}$=269.6 Hz, 1F), –118.6 (dd, $^{2}J_{FF}$=269.6, J_{HF}=13.0 Hz, 1F), –118.4 (d, $^{2}J_{FF}$=275.7 Hz, 1F),–123.6 (dd, *J*=275.7, J_{HF}=18.2 Hz, 1F) ppm. **MS** (ESI+) *m/z* 420 $(M + Na)^+$. **HRMS** (MS+) for $C_{17}H_{23}F_4NO_3S$ (M + H)+ calcd 420.1227, found 420.1232.

5.8.9 (R_s)-2-(*tert*-Butylsulfinylamino)-2,3,4-dideoxy-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranose (3.31R)



Ozone was bubbled through a solution of alkene ***ul*-3.29R** (475 mg, 1.20 mmol) in MeOH (15 mL) until a light blue colour was obtained (15 min). O_2 was bubbled through to remove excess ozone (10 min) and then, Me_2S (0.44 mL, 5.98 mmol, 5 equiv) was added and the reaction mixture was allowed to warm to rt and concentrated. Purification by column chromatography (petroleum ether 40–60 °C/acetone, 70:30 to 50:50) afforded 375 mg (1.16 mmol, 97%) of **3.31R** as a white solid. $\mathbf{R}_f$ 0.37 (petroleum ether 40–60 °C/acetone, 50:50). **IR** (neat) 3263 (m, w), 2964 (w), 1164 (m), 1107 (s), 1028 (s) cm^{-1}. **^{1}H NMR** (400 MHz, acetone-*d*6) δ 6.77 (br. s, 1H, OH-1α), 6.70 (br. s, 1H, OH-1β), 5.44 (br. s, 1H, H-1α), 5.19 (d, $^{3}J_{HH}$=8.3 Hz, 1H, NHβ), 4.94 (d, $^{3}J_{HH}$=7.8 Hz, 1H, H-1β), 4.45 – 4.33 (m, 1H, H-5α), 4.28 (d, $^{3}J_{HH}$=10.0 Hz, 1H, NHα), 4.24 (t, $^{3}J_{HH}$=6.1 Hz, 1H, OH-6β), 4.16 (t, $^{3}J_{HH}$=6.2 Hz, 1H, OH-6α), 3.98 – 3.82 (m, 4H, H-2α, H-5β, H-6_aα +β), 3.82 – 3.72 (m, 2H, H-6_bα +β), 3.67 – 3.52 (m, 1H, H-2β), 1.24 (s, 9H, $CH_{3,tBu}$α), 1.24 (s, 9H, $CH_{3,tBu}$β) ppm. **^{13}C NMR** (101 MHz, acetone-*d*6) δ 117.7 – 111.7 (m, 2 × CF_2), 95.7 (d, $^{3}J_{CF}$=8.8 Hz, C-1β), 93.0 (d, $^{3}J_{CF}$=8.1 Hz, C-1α), 74.2 (dd, $^{2}J_{CF}$=25.3, 22.4 Hz, C-5β), 69.3 (t, $^{2}J_{CF}$=23.5 Hz, C-5α), 64.0 (t, $^{2}J_{CF}$=17.2 Hz, C-2β), 59.5 (t, $^{2}J_{CF}$=17.6 Hz, C-2α), 59.1 – 58.8 (m, C-6α + β), 57.7 ($C_{q,tBu}$β), 57.2 ($C_{q,tBu}$α), 22.9 ($CH_{3,tBu}$β), 22.7 ($CH_{3,tBu}$α) ppm. **^{19}F NMR** (376 MHz, acetone-*d*6) δ –122.7 – –123.6 (m, $^{2}J_{FF}$=255.8 Hz, 1Fα), –126.1 (app. ddt, $^{2}J_{FF}$=258.4, *J*=24.3, 12.1 Hz, 1Fβ), –127.9 – –128.8 (m, 1Fα), –128.7 (dddd, $^{2}J_{FF}$=258.4, *J*=15.8, 9.8, 5.6 Hz, 1Fβ), –132.1 (app. ddt, $^{2}J_{FF}$=259.2, *J*=23.4, 13.9 Hz, 1Fβ), –133.0 (dddd, $^{2}J_{FF}$=259.2, *J*=19.1, 13.9, 4.8 Hz, 1Fα), –133.7 (m, $^{2}J_{FF}$=259.2 Hz, 1Fα), –135.4 (ddd, $^{2}J_{FF}$=259.2, $^{3}J_{FF}$=14.3, 10.8 Hz, 1Fβ) ppm. **MS** (ESI+) *m/z* 324 $(M + H)^+$. **HRMS** (MS+) for $C_{10}H_{18}F_4NO_4S$ (M + H)+ calcd 324.0887, found 324.0895.

5.8.10 2-Amino-2,3,4-dideoxy-3,3,4,4-tetrafluoro-D-*erythro*-hexopyranose hydrochloride (1.60·HCl)



A solution of sulfinamide **3.31R** (315 mg, 0.974 mmol, 1 equiv) in dry MeOH (2 mL) was added dropwise a solution of 4M HCl in dioxane (0.974 mL, 3.90 mmol, 4 equiv) and the reaction was stirred at rt for 0.75 h then evaporated *in vacuo* to near dryness. Et_2O (10 mL) was added in order to precipitate the hydrochloride salt and the supernatant was removed. The solid was washed once more with Et_2O (10 mL) then dried under vacuum to give 237 mg (0.927 mmol, 95%) of the aminosugar **1.60·HCl** as the hydrochloride salt. (α/β 60:40, MeOH). **IR** (neat) 3208 (m, br), 2882 (m, br), 1159 (s), 1099 (s), 1037 (s) cm^{-1}.

Data for α anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 5.55 (app. t, *J*=4.3 Hz, 1H, H-1), 4.50 – 4.35 (m, 1H, H-5), 4.19 – 4.07 (m, 1H, H-2), 3.94 (dd, $^2J_{HH}$=12.2, *J*=3.4 Hz, 1H, H-6_a), 3.79 (dd, $^2J_{HH}$=12.2, *J*=7.1 Hz, 1H, H-6_b) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 117.3 – 111.1 (m, 2 × CF_2), 90.5 (d, $^3J_{CF}$=8.1 Hz, C-1), 69.4 (ddd, $^2J_{CF}$=25.7, 21.3, *J*=1.5 Hz, C-5), 58.9 (dd, *J*=4.4, 2.2 Hz, C-6), 53.1 (br. t, $^2J_{CF}$=18.0 Hz, C-2) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –122.4 (dddd, $^2J_{FF}$=254.1, $^3J_{HF}$=23.2, $^3J_{FF}$=12.3, 10.8 Hz, 1F_{ax}), –126.4 – –127.2 (m, $^2J_{FF}$=254.1 Hz, 1F_{eq}),–133.9 (ddddd, $^2J_{FF}$=263.0, $^3J_{HF}$=24.3, $^3J_{FF}$=14.3, 10.3, *J*=3.5 Hz, 1F_{ax}), –136.4 (ddd, $^2J_{FF}$=263.0, $^3J_{FF}$=12.6, 8.0 Hz, 1F_{eq}) ppm.

Unambiguous resonances for β anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 5.07 (d, $^3J_{HH}$=8.3 Hz, 1H, H-1), 4.03 (app. ddt, *J*=24.0, 6.8, 3.4, Hz, 1H, H-5) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 117.3 – 111.1 (m, 2 × CF_2), 94.2 (d, *J*=8.1 Hz, C-1), 74.8 (ddd, $^2J_{CF}$=26.7, 21.2, *J*=1.5 Hz, C-5), 59.0 (dd, *J*=5.1, 2.2 Hz, C-6), 56.4 (br. t, $^2J_{CF}$=18.3 Hz, C-2) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –127.0 (dddd, $^2J_{FF}$=256.7, $^3J_{HF}$=24.0, $^3J_{FF}$=13.8, 10.6 Hz, 1F_{ax}), –128.5 (dddd, $^2J_{FF}$=256.7, $^3J_{FF}$=14.3, 9.5, *J*=5.2 Hz, 1F_{eq}), –132.5 (ddddd, $^2J_{FF}$=263.3, $^3J_{HF}$=24.3, $^3J_{FF}$=14.3, 10.6, *J*=3.5 Hz, 1F_{ax}), –137.4 (ddd, $^2J_{FF}$=263.3, $^3J_{FF}$=13.8, 9.5 Hz, 1F_{eq}) ppm.

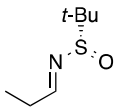
MS (ESI+) *m/z* 220 $(M + H)^+$. **HRMS** (MS+) for $C_6H_{10}F_4NO_3$ (M + H)+ calcd 220.0591, found 220.0593.

5.9 Honda-Reformatsky reactions with α-oxygenated sulfinylimines

5.9.1 General procedure for the synthesis of *N-tert*-butanesulfinylimines (Table 3.1)

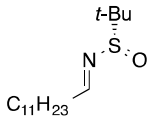
To a mixture of aldehyde (1 equiv) and sulfinamide (1.05 equiv) in CH_2Cl_2 was added $Ti(OEt)_4$ (3-5 equiv). After stirring at rt overnight, water was added. Stirring for a further 15 min was followed by filtration over a pad of $MgSO_4$ and Celite®. The filter cake was washed with EtOAc and the filtrate concentrated under reduced pressure. The residue was purified via filtration over a pad of silica to afford pure sulfinylimine (pale-yellow oils).

*5.9.1.1 (S_S,E)-N-(propylidene)-2-methyl-2-propanesulfinamide (**3.37S**)*



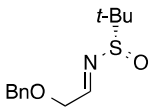
Propionaldehyde (0.100 g, 1.72 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.219 g, 1.81 mmol) and $Ti(OEt)_4$ (1.18 g, 5.17 mmol) yielded **3.37S** (0.201 g, 1.25 mmol, 72%) as a pale yellow oil. $\mathbf{R_f}$ 0.27 (hexane/EtOAc 75:25). $\mathbf{[\alpha]_D}$ +338.4 (c 0.12, $CHCl_3$, 26 °C), lit. (***ent*-3.37S**) $[\alpha]_D$ –328.5 (c 1.0, $CHCl_3$, 23 °C). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 (t, $^3J_{HH}$=4.3 Hz, 1H), 2.55 (dq, $^3J_{HH}$=7.4 Hz, $^3J_{HH}$=4.3 Hz, 2H), 1.20 (s, 9H), 1.20 (t, $^3J_{HH}$=7.4 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.3, 56.5, 29.5, 22.3 (3C), 9.6 ppm. NMR spectra correspond to the reported data for ***ent*-3.37S**.[115]

*5.9.1.2 (S_S,E)-N-[dodecylidene]-2-methyl-2-propanesulfinamide (**3.38S**)*



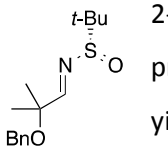
Dodecanal (0.30 mL, 0.249 g, 1.34 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.170 g, 1.41 mmol) and $Ti(OEt)_4$ (1.53 g, 6.70 mmol) yielded **3.38S** (0.366 g, 1.17 mmol, 87%) as a pale yellow oil. $\mathbf{R_f}$ 0.47 (hexane/EtOAc 75:25). $\mathbf{[\alpha]_D}$ +166.0 (c 0.21, $CHCl_3$, 28 °C). **IR** (neat) 2923 (s), 2854 (m), 1622 (m), 1457 (w), 1363 (w), 1087 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (t, $^3J_{HH}$=4.7 Hz, 1H), 2.52 (dt, $^3J_{HH}$=7.4 Hz, $^3J_{HH}$=4.7 Hz, 2H), 1.70–1.60 (m, 2H), 1.51–1.24 (m, 16H), 1.20 (s, 9H), 0.89 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8, 56.5, 36.1, 31.9, 29.6 (2C), 29.5, 29.3 (2C), 29.2, 25.5, 22.7, 22.3 (3C), 14.1 ppm. **HRMS** (MS+) for $C_{16}H_{34}NOS$ $(M+H)^+$ calcd 288.2356, found 288.2356.

*5.9.1.3 (S_S,E)-N-[2-Benzyloxyethylidene]-2-methyl-2-propanesulfinamide (**3.39S**)*



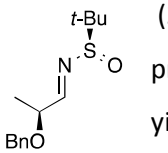
To benzyloxyacetaldehyde[65] (0.250 g, 1.67 mmol) in CH_2Cl_2 (3.5 mL) were added (*S*)-2-methyl-2-propanesulfinamide (0.212 g, 1.75 mmol) and $CuSO_4$ (0.558 g, 3.50 mmol). The resultant mixture was stirred at rt for 15 h then filtered over Celite® to afford the desired crude product. Purification over a short pad of silica eluting with PE/EtOAc 75:25 yielded **3.39S** (0.371 g, 1.46 mmol, 88%) as a pale yellow oil. $\mathbf{R_f}$ 0.21 (hexane/ethyl acetate 70:30). $\mathbf{[\alpha]_D}$ +161.6 (c 0.09, $CHCl_3$, 26 °C), lit. (***ent*-3.39S**)[116] $[\alpha]_D$ –212 (c 1.0, $CHCl_3$, 23 °C). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 (t, $^3J_{HH}$ 3.2 Hz, 1H), 7.40–7.29 (m, 5H), 4.65 (s, 2H), 4.45 (dd, $^2J_{HH}$=16.3, $^3J_{HH}$=3.2 Hz, 1H), 4.39 (dd, $^2J_{HH}$=16.3, $^3J_{HH}$=3.2 Hz, 1H), 1.23 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.7, 137.2, 128.5, 128.0, 127.9, 73.3, 71.3, 57.0, 22.4 ppm. NMR spectra correspond to the reported data for ***ent*-3.39S**.[116]

*5.9.1.4 (S_S,E)-N-[2-(Benzyloxy)-2-methylpropylidene]-2-methyl-2-propanesulfinamide (**3.40S**)*



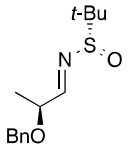
2-Benzyloxy-2-methylpropanal[100] (0.120 g, 0.673 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.086 g, 0.707 mmol) and $Ti(OEt)_4$ (0.768 g, 3.37 mmol) yielded **3.40S** (0.149 g, 0.529 mmol, 79%) as a pale yellow oil. $\mathbf{R_f}$ 0.47 (petroleum ether 40-60 °C/Et_2O 60:40). $\mathbf{[\alpha]_D}$ +210.6 (c 0.50, $CHCl_3$, 22 °C). **IR** (neat) 2979 (w), 1622 (w), 1160 (m), 1087 (s), 1059 (m). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.40–7.23 (m, 5H), 4.48 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.45 (d, $^2J_{HH}$=11.1 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H), 1.23 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 138.4, 128.4, 127.5, 127.6, 78.1, 66.4, 56.9, 24.4, 24.0, 22.5 ppm. **HRMS** (MS+) for $C_{15}H_{23}NNaO_2S$ $(M+Na)^+$ calcd 304.1342, found 304.1338.

*5.9.1.5 (R_S,E)-N-[(2S)-2-(Benzyloxy)propylidene]-2-methyl-2-propanesulfinamide (***ent*-3.41S**)*



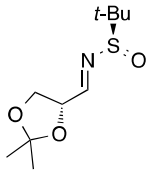
(2*S*)-2-Benzyloxypropanal[100] (0.150 g, 0.914 mmol), (*R*)-2-methyl-2-propanesulfinamide (0.122 g, 1.01 mmol) and $Ti(OEt)_4$ (0.625 g, 2.74 mmol) yielded ***ent*-41S** (0.200 g, 0.748 mmol, 82%) as a pale yellow oil. $\mathbf{R_f}$ 0.60 (hexane/EtOAc 50:50). $\mathbf{[\alpha]_D}$ –222 (c 0.52, EtOH, 22 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$=4.6 Hz, 1H), 7.41–7.23 (m, 5H), 4.66 (d, $^2J_{HH}$=11.7 Hz, 1H), 4.54 (d, $^2J_{HH}$=11.7 Hz, 1H), 4.35 (dq, $^3J_{HH}$=6.7 Hz, $^3J_{HH}$=4.6 Hz, 1H), 1.41 (d, $^3J_{HH}$=6.7 Hz, 3H), 1.22 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 137.6, 128.5, 127.9, 127.8, 76.3, 71.6, 56.9, 22.4, 18.7 ppm. NMR spectra correspond to the reported data.[93]

*5.9.1.6 (S_S,E)-N-[(2S)-2-(Benzyloxy)propylidene]-2-methyl-2-propanesulfinamide (**ent-3.41R**)*



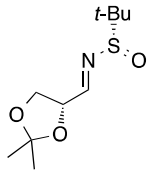
(2*S*)-2-Benzyloxypropanal[100] (0.150 g, 0.914 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.116 g, 0.959 mmol) and $Ti(OEt)_4$ (0.833 g, 3.65 mmol) yielded ***ent*-3.41R** (0.173 g, 0.647 mmol, 71%) as a pale yellow oil. $\mathbf{R_f}$ 0.40 (hexane/EtOAc 50:50). $\mathbf{[\alpha]_D}$ +67.3 (c 0.53, EtOH, 22 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, $^3J_{HH}$=4.5 Hz, 1H), 7.43–7.28 (m, 5H), 4.67 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.50 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.34 (dq, $^3J_{HH}$=6.6 Hz, $^3J_{HH}$=4.5 Hz, 1H), 1.43 (d, $^3J_{HH}$=6.6 Hz, 3H), 1.24 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 137.7, 128.5, 127.9, 127.8, 76.2, 71.5, 56.8, 22.5, 18.5 ppm. NMR spectra correspond to the reported data.[93]

*5.9.1.7 (R_S,E)-N-[(2S)-2,3-(Isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**3.42R**)*



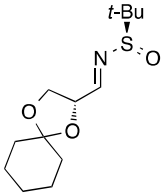
2,3-*O*,*O*-Isopropylidene-D-glyceraldehyde[91] (0.500 g, 3.84 mmol), (*R*)-2-methyl-2-propanesulfinamide (0.489 g, 4.03 mmol) and $Ti(OEt)_4$ (4.38 g, 19.2 mmol) yielded **3.42R** (0.771 g, 3.30 mmol, 86%) as a pale yellow oil. $\mathbf{R_f}$ 0.21 (hexane/EtOAc 70:30). $\mathbf{[\alpha]_D}$ −198.6 (c 0.84, $CHCl_3$, 26 °C). **IR** (neat) 2984 (m), 2873 (m), 1626 (s), 1060 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, $^3J_{HH}$=4.5 Hz, 1H), 4.83 (ddd, $^3J_{HH}$=7.6 Hz, $^3J_{HH}$=5.5 Hz, $^3J_{HH}$=4.5 Hz, 1H), 4.25 (dd, $^2J_{HH}$=8.7 Hz, $^3J_{HH}$=7.6 Hz, 1H), 4.00 (dd, $^2J_{HH}$=8.7 Hz, $^3J_{HH}$=5.5 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.20 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.4, 111.0, 76.7, 67.1, 57.2, 26.4, 25.4, 22.3 ppm. **HRMS** (MS+) for $C_{10}H_{19}NNaO_3S$ $(M+Na)^+$ calcd 256.0983, found 256.0978. NMR spectra correspond to the reported data.[92]

*5.9.1.8 (S_S,E)-N-[(2S)-2,3-(Isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**3.42S**)*



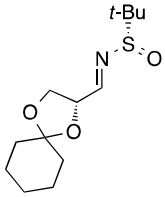
2,3-*O*,*O*-Isopropylidene-D-glyceraldehyde[91] (1.05 g, 8.07 mmol), (*S*)-2-methyl-2-propanesulfinamide (1.03 g, 8.47 mmol) and $Ti(OEt)_4$ (7.36 g, 32.3 mmol) yielded **3.42S** (1.50 g, 6.43 mmol, 80%) as a pale yellow oil. **R*f*** 0.6 (petroleum ether 40-60 °C/EtOAc 50:50). $\mathbf{[\alpha]_D}$ +248 (c 0.49, EtOH, 23 °C). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$=4.1 Hz, 1H), 4.85 (ddd, $^3J_{HH}$=6.8 Hz, $^3J_{HH}$=5.1 Hz, $^3J_{HH}$=4.1 Hz, 1H), 4.23 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=6.8 Hz, 1H), 4.05 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=5.1 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.21 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0, 110.8, 76.9, 67.2, 57.0, 26.4, 25.4, 22.3 ppm. NMR spectra correspond to the reported data.[92]

*5.9.1.9 (R_S,E)-N-[(2S)-2,3-Cyclohexylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**3.43R**)*



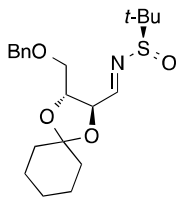
2,3-*O*,*O*-Cyclohexylidene-D-glyceraldehyde[101] (1.00 g, 5.88 mmol), (*R*)-2-methyl-2-propanesulfinamide (0.748 g, 6.17 mmol) and $Ti(OEt)_4$ (6.70 g, 29.4 mmol) yielded **3.43R** (1.41 g, 5.16 mmol, 88%) as a pale yellow oil. $\mathbf{R_f}$ 0.29 (hexane/EtOAc 70:30). $\mathbf{[\alpha]_D}$ –216.6 (c 0.49, $CHCl_3$, 20 °C). **IR** (neat) 2934 (m), 2863 (m), 1625 (s), 1084 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, $^3J_{HH}$=4.5 Hz, 1H), 4.83 (ddd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=5.5 Hz, $^3J_{HH}$=4.5 Hz, 1H), 4.24 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.01 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=5.5 Hz, 1H), 1.77–1.53 (m, 8H), 1.48–1.34 (m, 2H), 1.21 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8, 111.6, 76.5, 66.8, 57.2, 36.0, 35.0, 25.0, 23.83, 23.80, 22.4 ppm. **HRMS** (MS+) for $C_{13}H_{23}NNaO_3S$ $(M+Na)^+$ calcd 296.1291, found 296.1296.

*5.9.1.10 (S_S,E)-N-[(2S)-2,3-Cyclohexylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**3.43S**)*



2,3-*O*,*O*-Cyclohexylidene-D-glyceraldehyde[101] (1.0 g, 5.88 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.748 g, 6.17 mmol) and $Ti(OEt)_4$ (6.70 g, 29.4 mmol) yielded **3.43S** (1.43 g, 5.23 mmol, 89%) as a pale yellow oil. $\mathbf{R_f}$ 0.53 (petroleum ether 40-60 °C/EtOAc 60:40). $\mathbf{[\alpha]_D}$ +193 (c 0.53, EtOH, 22 °C). **IR** (neat) 2934 (m), 2863 (s), 1625 (m), 1364 (m), 1088 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$=4.2 Hz, 1H), 4.84 (ddd, $^3J_{HH}$=6.7 Hz, $^3J_{HH}$=5.1 Hz, $^3J_{HH}$=4.2 Hz, 1H), 4.22 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=6.7 Hz, 1H), 4.04 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=5.1 Hz, 1H), 1.73–1.54 (m, 8H), 1.48–1.37 (m, 2H), 1.20 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.3, 111.5, 76.7, 67.0, 57.1, 36.1, 35.0, 25.0, 23.9, 23.9, 22.4 ppm. **MS** (ESI+) (*m/z*) 274 $(M+H)^+$. **HRMS** (MS+) for $C_{13}H_{23}NNaO_3S$ $(M+Na)^+$ calcd 296.1291, found 296.1297.

*5.9.1.11 (R_S,E)-N-[(2R,3R)-4-(Benzyloxy)-2,3-(cyclohexylidenedioxy)-butylidene]-2-methyl-2-propanesulfinamide (**ent-3.44S**)*

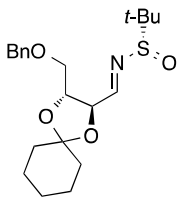


SO_3•pyridine (3.27 g, 20.5 mmol, 3.0 equiv), Et_3N (3.34 mL, 23.9 mmol, 3.5 equiv), DMSO (8 mL) and CH_2Cl_2 (17 mL) were combined and stirred at –20 °C for 0.5 h. The corresponding alcohol ($[\alpha]_D$ –4.02 (c 1.3, $CHCl_3$, 21 °C), lit. +0.90 (c 1.3, $CHCl_3$, 24 °C, enantiomer)[103] (2.00 g, 6.84 mmol, 1 equiv), DMSO (8 mL) and DCM were stirred at –20 °C in a separate flask and to this solution was added dropwise via cannula the solution of SO_3. The resultant mixture was allowed to stir below –10 °C for 1 h then at rt for 3 h. Quenching with saturated aqueous NH_4Cl solution and extraction with EtOAc

(2 × 15 mL) and Et_2O (2 × 15 mL) was followed by drying over $MgSO_4$ and concentrating *in vacuo* to afford bright yellow oil. Column chromatography (petroleum ether 40-60 °C/EtOAc 75:25 to 70:30) afforded 1.63 g (5.61 mmol, 82%) of the pure aldehyde **3.1h** as a colourless oil. R_f 0.31 (petroleum ether 40-60 °C/EtOAc 75:25). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.78 (d, $^3J_{HH}$=1.6 Hz, 1H), 7.40–7.28 (m, 5H), 4.62 (s, 2H), 4.32–4.22 (m, 2H), 3.67 (dd, $^3J_{HH}$=4.5 Hz, $^3J_{HH}$=1.1 Hz, 2H), 1.75–1.54 (m, 8H), 1.49–1.34 (m, 2H) ppm. The aldehyde was used immediately after purification.

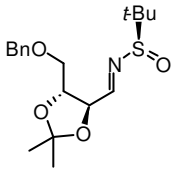
4-*O*-Benzyl-2,3-*O*,*O*-cyclohexylidene-D-threose **3.1h** obtained as described above (800 mg, 2.76 mmol), (*R*)-2-methyl-2-propanesulfinamide (367 mg, 3.03 mmol) and $Ti(OEt)_4$ (3.14 g, 13.8 mmol) yielded ***ent*-3.44S** (900 mg, 2.29 mmol, 83%) as a pale yellow oil. **R_f** 0.7 (petroleum ether 40-60 °C/EtOAc 50:50). **$[\alpha]_D$** –104 (c 0.67, EtOH, 23 °C). **IR** (neat) 2933 (m), 2861 (m), 1624 (m), 1364 (m), 1084 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, $^3J_{HH}$=4.7 Hz, 1H), 7.39–7.28 (m, 5H), 4.67–4.55 (m, 3H), 4.22 (ddd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=5.6 Hz, $^3J_{HH}$=4.4 Hz, 1H), 3.68 (dd, $^2J_{HH}$=10.4 Hz, $^3J_{HH}$=4.4 Hz, 1H), 3.64 (dd, $^2J_{HH}$=10.4 Hz, $^3J_{HH}$=5.6 Hz, 1H), 1.74–1.57 (m, 8H), 1.52–1.31 (m, 2H), 1.14 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.6, 137.7, 128.4 (2C), 127.8 (3C), 112.0, 79.0, 77.9, 73.6, 69.8, 57.1, 36.5, 36.1, 25.0, 23.9, 23.7, 22.3 (3C) ppm. **MS** (ESI+) (*m/z*) 416 $(M+Na)^+$. **HRMS** (MS+) for $C_{21}H_{31}NNaO_4S$ $(M+Na)^+$ calcd 416.1866, found 416.1873.

*5.9.1.12 (S_s,E)-N-[(2R,3R)-4-(benzyloxy)-2,3-(cyclohexylidenedioxy)-butylidene]-2-methyl-2-propanesulfinamide (**ent-3.44R**)*



4-*O*-Benzyl-2,3-*O*,*O*-cyclohexylidene-D-threose **3.1h** obtained as described above (900 mg, 3.1 mmol), (*S*)-2-methyl-2-propanesulfinamide (394 mg, 3.26 mmol) and $Ti(OEt)_4$ (3.54 g, 15.5 mmol) yielded ***ent*-3.44R** (1.03 g, 2.63 mmol, 85%) as a pale yellow oil. **R_f** 0.7 (petroleum ether 40-60 °C/EtOAc 50:50). **$[\alpha]_D$** +156 (c 0.47, EtOH, 23 °C). **IR** (neat) 2934 (m), 2862 (m), 1625 (m), 1364 (m), 1087 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, $^3J_{HH}$=4.2 Hz, 1H), 7.39–7.28 (m, 5H), 4.67–4.59 (m, 3H), 4.28 (ddd, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=5.2 Hz, $^3J_{HH}$=4.2 Hz, 1H), 3.72 (dd, $^2J_{HH}$=10.6 Hz, $^3J_{HH}$=4.2 Hz, 1H), 3.68 (dd, $^2J_{HH}$=10.6 Hz, $^3J_{HH}$=5.2 Hz, 1H), 1.76–1.57 (m, 8H), 1.48–1.35 (m, 2H), 1.20 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.2, 137.9, 128.4 (2C), 127.7 (3C), 111.9, 78.7, 77.8, 73.6, 69.7, 57.2, 36.5, 36.0, 25.0, 23.9, 23.7, 22.4 (3C) ppm. **MS** (ESI+) (*m/z)* 416 $(M+Na)^+$. **HRMS** (MS+) for $C_{21}H_{31}NNaO_4S$ $(M+Na)^+$ calcd 416.1866, found 416.1864.

*5.9.1.13 (R_S,E)-N-[(2R,3R)-4-(Benzyloxy)-2,3-(isopropylidenedioxy)-butylidene]-2-methyl-2-propanesulfinamide (**ent-3.45S**)*



To 4-*O*-benzyl-2,3-*O*,*O*-isopropylidene-D-threose[102] (1.00 g, 4.00 mmol) in CH_2Cl_2 (2 mL) were added (*R*)-2-methyl-2-propanesulfinamide (0.533 g, 4.40 mmol, 1.1 equiv) and $CuSO_4$ (1.40 g, 8.80 mmol, 2.2 equiv). The resultant mixture was stirred at rt for 17 h then filtered over Celite® to afford the desired crude product. Purification over a short pad of silica eluting with PE/EtOAc 80:20 yielded **3.45S** (0.758 g, 2.14 mmol, 54%) as a pale yellow oil. $\mathbf{R_f}$ 0.6 (petroleum ether 40-60 °C/EtOAc 50:50). $\mathbf{[\alpha]_D}$ –88 (c 0.66, EtOH, 19 °C). **IR** (neat) 2984 (m), 1625 (m), 1455 (m), 1365 (m), 1215 (m), 1085 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J*=4.6 Hz, 1H), 7.39 – 7.25 (m, 5H), 4.57 (d, $^2J_{HH}$=12.2 Hz, 1H), 4.60 (dd, $^3J_{HH}$=7.7, 4.6 Hz, 1H), 4.64 (d, $^2J_{HH}$=12.2 Hz, 1H), 4.22 (ddd, $^3J_{HH}$=7.7, 5.6, 4.0 Hz, 1H), 3.64 (dd, $^2J_{HH}$=10.4, $^3J_{HH}$=5.6 Hz, 1H), 3.68 (dd, $^2J_{HH}$=10.4, $^3J_{HH}$=4.0 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.14 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3, 137.6, 128.4 (2C), 127.8 (3C), 111.3, 79.1, 78.3, 73.6, 69.5, 57.0, 26.9, 26.5, 22.3 ppm. **MS** (ESI+) (*m/z)* 376 $(M+Na)^+$. **HRMS** (MS+) for $C_{18}H_{27}NNaO_4S$ $(M+Na)^+$ calcd 376.1553, found 376.1550.

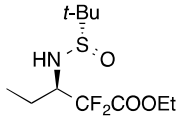
5.9.2 General procedure for the Honda-Reformatski reaction (Table 3.3).

A mixture of sulfinylimine (1 equiv), $RhCl(PPh_3)_3$ (3 mol%) in THF (7.5 mL/mmol) was cooled to –20 °C. **1** (3 equiv) was added immediately followed by dropwise addition of Et_2Zn (1.0M in hexane, 2 equiv). The mixture was allowed to warm up to 0 °C over 30 min and stirring was continued for 1 h. Quenching with sat. NH_4Cl was followed by extraction with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography gave the products as pale-yellow oils unless mentioned otherwise.

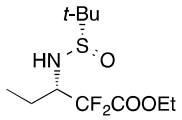
*5.9.2.1 Reaction with sulfinylimine **3.37S***

100 mg, 0.620 mmol yielded **3.46S** (53:47 *dr*). Chromatography (petroleum ether 40-60 °C/EtOAc 70:30) afforded an inseparable mixture of diastereoisomers (114 mg, 0.400 mmol, 64%). Analytical samples of pure diastereoisomers were obtained by HPLC (hexane/EtOAc 70:30).

Major isomer: (3*R*,*SS*)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate *ul*-3.46S (pale yellow oil): $\mathbf{R_f}$ 0.20 (hexane/EtOAc 70:30). $\mathbf{[\alpha]_D}$ +62.9 (c 0.19, $CHCl_3$, 21 °C). **IR** (neat) 3207 (br), 2982 (m), 1773(s), 1062 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.32 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.2 Hz, 1H), 4.29 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.1 Hz, 1H), 3.81–3.66 (m, 1H), 3.15 (d, $^3J_{HH}$=8.9 Hz, 1H), 1.98–1.86 (m, 1H), 1.65–1.52 (m, 1H), 1.36 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.20 (s, 9H), 1.14 (t, $^3J_{HH}$=7.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$=32.3 Hz), 114.8 (t, $^1J_{CF}$=255.7 Hz), 62.8, 60.8 (dd, $^2J_{CF}$=25.7, 24.2 Hz), 56.5, 22.6, 22.4 (3C), 13.8, 10.0 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –110.4 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=7.5 Hz), –119.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz) ppm. **MS** (ESI+) (*m/z*) 349 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{11}H_{21}F_2NNaO_3S$ $(M + Na)^+$ calcd 308.1102, found 308.1108.



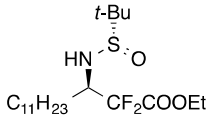
Minor isomer: (3*S*,*SS*)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate *l*-3.46S (pale yellow oil): $\mathbf{R_f}$ 0.23 (hexane/EtOAc 70:30). $\mathbf{[\alpha]_D}$ +26.6 (c 0.51, $CHCl_3$, 19 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.39 (q, $^3J_{HH}$=7.1 Hz, 2H), 3.80–3.66 (m, 1H), 3.57 (d, $^3J_{HH}$=9.3 Hz, 1H), 1.91–1.78 (m, 1H), 1.66–1.52 (m, 1H), 1.38 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.24 (s, 9H), 1.06 (t, $^3J_{HH}$=7.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$=31.9 Hz), 114.7 (t, $^1J_{CF}$=256.4 Hz), 63.3, 60.4 (dd, $^2J_{CF}$=25.3, 23.8 Hz), 56.9, 22.7 (3C), 22.3, 13.8, 10.3 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –109.9 (dd, $^2J_{FF}$=264.3, $^3J_{HF}$=7.5 Hz),–118.4 (dd, $^2J_{FF}$=264.3 Hz, $^3J_{HF}$=15.6 Hz) ppm. **MS** (ESI+) (*m/z*) 308 $(M+Na)^+$. **HRMS** (MS+) for $C_{11}H_{21}F_2NNaO_3S$ $(M + Na)^+$ calcd 308.1102, found 308.1106.



*5.9.2.2 Reaction with sulfinylimine **3.38S***

150 mg, 0.522 mmol yielded **3.47S** (53:47 *dr*). Chromatography (hexane/EtOAc 90:10→65:35) afforded an inseparable mixture of diastereoisomers (125 mg, 0.304 mmol, 58%). Analytical samples of pure diastereoisomers were obtained by HPLC (hexane/EtOAc 75:25).

Major isomer: (3*R*,S_S)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluorotetradecanoate *ul*-3.47S (pale yellow oil): $\mathbf{R_f}$ 0.19 (hexane/EtOAc 75:25). $\mathbf{[\alpha]_D}$ +43.9 (c 0.54, $CHCl_3$, 21 °C). **IR** (neat) 3206 (br w), 2924 (s), 2854 (s), 1774 (s), 1057 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33 (dq, $^2J_{HH}$=10.9, $^3J_{HH}$=7.2 Hz, 1H), 4.29 (dq, $^2J_{HH}$=10.9, $^3J_{HH}$=7.2 Hz, 1H), 3.79 (ddddd app. as ddtd, $^3J_{HF}$=16.1, $^3J_{HH}$=8.8, $^3J_{HF}$=8.6, $^3J_{HH}$=8.6, $^3J_{HH}$=3.8 Hz, 1H), 3.10 (d, $^3J_{HH}$=8.8 Hz, 1H), 1.87–1.76 (m, 1H), 1.73–1.59 (m, 1H), 1.59–1.22 (m, 18H), 1.36 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.20 (s, 9H), 0.88 (t, $^3J_{HH}$=7.0 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{CF}$=33.0 Hz), 114.9 (t, $^1J_{CF}$=255.4 Hz), 62.9, 59.4 (dd, $^2J_{CF}$=26.3 Hz, $^2J_{CF}$=23.4 Hz), 56.6, 31.9, 29.6 (4C), 29.3, 29.3 (2C), 25.2, 22.7, 22.5 (3C), 14.1, 13.9 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –110.8 (dd, $^2J_{FF}$=261.1 Hz, $^3J_{HF}$=8.6 Hz), –118.8 (dd, $^2J_{FF}$=261.1 Hz, $^3J_{HF}$=16.1 Hz) ppm. **MS** (ESI+)



(*m/z*) 475 (M+Na+MeCN)$^+$. **HRMS** (MS+) for $C_{20}H_{39}F_2NNaO_3S$ (M+Na)$^+$ calcd 434.2511, found 434.2516.

Minor isomer: (3*S*,*S*$_S$)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluorotetradecanoate *l*-3.47S (pale yellow oil): R_f 0.17 (hexane/EtOAc 70:30). $[\alpha]_D$ +61.9 (c 0.59, $CHCl_3$, 23 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.38 (q, $^3J_{HH}$=7.2 Hz, 2H), 3.86–3.72 (m, 1H), 3.56 (d, $^3J_{HH}$=9.5 Hz, 1H), 1.80–1.68 (m, 1H), 1.63–1.49 (m, 2H), 1.41–1.24 (m, 17H), 1.37 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.23 (s, 9H), 0.89 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$=32.2 Hz), 114.7 (t, $^1J_{CF}$=256.1 Hz), 63.3, 58.9 (t, $^2J_{CF}$=24.9 Hz), 56.9, 31.9, 29.6 (2C), 29.5, 29.3 (2C), 29.1, 28.9, 25.4, 22.7 (3C), 22.7, 14.1, 13.9 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –110.1 (dd, $^2J_{FF}$=264.3, $^3J_{HF}$=7.5 Hz, 1F), –118.3 (dd, $^2J_{FF}$=264.3, $^3J_{HF}$=16.1 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 475 (M+Na+MeCN)$^+$. **HRMS** (MS+) for $C_{20}H_{39}F_2NNaO_3S$ (M+Na)$^+$ calcd 434.2511, found 434.2513.

*5.9.2.3 Reaction with sulfinylimine **3.39S***

100 mg, 0.395 mmol yielded **3.48S** (88:12 *dr*). Chromatography (hexane/EtOAc 75:25→65:35) afforded an inseparable mixture of diastereoisomers (68 mg, 0.180 mmol, 46%).

Major isomer (3*R*,*S*$_S$)-ethyl-4-(benzyloxy)-3-(*tert*-butylsulfinamino)-2,2-difluorobutanoate *ul*-3.48S. Analytically pure sample of the major diastereoisomer (pale yellow oil) was obtained by HPLC (hexane/EtOAc 70:30): R_f 0.31 (hexane/EtOAc 40:60). $[\alpha]_D$ +33.1 (c 0.62, $CHCl_3$, 19 °C). **IR** (neat) 3209 (br w), 2982 (br w), 2871 (br w), 1771 (s), 1077 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 4.56 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.49 (d, $^2J_{HH}$=11.6 Hz, 1H), 4.15 (q, $^3J_{HH}$=7.2 Hz, 2H), 4.08–3.95 (m, 2H), 3.92–3.86 (m, 1H), 3.80–3.73 (m, 1H), 1.24 (t, *J*=7.2 Hz, 3H), 1.23 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (t, $^2J_{CF}$=32.2 Hz), 137.2, 128.4 (2C), 127.84, 127.79 (2C), 113.8 (t, $^1J_{CF}$=256.1 Hz), 73.6, 67.6, 62.9, 58.6 (t, $^2J_{CF}$=24.9 Hz), 56.7, 22.4 (3C), 13.8 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –112.7 (dd, $^2J_{FF}$=261.8 Hz, $^3J_{HF}$ 8.7 Hz), –115.7 (dd, $^2J_{FF}$=261.8 Hz, $^3J_{HF}$=13.0 Hz) ppm. **MS** (ESI+) (*m/z*) 400 (M+Na)$^+$. **HRMS** (MS+) for $C_{17}H_{25}F_2NNaO_4S$ (M+Na)$^+$ calcd 400.1365, found 400.1364.

*5.9.2.4 Reaction with sulfinylimine **ent-3.41S***

100 mg, 0.374 mmol yielded ***ent-3*.50S** (94:6 *dr*). Chromatography (petroleum ether 40-60 °C/Et_2O 40:60→20:80) afforded ***ent-ul-3*.50S** (80 mg, 0.204 mmol, 54%) as a white solid and ***ent-l*-3.50S** (4 mg, 0.010 mmol, 3%) as a pale yellow oil.

Major isomer: (3*S*,4*S*,*R*$_S$)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate *ent-ul*-3.50S: **R$_f$** 0.10 (petroleum ether 40-60 °C/Et$_2$O 40:60). **Mp** 109–111 °C. **[α]$_D$** –4.2 (c 0.14, $CHCl_3$, 23 °C). **IR** (neat) 3213 (w, br), 2982 (w), 1771 (s), 1099 (s), 1054 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 4.57 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.38 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.05–3.85 (m, 3H), 3.80 (dq app. as quin, $^3J_{HH}$ 6.3=Hz, 1H), 3.71 (d, $^3J_{HH}$=9.5 Hz, 1H), 1.44 (d, $^3J_{HH}$=6.3 Hz, 3H), 1.24 (s, 9H), 1.16 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0 (t, $^2J_{CF}$=32.2 Hz), 137.4, 128.3 (2C), 128.2 (2C), 127.9, 114.2 (t, $^1J_{CF}$=254.7 Hz), 74.9, 71.4, 63.3 (t, $^2J_{CF}$=23.4 Hz), 62.6, 57.0, 22.5 (3C), 16.4, 13.7 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –110.0 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), –115.2 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=12.9 Hz). **MS** (ESI+) (*m/z*) 414 $(M+Na)^+$. **HRMS** (MS+) for $C_{18}H_{27}F_2NNaO_4S$ $(M+Na)^+$ calcd 414.1521, found 414.1525.

Minor isomer: (3*R*,4*S*,*R*$_S$)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate *ent-l*-3.50S: **R$_f$** 0.20 (petroleum ether 40-60 °C/Et$_2$O 40:60). **[α]$_D$** –33.5 (c 0.07, $CHCl_3$, 23 °C). **IR** (neat) 2980 (w), 1770 (m), 1108 (s), 1082 (s), 1026 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 4.56 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.36 (d, $^2J_{HH}$=11.1 Hz, 1H), 4.31 (d, $^3J_{HH}$=10.5 Hz, 1H), 4.09 (qd, $^3J_{HH}$=7.1 Hz, $^2J_{HH}$=6.7 Hz, 1H), 4.07 (qd, $^3J_{HH}$=7.1 Hz, $^2J_{HH}$=6.7 Hz, 1H), 4.00 (qt, $^3J_{HH}$=6.3 Hz, $^3J_{HH}$=1.7 Hz, 1H), 3.74 (dddd, $^3J_{HF}$=12.4 Hz, $^3J_{HH}$=10.5 Hz, $^3J_{HF}$=8.7 Hz, $^3J_{HH}$=1.8 Hz, 1H), 1.29 (d, $^3J_{HH}$=6.3 Hz, 3H), 1.27 (s, 9H), 1.20 (t, $^3J_{HH}$=7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7, 128.3 (2C), 127.8 (3C), 113.6 (t, $^1J_{CF}$=257.6 Hz), 72.1 (d, $^3J_{CF}$=2.9 Hz), 71.1, 63.0 (t, $^2J_{CF}$=24.9 Hz), 63.0, 57.2, 22.9 (3C), 16.6, 13.7 ppm (The C=O signal was not observed). **^{19}F NMR** (282 MHz, $CDCl_3$) δ –108.0 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.7 Hz), –114.6 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=12.4 Hz) ppm. **MS** (ESI) (*m/z*) 455 $(M+Na+MeCN)^+$. **HRMS** (ESI) for $C_{18}H_{27}F_2NNaO_4S$ $(M + Na)^+$ calcd 414.1521, found 414.1509.

*5.9.2.5 Reaction with sulfinylimine **ent-3.41R***

100 mg, 0.374 mmol yielded ***ent*-3.50R** (54:46 *dr*). Chromatography (petroleum ether 40-60 °C/Et$_2$O 40:60→20:80) afforded ***ent-ul*-3.50R** (37 mg, 0.095 mmol, 25%) and ***ent-l*-3.50R** (31 mg, 0.079 mmol, 21%).

Major isomer: (3*R*,4*S*,*S*$_S$)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate *ent-ul*-3.50R (pale yellow oil): **R$_f$** 0.38 (petroleum ether 40-60 °C/Et$_2$O 20:80). **[α]$_D$** +30.0 (c 0.62, $CHCl_3$, 23 °C). **IR** (neat) 3353 (w, br), 2979 (w), 1765 (m), 1079 (s), 1021 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 4.60 (d, $^2J_{HH}$=11.0 Hz, 1H), 4.33 (d, $^2J_{HH}$=11.0 Hz, 1H), 4.30 (d, $^3J_{HH}$=9.1 Hz, 1H), 4.09–3.98 (m, 3H), 3.66 (dddd, $^3J_{HF}$=12.8, $^3J_{HH}$=9.1 Hz, $^3J_{HF}$=8.9 Hz, $^3J_{HH}$=0.9 Hz, 1H), 1.42 (d, $^3J_{HH}$=6.4

Hz, 3H), 1.24 (s, 9H), 1.16 (t, $^{3}J_{HH}$=7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (dd, $^{2}J_{CF}$=33.7, 30.7 Hz), 137.5, 128.3 (2C), 127.8 (2C), 127.7, 113.8 (t, $^{1}J_{CF}$=255.4 Hz), 70.7, 70.4 (d, $^{3}J_{CF}$=2.9 Hz), 64.1 (dd, $^{2}J_{CF}$=27.8 Hz, $^{2}J_{CF}$=23.4 Hz), 62.7, 56.8, 22.5 (3C), 16.6, 13.7 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –109.9 (dd, $^{2}J_{FF}$=257.9 Hz, $^{3}J_{HF}$=8.9 Hz), –114.7 (dd, $^{2}J_{FF}$=257.9 Hz, $^{3}J_{HF}$=12.8 Hz) ppm. **MS** (ESI+) (*m/z*) 414 $(M+Na)^+$. **HRMS** (MS+) for $C_{18}H_{27}F_2NNaO_4S$ $(M+Na)^+$ calcd 414.1521, found 414.1526.

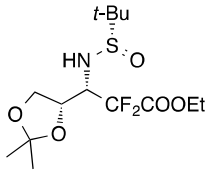
Minor isomer: (3*S*,4*S*,*S*$_S$)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate *ent-l*-3.50R (pale yellow oil): **R_f** 0.22 (petroleum ether 40-60 °C/Et_2O 20:80). **[α]$_D$** +37.7 (c 0.53, $CHCl_3$, 23 °C). **IR** (neat) 3213 (w, br), 2981 (w), 1770 (m), 1097 (s), 1055 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 4.51 (d, $^{2}J_{HH}$=11.2 Hz, 1H), 4.39 (d, $^{2}J_{HH}$=11.2 Hz, 1H), 4.08–3.92 (m, 3H), 3.76–3.68 (m, 1H), 3.68 (d, $^{3}J_{HH}$=9.3 Hz, 1H), 1.32 (d, $^{3}J_{HH}$=6.1 Hz, 3H), 1.24 (s, 9H), 1.18 (t, $^{3}J_{HH}$=7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.7 (dd, $^{2}J_{CF}$=32.2 Hz, $^{2}J_{CF}$=30.7 Hz), 137.4, 128.3 (2C), 128.0 (2C), 127.8, 113.8 (t, $^{1}J_{CF}$=254.7 Hz), 73.9, 71.0, 62.8, 62.7 (dd, $^{2}J_{CF}$=23.4 Hz, $^{2}J_{CF}$=22.0 Hz), 57.1, 22.7 (3C), 16.6, 13.7 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –109.6 (dd, $^{2}J_{FF}$=262.2 Hz, $^{3}J_{HF}$=8.6 Hz), –117.3 (dd, $^{2}J_{FF}$=262.2 Hz, $^{3}J_{HF}$=17.2 Hz) ppm. **MS** (ESI) (*m/z*) 455 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{18}H_{27}F_2NNaO_4S$ $(M+Na)^+$ calcd 414.1521, found 414.1524.

*5.9.2.6 Reaction with sulfinylimine **3.42S***

109 mg, 0.467 mmol yielded ***ul*-3.51S** as a single diastereoisomer. Chromatography (petroleum ether 40-60 °C/EtOAc 70:30→50:50) afforded ***ul*-3.51S** (103 mg, 0.288 mmol, 62%) as a white solid.

Major isomer: (3*R*,4*S*,*S*$_S$)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate *ul*-3.51S: **R_f** 0.26 (petroleum ether 40-60 °C/EtOAc 50:50). **Mp** 88–90 °C. **[α]$_D$** +30.3 (c 0.29, $CHCl_3$, 23 °C). **IR** (neat) 3194 (w), 2986 (w), 1777 (m), 1761 (m), 1053 (s). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.38–4.11 (m, 5H), 3.96 (dddd, $^{3}J_{HF}$=17.4 Hz, $^{3}J_{HH}$=8.7 Hz, $^{3}J_{HF}$=8.2 Hz, $^{3}J_{HH}$=7.2 Hz, 1H), 3.54 (d, $^{3}J_{HH}$=8.7 Hz, 1H), 1.39 (s, 3H), 1.34 (t, $^{3}J_{HH}$=7.2 Hz, 3H), 1.29 (s, 3H), 1.21 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.9 (t, $^{2}J_{CF}$=30.8 Hz), 113.8 (dd, $^{1}J_{CF}$=256.4 Hz, $^{1}J_{CF}$=252.5 Hz), 110.6, 73.6, 66.8, 63.0, 61.1 (dd, $^{2}J_{CF}$=22.6 Hz, $^{2}J_{CF}$=21.5 Hz), 57.1, 25.9, 24.9, 22.4 (3C), 13.7 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –110.0 (dd, $^{2}J_{FF}$=262.6 Hz, $^{3}J_{HF}$=8.2 Hz), –119.4 (dd, $^{2}J_{FF}$=262.6 Hz, $^{3}J_{HF}$=17.4 Hz) ppm. **MS** (ESI+) (*m/z*) 421 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{14}H_{25}F_2NNaO_5S$ $(M+Na)^+$ calcd 380.1314, found 380.1312.

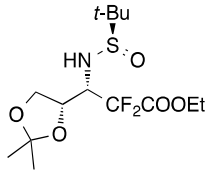
Minor isomer: (3*S*,4*S*,*S*$_S$)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate *l*-3.51S (isolated from an unselective reaction, pale yellow oil): **[α]$_D$** +6.2 (*c* 0.17, $CHCl_3$, 23 °C). **IR** (neat) 2991 (w), 1770 (s), 1137 (s), 1123 (s), 1107 (s) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.51 (ddd, $^3J_{HH}$=7.1 Hz, $^3J_{HH}$=6.1 Hz, $^3J_{HH}$=2.2 Hz, 1H), 4.45–4.32 (m, 2H), 4.14 (d, $^3J_{HH}$=10.4 Hz, 1H), 4.11 (dd, $^2J_{HH}$=8.2 Hz, $^3J_{HH}$=7.1 Hz, 1H), 3.85 (dddd, $^3J_{HF}$=16.3 Hz, $^3J_{HH}$=10.4 Hz, $^3J_{HF}$=6.1 Hz, $^3J_{HH}$=2.2 Hz, 1H), 3.80 (dd, $^2J_{HH}$=8.2 Hz, $^3J_{HH}$=6.1 Hz, 1H), 1.44 (s, 3H), 1.38 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.33 (s, 3H), 1.26 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$=31.4 Hz), 113.5 (dd, $^1J_{CF}$=261 Hz, $^1J_{CF}$=256 Hz), 110.2, 72.1 (d, $^3J_{CF}$=3.3 Hz), 66.1, 63.5, 59.4 (t, $^2J_{CF}$=24.8 Hz), 57.3, 26.1, 24.4, 22.6 (3C), 13.7 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –107.0 (dd, $^2J_{FF}$=265.7 Hz, $^3J_{HF}$=6.1 Hz), –117.9 (dd, $^2J_{FF}$=265.7 Hz, $^3J_{HF}$=16.3 Hz) ppm. **HRMS** (MS+) for $C_{14}H_{25}F_2NNaO_5S$ $(M+Na)^+$ calcd 380.1314, found 380.1305.



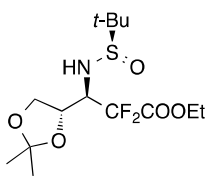
*5.9.2.7 Reaction with sulfinylimine **3.42R***

150 mg, 0.643 mmol yielded **3.51R** (88:12 *dr*). Chromatography (petroleum ether 40-60 °C/EtOAc 75:25→70:30) afforded ***ul*-3.51R** (120 mg, 0.336 mmol, 52%) and ***l*-3.51R** (15 mg, 0.042 mmol, 7%) as white solids.

Major isomer: (3*S*,4*S*,*R*$_S$)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate *ul*-3.51R: **R$_f$** 0.50 (hexane/EtOAc 50:50). **Mp** 84–86 °C. **[α]$_D$** –62.5 (c 0.81, $CHCl_3$, 21 °C). **IR** (neat) 3313 (br w), 2985 (br m), 1771 (s), 1077 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.54–4.40 (m, 1H), 4.38–4.25 (m, 3H), 4.15 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=7.8 Hz, 1H), 4.10 (dd, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=6.6 Hz, 1H), 3.91–3.77 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.24 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$=30.7 Hz), 113.9 (dd, $^1J_{CF}$=259.1 Hz, $^1J_{CF}$=254.7 Hz), 110.4, 70.8 (d, $^3J_{CF}$=2.9 Hz), 66.2, 63.0, 57.9 (t, $^2J_{CF}$=25.6 Hz), 56.7, 26.2, 25.6, 22.5 (3C), 13.9 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –108.9 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), –118.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz) ppm. **MS** (ESI+) (*m/z*) 421 ((M+Na+MeCN)$^+$. **HRMS** (MS+) for $C_{14}H_{26}F_2NO_5S$ $(M+H)^+$ calcd 358.1500, found 358.1494.



Minor isomer: (3*R*,4*S*,*R*$_S$)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate *l*-3.51R: **R$_f$** 0.32 (hexane/EtOAc 50:50). **Mp** 86–88 °C . **[α]$_D$** –22.6 (c 0.06, $CHCl_3$, 22 °C). **IR** (neat) 3205 (br w), 2986 (br m), 1775 (s), 1065 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.43–4.22 (m, 3H), 4.14 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=6.4 Hz, 1H), 4.07–3.94 (m, 1H), 3.88 (dd, $^2J_{HH}$=8.6 Hz, $^3J_{HH}$=6.3 Hz, 1H), 3.65 (d, $^3J_{HH}$=9.0 Hz, 1H), 1.39 (s, 3H), 1.38 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.33 (s, 3H),



1.25 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6 (t, $^2J_{CF}$=30.8 Hz), 113.6 (dd, $^1J_{CF}$=257.5, 253.8 Hz), 110.5, 73.7 (d, $^3J_{CF}$=2.9 Hz), 67.1, 63.3, 61.0 (t, $^2J_{CF}$=22.0 Hz), 57.2, 26.1, 25.1, 22.6 (3C), 13.8 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ −109.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$ 8.6 Hz), −118.1 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=12.9 Hz) ppm. **MS** (ESI+) (*m/z*) 421 ((M+Na+MeCN)$^+$, 100). **HRMS** (MS+) for $C_{14}H_{26}F_2NO_5S$ (M+H)$^+$ calcd 358.1500, found 358.1498.

*5.9.2.8 Reaction with sulfinylimine **3.43S***

100 mg, 0.366 mmol yielded ***ul*-3.52S** (single diastereoisomer). Chromatography (petroleum ether 40-60 °C/EtOAc 65:35→50:50) afforded ***ul*-3.52S** (75 mg, 0.189 mmol, 52%).

(3*R*,4*S*,*S*$_S$)-Ethyl-4,5-cyclohexylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate *ul*-3.52S (white solid): **R_f** 0.23 (PE 40-60 °C/EtOAc 50:50). **Mp** 112–116 °C. **[α]$_D$** +28.3 (c 0.56, $CHCl_3$, 23 °C). **IR** (neat) 3203 (br, w), 2937 (m), 1761 (m), 1092 (m), 1050 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.37–4.06 (m, 5H), 3.96 (dddd, $^3J_{HF}$=17.2 Hz, $^3J_{HF}$=8.6 Hz, $^3J_{HH}$=8.5 Hz, $^3J_{HH}$=7.3 Hz, 1H), 3.54 (d, $^3J_{HH}$=8.5 Hz, 1H), 1.70–1.45 (m, 8H), 1.44–1.28 (m, 2H), 1.35 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.21 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$=30.7 Hz), 113.9 (dd, $^1J_{CF}$=256.1 Hz, $^1J_{CF}$=251.8 Hz), 111.3, 73.2, 66.5, 62.9, 61.1 (t, $^2J_{CF}$=22.0 Hz), 57.1, 35.6, 34.2, 24.9, 23.8, 23.6, 22.4 (3C), 13.8 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ −109.5 (dd, $^2J_{FF}$=264.3 Hz, $^3J_{HF}$=8.6 Hz), −118.9 (dd, $^2J_{FF}$=264.3 Hz, $^3J_{HF}$=17.2 Hz) ppm. **MS** (ESI+) (*m/z*) 461 (M+Na+MeCN)$^+$. **HRMS** (MS+) for $C_{17}H_{30}F_2NO_5S$ (M+H)$^+$ calcd 398.1807, found 398.1804.

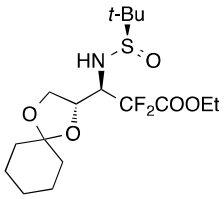
*5.9.2.9 Reaction with sulfinylimine **3.43R***

100 mg, 0.366 mmol yielded **3.52R** (81:19 *dr*). Chromatography (petroleum ether 40-60 °C/EtOAc 80:20→65:35) afforded ***ul*-3.52R** (70 mg, 0.176 mmol, 48%) and ***l*-3.52R** (12 mg, 0.030 mmol, 8%) as white solids.

Major isomer: (3*S*,4*S*,*R*$_S$)-ethyl-4,5-cyclohexylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate *ul*-3.52R: **R_f** 0.21 (petroleum ether 40-60 °C/EtOAc 65:35). **Mp** 72–75 °C. **[α]$_D$** −29.9 (c 0.68, $CHCl_3$, 21 °C). **IR** (neat) 3311 (br w), 2935 (m), 1770 (s), 1075 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.43 (t, $^3J_{HH}$=7.2 Hz, 1H), 4.39–4.24 (m, 3H), 4.16–4.07 (m, 2H), 3.90–3.76 (m, 1H), 1.70–1.51 (m, 8H), 1.46–1.33 (m, 2H), 1.37 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.25 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$=30.7 Hz), 113.9 (t, $^1J_{CF}$=259.1 Hz), 111.0, 70.5 (d, $^3J_{CF}$=2.9 Hz), 65.9, 63.0, 58.0 (t, $^2J_{CF}$=26.3 Hz), 56.7, 35.7, 35.4, 25.0, 23.9, 23.7, 22.5 (3C), 13.9 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ −108.9 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=8.6 Hz), −117.8 (dd, $^2J_{FF}$=262.2 Hz, $^3J_{HF}$=17.2 Hz)

ppm. **MS** (ESI+) (*m/z*) 461 $(M+Na+MeCN)^+$. **HRMS** (MS+) for $C_{17}H_{30}F_2NO_5S$ $(M+H)^+$ calcd 398.1807, found 398.1808.

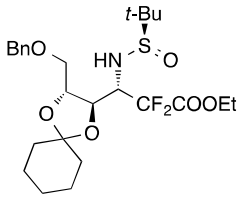
Minor isomer: (3*R*,4*S*,*R*$_S$)-ethyl-4,5-cyclohexylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate *I*-3.52R: R_f 0.12 (petroleum ether 40-60 °C/EtOAc 65:35). **Mp** 122–124 °C **$[\alpha]_D$** –39.0 (c 0.50, $CHCl_3$, 19 °C). **IR** (neat) 3204 (br w), 2937 (m), 1762 (s), 1053 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.36 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.2 Hz, 1H), 4.30 (dq, $^2J_{HH}$=10.7, $^3J_{HH}$=7.2 Hz, 1H), 4.25–4.18 (m, 1H), 4.15–4.08 (m, 1H), 3.98 (dddd app. ddt, $^3J_{HF}$=16.1, $^3J_{HH}$=9.1, $^3J_{HF}$=$^3J_{HH}$=8.6 Hz, 1H), 3.83 (dd, $^3J_{HH}$=8.6, 6.3 Hz, 1H), 3.67 (d, $^3J_{HH}$=9.1 Hz, 1H), 1.63–1.48 (m, 8H), 1.43–1.31 (m, 2H), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.23 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6 (t, $^2J_{CF}$=30.7 Hz), 113.7 (dd, $^1J_{CF}$=256.1 Hz, $^1J_{CF}$ 253.2 Hz), 111.2, 73.2 (br. s), 66.8, 63.2, 61.1 (t, $^2J_{CF}$=22.0 Hz), 57.1, 35.8, 34.4, 24.9, 23.8, 23.6, 22.6 (3C), 13.8 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –108.6 (dd, $^2J_{FF}$=262.5, $^3J_{HF}$=8.6 Hz), –118.3 (d, $^2J_{FF}$=262.5, $^3J_{HF}$=16.1 Hz) ppm. **MS** (ESI+) (*m/z*) 461 (M+Na+MeCN. **HRMS** (MS+) for $C_{17}H_{30}F_2NO_5S$ $(M+H)^+$ calcd 398.1807, found 398.1814.



*5.9.2.10 Reaction with sulfinylimine **ent-3.44S***

2.06 g, 5.24 mmol yielded ***ent-ul*-3.53S** (single diastereoisomer). Chromatography (petroleum ether 40-60 °C/EtOAc 75:25→60:40) afforded ***ent-ul*-3.53S** (1.81 g, 3.50 mmol, 67%).

(3*S*,4*R*,5*R*,*R*$_S$)-Ethyl-[6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexylidenedioxy)-2,2-difluorohexanoate *ent-ul*-3.53S (pale yellow oil): R_f 0.35 (petroleum ether 40-60 °C/EtOAc 50:50). **$[\alpha]_D$** +43.2 (c 0.35, $CHCl_3$, 22 °C). **IR** (neat) 3244 (w), 2936 (m), 1774 (m), 1759 (m), 1369 (m), 1060 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 4.62 (d, $^3J_{HH}$=6.4 Hz, 1H), 4.56 (s, 2H), 4.49 (ddd, $^3J_{HH}$=8.8 Hz, $^3J_{HH}$=6.8 Hz, $^3J_{HH}$=4.4 Hz, 1H), 4.32 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.1 Hz, 1H), 4.28 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.1 Hz, 1H), 4.13 (dd, $^3J_{HH}$=8.5 Hz, $^3J_{HH}$=6.8 Hz, 1H), 3.99 (dddd, $^3J_{HF}$=17.2 Hz, $^3J_{HH}$=8.5 Hz, $^3J_{HF}$=7.5 Hz, $^3J_{HH}$=6.4 Hz, 1H), 3.88 (dd, $^2J_{HH}$=8.8 Hz, $^3J_{HH}$=4.4 Hz, 1H), 3.38 (dd app. t, $^2J_{HH}$=8.8 Hz, $^3J_{HH}$ 8.8 Hz, 1H), 1.74–1.61 (m, 1H), 1.61–1.45 (m, 7H), 1.36 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.44–1.26 (m, 2H), 1.08 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{CF}$=30.7 Hz), 136.9, 128.6 (2C), 128.1 (3C), 114.0 (dd, $^1J_{CF}$=257.6 Hz, $^1J_{CF}$=251.8 Hz), 111.6, 76.5, 76.2, 73.9, 71.1, 62.8, 61.7 (t, $^2J_{CF}$=22.0 Hz), 56.4, 36.3, 35.7, 24.9, 23.7, 23.6, 22.5 (3C), 13.8 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –110.8 (dd, $^2J_{FF}$=260.0 Hz, $^3J_{HF}$=7.5 Hz), –121.4 (dd, $^2J_{FF}$=260.0 Hz, $^3J_{HF}$=17.2 Hz) ppm. **MS** (ESI+) (*m/z*) 540 $(M+Na)^+$. **HRMS** (MS+) for $C_{25}H_{38}F_2NO_6S$ $(M+H)^+$ calcd 518.2382, found 518.2377.



*5.9.2.11 Reaction with sulfinylimine **ent-3.44R***

100 mg, 0.254 mmol yielded ***ent*-3.53R** (60:40 *dr*). Chromatography (petroleum ether 40-60 °C/EtOAc 75:25→70:30) afforded ***ent-ul*-3.53R** (41 mg, 0.079 mmol, 31%) and ***ent-l*-3.53R** (22 mg, 0.043 mmol, 17%).

Major isomer: (3*R*,4*R*,5*R*,S_S)-ethyl-6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexylidenedioxy)-2,2-difluorohexanoate *ent-ul*-3.53R (pale yellow oil): $\mathbf{R_f}$ 0.37 (petroleum ether 40-60 °C/EtOAc 70:30). $\mathbf{[\alpha]_D}$ +50.8 (*c* 0.53, $CHCl_3$, 20 °C). **IR** (neat) 2936 (s), 2863 (w), 1773 (m), 1760 (m), 1073 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 4.63 (d, $^2J_{HH}$=12.1 Hz, 1H), 4.59 (d, $^2J_{HH}$=12.1 Hz, 1H), 4.51–4.44 (m, 2H), 4.30 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.26 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.20 (d, $^3J_{HH}$=8.7 Hz, 1H), 4.05 (ddd, $^3J_{HF}$=17.2 Hz, $^3J_{HH}$=8.7 Hz, $^3J_{HH}$=7.5 Hz, 1H), 3.78 (dd, $^2J_{HH}$=10.1 Hz, $^3J_{HH}$=4.2 Hz, 1H), 3.62 (dd, $^2J_{HH}$=10.1 Hz, $^3J_{HH}$=6.4 Hz, 1H), 1.77–1.47 (m, 8H), 1.44–1.30 (m, 2H), 1.33 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.24 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$=33.7 Hz), 137.9, 128.3 (2C), 127.6 (3C), 114.0 (dd, $^1J_{CF}$=259.1 Hz, $^1J_{CF}$=254.7 Hz), 110.8, 74.3, 74.2 (d, $^3J_{CF}$=2.9 Hz), 73.6, 69.5, 62.9, 57.7 (t, $^2J_{CF}$=24.9 Hz), 56.7, 36.6, 36.1, 24.9, 23.8, 23.7, 22.5 (3C), 13.9 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –109.1 (dd, $^2J_{FF}$=257.9 Hz, $^3J_{HF}$=7.5 Hz), –117.9 (dd, $^2J_{FF}$=257.9 Hz, $^3J_{HF}$=17.2 Hz) ppm. **MS** (ESI+) (*m/z*) 540 $(M+Na)^+$. **HRMS** (MS+) for $C_{25}H_{38}F_2NO_6S$ $(M+H)^+$ calcd 518.2382, found 518.2378.

Minor isomer: (3*S*,4*R*,5*R*,S_S)-ethyl-6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexylidenedioxy)-2,2-difluorohexanoate *ent-l*-3.53R (pale yellow oil): $\mathbf{R_f}$ 0.18 (petroleum ether 40-60 °C/EtOAc 70:30). $\mathbf{[\alpha]_D}$ +28.3 (c 0.72, $CHCl_3$, 20 °C). **IR** (neat) 2936 (s), 2863 (w), 1773 (m), 1760 (m), 1057 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H), 4.57 (s, 2H), 4.36 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.31 (dq, $^2J_{HH}$=10.7 Hz, $^3J_{HH}$=7.2 Hz, 1H), 4.30–4.23 (m, 1H), 4.09–3.95 (m, 2H), 3.83 (d, $^3J_{HH}$=9.2 Hz, 1H), 3.63 (dd, $^2J_{HH}$=10.0 Hz, $^3J_{HH}$=5.3 Hz, 1H), 3.58 (dd, $^2J_{HH}$=10.0 Hz, $^3J_{HH}$=4.9 Hz, 1H), 1.68–1.47 (m, 8H), 1.41–1.32 (m, 2H), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.15 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$=31.1 Hz), 137.6, 128.5 (2C), 128.0 (2C), 127.9, 113.8 (dd, $^1J_{CF}$=256.5 Hz, $^1J_{CF}$=255.0 Hz), 111.4, 77.5, 76.0 (t, $^3J_{CF}$=2.6 Hz), 73.7, 71.1, 63.2 , 60.7 (t, $^2J_{CF}$=22.7 Hz), 57.2, 36.4, 36.3, 25.0, 23.8, 23.7, 22.5 (3C), 13.8 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ –108.4 (d, $^2J_{FF}$=262.2 Hz), –116.8 (d, $^2J_{FF}$=262.2 Hz) ppm. **MS** (ESI+) (*m/z*) 540 $(M+Na)^+$. **HRMS** (MS+) for $C_{25}H_{37}F_2NNaO_6S$ $(M+Na)^+$ calcd 540.2202, found 540.2192.

*5.9.2.12 Reaction with sulfinylimine **ent-3.45S***

1.10 g, 3.11 mmol yielded ***ent-ul*-3.54S** (single diastereoisomer). Chromatography (hexane/EtOAc 80:20→60:40) afforded ***ent-ul*-3.54S** (1.04 g, 2.17 mmol, 70%).

(3*S*,4*R*,5*R*,R_S)-Ethyl-[6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(isopropylidenedioxy)-2,2-difluorohexanoate *ent-ul*-3.54S (pale yellow oil): $\mathbf{R_f}$ 0.28 (petroleum ether 40-60 °C/EtOAc 50:50). $\mathbf{[\alpha]_D}$ –50 (c 0.75, $CHCl_3$, 19 °C). **IR** (neat) 3423 (w), 2986 (m), 1774 (m), 1760 (m), 1209 (m), 1073 (s). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.40 – 7.26 (m, 5H), 4.63 (d, $^2J_{HH}$=11.8 Hz, 1H), 4.59 (d, $^2J_{HH}$=11.8 Hz, 1 H), 4.42 (ddd, $^3J_{HH}$=7.0, 5.7, 5.2 Hz, 1H), 4.32 (dq, $^2J_{HH}$=10.8, $^3J_{HH}$=7.2 Hz, 1H), 4.26 (dq, $^2J_{HH}$=10.8, $^3J_{HH}$=7.1 Hz, 1 H), 4.11 (dd, $^2J_{HH}$=8.9, 7.0 Hz, 1H), 3.98 (ddd, $^3J_{HF}$=18.6, $^3J_{HH}$=8.9, $^3J_{HF}$=6.8 Hz, 1H), 3.76 (dd, $^2J_{HH}$=9.9, $^3J_{HH}$=5.2 Hz, 1H), 3.62 (dd, $^2J_{HH}$=9.9, $^3J_{HH}$=5.7 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 1.34 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.15 (s, 9H) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 164.7 (t, *J*=30.8 Hz), 139.2, 129.7, 129.4, 129.1, 115.6 (dd, *J*=249.4, 257.5 Hz), 112.2, 79.7, 76.9 (dd, *J*=1.5, 4.4 Hz), 74.9, 72.2, 64.3, 63.8 (dd, *J*=20.9, 22.4 Hz), 58.3, 27.5, 26.9, 23.2, 14.3 ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –109.3 (dd, $^2J_{FF}$=260.1, $^3J_{HF}$=6.9 Hz, 1F), –122.2 (dd, $^2J_{FF}$=260.1, $^3J_{HF}$=18.6 Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 478 $(M+H)^+$. **HRMS** (MS+) for $C_{22}H_{33}F_2NNaO_6S$ $(M+Na)^+$ calcd 500.1889, found 500.1867.

*5.9.2.13 (3R,SS)-3-(tert-Butylsulfinylamido)-2,2-difluoropentanoic acid (**ul-3.55S**):*

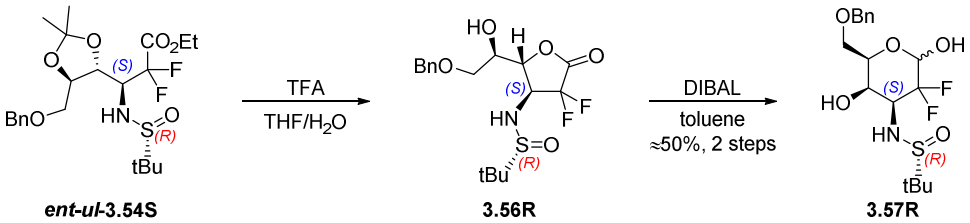
To a round-bottomed flask containing ***ul*-3.46S** (36 mg, 0.126 mmol, 1 equiv) in THF/H_2O (1:2, 3 mL) was added LiOH (15.1 mg, 0.63 mmol, 5 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h then acidified with 2M aq. HCl to pH = 2 and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give ***ul*-3.55S** (31 mg, 0.121 mmol, 96%) as a white solid. Recrystallisation from $CHCl_3$ afforded crystals suitable for X-ray analysis.

Mp: 126-128 °C. $\mathbf{[\alpha]_D}$ +50.8 (c 0.90, CH_3OH). **IR** (neat) 3275 (w, br), 2969 (w), 1748 (m), 1096 (m), 1002 (s). **^{1}H NMR** (400 MHz, CD_3OD) δ 3.70–3.56 (m, 1H), 1.83 (dqd, $^2J_{HH}$=14.4 Hz, $^3J_{HH}$=7.4, $^3J_{HH}$=3.5 Hz, 1H), 1.65 (ddq, $^2J_{HH}$=14.4 Hz, $^3J_{HH}$=10.2, $^3J_{HH}$=7.4 Hz, 1H), 1.22 (s, 9H), 1.10 (t, $^3J_{HH}$=7.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 166.4 (t, $^2J_{CF}$=33.0 Hz), 119.7–113.7 (m), 63.6 (dd, $^2J_{CF}$=26.4, 23.5 Hz), 58.1, 23.4, 22.6 (3C), 11.1 ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –112.1 (dd, $^2J_{FF}$=258.4 Hz, $^3J_{HF}$=6.1 Hz, 1F), –119.8 (dd, $^2J_{FF}$=258.4 Hz, $^3J_{HF}$=16.5 Hz, 1F) ppm. **MS**

(ESI+) (*m/z*) 258 $(M+H)^+$. **HRMS** (MS+) for $C_9H_{17}F_2NNaO_3S$ $(M+Na)^+$ calcd 280.0789, found 280.0789.

5.10 Synthesis of 1.61

5.10.1 (R_S)-6-*O*-Benzyl-3-(*tert*-butylsulfinylamino)-2,3-dideoxy-2,2-difluoro-D-*lyxo*-hexopyranose 3.57R



***ent-ul*-3.54S** **3.56R** **3.57R**

The ester ***ent-ul*-3.54S** (500 mg, 1.05 mmol) was stirred in a 10:5:1 mixture of TFA/THF/H_2O at rt for 2 h. Evaporation afforded 417 mg of a 0.85:1 mixture of TFA and the desired lactone **3.56R**. Calculated amount of product: 330 mg (0.853 mmol, ≈80%). The mixture obtained was dissolved in toluene (3.5 mL) and the temperature cooled to –78 °C. DIBAL (1M in hexane, 2.13 mL, 2.13 mmol, ≈2.5 equiv) was added over 10 min and the reaction mixture was stirred at –78 °C for 4.5 h after which the presence of starting material was evidenced by ^{19}F NMR. DIBAL (1M in hexane, 0.43 mL, 0.43 mmol, ≈0.5 equiv) was added and the reaction mixture was stirred at –70 °C for 1 h. The reaction was quenched with MeOH (1 mL), then diluted with 1M HCl (aq, 5mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Column chromatography (petroleum ether 40-60 °C/iPrOH 90:10 to 80:20) followed by HPLC (hexane/iPrOH 90:10) afforded 206 mg (0.524 mmol, 50%) of hexopyranose **3.57R** as white solid. **IR** (neat) 3304 (br, w), 2928 (w), 1251 (m), 1055 (s), 1029 (s).

Data for the α-anomer: $[\alpha]_D$ +14 (c 0.52, MeOH, 20 °C). **^{1}H NMR** (400 MHz, acetone-*d*6) δ 7.39 – 7.24 (m, 5H, H_{Ar}), 6.53 (br d, *J*=2.7 Hz, 1H, OH-1), 5.14 (br dd, *J*=6.5, 3.1 Hz, 1H, H-1), 4.59 – 4.51 (m, 2H, CH_2Ph), 4.49 – 4.42 (m, 2H, H-5 and NH), 4.37 (d, *J*=7.3 Hz, 1H, OH-4), 4.16 – 4.09 (m, 1H, H-4), 3.87 (dddd, *J*=24.8, 9.9, 6.1, 4.3 Hz, 1H, H-3), 3.76 (dd, *J*=9.9, 5.8 Hz, 1H, H-6_a), 3.63 (dd, *J*=9.9, 6.3 Hz, 1H, H-6_b), 1.23 (s, 9H, $CH_{3,tBu}$) ppm. **^{13}C NMR** (101 MHz, acetone-*d*6) δ 139.6 ($C_{q,Ar}$), 129.1 (CH_{Ar}), 128.3 (CH_{Ar}), 128.5 (CH_{Ar}), 117.1 (dd, *J*=253.8, 245.0 Hz, C-2), 92.3 (dd, *J*=37.4, 28.6 Hz, C-1), 73.8 ($\underline{C}H_2Ph$), 70.7 (d, *J*=5.9 Hz, C-4), 70.1 (C-6), 69.8 (C-5), 57.0 ($C_{q,tBu}$), 56.9 (t, *J*=18.0 Hz, C-3), 22.8 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, acetone-*d*6) δ –115.2 (dt, *J*=251.4, 5.1 Hz, 1F), –117.0 (ddd, *J*=251.4, 24.8, 6.8 Hz, 1F) ppm.

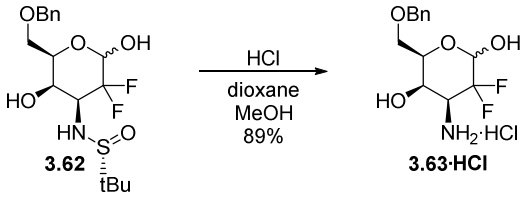
Data for the β-anomer: **^{1}H NMR** (400 MHz, acetone-*d*6) δ 7.41 – 7.24 (m, 5H, H_{Ar}), 6.27 (br d, *J*=8.7 Hz, 1H, OH-1), 4.90 (dd, *J*=16.4, 8.7 Hz, 1H, H-1), 4.56 (s, 2H, $C\underline{H}_2Ph$), 4.43 (br d, *J*=9.6 Hz, 1H, NH), 4.32 (d, *J*=7.4 Hz, 1H, OH-4), 4.10 – 4.04 (m, 1H, H-4), 4.01 (app. td, *J*=6.0, 1.3 Hz, 1H, H-5), 3.88 – 3.74 (m, 1H, H-3), 3.77 (dd, *J*=9.9, 5.9 Hz, 1H, H-6_a), 3.67 (dd, *J*=9.9, 6.2 Hz, 1H, H-6_b), 1.22 (s, 9H, $CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, acetone-*d*6) δ –116.4 – –117.2 (m, *J*=248.0 Hz, 1F), –134.4 (ddd, *J*=248.0, 23.4, 16.5 Hz, 1F) ppm.

MS (ESI+) (*m/z*) 416 $(M+Na)^+$.

*5.10.1.1 (R_S)-6-O-Benzyl-3-(tert-butylsulfinylamino)-2,3-dideoxy-2,2-difluoro-D-lyxo-hexono-1,4-lactone (**3.56R**)*

Analytical sample of the lactone was obtained *via* column chromatography (petroleum ether 40-60 °C/EtOAc 70:30 to 50:50). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H, H_{Ar}), 4.64 – 4.47 (m, 3H, $C\underline{H}_2Ph$ and H-3), 4.37 (dd, *J*=8.9, 1.8 Hz, 1H, H-4), 4.32 (ddd, *J*=6.4, 5.9, 1.8 Hz, 1H, H-5), 3.95 (d, *J*=9.8 Hz, 1H, NH), 3.71 (dd, *J*=9.6, 6.4 Hz, 1H, H-6_a), 3.63 (dd, *J*=9.6, 5.9 Hz, 1H, H-6_b), 1.26 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (dd, *J*=33.8, 29.3 Hz, C=O), 137.2 ($C_{q,Ar}$), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 112.1 (dd, *J*=265.6, 248.7 Hz, CF_2), 79.9 (d, *J*=7.3 Hz, C-4), 73.7 ($\underline{C}H_2Ph$), 69.8 (C-6), 65.6 (C-5), 57.5 (dd, *J*=22.7, 16.9 Hz, C-3), 57.4 ($C_{q,tBu}$), 22.4 ($CH_{3,tBu}$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –119.3 (dd, *J*=276.6, 19.1 Hz, 1F), –121.4 (dd, *J*=276.6, 10.4 Hz, 1F).

5.10.2 3-Amino-6-*O*-benzyl-2,3-dideoxy-2,2-difluoro-D-*lyxo*-hexopyranose hydrochloride 3.58·HCl



A solution of sulfinamide **3.57R** (270 mg, 0.686 mmol, 1 equiv) in MeOH (1.2 mL) and 4M HCl in dioxane (0.34 mL, 1.37 mmol, 2 equiv) was stirred at rt for 1 h then evaporated *in vacuo* to near dryness. Et_2O (5 mL) was added in order to precipitate the hydrochloride salt and the supernatant was removed. The solid was washed once more with Et_2O (5 mL) then dried under vacuum to yield 199 mg (0.611 mmol, 89%) of the **3.58·HCl** as a white solid consisting of a 90:10 α/β mixture of anomers. **IR** (neat) 3214 (br, w), 2876 (m), 1519 (m), 1149 (s), 1076 (s).

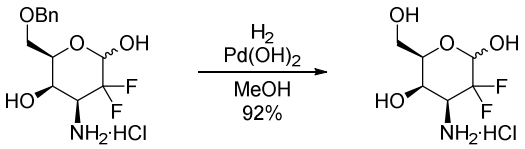
Data for the α-anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 7.38 – 7.25 (m, 5H, H_{Ar}), 5.16 (d, *J*=7.3 Hz, 1H, H-1), 4.60 (d, *J*=11.8 Hz, 1H, $C\underline{H}HPh$), 4.56 (d, *J*=11.8 Hz, 1H, $CH\underline{H}Ph$), 4.41 (td, *J*=6.3, 1.1 Hz, 1H, H-5), 4.17 – 4.13 (m, 1H, H-4), 3.95 (ddd, *J*=23.8, 5.0, 4.2 Hz, 1H, H-3), 3.75 (dd, *J*=10.0, 6.1

Hz, 1H, H-6_a), 3.65 (dd, *J*=10.0, 6.5 Hz, 1H, H-6_b) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 139.5 ($C_{q,Ar}$), 129.5 (CH_{Ar}), 129.1 (CH_{Ar}), 128.9 (CH_{Ar}), 116.6 (dd, *J*=254.6, 248.0 Hz, C-2), 92.0 (dd, *J*=35.9, 27.1 Hz, C-1), 74.6 (CH_2Ph), 69.8 (C-6), 69.3 (C-5), 67.3 (d, *J*=5.1 Hz, C-4), 51.6 (t, *J*=18.7 Hz, C-3) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –115.6 (m, *J*=248.8 Hz, 1F), –118.0 (m, *J*=248.8, 23.4 Hz, 1F) ppm.

Unambiguous resonances for the β-anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 4.93 (d, *J*=16.3 Hz, 1H, H-1β) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –116.7 (br dt, *J*=247.1, 4.3 Hz, 1F), –134.4 (m, *J*=247.1 Hz, 1F) ppm.

MS (ESI+) (*m/z*) 290 $(M+H)^+$. **HRMS** (MS+) for $C_{13}H_{18}F_2NO_4$ $(M+H)^+$ calcd 290.1198, found 290.1203.

5.10.3 3-Amino-2,3-dideoxy-2,2-difluoro-D-*lyxo*-hexopyranose hydrochloride 1.61·HCl



3.63 **1.61·HCl**

To a solution of **3.58·HCl** (187 mg, 0.574 mmol, 1 equiv) in MeOH (10 mL) was added $Pd(OH)_2$/C (20%, 101 mg, 0.144 mmol, 0.25 equiv) and H_2 was bubbled through the solution via a needle for 10 min. The reaction mixture was left stirring at rt under H_2 for 2.5 h then filtered over a pad of Celite® and concentrated *in vacuo* to near dryness. Et_2O (5 mL) was added in order to precipitate the hydrochloride salt and the supernatant was removed. The solid was washed once more with Et_2O (5 mL) then dried under vacuum to yield 125 mg (0.531 mmol, 92%) of the **1.61·HCl** as a white solid consisting of a 90:10 α/β mixture of anomers.

Data for the α-anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 5.15 (d, *J*=7.3 Hz, 1H, H-1), 4.23 (td, *J*=6.3, 1.1 Hz, 1H, H-5), 4.19 – 4.12 (m, 1H, H-4), 3.98 – 3.88 (m, 1H, H-3), 3.76 (dd, *J*=11.3, 6.1 Hz, 1H, H-6_a), 3.72 (dd, *J*=11.3, 6.6 Hz, 1H, H-6_b) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 116.6 (dd, *J*=254.6, 248.3 Hz), 91.9 (dd, *J*=35.9, 27.1 Hz, C-1), 70.9 (C-5), 67.0 (d, *J*=5.9 Hz, C-4), 61.7 (C-6), 51.6 (t, *J*=18.9 Hz, C-3) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –115.7 (dt, *J*=248.8, 4.3 Hz, 1F), –118.0 (ddd, *J*=248.8, 23.4, 6.9 Hz, 1F) ppm.

Unambiguous resonances for the β-anomer: **^{1}H NMR** (400 MHz, CD_3OD) δ 4.92 (d, *J*=16.4 Hz, 1H, H-1) ppm. **^{13}C NMR** (101 MHz, CD_3OD) δ 116.3 (br dd, *J*=259.3, 250.2 Hz), 93.9 (br dd, *J*=28.1, 20.0 Hz, C-1), 77.3 (C-5), 66.8 (d, *J*=6.6 Hz, C-4), 61.7 (C-6), 54.5 (t, *J*=19.1 Hz, C-3) ppm. **^{19}F NMR** (376 MHz, CD_3OD) δ –116.8 (dt, *J*=246.7, 4.6 Hz, 1F), –134.4 (ddd, *J*=246.7, 22.5, 16.5

Hz, 1F) ppm. **MS** (ESI+) (*m/z*) 200 $(M+H)^+$. **HRMS** (MS^+) for $C_6H_{12}F_2NO_4$ $(M + Na)^+$ calcd 200.0729, found 200.0728.

Chapter 6: References

(1) Pauling, L. *J. Am. Chem. Soc.* **1932**, *54*, 3570-3582.

(2) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441-451.

(3) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, **1994**.

(4) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308-319.

(5) Sun, A.; Lankin, D. C.; Hardcastle, K.; Snyder, J. P. *Chem. Eur. J.* **2005**, *11*, 1579-1591.

(6) Gooseman, N. E. J.; O'Hagan, D.; Peach, M. J. G.; Slawin, A. M. Z.; Tozer, D. J.; Young, R. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5904-5908.

(7) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330.

(8) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2013**, *114*, 2432-2506.

(9) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15-24.

(10) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071-1081.

(11) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. *Pure Appl. Chem.* **2011**, *83*, 1619-1636.

(12) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. *Pure Appl. Chem.* **2011**, *83*, 1637-1641.

(13) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881-1886.

(14) Dunitz, J. D.; Taylor, R. *Chem. Eur. J.* **1997**, *3*, 89-98.

(15) Carosati, E.; Sciabola, S.; Cruciani, G. *J. Med. Chem.* **2004**, *47*, 5114-5125.

(16) Schneider, H.-J. *Chem. Sci.* **2012**, *3*, 1381-1394.

(17) Barbarich, T. J.; Rithner, C. D.; Miller, S. M.; Anderson, O. P.; Strauss, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 4280-4281.

(18) Biamonte, M. A.; Vasella, A. *Helv. Chim. Acta* **1998**, *81*, 695-717.

(19) Zapata, A.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 1169-1191.

(20) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2007**, *90*, 1874-1888.

(21) Giuffredi, G. T.; Gouverneur, V.; Bernet, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 10524-10528.

(22) Ouvrard, C.; Berthelot, M.; Laurence, C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1357-1362.

(23) Dalvit, C.; Invernizzi, C.; Vulpetti, A. *Chem. Eur. J.* **2014**, *20*, 11058-11068.

(24) Rademacher, T. W.; Parekh, R. B.; Dwek, R. A. *Annu. Rev. Biochem.* **1988**, *57*, 785-838.

(25) Varki, A. *Glycobiology* **1993**, *3*, 97-130.

(26) Kiessling, L. L.; Splain, R. A. *Annu. Rev. Biochem.* **2010**, *79*, 619-653.

(27) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300-2324.

(28) Quiocho, F. A. *Pure Appl. Chem.* **1989**, *61*, 1293-1306.

(29) Lemieux, R. U. *Acc. Chem. Res.* **1996**, *29*, 373-380.

(30) Davis, A. M.; Teague, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 736-749.

(31) Vyas, N.; Vyas, M.; Quiocho, F. *Science* **1988**, *242*, 1290-1295.

(32) Gao, J.; Qiao, S.; Whitesides, G. M. *J. Med. Chem.* **1995**, *38*, 2292-2301.

(33) Mecinović, J.; Snyder, P. W.; Mirica, K. A.; Bai, S.; Mack, E. T.; Kwant, R. L.; Moustakas, D. T.; Héroux, A.; Whitesides, G. M. *J. Am. Chem. Soc.* **2011**, *133*, 14017-14026.

(34) Olsen, J. A.; Banner, D. W.; Seiler, P.; Wagner, B.; Tschopp, T.; Obst-Sander, U.; Kansy, M.; Müller, K.; Diederich, F. *ChemBioChem* **2004**, *5*, 666-675.

(35) Dalvit, C.; Vulpetti, A. *ChemMedChem* **2011**, *6*, 104-114.

(36) Dalvit, C.; Vulpetti, A. *ChemMedChem* **2012**, *7*, 262-272.

(37) Kim, H. W.; Rossi, P.; Shoemaker, R. K.; DiMagno, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 9082-9083.

(38) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem* **2004**, *5*, 622-627.

(39) Street, I. P.; Armstrong, C. R.; Withers, S. G. *Biochemistry* **1986**, *25*, 6021-6027.

(40) McCarter, J. D.; Adam, M. J.; Hartman, N. G.; Withers, S. G. *Biochem. J.* **1994**, *301*, 343-348.

(41) Riley, G. J.; Taylor, N. F. *Biochem. J.* **1973**, *135*, 773-777.

(42) Potts, J. R.; Hounslow, A. M.; Kuchel, P. W. *Biochem. J.* **1990**, *266*, 925-928.

(43) Potts, J. R.; Kuchel, P. W. *Biochem. J.* **1992**, *281*, 753-759.

(44) O'Connell, T. M.; Gabel, S. A.; London, R. E. *Biochemistry* **1994**, *33*, 10985-10992.

(45) Bresciani, S.; Lebl, T.; Slawin, A. M. Z.; O'Hagan, D. *Chem. Commun.* **2010**, *46*, 5434-5436.

(46) Boydell, A. J.; Vinader, V.; Linclau, B. *Angew. Chem. Int. Ed.* **2004**, *43*, 5677-5679.

(47) Timofte, R. S.; Linclau, B. *Org. Lett.* **2008**, *10*, 3673-3676.

(48) Linclau, B.; Boydell, A. J.; Timofte, R. S.; Brown, K. J.; Vinader, V.; Weymouth-Wilson, A. C. *Org. Biomol. Chem.* **2009**, *7*, 803-814.

(49) Ioannou, A.; Cini, E.; Timofte, R. S.; Flitsch, S. L.; Turner, N. J.; Linclau, B. *Chem. Commun.* **2011**, *47*, 11228-11230.

(50) N'Go, I.; Golten, S.; Ardá, A.; Cañada, J.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P. *Chem. Eur. J.* **2014**, *20*, 106-112.

(51) Graton, J.; Wang, Z.; Brossard, A.-M.; Gonçalves Monteiro, D.; Le Questel, J.-Y.; Linclau, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 6176-6180.

(52) Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. *J. Med. Chem.* **2009**, *52*, 4073-4086.

(53) Laurence, C.; Berthelot, M.; Helbert, M.; Sraidi, K. *J. Phys. Chem.* **1989**, *93*, 3799-3802.

(54) Graton, J.; Laurence, C.; Berthelot, M.; Le Questel, J.-Y.; Besseau, F.; D. Raczynska, E. *J. Chem. Soc., Perkin Trans. 2* **1999**, 997-1002.

(55) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795-798.

(56) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, **1965**.

(57) Titov, E. V.; Korzhenevskaya, N. G.; Gandel'sman, L. Z.; Dronkina, M. I.; Khomenko, L. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1983**, *53*, 2117-2119.

(58) Richard, J. P.; Toteva, M. M.; Crugeiras, J. *J. Am. Chem. Soc.* **2000**, *122*, 1664-1674.

(59) Konno, T.; Takano, S.; Takahashi, Y.; Konishi, H.; Tanaka, Y.; Ishihara, T. *Synthesis* **2011**, *2011*, 33-44.

(60) Konno, T.; Hoshino, T.; Kida, T.; Takano, S.; Ishihara, T. *J. Fluorine Chem.* **2013**, *152*, 106-113.

(61) Posner, G. H.; Nelson, T. D. *Tetrahedron* **1990**, *46*, 4573-4586.

(62) Vijgen, S.; Nauwelaerts, K.; Wang, J.; Van Aerschot, A.; Lagoja, I.; Herdewijn, P. *J. Org. Chem.* **2005**, *70*, 4591-4597.

(63) Zhou, W.; Gumina, G.; Chong, Y.; Wang, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2004**, *47*, 3399-3408.

(64) Nishizono, N.; Akama, Y.; Agata, M.; Sugo, M.; Yamaguchi, Y.; Oda, K. *Tetrahedron* **2011**, *67*, 358-363.

(65) Pollex, A.; Millet, A.; Müller, J.; Hiersemann, M.; Abraham, L. *J. Org. Chem.* **2005**, *70*, 5579-5591.

(66) Denmark, S. E.; Ghosh, S. K. *Tetrahedron* **2007**, *63*, 8636-8644.

(67) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* **2004**, 470-471.

(68) Rausch, D. A.; Lovelace, A. M.; Coleman, J. L. E. *J. Org. Chem.* **1956**, *21*, 1328-1330.

(69) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675-3680.

(70) Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728-6734.

(71) Klausener, A.; Runsink, J.; Scharf, H.-D. *Liebigs Ann. Chem.* **1984**, *1984*, 783-790.

(72) Lichtenthaler, F. W.; Lergenmüller, M.; Peters, S.; Varga, Z. *Tetrahedron: Asymmetry* **2003**, *14*, 727-736.

(73) Ishiwata, A.; Sakurai, A.; Nishimiya, Y.; Tsuda, S.; Ito, Y. *J. Am. Chem. Soc.* **2011**, *133*, 19524-19535.

(74) Sail, D.; Kováč, P. *Carbohydr. Res.* **2012**, *357*, 47-52.

(75) Yang, J.; Fu, X.; Jia, Q.; Shen, J.; Biggins, J. B.; Jiang, J.; Zhao, J.; Schmidt, J. J.; Wang, P. G.; Thorson, J. S. *Org. Lett.* **2003**, *5*, 2223-2226.

(76) Hodosi, G.; Kováč, P. *Carbohydr. Res.* **1997**, *303*, 239-243.

(77) Izatt, R. M.; Rytting, J. H.; Hansen, L. D.; Christensen, J. J. *J. Am. Chem. Soc.* **1966**, *88*, 2641-2645.

(78) Périon, R.; Lemée, L. c.; Ferrières, V.; Duval, R.; Plusquellec, D. *Carbohydr. Res.* **2003**, *338*, 2779-2792.

(79) Wray, V. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1598-1605.

(80) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-3740.

(81) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278-1284.

(82) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883-8904.

(83) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303-310.

(84) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589-590.

(85) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882-5886.

(86) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693-1696.

(87) March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. *Chem. Biodiversity* **2012**, *9*, 2410-2441.

(88) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D. O.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448-7454.

(89) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276-8279.

(90) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387-6389.

(91) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6.

(92) Buesking, A. W.; Baguley, T. D.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 964-967.

(93) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948-9957.

(94) Bergeron, M.; Johnson, T.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2011**, *50*, 11112-11116.

(95) Fontenelle, C. Q.; Conroy, M.; Light, M.; Poisson, T.; Pannecoucke, X.; Linclau, B. *J. Org. Chem.* **2014**, *79*, 4186-4195.

(96) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5291-5294.

(97) Baldwin, J. E.; Lynch, G. P.; Schofield, C. J. *Tetrahedron* **1992**, *48*, 9085-9100.

(98) Dondoni, A.; Massi, A.; Sabbatini, S. *Chem. Eur. J.* **2005**, *11*, 7110-7125.

(99) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403-1406.

(100) Enders, D.; Berg, S. v.; Jandeleit, B. *Org. Synth.* **2002**, *78*, 177.

(101) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585-587.

(102) Dondoni, A.; Merino, P. *Synthesis* **1992**, *1992*, 196-200.

(103) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Heterocycles* **1988**, *27*, 495-508.

(104) Poisson, T.; Belhomme, M.-C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277-9285.

(105) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 2270-2273.

(106) Adrian, J. C.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143-2150.

(107) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920-2930.

(108) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051-2054.

(109) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291-9294.

(110) Pakulski, Z.; Zamojski, A. *Tetrahedron* **1995**, *51*, 871-908.

(111) Brown, K. J. Ph. D. Thesis, University of Southampton, 2011.

(112) Seneci, P.; Leger, I.; Souchet, M.; Nadler, G. *Tetrahedron* **1997**, *53*, 17097-17114.

(113) Phukan, P.; Madan Mohan, J.; Sudalai, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3685-3689.

(114) Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J.* **2005**, *11*, 5269-5278.

(115) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913-9914.

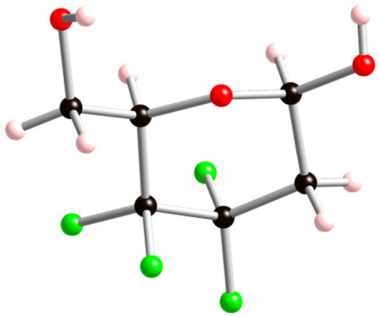
(116) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772-8778.

Chapter 7: Appendices

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2012sot0091** (CF003Arc2)
Empirical formula	$C_6H_8F_4O_3$
Formula weight	204.12
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.366(4) Å
	b = 9.179(5) Å
	c = 9.448(5) Å
Volume	725.5(6) Å^3
Z	4
Density (calculated)	1.869 Mg / m^3
Absorption coefficient	0.208 mm^{-1}
$F(000)$	416
Crystal	Block; Colourless
Crystal size	0.21 × 0.18 × 0.07 mm^3
θ range for data collection	3.09 – 27.47°
Index ranges	$-10 \le h \le 9$, $-7 \le k \le 11$, $-10 \le l \le 12$
Reflections collected	3335
Independent reflections	972 [R_{int} = 0.0294]
Completeness to θ = 27.47°	98.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9856 and 0.9576
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	972 / 0 / 126
Goodness-of-fit on F^2	0.920
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0333, $wR2$ = 0.0819
R indices (all data)	$R1$ = 0.0376, $wR2$ = 0.0842
Largest diff. peak and hole	0.322 and –0.191 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogens were located in the difference map, OH were freely refined and CH were placed in calculated positions and refined using a riding model

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	14872(3)	4702(3)	6228(3)	12(1)	1
C2	14034(3)	3352(3)	6773(3)	12(1)	1
C3	12392(3)	3252(3)	6112(3)	13(1)	1
C4	11457(3)	4670(3)	6221(3)	12(1)	1
C5	12452(3)	5987(3)	5777(3)	11(1)	1
C6	11615(3)	7407(3)	6062(3)	14(1)	1
O1	16322(2)	4872(2)	6929(2)	14(1)	1
O6	13917(2)	5964(2)	6547(2)	12(1)	1
O7	12499(2)	8589(2)	5464(2)	15(1)	1
F3A	12534(2)	2941(2)	4703(2)	19(1)	1
F3E	11524(2)	2149(2)	6688(2)	20(1)	1
F4A	10944(2)	4818(2)	7586(2)	17(1)	1
F4E	10113(2)	4582(2)	5409(2)	20(1)	1

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

C1–O1	1.391(3)	C4–F4E	1.363(3)
C1–O6	1.439(3)	C4–F4A	1.366(3)
C1–C2	1.514(3)	C4–C5	1.526(4)
C2–C3	1.511(3)	C5–O6	1.425(3)
C3–F3E	1.360(3)	C5–C6	1.504(3)
C3–F3A	1.367(3)	C6–O7	1.430(3)
C3–C4	1.522(3)		
O1–C1–O6	107.1(2)	F4E–C4–C5	110.1(2)
O1–C1–C2	109.5(2)	F4A–C4–C5	110.6(2)
O6–C1–C2	109.3(2)	F4E–C4–C3	109.6(2)
C3–C2–C1	109.2(2)	F4A–C4–C3	108.1(2)
F3E–C3–F3A	106.3(2)	C5–C4–C3	112.2(2)
F3E–C3–C2	111.4(2)	O6–C5–C6	108.8(2)
F3A–C3–C2	109.7(2)	O6–C5–C4	108.5(2)
F3E–C3–C4	109.6(2)	C6–C5–C4	112.5(2)
F3A–C3–C4	106.82(19)	O7–C6–C5	110.2(2)
C2–C3–C4	112.8(2)	C5–O6–C1	112.48(18)
F4E–C4–F4A	106.13(19)		

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}
C1	10(1)	12(1)	16(1)	−2(1)	1(1)	1(1)
C2	12(1)	9(1)	16(1)	0(1)	0(1)	0(1)
C3	15(1)	10(1)	15(1)	2(1)	1(1)	−1(1)
C4	13(1)	13(1)	11(1)	0(1)	−2(1)	−1(1)
C5	11(1)	12(1)	12(1)	1(1)	−2(1)	−1(1)
C6	14(1)	12(1)	16(1)	−1(1)	1(1)	2(1)
O1	9(1)	14(1)	20(1)	2(1)	−2(1)	−2(1)
O6	9(1)	9(1)	18(1)	−2(1)	−2(1)	1(1)
O7	16(1)	10(1)	20(1)	3(1)	−2(1)	−4(1)
F3A	20(1)	20(1)	16(1)	−6(1)	−3(1)	2(1)
F3E	15(1)	12(1)	33(1)	5(1)	1(1)	−4(1)
F4A	19(1)	16(1)	17(1)	1(1)	5(1)	1(1)
F4E	14(1)	16(1)	30(1)	0(1)	−10(1)	1(1)

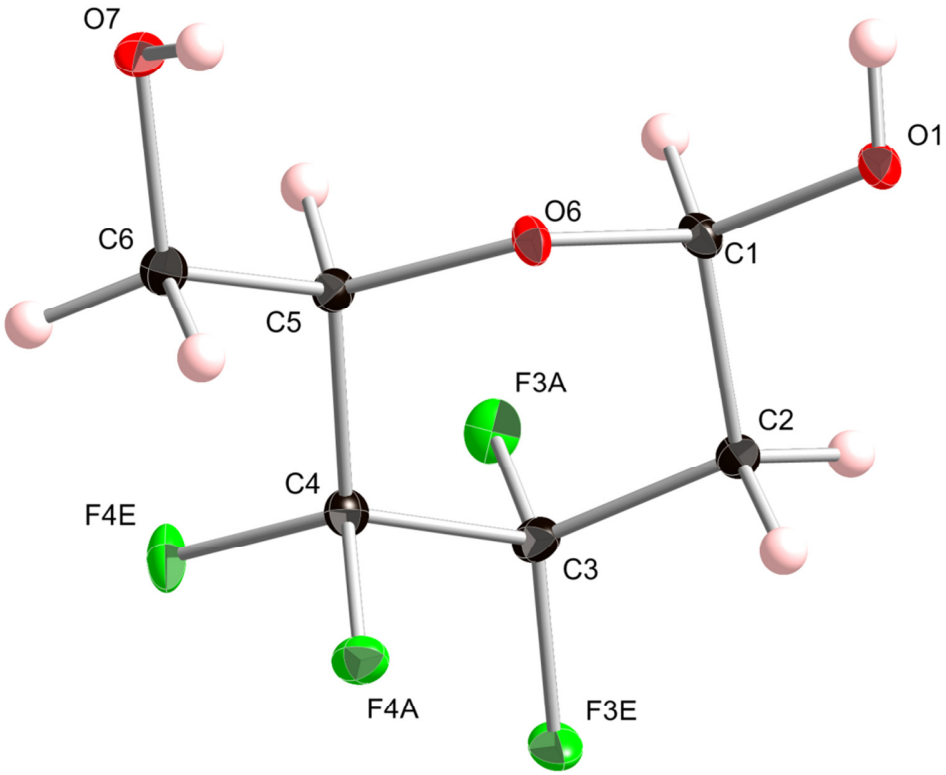
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	*S.o.f.*
H1	15051	4624	5184	15	1
H2A	14665	2474	6530	15	1
H2B	13936	3402	7817	15	1
H5	12692	5915	4743	13	1
H6A	10529	7381	5646	17	1
H6B	11507	7551	7096	17	1
H01	16850(40)	5370(40)	6450(40)	38(11)	1
H07	12960(40)	9010(40)	6190(40)	55(12)	1

Table 6. Hydrogen bonds [Å and °].

D–H···A	$d(D$–H)	d(H···A)	$d(D$···A)	∠(DHA)
O1–H01···O7^{i}	0.78(3)	2.11(3)	2.842(3)	155(3)
O7–H07···O1^{ii}	0.87(4)	2.04(4)	2.903(3)	170(4)

Symmetry transformations used to generate equivalent atoms:
(i) x+1/2,−y+3/2,−z+1 (ii) −x+3,y+1/2,−z+3/2



Thermal ellipsoids drawn at the 35% probability level.

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.

Identification code	**2012sot0015** (CF6141-95Brc)
Empirical formula	$C_{13}H_{14}F_4O_4$
Formula weight	310.24
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 8.8199(3) Å
	b = 5.5422(2) Å β = 91.413(2)°
	c = 28.0430(7) Å
Volume	1370.37(8) Å^3
Z	4
Density (calculated)	1.504 Mg / m^3
Absorption coefficient	0.144 mm^{-1}
$F(000)$	640
Crystal	Block; Colourless
Crystal size	0.33 × 0.14 × 0.07 mm^3
θ range for data collection	3.67 – 27.48°
Index ranges	$-10 \le h \le 11$, $-7 \le k \le 6$, $-36 \le l \le 36$
Reflections collected	11472
Independent reflections	3061 [R_{int} = 0.0300]
Completeness to θ = 27.48°	97.3 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9900 and 0.9539
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3061 / 19 / 199
Goodness-of-fit on F^2	1.130
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0471, $wR2$ = 0.1156
R indices (all data)	$R1$ = 0.0506, $wR2$ = 0.1180
Largest diff. peak and hole	0.304 and –0.223 e Å^{-3}

Diffractometer: Rigaku R-Axis Spider including curved Fujifilm image plate and a graphite monochromated sealed tube Mo generator. Cell determination, Data collection, Data reduction and cell refinement & Absorption correction: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , Structure solution: SHELXS97 (G. M. Sheldrick, Acta Cryst. (1990) A46 467 473). Structure refinement: SHELXL97 (G. M. Sheldrick (1997), University of Gttingen, Germany). Graphics: CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except those of the OH which were fully the refined. The orientation of the BnO group is disordered over two positions.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
F3A	826(1)	1322(2)	1682(1)	43(1)	1
F3E	968(1)	–2594(2)	1587(1)	42(1)	1
F4A	3884(1)	–2298(2)	1383(1)	35(1)	1
F4E	2605(1)	435(2)	987(1)	42(1)	1
O1	4514(1)	1247(2)	2118(1)	22(1)	1
O2	2852(1)	–3075(2)	2336(1)	26(1)	1
O3	853(2)	–612(3)	2545(1)	36(1)	1
C1	3206(2)	1256(3)	2413(1)	24(1)	1
C2	2169(2)	–832(3)	2277(1)	23(1)	1
C3	1750(2)	–637(3)	1744(1)	26(1)	1
C4	3116(2)	–193(3)	1432(1)	26(1)	1
C5	4154(2)	1768(3)	1631(1)	22(1)	1
C6A	5612(2)	1896(3)	1361(1)	27(1)	0.533(5)
O6A	6380(20)	4050(30)	1485(6)	31(1)	0.533(5)
C7A	7882(16)	4070(30)	1292(3)	37(2)	0.533(5)
C8A	7787(5)	4334(9)	755(2)	31(1)	0.533(5)
C9A	7202(6)	6409(8)	542(2)	40(1)	0.533(5)
C10A	7115(6)	6590(9)	48(2)	47(1)	0.533(5)
C11A	7613(6)	4696(10)	–233(2)	49(1)	0.533(5)
C12A	8198(7)	2621(9)	–20(2)	49(1)	0.533(5)
C13A	8286(6)	2440(8)	474(2)	40(1)	0.533(5)
C6B	5612(2)	1896(3)	1361(1)	27(1)	0.467(5)
O6B	6350(20)	4030(30)	1517(7)	31(1)	0.467(5)
C7B	7759(18)	4500(40)	1286(4)	37(2)	0.467(5)
C8B	7688(6)	4517(11)	744(2)	31(1)	0.467(5)
C9B	6641(6)	6026(11)	517(2)	40(1)	0.467(5)
C10B	6575(6)	6152(12)	22(2)	47(1)	0.467(5)
C11B	7557(7)	4769(13)	–246(2)	49(1)	0.467(5)
C12B	8605(7)	3260(12)	–18(2)	49(1)	0.467(5)
C13B	8671(6)	3135(10)	477(2)	40(1)	0.467(5)

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

F3A–C3	1.3664(19)	C7A–C8A	1.513(8)
F3E–C3	1.353(2)	C8A–C9A	1.3900
F4A–C4	1.358(2)	C8A–C13A	1.3900
F4E–C4	1.3605(17)	C9A–C10A	1.3900
O1–C5	1.4241(16)	C10A–C11A	1.3900
O1–C1	1.4364(18)	C11A–C12A	1.3900
O2–C2	1.3895(19)	C12A–C13A	1.3900
O3–C2	1.4042(19)	O6B–C7B	1.438(10)
C1–C2	1.518(2)	C7B–C8B	1.518(9)
C2–C3	1.534(2)	C8B–C9B	1.3900
C3–C4	1.527(2)	C8B–C13B	1.3900
C4–C5	1.518(2)	C9B–C10B	1.3900
C5–C6A	1.510(2)	C10B–C11B	1.3900
C6A–O6A	1.413(9)	C11B–C12B	1.3900
O6A–C7A	1.445(10)	C12B–C13B	1.3900
C5–O1–C1	112.82(11)	C6A–C5–C4	111.18(13)
O1–C1–C2	109.87(12)	O6A–C6A–C5	108.9(6)
O2–C2–O3	112.04(13)	C6A–O6A–C7A	110.6(12)
O2–C2–C1	113.24(13)	O6A–C7A–C8A	110.1(11)
O3–C2–C1	107.44(13)	C9A–C8A–C13A	120.0
O2–C2–C3	105.84(13)	C9A–C8A–C7A	121.2(7)
O3–C2–C3	109.51(13)	C13A–C8A–C7A	118.8(7)
C1–C2–C3	108.69(12)	C8A–C9A–C10A	120.0
F3E–C3–F3A	107.30(12)	C9A–C10A–C11A	120.0
F3E–C3–C4	110.23(14)	C12A–C11A–C10A	120.0
F3A–C3–C4	106.01(13)	C13A–C12A–C11A	120.0
F3E–C3–C2	111.65(13)	C12A–C13A–C8A	120.0
F3A–C3–C2	107.96(14)	O6B–C7B–C8B	115.9(12)
C4–C3–C2	113.32(12)	C9B–C8B–C13B	120.0
F4A–C4–F4E	106.41(13)	C9B–C8B–C7B	118.3(8)
F4A–C4–C5	110.77(13)	C13B–C8B–C7B	121.7(8)
F4E–C4–C5	109.75(13)	C10B–C9B–C8B	120.0
F4A–C4–C3	108.78(13)	C9B–C10B–C11B	120.0
F4E–C4–C3	108.57(13)	C10B–C11B–C12B	120.0
C5–C4–C3	112.36(13)	C13B–C12B–C11B	120.0
O1–C5–C6A	108.51(12)	C12B–C13B–C8B	120.0
O1–C5–C4	109.08(12)		

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}
F3A	27(1)	46(1)	56(1)	20(1)	−5(1)	13(1)
F3E	38(1)	47(1)	39(1)	5(1)	−13(1)	−20(1)
F4A	45(1)	24(1)	34(1)	−7(1)	9(1)	−1(1)
F4E	53(1)	50(1)	23(1)	10(1)	−12(1)	−14(1)
O1	22(1)	25(1)	18(1)	2(1)	1(1)	−3(1)
O2	29(1)	19(1)	30(1)	4(1)	−6(1)	0(1)
O3	27(1)	39(1)	43(1)	3(1)	14(1)	−2(1)
C1	27(1)	22(1)	24(1)	−1(1)	7(1)	−2(1)
C2	21(1)	21(1)	26(1)	4(1)	3(1)	1(1)
C3	21(1)	25(1)	32(1)	6(1)	−7(1)	0(1)
C4	33(1)	24(1)	20(1)	2(1)	−3(1)	−1(1)
C5	25(1)	22(1)	19(1)	3(1)	1(1)	−1(1)
C6A	30(1)	30(1)	23(1)	0(1)	6(1)	−2(1)
O6A	26(1)	44(1)	22(2)	−3(1)	5(1)	−11(1)
C7A	20(2)	63(5)	27(1)	2(2)	2(1)	−6(3)
C8A	24(1)	45(1)	25(1)	0(1)	5(1)	−10(1)
C9A	49(3)	37(2)	33(1)	0(1)	13(2)	−4(2)
C10A	63(4)	43(2)	37(1)	13(2)	4(2)	−5(2)
C11A	66(2)	58(1)	24(1)	−1(1)	6(1)	−17(1)
C12A	56(3)	52(3)	38(1)	−16(2)	13(2)	−9(2)
C13A	32(2)	46(3)	41(1)	−1(2)	4(2)	−5(2)
C6B	30(1)	30(1)	23(1)	0(1)	6(1)	−2(1)
O6B	26(1)	44(1)	22(2)	−3(1)	5(1)	−11(1)
C7B	20(2)	63(5)	27(1)	2(2)	2(1)	−6(3)
C8B	24(1)	45(1)	25(1)	0(1)	5(1)	−10(1)
C9B	49(3)	37(2)	33(1)	0(1)	13(2)	−4(2)
C10B	63(4)	43(2)	37(1)	13(2)	4(2)	−5(2)
C11B	66(2)	58(1)	24(1)	−1(1)	6(1)	−17(1)
C12B	56(3)	52(3)	38(1)	−16(2)	13(2)	−9(2)
C13B	32(2)	46(3)	41(1)	−1(2)	4(2)	−5(2)

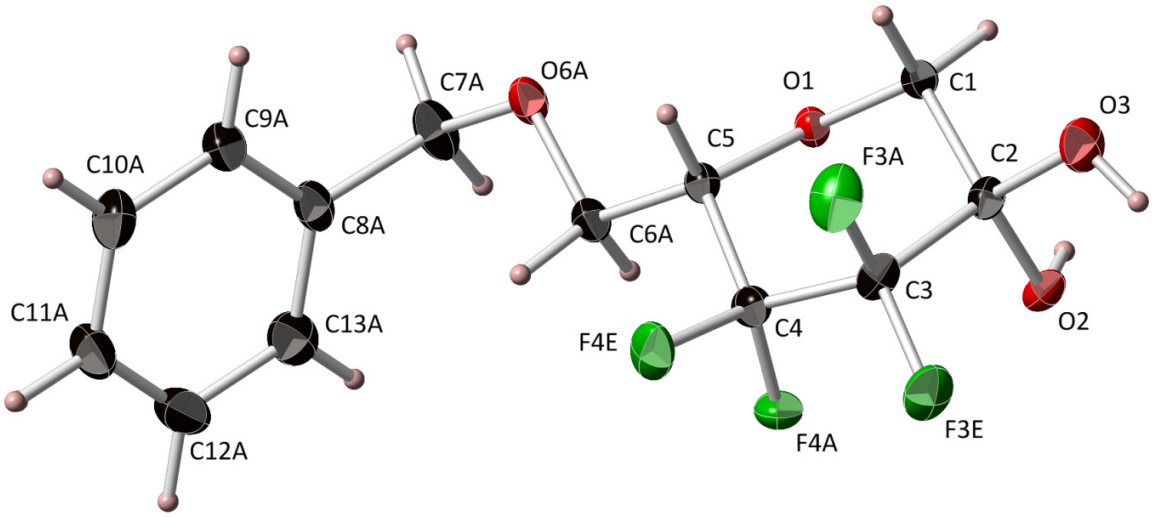
Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	3540(30)	−2980(50)	2546(9)	49(7)	1
H3	430(40)	−1900(70)	2562(12)	93(12)	1
H1A	2652	2799	2372	29	1
H1B	3529	1109	2753	29	1
H5	3622	3359	1609	27	1
H6A1	6259	489	1443	33	0.533(5)
H6A2	5387	1863	1014	33	0.533(5)
H7A1	8412	2552	1377	44	0.533(5)
H7A2	8471	5431	1432	44	0.533(5)
H9A	6861	7703	734	47	0.533(5)
H10A	6715	8008	−98	57	0.533(5)
H11A	7553	4820	−571	59	0.533(5)
H12A	8539	1327	−212	59	0.533(5)
H13A	8686	1022	620	47	0.533(5)
H6B1	6253	468	1432	33	0.467(5)
H6B2	5396	1956	1013	33	0.467(5)
H7B1	8504	3264	1391	44	0.467(5)
H7B2	8147	6086	1396	44	0.467(5)
H9B	5969	6971	699	47	0.467(5)
H10B	5859	7183	−134	57	0.467(5)
H11B	7512	4855	−584	59	0.467(5)
H12B	9276	2315	−201	59	0.467(5)
H13B	9387	2103	633	47	0.467(5)

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H2···O1^{i}	0.84(3)	1.98(3)	2.7756(16)	158(2)
O3–H3···O3^{ii}	0.81(4)	2.36(4)	3.1600(13)	169(3)
O3–H3···F3A^{ii}	0.81(4)	2.61(4)	3.1520(18)	126(3)

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

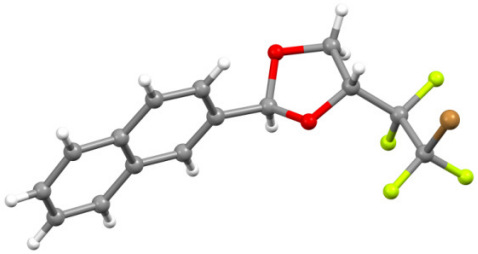


Thermal ellipsoids drawn at the 35% probability level, BnO disorder omitted for clarity.

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2013sot0064**
Empirical formula	$C_{15}H_{11}BrF_4O_2$
Formula weight	379.15
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P*21/*n*
Unit cell dimensions	a = 9.2027(12) Å
	b = 5.9660(6) Å β = 99.679(2)°
	c = 25.780(3) Å
Volume	1395.2(3) Å^3
Z	4
Density (calculated)	1.805 Mg / m^3
Absorption coefficient	2.996 mm^{-1}
F(000)	752
Crystal	Block; Colourless
Crystal size	0.320 × 0.220 × 0.050 mm^3
θ range for data collection	3.002 – 27.484°
Index ranges	$-11 \le h \le 11$, $-7 \le k \le 6$, $-33 \le l \le 33$
Reflections collected	10862
Independent reflections	3170 [R_{int} = 0.0248]
Completeness to θ = 25.242°	98.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.653
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3170 / 0 / 199
Goodness-of-fit on F^2	1.035
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0295, *wR2* = 0.0767
R indices (all data)	*R1* = 0.0318, *wR2* = 0.0782
Extinction coefficient	n/a
Largest diff. peak and hole	0.920 and –0.673 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst.* **A64**, 112-122). **Structure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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	1861(1)	8464(1)	305(1)	25(1)	1
F1	3441(1)	5849(2)	–945(1)	24(1)	1
F2	4567(1)	7548(2)	–238(1)	21(1)	1
F3	802(1)	6345(2)	–600(1)	28(1)	1
F4	2491(1)	4499(2)	–88(1)	27(1)	1
O1	3566(2)	11472(2)	–1587(1)	18(1)	1
O2	1768(1)	9622(2)	–1263(1)	20(1)	1
C1	697(2)	13533(3)	–1962(1)	17(1)	1
C2	–398(2)	14665(3)	–2284(1)	17(1)	1
C3	–1099(2)	13709(3)	–2767(1)	14(1)	1
C4	–2303(2)	14780(3)	–3092(1)	17(1)	1
C5	–3009(2)	13756(3)	–3540(1)	18(1)	1
C6	–2518(2)	11657(3)	–3697(1)	18(1)	1
C7	–1351(2)	10591(3)	–3394(1)	16(1)	1
C8	–628(2)	11573(3)	–2919(1)	14(1)	1
C9	529(2)	10448(3)	–2581(1)	15(1)	1
C10	1157(2)	11391(3)	–2112(1)	15(1)	1
C11	2309(2)	10124(3)	–1744(1)	16(1)	1
C12	4289(2)	10504(3)	–1106(1)	19(1)	1
C13	2985(2)	9724(3)	–846(1)	16(1)	1
C14	3272(2)	7441(3)	–584(1)	16(1)	1
C15	2098(2)	6558(3)	–278(1)	18(1)	1

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

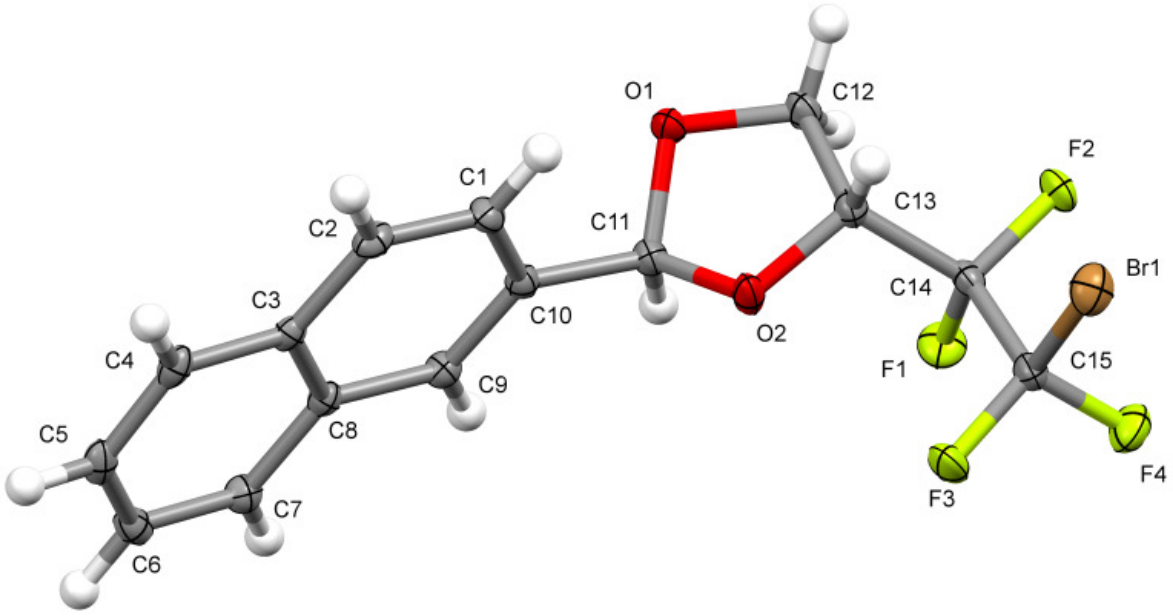
Br1–C15	1.927(2)	C3–C8	1.423(2)
F1–C14	1.356(2)	C3–C4	1.423(2)
F2–C14	1.365(2)	C4–C5	1.370(3)
F3–C15	1.339(2)	C5–C6	1.414(3)
F4–C15	1.349(2)	C6–C7	1.373(3)
O1–C11	1.412(2)	C7–C8	1.419(3)
O1–C12	1.427(2)	C8–C9	1.426(2)
O2–C13	1.418(2)	C9–C10	1.369(3)
O2–C11	1.444(2)	C10–C11	1.502(2)
C1–C2	1.371(3)	C12–C13	1.542(3)
C1–C10	1.420(3)	C13–C14	1.523(3)
C2–C3	1.421(3)	C14–C15	1.534(3)
C11–O1–C12	105.04(14)	O1–C11–C10	110.63(15)
C13–O2–C11	107.50(14)	O2–C11–C10	109.76(15)
C2–C1–C10	120.09(17)	O1–C12–C13	102.49(14)
C1–C2–C3	120.75(17)	O2–C13–C14	110.73(15)
C2–C3–C8	119.14(17)	O2–C13–C12	104.84(15)
C2–C3–C4	121.95(17)	C14–C13–C12	111.85(15)
C8–C3–C4	118.86(17)	F1–C14–F2	107.05(15)
C5–C4–C3	120.54(18)	F1–C14–C13	110.76(15)
C4–C5–C6	120.53(17)	F2–C14–C13	108.40(15)
C7–C6–C5	120.25(18)	F1–C14–C15	106.46(15)
C6–C7–C8	120.56(18)	F2–C14–C15	106.99(15)
C7–C8–C3	119.21(17)	C13–C14–C15	116.72(16)
C7–C8–C9	121.86(17)	F3–C15–F4	107.14(15)
C3–C8–C9	118.90(17)	F3–C15–C14	110.21(16)
C10–C9–C8	120.51(17)	F4–C15–C14	109.33(16)
C9–C10–C1	120.58(17)	F3–C15–Br1	109.45(14)
C9–C10–C11	119.93(17)	F4–C15–Br1	108.19(13)
C1–C10–C11	119.45(16)	C14–C15–Br1	112.36(12)
O1–C11–O2	104.78(14)		

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	29(1)	26(1)	21(1)	0(1)	9(1)	4(1)
F1	32(1)	19(1)	23(1)	–6(1)	6(1)	3(1)
F2	14(1)	26(1)	21(1)	3(1)	–4(1)	2(1)
F3	19(1)	40(1)	22(1)	7(1)	–6(1)	–11(1)
F4	36(1)	17(1)	27(1)	5(1)	4(1)	2(1)
O1	14(1)	22(1)	17(1)	4(1)	0(1)	–3(1)
O2	13(1)	30(1)	17(1)	9(1)	–1(1)	–2(1)
C1	20(1)	17(1)	14(1)	–2(1)	2(1)	–2(1)
C2	21(1)	13(1)	18(1)	–2(1)	7(1)	0(1)
C3	14(1)	14(1)	14(1)	2(1)	6(1)	0(1)
C4	17(1)	17(1)	18(1)	5(1)	8(1)	3(1)
C5	13(1)	25(1)	17(1)	7(1)	5(1)	3(1)
C6	16(1)	25(1)	14(1)	–1(1)	3(1)	–3(1)
C7	18(1)	17(1)	16(1)	–1(1)	5(1)	–1(1)
C8	13(1)	14(1)	14(1)	1(1)	5(1)	0(1)
C9	16(1)	14(1)	16(1)	0(1)	4(1)	0(1)
C10	14(1)	16(1)	14(1)	2(1)	2(1)	0(1)
C11	16(1)	17(1)	15(1)	1(1)	1(1)	–1(1)
C12	14(1)	24(1)	18(1)	2(1)	–1(1)	0(1)
C13	16(1)	18(1)	14(1)	1(1)	1(1)	1(1)
C14	16(1)	18(1)	14(1)	–2(1)	–3(1)	1(1)
C15	19(1)	18(1)	16(1)	1(1)	–2(1)	–1(1)

Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	1149	14182	−1639	20	1
H2	−692	16105	−2183	20	1
H4	−2619	16216	−2997	20	1
H5	−3835	14463	−3746	22	1
H6	−2998	10981	−4014	22	1
H7	−1025	9185	−3504	20	1
H9	867	9034	−2681	18	1
H11	2584	8714	−1914	20	1
H12A	4901	11625	−885	23	1
H12B	4918	9224	−1172	23	1
H13	2788	10855	−580	20	1

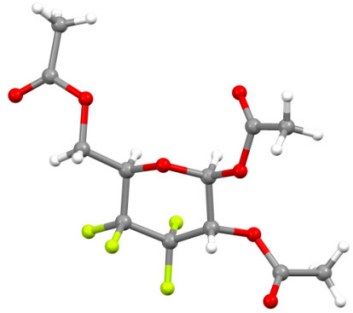


Thermal ellipsoids drawn at the 50% probability level.

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2013sot0083**
Empirical formula	$C_{12}H_{14}F_4O_7$
Formula weight	346.23
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 19.9933(11) Å
	b = 10.6809(8) Å β = 110.869(2)°
	c = 15.0590(14) Å
Volume	3004.8(4) Å^3
Z	8 (Z' = 2)
Density (calculated)	1.531 Mg / m^3
Absorption coefficient	0.154 mm^{-1}
$F(000)$	1424
Crystal	Prism; Colourless
Crystal size	0.300 × 0.200 × 0.120 mm^3
θ range for data collection	2.939 – 25.025°
Index ranges	$-23 \le h \le 23$, $-12 \le k \le 12$, $-15 \le l \le 17$
Reflections collected	22730
Independent reflections	5245 [R_{int} = 0.1144]
Completeness to θ = 25.242°	96.4 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.790
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5245 / 0 / 421
Goodness-of-fit on F^2	0.961
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0373, $wR2$ = 0.0940
R indices (all data)	$R1$ = 0.0597, $wR2$ = 0.1028
Extinction coefficient	n/a
Largest diff. peak and hole	0.199 and –0.205 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst.* **A64**, 112-122). **Structure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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	10292(1)	7597(1)	6274(1)	61(1)	1
F13E	10009(1)	5751(1)	6626(1)	62(1)	1
F14A	8666(1)	6004(1)	5384(1)	51(1)	1
F14E	9451(1)	6433(1)	4730(1)	57(1)	1
O101	8681(1)	8967(1)	7318(1)	42(1)	1
O102	8466(1)	10926(1)	6743(1)	56(1)	1
O103	9935(1)	6204(2)	8745(1)	64(1)	1
O104	10085(1)	7842(1)	7901(1)	47(1)	1
O105	8524(1)	8466(1)	5792(1)	40(1)	1
O106	8101(1)	9450(1)	3830(1)	50(1)	1
O107	8198(1)	9014(2)	2423(1)	64(1)	1
C101	9054(1)	8688(2)	6698(1)	38(1)	1
C102	9478(1)	7497(2)	7090(1)	38(1)	1
C103	9742(1)	6910(2)	6353(1)	42(1)	1
C104	9163(1)	6862(2)	5368(1)	41(1)	1
C105	8823(1)	8137(2)	5087(1)	39(1)	1
C106	8407(1)	10144(2)	7273(1)	40(1)	1
C107	8038(1)	10288(2)	7968(2)	61(1)	1
C108	10909(1)	7641(2)	9457(2)	67(1)	1
C109	10261(1)	7117(2)	8695(1)	48(1)	1
C110	8238(1)	8155(2)	4118(1)	47(1)	1
C111	7983(1)	11125(2)	2779(2)	68(1)	1
C112	8110(1)	9759(2)	2964(1)	45(1)	1
F23A	4731(1)	7565(1)	6076(1)	57(1)	1
F23E	5093(1)	9391(1)	6696(1)	60(1)	1
F24A	6405(1)	8984(1)	6651(1)	53(1)	1
F24E	5576(1)	8594(1)	5279(1)	55(1)	1
O201	6342(1)	6076(1)	8599(1)	39(1)	1
O202	6435(1)	4065(1)	8214(1)	54(1)	1
O203	5168(1)	8975(2)	8869(1)	73(1)	1
O204	4975(1)	7311(1)	7903(1)	48(1)	1
O205	6482(1)	6520(1)	7200(1)	40(1)	1
O206	7003(1)	5968(1)	4242(1)	59(1)	1
O207	6802(1)	5465(1)	5570(1)	51(1)	1
C201	5963(1)	6371(2)	7635(1)	37(1)	1
C202	5579(1)	7605(2)	7641(1)	38(1)	1
C203	5312(1)	8199(2)	6663(1)	42(1)	1
C204	5872(1)	8165(2)	6184(1)	42(1)	1
C205	6168(1)	6859(2)	6218(1)	38(1)	1
C206	6554(1)	4860(2)	8805(1)	39(1)	1
C207	6942(1)	4704(2)	9848(1)	53(1)	1
C208	4171(1)	7608(3)	8695(2)	80(1)	1

C209	4821(1)	8078(2)	8524(2)	55(1)	1
C210	6727(1)	6770(2)	5754(1)	45(1)	1
C211	6988(2)	3810(2)	4674(2)	80(1)	1
C212	6936(1)	5191(2)	4778(1)	46(1)	1

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

F13A–C103	1.363(2)	F23A–C203	1.363(2)
F13E–C103	1.353(2)	F23E–C203	1.354(2)
F14A–C104	1.358(2)	F24A–C204	1.365(2)
F14E–C104	1.363(2)	F24E–C204	1.358(2)
O101–C106	1.363(2)	O201–C206	1.368(2)
O101–C101	1.418(2)	O201–C201	1.412(2)
O102–C106	1.190(2)	O202–C206	1.191(2)
O103–C109	1.190(2)	O203–C209	1.189(3)
O104–C109	1.361(2)	O204–C209	1.358(2)
O104–C102	1.429(2)	O204–C202	1.4312(19)
O105–C101	1.418(2)	O205–C201	1.4204(19)
O105–C105	1.434(2)	O205–C205	1.433(2)
O106–C112	1.351(2)	O206–C212	1.198(2)
O106–C110	1.447(2)	O207–C212	1.345(2)
O107–C112	1.197(2)	O207–C210	1.440(2)
C101–C102	1.526(2)	C201–C202	1.527(2)
C102–C103	1.523(2)	C202–C203	1.516(3)
C103–C104	1.523(3)	C203–C204	1.533(2)
C104–C105	1.514(2)	C204–C205	1.509(3)
C105–C110	1.509(3)	C205–C210	1.518(2)
C106–C107	1.488(3)	C206–C207	1.492(3)
C108–C109	1.500(3)	C208–C209	1.498(3)
C111–C112	1.490(3)	C211–C212	1.490(3)
C106–O101–C101	117.21(14)	F14E–C104–C103	109.49(15)
C109–O104–C102	118.62(15)	C105–C104–C103	110.63(15)
C101–O105–C105	112.90(13)	O105–C105–C110	109.23(14)
C112–O106–C110	117.20(15)	O105–C105–C104	106.14(13)
O101–C101–O105	106.37(13)	C110–C105–C104	113.48(15)
O101–C101–C102	105.73(14)	O102–C106–O101	123.17(17)
O105–C101–C102	110.77(14)	O102–C106–C107	126.25(18)
O104–C102–C103	108.64(14)	O101–C106–C107	110.57(16)
O104–C102–C101	107.56(14)	O103–C109–O104	123.07(19)
C103–C102–C101	110.52(14)	O103–C109–C108	126.9(2)
F13E–C103–F13A	106.05(14)	O104–C109–C108	110.02(19)
F13E–C103–C104	110.23(15)	O106–C110–C105	107.57(15)
F13A–C103–C104	106.86(15)	O107–C112–O106	123.38(19)
F13E–C103–C102	110.88(15)	O107–C112–C111	125.5(2)
F13A–C103–C102	109.97(15)	O106–C112–C111	111.06(18)
C104–C103–C102	112.56(14)	C206–O201–C201	117.00(14)
F14A–C104–F14E	106.29(14)	C209–O204–C202	118.58(17)
F14A–C104–C105	110.65(15)	C201–O205–C205	112.39(13)
F14E–C104–C105	111.46(14)	C212–O207–C210	116.66(14)
F14A–C104–C103	108.19(14)	O201–C201–O205	106.66(13)

O201–C201–C202	105.84(13)	F24A–C204–C203	108.00(14)
O205–C201–C202	110.92(14)	C205–C204–C203	110.43(15)
O204–C202–C203	108.71(14)	O205–C205–C204	106.90(14)
O204–C202–C201	106.71(14)	O205–C205–C210	109.63(15)
C203–C202–C201	111.05(14)	C204–C205–C210	112.70(15)
F23E–C203–F23A	106.18(15)	O202–C206–O201	122.93(17)
F23E–C203–C202	111.39(15)	O202–C206–C207	126.71(18)
F23A–C203–C202	110.21(15)	O201–C206–C207	110.36(16)
F23E–C203–C204	109.84(15)	O203–C209–O204	123.1(2)
F23A–C203–C204	106.27(14)	O203–C209–C208	127.0(2)
C202–C203–C204	112.62(15)	O204–C209–C208	109.9(2)
F24E–C204–F24A	106.38(14)	O207–C210–C205	107.08(14)
F24E–C204–C205	111.82(15)	O206–C212–O207	123.54(18)
F24A–C204–C205	110.53(15)	O206–C212–C211	125.84(19)
F24E–C204–C203	109.53(15)	O207–C212–C211	110.62(17)

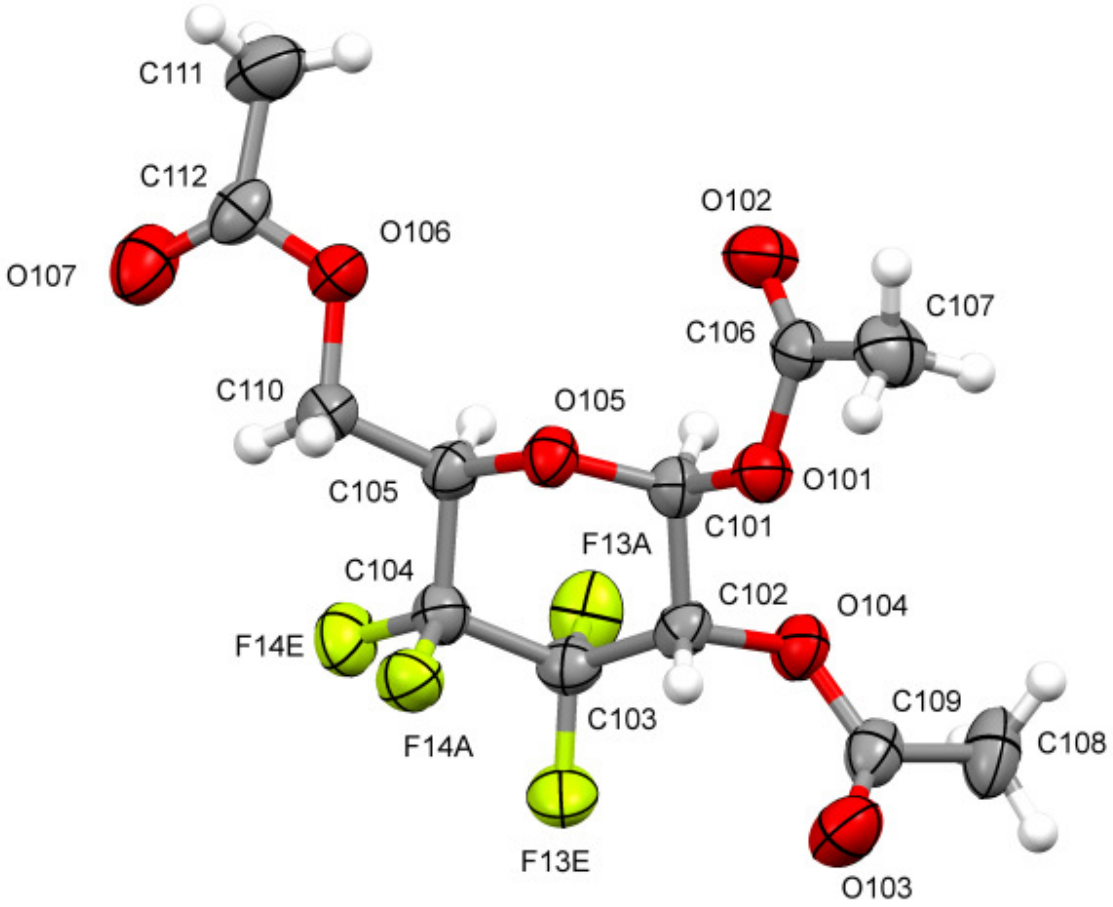
Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F13A	37(1)	87(1)	60(1)	−5(1)	20(1)	−8(1)
F13E	64(1)	57(1)	56(1)	1(1)	9(1)	26(1)
F14A	50(1)	44(1)	54(1)	2(1)	10(1)	−6(1)
F14E	61(1)	66(1)	48(1)	−6(1)	24(1)	14(1)
O101	49(1)	40(1)	41(1)	0(1)	22(1)	3(1)
O102	65(1)	44(1)	63(1)	6(1)	28(1)	5(1)
O103	70(1)	68(1)	51(1)	15(1)	18(1)	2(1)
O104	40(1)	51(1)	39(1)	−1(1)	4(1)	−3(1)
O105	37(1)	47(1)	35(1)	−1(1)	10(1)	5(1)
O106	65(1)	45(1)	38(1)	5(1)	16(1)	9(1)
O107	62(1)	86(1)	48(1)	3(1)	23(1)	21(1)
C101	36(1)	40(1)	36(1)	−2(1)	13(1)	−1(1)
C102	34(1)	43(1)	34(1)	2(1)	8(1)	−1(1)
C103	38(1)	42(1)	46(1)	3(1)	13(1)	5(1)
C104	42(1)	42(1)	40(1)	−2(1)	16(1)	1(1)
C105	41(1)	42(1)	35(1)	1(1)	15(1)	1(1)
C106	38(1)	40(1)	38(1)	−4(1)	7(1)	−1(1)
C107	72(2)	59(1)	64(1)	−3(1)	37(1)	9(1)
C108	50(1)	102(2)	40(1)	−13(1)	6(1)	10(1)
C109	45(1)	61(1)	38(1)	−1(1)	15(1)	13(1)
C110	56(1)	41(1)	40(1)	2(1)	11(1)	4(1)
C111	72(2)	62(2)	64(2)	20(1)	18(1)	−1(1)
C112	32(1)	60(1)	40(1)	9(1)	10(1)	4(1)
F23A	37(1)	83(1)	47(1)	−1(1)	8(1)	−2(1)
F23E	72(1)	50(1)	68(1)	13(1)	36(1)	24(1)
F24A	53(1)	49(1)	58(1)	−5(1)	22(1)	−10(1)
F24E	62(1)	63(1)	39(1)	15(1)	18(1)	12(1)
O201	44(1)	40(1)	32(1)	2(1)	12(1)	2(1)
O202	58(1)	42(1)	54(1)	−7(1)	13(1)	1(1)
O203	81(1)	85(1)	58(1)	−14(1)	30(1)	18(1)
O204	45(1)	55(1)	53(1)	4(1)	28(1)	3(1)
O205	36(1)	51(1)	35(1)	5(1)	15(1)	6(1)
O206	68(1)	66(1)	57(1)	6(1)	39(1)	6(1)
O207	66(1)	46(1)	51(1)	5(1)	34(1)	9(1)
C201	36(1)	41(1)	34(1)	−1(1)	12(1)	−2(1)
C202	34(1)	45(1)	38(1)	0(1)	16(1)	1(1)
C203	39(1)	43(1)	44(1)	2(1)	14(1)	6(1)
C204	42(1)	48(1)	34(1)	4(1)	12(1)	−1(1)
C205	38(1)	44(1)	32(1)	0(1)	13(1)	1(1)
C206	34(1)	40(1)	45(1)	4(1)	17(1)	0(1)
C207	61(1)	50(1)	45(1)	10(1)	17(1)	5(1)
C208	58(2)	136(2)	59(2)	35(2)	35(1)	33(2)

C209	55(1)	75(2)	38(1)	13(1)	21(1)	25(1)
C210	52(1)	45(1)	45(1)	2(1)	25(1)	4(1)
C211	105(2)	56(2)	104(2)	−14(1)	69(2)	−1(1)
C212	38(1)	56(1)	49(1)	−2(1)	22(1)	2(1)

Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H101	9371	9378	6676	45	1
H102	9180	6899	7276	46	1
H105	9192	8746	5101	47	1
H10A	7716	10987	7788	92	1
H10B	8386	10429	8590	92	1
H10C	7773	9540	7973	92	1
H10D	11064	7072	9985	100	1
H10E	10792	8433	9664	100	1
H10F	11286	7752	9210	100	1
H11A	8389	7696	3666	57	1
H11B	7808	7767	4147	57	1
H11C	7531	11250	2276	102	1
H11D	8359	11472	2597	102	1
H11E	7979	11533	3345	102	1
H201	5621	5708	7323	44	1
H202	5900	8182	8105	46	1
H205	5774	6282	5898	45	1
H20A	7251	3987	9959	79	1
H20B	6602	4586	10158	79	1
H20C	7223	5438	10097	79	1
H20D	4046	8183	9101	121	1
H20E	4271	6801	8995	121	1
H20F	3780	7539	8100	121	1
H21A	6575	7241	5164	55	1
H21B	7180	7108	6172	55	1
H21C	7382	3625	4472	120	1
H21D	6552	3504	4210	120	1
H21E	7065	3412	5274	120	1

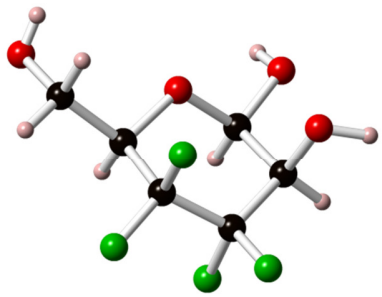


Molecule 1: Thermal ellipsoids drawn at the 50% probability level. Second molecule labelled in a similar fashion.

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2012sot0017** (CF6141-85Arc)
Empirical formula	$C_6H_8F_4O_4$
Formula weight	220.12
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.352(3) Å
	b = 9.152(4) Å
	c = 9.948(3) Å
Volume	760.4(5) Å^3
Z	4
Density (calculated)	1.923 Mg / m^3
Absorption coefficient	0.216 mm^{-1}
$F(000)$	448
Crystal	Block; Colourless
Crystal size	0.22 × 0.20 × 0.14 mm^3
θ range for data collection	3.02 – 27.48°
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-12 \le l \le 10$
Reflections collected	5341
Independent reflections	1020 [R_{int} = 0.0684]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9704 and 0.9541
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1020 / 0 / 139
Goodness-of-fit on F^2	0.994
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0463, $wR2$ = 0.1118
R indices (all data)	$R1$ = 0.0541, $wR2$ = 0.1142
Largest diff. peak and hole	0.392 and –0.361 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except the OH which were freely refined.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
F3A	2394(3)	8051(3)	–213(2)	18(1)	1
F3E	1549(3)	7164(3)	1704(2)	18(1)	1
F4A	1117(3)	9835(2)	2707(2)	15(1)	1
F4E	30(2)	9648(3)	723(2)	17(1)	1
O1	6411(3)	9846(3)	1609(3)	15(1)	1
O2	4142(3)	8360(3)	3049(3)	13(1)	1
O5	3988(3)	10965(3)	1482(2)	12(1)	1
O6	2490(4)	13665(3)	693(3)	19(1)	1
C1	4891(4)	9693(5)	1069(4)	10(1)	1
C2	4095(5)	8330(4)	1628(4)	11(1)	1
C3	2381(5)	8293(5)	1156(4)	12(1)	1
C4	1464(5)	9717(5)	1370(4)	13(1)	1
C5	2417(5)	11031(4)	878(4)	10(1)	1
C6	1651(5)	12482(4)	1288(4)	15(1)	1

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

F3A–C3	1.380(4)	O5–C1	1.446(5)
F3E–C3	1.359(4)	O6–C6	1.420(5)
F4A–C4	1.366(4)	C1–C2	1.519(5)
F4E–C4	1.360(4)	C2–C3	1.507(6)
O1–C1	1.386(5)	C3–C4	1.527(6)
O2–C2	1.415(4)	C4–C5	1.523(6)
O5–C5	1.444(5)	C5–C6	1.529(5)
C5–O5–C1	112.9(3)	C2–C3–C4	114.5(3)
O1–C1–O5	106.6(3)	F4E–C4–F4A	106.1(3)
O1–C1–C2	110.0(3)	F4E–C4–C5	110.2(3)
O5–C1–C2	109.2(3)	F4A–C4–C5	111.2(3)
O2–C2–C3	109.8(3)	F4E–C4–C3	109.6(3)
O2–C2–C1	109.8(3)	F4A–C4–C3	108.0(3)
C3–C2–C1	108.7(3)	C5–C4–C3	111.5(3)
F3E–C3–F3A	106.1(3)	O5–C5–C4	108.0(3)
F3E–C3–C2	112.2(3)	O5–C5–C6	107.8(3)
F3A–C3–C2	107.7(3)	C4–C5–C6	112.4(3)
F3E–C3–C4	109.7(3)	O6–C6–C5	110.1(3)
F3A–C3–C4	106.2(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}
F3A	18(1)	19(1)	16(1)	–6(1)	–3(1)	–1(1)
F3E	16(1)	10(1)	29(1)	3(1)	2(1)	–5(1)
F4A	15(1)	16(1)	14(1)	1(1)	5(1)	2(1)
F4E	9(1)	18(1)	26(1)	1(1)	–5(1)	–3(1)
O1	10(1)	18(2)	18(2)	1(1)	–1(1)	–1(1)
O2	18(2)	12(2)	11(1)	2(1)	–1(1)	5(1)
O5	10(1)	11(1)	15(1)	1(1)	–2(1)	3(1)
O6	19(2)	12(2)	26(2)	5(1)	–9(2)	–4(1)
C1	7(2)	11(2)	13(2)	1(2)	0(2)	0(2)
C2	15(2)	8(2)	10(2)	–1(2)	3(2)	1(2)
C3	15(2)	13(2)	9(2)	1(2)	0(2)	–5(2)
C4	10(2)	17(2)	11(2)	–2(2)	0(2)	0(2)
C5	9(2)	13(2)	9(2)	2(2)	–3(2)	–4(2)
C6	14(2)	12(2)	18(2)	1(2)	–3(2)	2(2)

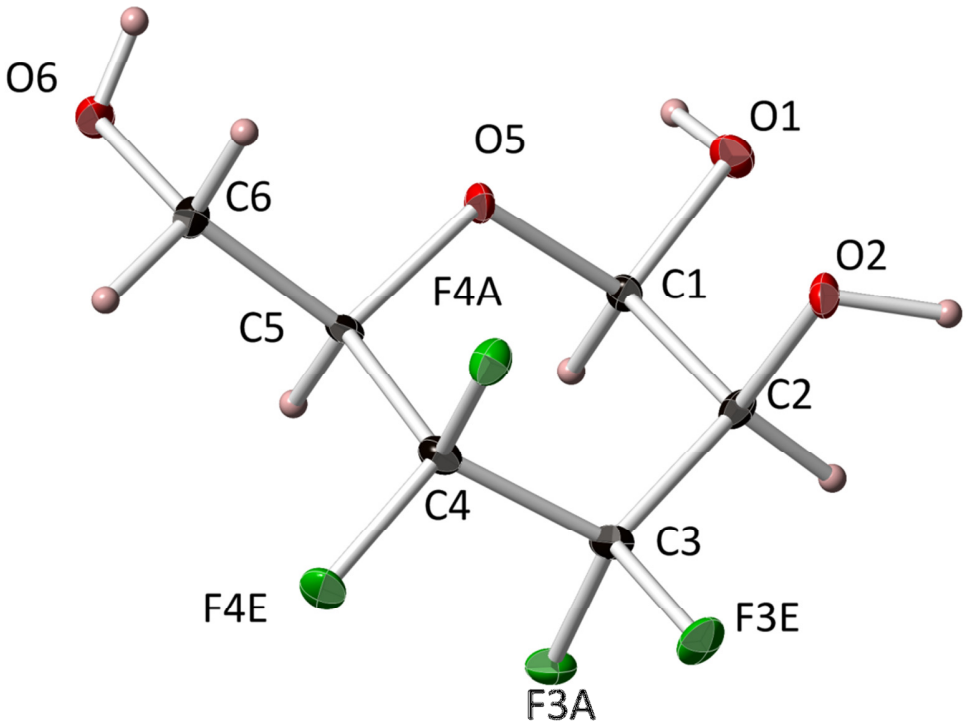
Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	4949	9640	66	12	1
H2A	4670	7443	1294	13	1
H5	2520	10989	−123	12	1
H6A	518	12500	995	18	1
H6B	1675	12580	2279	18	1
H1	7020(80)	10480(80)	1040(70)	90(30)	1
H2	4740(60)	7550(50)	3280(40)	23(13)	1
H6	2960(70)	13940(70)	1300(50)	50(20)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O1–H1···O6^{i}	0.95(7)	1.94(7)	2.812(4)	152(6)
O2–H2···O5^{ii}	0.92(5)	1.82(5)	2.731(4)	172(4)
O2–H2···O1^{ii}	0.92(5)	2.66(4)	3.267(5)	124(3)
O6–H6···O1^{iii}	0.76(6)	2.30(6)	3.036(4)	162(6)
O6–H6···O2^{iii}	0.76(6)	2.56(6)	3.091(4)	128(5)

Symmetry transformations used to generate equivalent atoms:
(i) x+1/2,−y+5/2,−z (ii) −x+1,y−1/2,−z+1/2 (iii) −x+1,y+1/2,−z+1/2

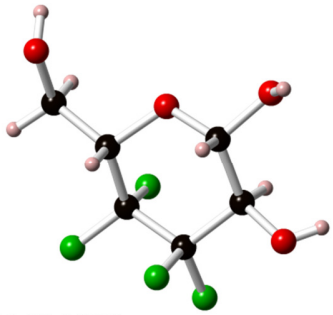


Thermal ellipsoids drawn at the 35% probability level.

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2012sot0016** (CF6141-86Arc)
Empirical formula	$C_6H_8F_4O_4$
Formula weight	220.12
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.179(5) Å
	b = 9.212(4) Å β = 95.815(9)°
	c = 7.815(4) Å
Volume	800.7(6) Å^3
Z	4
Density (calculated)	1.826 Mg / m^3
Absorption coefficient	0.205 mm^{-1}
$F(000)$	448
Crystal	Fragment; Colourless
Crystal size	0.20 × 0.12 × 0.08 mm^3
θ range for data collection	3.43 – 27.45°
Index ranges	$-14 \le h \le 8$, $-10 \le k \le 11$, $-10 \le l \le 10$
Reflections collected	4241
Independent reflections	1804 [R_{int} = 0.0155]
Completeness to θ = 27.45°	98.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9838 and 0.9602
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1804 / 0 / 159
Goodness-of-fit on F^2	1.061
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0298, $wR2$ = 0.0734
R indices (all data)	$R1$ = 0.0348, $wR2$ = 0.0761
Largest diff. peak and hole	0.394 and –0.233 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **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:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were located from the difference map and freely refined.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	999(1)	4250(1)	1869(2)	15(1)	1
C2	1903(1)	3855(1)	3407(2)	16(1)	1
C3	3005(1)	4816(1)	3504(2)	18(1)	1
C4	3492(1)	4996(1)	1755(2)	18(1)	1
C5	2486(1)	5430(1)	390(2)	15(1)	1
C6	2895(1)	5552(2)	−1394(2)	17(1)	1
O1	182(1)	3112(1)	1589(1)	18(1)	1
O2	1380(1)	4032(1)	4964(1)	21(1)	1
O5	1586(1)	4327(1)	333(1)	16(1)	1
O6	1908(1)	6076(1)	−2535(1)	18(1)	1
F3A	2719(1)	6170(1)	4034(1)	24(1)	1
F3E	3873(1)	4302(1)	4682(1)	29(1)	1
F4A	3995(1)	3720(1)	1337(1)	25(1)	1
F4E	4377(1)	6011(1)	1880(1)	25(1)	1

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

C1–O1	1.3937(15)	C3–C4	1.5305(18)
C1–O5	1.4268(15)	C4–F4A	1.3570(16)
C1–C2	1.5331(17)	C4–F4E	1.3577(15)
C2–O2	1.4118(16)	C4–C5	1.5229(17)
C2–C3	1.5130(18)	C5–O5	1.4279(15)
C3–F3E	1.3540(14)	C5–C6	1.5150(18)
C3–F3A	1.3625(16)	C6–O6	1.4308(15)

O1–C1–O5	104.78(9)	F4A–C4–F4E	107.31(10)
O1–C1–C2	108.32(10)	F4A–C4–C5	110.69(10)
O5–C1–C2	110.43(10)	F4E–C4–C5	110.52(10)
O2–C2–C3	107.20(10)	F4A–C4–C3	108.34(10)
O2–C2–C1	110.55(11)	F4E–C4–C3	109.45(10)
C3–C2–C1	111.63(10)	C5–C4–C3	110.46(10)
F3E–C3–F3A	106.69(10)	O5–C5–C6	107.55(10)
F3E–C3–C2	110.65(10)	O5–C5–C4	107.65(10)
F3A–C3–C2	109.65(10)	C6–C5–C4	113.19(11)
F3E–C3–C4	110.49(10)	O6–C6–C5	108.22(10)
F3A–C3–C4	106.77(10)	C1–O5–C5	113.06(9)
C2–C3–C4	112.35(10)		

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}
C1	15(1)	14(1)	15(1)	−1(1)	3(1)	−1(1)
C2	19(1)	15(1)	14(1)	0(1)	3(1)	−1(1)
C3	19(1)	21(1)	14(1)	1(1)	−2(1)	−2(1)
C4	15(1)	20(1)	19(1)	0(1)	2(1)	−2(1)
C5	15(1)	16(1)	15(1)	−1(1)	2(1)	−1(1)
C6	15(1)	20(1)	15(1)	0(1)	3(1)	0(1)
O1	14(1)	18(1)	24(1)	−3(1)	4(1)	−2(1)
O2	27(1)	20(1)	16(1)	0(1)	6(1)	−7(1)
O5	15(1)	18(1)	14(1)	−2(1)	3(1)	−3(1)
O6	19(1)	22(1)	14(1)	−2(1)	2(1)	0(1)
F3A	36(1)	18(1)	18(1)	−5(1)	7(1)	−10(1)
F3E	22(1)	41(1)	22(1)	11(1)	−8(1)	−6(1)
F4A	20(1)	27(1)	28(1)	1(1)	5(1)	8(1)
F4E	18(1)	34(1)	22(1)	3(1)	0(1)	−11(1)

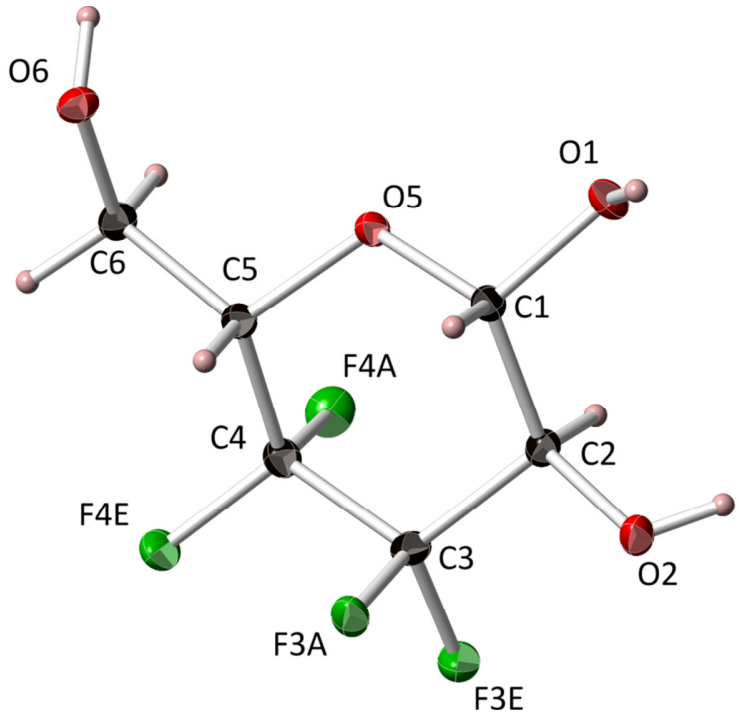
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	576(12)	5170(16)	2090(17)	13(3)	1
H2A	2142(12)	2878(16)	3237(17)	14(3)	1
H5	2169(12)	6358(16)	753(17)	14(3)	1
H6B	3542(14)	6249(16)	−1389(19)	20(4)	1
H6A	3169(12)	4583(16)	−1795(17)	14(3)	1
H1	−502(18)	3430(20)	1840(20)	47(5)	1
H2	995(18)	3330(20)	5170(20)	43(5)	1
H6	1780(17)	5490(20)	−3380(20)	41(5)	1

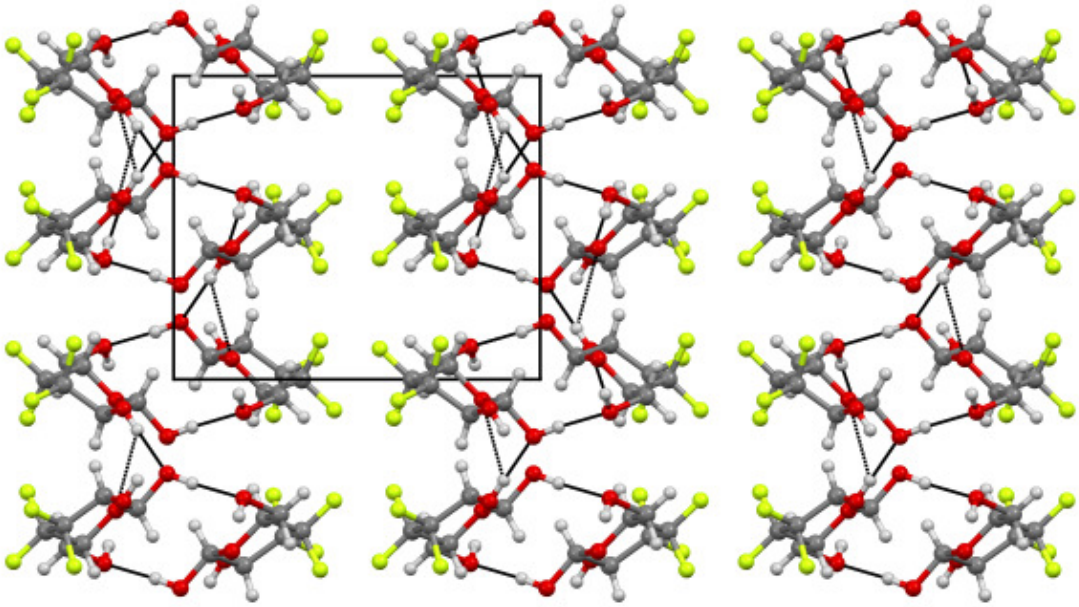
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H2···O1^{i}	0.80(2)	2.01(2)	2.7662(16)	157.7(19)
O2–H2···O5^{i}	0.80(2)	2.53(2)	3.1138(19)	130.4(17)
O1–H1···O6^{ii}	0.86(2)	1.77(2)	2.6287(16)	173.0(19)
O6–H6···O2^{iii}	0.855(19)	1.886(19)	2.7352(16)	172.0(18)
O6–H6···F3A^{iii}	0.855(19)	2.452(19)	2.9179(16)	114.9(15)

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



Thermal ellipsoids drawn at the 35% probability level.



Packing arrangement viewed down the c-axis.

ncs | UK National Crystallography Service

Table 1. Crystal data and structure refinement details.

Identification code	**2013ncs0664a**	
Empirical formula	$C_{10}H_{17}F_4NO_4S$	
Formula weight	323.30	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	*P*1211	
Unit cell dimensions	a = **12.5384(9) Å**	α = **90**°
	b = **10.8313(8) Å**	β = **92.887(2)**°
	c = **27.1058(19) Å**	γ = **90**°
Volume	3676.5(5) Å^3	
Z	10	
Density (calculated)	1.460 Mg / m^3	
Absorption coefficient	0.276 mm^{-1}	
F(000)	1680	
Crystal	Plate; colourless	
Crystal size	0.19 × 0.12 × 0.1 mm^3	
θ range for data collection	2.257 – 27.466°	
Index ranges	$-13 \le h \le 16$, $-13 \le k \le 14$, $-35 \le l \le 28$	
Reflections collected	26412	
Independent reflections	14253 [R_{int} = 0.0505]	
Completeness to θ = 25.242°	97.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	1.000 and 0.464	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	14253 / 1 / 938	
Goodness-of-fit on F^2	1.055	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0525, *wR2* = 0.1317	
R indices (all data)	*R1* = 0.0585, *wR2* = 0.1357	
Absolute structure parameter	0.05(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.737 and –0.848 e Å^{-3}	

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with VHF *Varimax* optics (70µm focus). **Cell determination and data collection**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Data reduction, cell refinement and absorption correction**: *CrystalClear-SM Expert 3.1 b27 (Rigaku, 2013).* **Structure solution**: *SUPERFLIP* (Palatinus, L. & Chapuis, G. (2007). J. Appl. Cryst. 40, 786-790). **Structure refinement**: *SHELXL-2012* (Sheldrick, G.M. (2012) **Graphics:** *OLEX2* (Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). J. Appl. Cryst. 42, 339-341).

Special details:

The Model has the following chirality C1 R
C4 R
C5 S

Each of the 5 crystallographically independent molecules in the asymmetric unit displays the same configuration at the equivalent stereocentres

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	8765(1)	5273(1)	849(1)	18(1)	1
F1	8591(2)	235(3)	883(1)	22(1)	1
F2	9973(2)	–185(3)	1376(1)	30(1)	1
F3	10159(2)	1889(3)	779(1)	29(1)	1
F4	10320(2)	2170(3)	1580(1)	24(1)	1
O1	7599(2)	1501(3)	1615(1)	17(1)	1
O2	8019(3)	–473(3)	1850(1)	21(1)	1
O3	8242(2)	6131(3)	1202(1)	20(1)	1
O4	6448(3)	3222(3)	1021(1)	25(1)	1
N1	9287(3)	4095(3)	1168(1)	17(1)	1
C1	8442(3)	659(4)	1737(2)	17(1)	1
C2	9150(3)	621(4)	1295(2)	18(1)	1
C3	9598(3)	1910(4)	1195(2)	19(1)	1
C4	8738(3)	2909(4)	1164(1)	15(1)	1
C5	7953(3)	2758(4)	1586(1)	14(1)	1
C6	10006(4)	6074(4)	702(2)	25(1)	1
C7	9617(5)	7245(5)	426(2)	34(1)	1
C8	10615(4)	5229(6)	357(2)	38(1)	1
C9	10655(4)	6400(5)	1174(2)	33(1)	1
C10	6944(3)	3506(4)	1491(2)	20(1)	1
S11	7093(1)	5301(1)	4885(1)	22(1)	1
F11	6897(2)	258(3)	4932(1)	27(1)	1
F12	8107(2)	–150(3)	5519(1)	28(1)	1
F13	8482(2)	1904(3)	4930(1)	33(1)	1
F14	8392(2)	2215(3)	5725(1)	23(1)	1
O11	5678(2)	1551(3)	5572(1)	18(1)	1
O12	6007(3)	–414(3)	5842(1)	21(1)	1
O13	6481(3)	6179(3)	5193(1)	25(1)	1
O14	4711(3)	3237(3)	4910(1)	24(1)	1
N11	7514(3)	4127(4)	5236(1)	19(1)	1
C11	6471(3)	713(4)	5759(2)	17(1)	1
C12	7318(4)	659(4)	5375(2)	21(1)	1
C13	7802(4)	1943(4)	5302(2)	21(1)	1
C14	6961(3)	2944(4)	5205(2)	18(1)	1
C15	6050(3)	2808(4)	5563(2)	18(1)	1
C16	8375(4)	6071(5)	4816(2)	28(1)	1
C17	8089(5)	7286(5)	4541(2)	41(1)	1
C18	9036(4)	5231(6)	4495(2)	40(1)	1
C19	8920(4)	6354(5)	5319(2)	34(1)	1
C20	5073(3)	3566(4)	5397(2)	20(1)	1
S21	5354(1)	5254(1)	8823(1)	19(1)	1
F21	5216(2)	229(3)	8876(1)	29(1)	1
F22	6384(2)	–164(3)	9483(1)	36(1)	1
F23	6782(2)	1897(3)	8906(1)	31(1)	1
F24	6623(2)	2196(3)	9697(1)	32(1)	1
O21	3920(3)	1506(3)	9498(1)	21(1)	1
O22	4233(3)	–476(3)	9751(1)	26(1)	1
O23	4691(3)	6132(3)	9105(1)	24(1)	1
O24	2962(2)	3199(3)	8846(1)	19(1)	1
N21	5750(3)	4102(4)	9191(1)	19(1)	1
C21	4693(4)	658(4)	9689(2)	23(1)	1
C22	5589(4)	630(4)	9326(2)	26(1)	1
C23	6065(4)	1923(4)	9265(2)	25(1)	1
C24	5218(3)	2911(4)	9154(2)	19(1)	1
C25	4290(3)	2769(4)	9505(2)	19(1)	1
C26	6643(4)	6045(5)	8773(2)	24(1)	1
C27	6382(4)	7201(5)	8468(2)	34(1)	1
C28	7350(4)	5173(5)	8492(2)	31(1)	1
C29	7121(4)	6396(5)	9285(2)	31(1)	1
C30	3323(3)	3531(4)	9340(2)	20(1)	1
S31	3231(1)	5298(1)	2745(1)	21(1)	1

F31	3134(2)	283(3)	2776(1)	29(1)	1
F32	4438(2)	−125(3)	3323(1)	31(1)	1
F33	4689(2)	1977(3)	2743(1)	29(1)	1
F34	4709(2)	2234(3)	3545(1)	24(1)	1
O31	2008(2)	1510(3)	3475(1)	18(1)	1
O32	2385(3)	−480(3)	3695(1)	23(1)	1
O33	2604(3)	6151(3)	3054(1)	25(1)	1
O34	870(3)	3219(3)	2894(1)	25(1)	1
N31	3707(3)	4148(4)	3095(1)	18(1)	1
C31	2827(3)	668(4)	3618(2)	17(1)	1
C32	3617(4)	668(4)	3205(2)	22(1)	1
C33	4058(4)	1969(4)	3133(2)	22(1)	1
C34	3182(3)	2944(4)	3074(2)	17(1)	1
C35	2359(3)	2772(4)	3471(2)	16(1)	1
C36	4494(4)	6126(5)	2652(2)	28(1)	1
C37	4153(5)	7251(5)	2341(2)	39(1)	1
C38	5202(4)	5256(6)	2366(2)	36(1)	1
C39	5020(4)	6533(5)	3149(2)	31(1)	1
C40	1348(3)	3527(4)	3363(2)	20(1)	1
S41	832(1)	5282(1)	6778(1)	21(1)	1
F41	698(2)	256(3)	6809(1)	30(1)	1
F42	2122(2)	−164(3)	7277(1)	30(1)	1
F43	2244(2)	1934(3)	6687(1)	30(1)	1
F44	2458(2)	2189(3)	7484(1)	24(1)	1
O41	−233(2)	1494(3)	7567(1)	17(1)	1
O42	201(3)	−490(3)	7782(1)	22(1)	1
O43	317(3)	6139(3)	7132(1)	24(1)	1
O44	−1462(3)	3249(3)	7028(1)	27(1)	1
N41	1388(3)	4114(3)	7095(1)	19(1)	1
C41	608(4)	653(4)	7672(2)	19(1)	1
C42	1278(4)	638(4)	7213(2)	22(1)	1
C43	1710(4)	1933(4)	7110(2)	22(1)	1
C44	848(4)	2923(4)	7101(2)	18(1)	1
C45	123(3)	2760(4)	7542(2)	18(1)	1
C46	2059(4)	6099(4)	6609(2)	26(1)	1
C47	1640(5)	7248(5)	6331(2)	35(1)	1
C48	2680(5)	5255(6)	6280(2)	43(1)	1
C49	2709(4)	6484(5)	7078(2)	28(1)	1
C50	−891(4)	3516(4)	7483(2)	21(1)	1

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

S1–O3	1.507(3)	C15–C20	1.523(6)
S1–N1	1.657(4)	C16–C17	1.546(8)
S1–C6	1.842(5)	C16–C18	1.531(7)
F1–C2	1.355(5)	C16–C19	1.524(7)
F2–C2	1.361(5)	C17–H17A	0.9800
F3–C3	1.357(5)	C17–H17B	0.9800
F4–C3	1.377(5)	C17–H17C	0.9800
O1–C1	1.423(5)	C18–H18A	0.9800
O1–C5	1.435(5)	C18–H18B	0.9800
O2–H2	0.8400	C18–H18C	0.9800
O2–C1	1.378(5)	C19–H19A	0.9800
O4–H4	0.8400	C19–H19B	0.9800
O4–C10	1.423(5)	C19–H19C	0.9800
N1–H1	0.85(5)	C20–H20A	0.9900
N1–C4	1.457(5)	C20–H20B	0.9900
C1–H1A	1.0000	S21–O23	1.497(3)
C1–C2	1.528(6)	S21–N21	1.659(4)
C2–C3	1.534(6)	S21–C26	1.840(5)
C3–C4	1.527(6)	F21–C22	1.355(5)
C4–H4A	1.0000	F22–C22	1.368(5)
C4–C5	1.555(5)	F23–C23	1.357(6)
C5–H5	1.0000	F24–C23	1.366(5)
C5–C10	1.513(6)	O21–C21	1.414(5)
C6–C7	1.538(7)	O21–C25	1.443(5)
C6–C8	1.538(7)	O22–H22	0.8400
C6–C9	1.524(7)	O22–C21	1.372(5)
C7–H7A	0.9800	O24–H24	0.8400
C7–H7B	0.9800	O24–C30	1.436(5)
C7–H7C	0.9800	N21–H21	0.81(6)
C8–H8A	0.9800	N21–C24	1.454(6)
C8–H8B	0.9800	C21–H21A	1.0000
C8–H8C	0.9800	C21–C22	1.531(7)
C9–H9A	0.9800	C22–C23	1.534(7)
C9–H9B	0.9800	C23–C24	1.527(6)
C9–H9C	0.9800	C24–H24A	1.0000
C10–H10A	0.9900	C24–C25	1.546(6)
C10–H10B	0.9900	C25–H25	1.0000
S11–O13	1.501(4)	C25–C30	1.516(6)
S11–N11	1.658(4)	C26–C27	1.527(7)
S11–C16	1.829(5)	C26–C28	1.525(7)
F11–C12	1.361(5)	C26–C29	1.531(6)
F12–C12	1.364(5)	C27–H27A	0.9800
F13–C13	1.353(5)	C27–H27B	0.9800
F14–C13	1.365(5)	C27–H27C	0.9800
O11–C11	1.421(5)	C28–H28A	0.9800
O11–C15	1.440(5)	C28–H28B	0.9800
O12–H12	0.8400	C28–H28C	0.9800
O12–C11	1.376(5)	C29–H29A	0.9800
O14–H14	0.8400	C29–H29B	0.9800
O14–C20	1.420(5)	C29–H29C	0.9800
N11–H11	0.78(6)	C30–H30A	0.9900
N11–C14	1.457(6)	C30–H30B	0.9900
C11–H11A	1.0000	S31–O33	1.497(3)
C11–C12	1.524(6)	S31–N31	1.658(4)
C12–C13	1.534(6)	S31–C36	1.849(5)
C13–C14	1.527(6)	F31–C32	1.350(5)
C14–H14A	1.0000	F32–C32	1.367(5)
C14–C15	1.544(6)	F33–C33	1.353(5)
C15–H15	1.0000	F34–C33	1.379(5)

O31–C31	1.414(5)	C48–H48C	0.9800
O31–C35	1.435(5)	C49–H49A	0.9800
O32–H32	0.8400	C49–H49B	0.9800
O32–C31	1.381(5)	C49–H49C	0.9800
O34–H34	0.8400	C50–H50A	0.9900
O34–C40	1.419(5)	C50–H50B	0.9900
N31–H31	0.83(6)		
N31–C34	1.460(5)	O3–S1–N1	108.50(18)
C31–H31A	1.0000	O3–S1–C6	104.3(2)
C31–C32	1.531(6)	N1–S1–C6	99.2(2)
C32–C33	1.529(6)	C1–O1–C5	113.0(3)
C33–C34	1.527(6)	C1–O2–H2	109.5
C34–H34A	1.0000	C10–O4–H4	109.5
C34–C35	1.540(6)	S1–N1–H1	113(4)
C35–H35	1.0000	C4–N1–S1	120.0(3)
C35–C40	1.524(6)	C4–N1–H1	119(4)
C36–C37	1.531(7)	O1–C1–H1A	109.1
C36–C38	1.530(7)	O1–C1–C2	106.8(3)
C36–C39	1.536(7)	O2–C1–O1	109.4(3)
C37–H37A	0.9800	O2–C1–H1A	109.1
C37–H37B	0.9800	O2–C1–C2	113.4(3)
C37–H37C	0.9800	C2–C1–H1A	109.1
C38–H38A	0.9800	F1–C2–F2	107.0(3)
C38–H38B	0.9800	F1–C2–C1	111.0(3)
C38–H38C	0.9800	F1–C2–C3	108.3(4)
C39–H39A	0.9800	F2–C2–C1	110.9(3)
C39–H39B	0.9800	F2–C2–C3	109.4(3)
C39–H39C	0.9800	C1–C2–C3	110.3(3)
C40–H40A	0.9900	F3–C3–F4	106.5(3)
C40–H40B	0.9900	F3–C3–C2	109.9(4)
S41–O43	1.505(4)	F3–C3–C4	111.1(4)
S41–N41	1.663(4)	F4–C3–C2	106.5(3)
S41–C46	1.852(5)	F4–C3–C4	109.4(3)
F41–C42	1.350(5)	C4–C3–C2	113.0(3)
F42–C42	1.373(5)	N1–C4–C3	107.0(3)
F43–C43	1.357(5)	N1–C4–H4A	108.4
F44–C43	1.373(5)	N1–C4–C5	113.8(3)
O41–C41	1.412(5)	C3–C4–H4A	108.4
O41–C45	1.445(5)	C3–C4–C5	110.9(3)
O42–H42	0.8400	C5–C4–H4A	108.4
O42–C41	1.378(5)	O1–C5–C4	110.4(3)
O44–H44	0.8400	O1–C5–H5	109.8
O44–C50	1.425(5)	O1–C5–C10	105.0(3)
N41–H41	0.7967	C4–C5–H5	109.8
N41–C44	1.458(6)	C10–C5–C4	111.9(3)
C41–H41A	1.0000	C10–C5–H5	109.8
C41–C42	1.535(6)	C7–C6–S1	104.1(3)
C42–C43	1.535(7)	C8–C6–S1	107.6(3)
C43–C44	1.522(6)	C8–C6–C7	110.5(4)
C44–H44A	1.0000	C9–C6–S1	110.3(3)
C44–C45	1.549(6)	C9–C6–C7	111.1(4)
C45–H45	1.0000	C9–C6–C8	112.8(4)
C45–C50	1.514(6)	C6–C7–H7A	109.5
C46–C47	1.535(7)	C6–C7–H7B	109.5
C46–C48	1.519(7)	C6–C7–H7C	109.5
C46–C49	1.532(6)	H7A–C7–H7B	109.5
C47–H47A	0.9800	H7A–C7–H7C	109.5
C47–H47B	0.9800	H7B–C7–H7C	109.5
C47–H47C	0.9800	C6–C8–H8A	109.5
C48–H48A	0.9800	C6–C8–H8B	109.5
C48–H48B	0.9800	C6–C8–H8C	109.5

H8A–C8–H8B	109.5	C16–C17–H17B	109.5
H8A–C8–H8C	109.5	C16–C17–H17C	109.5
H8B–C8–H8C	109.5	H17A–C17–H17B	109.5
C6–C9–H9A	109.5	H17A–C17–H17C	109.5
C6–C9–H9B	109.5	H17B–C17–H17C	109.5
C6–C9–H9C	109.5	C16–C18–H18A	109.5
H9A–C9–H9B	109.5	C16–C18–H18B	109.5
H9A–C9–H9C	109.5	C16–C18–H18C	109.5
H9B–C9–H9C	109.5	H18A–C18–H18B	109.5
O4–C10–C5	111.2(3)	H18A–C18–H18C	109.5
O4–C10–H10A	109.4	H18B–C18–H18C	109.5
O4–C10–H10B	109.4	C16–C19–H19A	109.5
C5–C10–H10A	109.4	C16–C19–H19B	109.5
C5–C10–H10B	109.4	C16–C19–H19C	109.5
H10A–C10–H10B	108.0	H19A–C19–H19B	109.5
O13–S11–N11	108.9(2)	H19A–C19–H19C	109.5
O13–S11–C16	104.2(2)	H19B–C19–H19C	109.5
N11–S11–C16	98.7(2)	O14–C20–C15	110.8(4)
C11–O11–C15	112.9(3)	O14–C20–H20A	109.5
C11–O12–H12	109.5	O14–C20–H20B	109.5
C20–O14–H14	109.5	C15–C20–H20A	109.5
S11–N11–H11	117(4)	C15–C20–H20B	109.5
C14–N11–S11	120.2(3)	H20A–C20–H20B	108.1
C14–N11–H11	113(4)	O23–S21–N21	109.1(2)
O11–C11–H11A	109.3	O23–S21–C26	104.7(2)
O11–C11–C12	106.3(3)	N21–S21–C26	99.0(2)
O12–C11–O11	109.4(3)	C21–O21–C25	113.4(3)
O12–C11–H11A	109.3	C21–O22–H22	109.5
O12–C11–C12	113.2(4)	C30–O24–H24	109.5
C12–C11–H11A	109.3	S21–N21–H21	115(4)
F11–C12–F12	106.8(4)	C24–N21–S21	120.2(3)
F11–C12–C11	111.2(4)	C24–N21–H21	114(4)
F11–C12–C13	108.3(4)	O21–C21–H21A	109.0
F12–C12–C11	110.6(4)	O21–C21–C22	106.8(4)
F12–C12–C13	109.5(4)	O22–C21–O21	110.0(4)
C11–C12–C13	110.4(4)	O22–C21–H21A	109.0
F13–C13–F14	107.4(4)	O22–C21–C22	112.9(4)
F13–C13–C12	109.7(4)	C22–C21–H21A	109.0
F13–C13–C14	110.5(4)	F21–C22–F22	106.9(4)
F14–C13–C12	106.7(3)	F21–C22–C21	110.7(4)
F14–C13–C14	109.4(4)	F21–C22–C23	108.3(4)
C14–C13–C12	113.1(4)	F22–C22–C21	111.0(4)
N11–C14–C13	106.9(4)	F22–C22–C23	109.0(4)
N11–C14–H14A	108.3	C21–C22–C23	110.7(4)
N11–C14–C15	114.4(4)	F23–C23–F24	106.8(4)
C13–C14–H14A	108.3	F23–C23–C22	109.5(4)
C13–C14–C15	110.5(3)	F23–C23–C24	110.7(4)
C15–C14–H14A	108.3	F24–C23–C22	106.9(4)
O11–C15–C14	110.6(4)	F24–C23–C24	109.7(4)
O11–C15–H15	109.8	C24–C23–C22	112.9(4)
O11–C15–C20	105.0(3)	N21–C24–C23	107.2(4)
C14–C15–H15	109.8	N21–C24–H24A	108.5
C20–C15–C14	111.8(3)	N21–C24–C25	113.8(4)
C20–C15–H15	109.8	C23–C24–H24A	108.5
C17–C16–S11	104.7(4)	C23–C24–C25	110.3(4)
C18–C16–S11	107.0(4)	C25–C24–H24A	108.5
C18–C16–C17	110.5(4)	O21–C25–C24	109.7(4)
C19–C16–S11	110.9(3)	O21–C25–H25	109.9
C19–C16–C17	110.0(5)	O21–C25–C30	105.1(3)
C19–C16–C18	113.3(5)	C24–C25–H25	109.9
C16–C17–H17A	109.5	C30–C25–C24	112.3(4)

C30–C25–H25	109.9	C33–C34–H34A	108.7
C27–C26–S21	104.9(3)	C33–C34–C35	110.2(3)
C27–C26–C29	110.5(4)	C35–C34–H34A	108.7
C28–C26–S21	106.5(3)	O31–C35–C34	109.7(3)
C28–C26–C27	110.6(4)	O31–C35–H35	109.8
C28–C26–C29	113.3(4)	O31–C35–C40	105.1(3)
C29–C26–S21	110.7(3)	C34–C35–H35	109.8
C26–C27–H27A	109.5	C40–C35–C34	112.4(3)
C26–C27–H27B	109.5	C40–C35–H35	109.8
C26–C27–H27C	109.5	C37–C36–S31	104.1(4)
H27A–C27–H27B	109.5	C37–C36–C39	110.5(4)
H27A–C27–H27C	109.5	C38–C36–S31	107.1(4)
H27B–C27–H27C	109.5	C38–C36–C37	111.4(4)
C26–C28–H28A	109.5	C38–C36–C39	112.8(5)
C26–C28–H28B	109.5	C39–C36–S31	110.6(3)
C26–C28–H28C	109.5	C36–C37–H37A	109.5
H28A–C28–H28B	109.5	C36–C37–H37B	109.5
H28A–C28–H28C	109.5	C36–C37–H37C	109.5
H28B–C28–H28C	109.5	H37A–C37–H37B	109.5
C26–C29–H29A	109.5	H37A–C37–H37C	109.5
C26–C29–H29B	109.5	H37B–C37–H37C	109.5
C26–C29–H29C	109.5	C36–C38–H38A	109.5
H29A–C29–H29B	109.5	C36–C38–H38B	109.5
H29A–C29–H29C	109.5	C36–C38–H38C	109.5
H29B–C29–H29C	109.5	H38A–C38–H38B	109.5
O24–C30–C25	110.3(3)	H38A–C38–H38C	109.5
O24–C30–H30A	109.6	H38B–C38–H38C	109.5
O24–C30–H30B	109.6	C36–C39–H39A	109.5
C25–C30–H30A	109.6	C36–C39–H39B	109.5
C25–C30–H30B	109.6	C36–C39–H39C	109.5
H30A–C30–H30B	108.1	H39A–C39–H39B	109.5
O33–S31–N31	109.07(19)	H39A–C39–H39C	109.5
O33–S31–C36	104.8(2)	H39B–C39–H39C	109.5
N31–S31–C36	99.0(2)	O34–C40–C35	110.8(4)
C31–O31–C35	113.4(3)	O34–C40–H40A	109.5
C31–O32–H32	109.5	O34–C40–H40B	109.5
C40–O34–H34	109.5	C35–C40–H40A	109.5
S31–N31–H31	115(4)	C35–C40–H40B	109.5
C34–N31–S31	120.0(3)	H40A–C40–H40B	108.1
C34–N31–H31	120(4)	O43–S41–N41	108.73(19)
O31–C31–H31A	109.3	O43–S41–C46	104.6(2)
O31–C31–C32	106.7(3)	N41–S41–C46	99.2(2)
O32–C31–O31	109.3(3)	C41–O41–C45	113.1(3)
O32–C31–H31A	109.3	C41–O42–H42	109.5
O32–C31–C32	112.9(4)	C50–O44–H44	109.5
C32–C31–H31A	109.3	S41–N41–H41	121.3
F31–C32–F32	107.8(4)	C44–N41–S41	119.7(3)
F31–C32–C31	110.5(4)	C44–N41–H41	112.6
F31–C32–C33	109.0(4)	O41–C41–H41A	109.2
F32–C32–C31	109.7(4)	O41–C41–C42	106.1(3)
F32–C32–C33	109.6(4)	O42–C41–O41	110.0(4)
C33–C32–C31	110.2(4)	O42–C41–H41A	109.2
F33–C33–F34	106.6(4)	O42–C41–C42	112.9(4)
F33–C33–C32	109.6(4)	C42–C41–H41A	109.2
F33–C33–C34	111.0(4)	F41–C42–F42	106.8(4)
F34–C33–C32	107.0(4)	F41–C42–C41	111.5(4)
F34–C33–C34	109.6(3)	F41–C42–C43	108.3(4)
C34–C33–C32	112.8(4)	F42–C42–C41	110.8(4)
N31–C34–C33	107.1(3)	F42–C42–C43	108.9(4)
N31–C34–H34A	108.7	C43–C42–C41	110.5(4)
N31–C34–C35	113.4(3)	F43–C43–F44	106.0(4)

F43–C43–C42	110.4(4)	C46–C47–H47B	109.5
F43–C43–C44	111.4(4)	C46–C47–H47C	109.5
F44–C43–C42	106.5(4)	H47A–C47–H47B	109.5
F44–C43–C44	109.2(3)	H47A–C47–H47C	109.5
C44–C43–C42	112.9(4)	H47B–C47–H47C	109.5
N41–C44–C43	107.1(4)	C46–C48–H48A	109.5
N41–C44–H44A	108.5	C46–C48–H48B	109.5
N41–C44–C45	113.6(4)	C46–C48–H48C	109.5
C43–C44–H44A	108.5	H48A–C48–H48B	109.5
C43–C44–C45	110.5(3)	H48A–C48–H48C	109.5
C45–C44–H44A	108.5	H48B–C48–H48C	109.5
O41–C45–C44	109.8(3)	C46–C49–H49A	109.5
O41–C45–H45	109.9	C46–C49–H49B	109.5
O41–C45–C50	105.0(3)	C46–C49–H49C	109.5
C44–C45–H45	109.9	H49A–C49–H49B	109.5
C50–C45–C44	112.3(3)	H49A–C49–H49C	109.5
C50–C45–H45	109.9	H49B–C49–H49C	109.5
C47–C46–S41	103.9(4)	O44–C50–C45	111.3(4)
C48–C46–S41	108.3(4)	O44–C50–H50A	109.4
C48–C46–C47	111.9(4)	O44–C50–H50B	109.4
C48–C46–C49	112.6(5)	C45–C50–H50A	109.4
C49–C46–S41	109.8(3)	C45–C50–H50B	109.4
C49–C46–C47	110.0(4)	H50A–C50–H50B	108.0
C46–C47–H47A	109.5		

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}
S1	20(1)	14(1)	19(1)	2(1)	2(1)	1(1)
F1	25(1)	17(1)	24(1)	−4(1)	5(1)	−5(1)
F2	22(1)	14(1)	53(2)	0(1)	3(1)	6(1)
F3	30(2)	19(1)	41(2)	−5(1)	22(1)	−1(1)
F4	19(1)	17(1)	37(2)	−2(1)	−6(1)	0(1)
O1	18(1)	12(2)	20(1)	1(1)	0(1)	0(1)
O2	27(2)	14(2)	21(1)	5(1)	−9(1)	−5(1)
O3	21(2)	17(2)	23(2)	3(1)	2(1)	2(1)
O4	20(2)	14(2)	39(2)	4(1)	−11(1)	−2(1)
N1	16(2)	13(2)	21(2)	2(1)	−3(1)	0(1)
C1	20(2)	10(2)	20(2)	1(2)	−7(2)	0(2)
C2	20(2)	11(2)	25(2)	−3(2)	0(2)	0(2)
C3	16(2)	14(2)	25(2)	−2(2)	5(2)	−1(2)
C4	15(2)	12(2)	18(2)	0(2)	0(1)	1(2)
C5	13(2)	15(2)	15(2)	−1(2)	1(1)	−1(2)
C6	30(2)	18(2)	28(2)	6(2)	15(2)	−3(2)
C7	47(3)	19(3)	36(3)	5(2)	16(2)	−3(2)
C8	40(3)	25(3)	50(3)	−4(3)	31(2)	−2(3)
C9	28(3)	31(3)	41(3)	3(2)	9(2)	−10(2)
C10	17(2)	15(2)	27(2)	0(2)	4(2)	2(2)
S11	28(1)	15(1)	22(1)	3(1)	0(1)	−1(1)
F11	40(2)	20(1)	21(1)	−6(1)	2(1)	−2(1)
F12	27(1)	17(1)	42(2)	4(1)	5(1)	8(1)
F13	35(2)	22(2)	44(2)	0(1)	24(1)	2(1)
F14	18(1)	18(1)	33(1)	3(1)	−3(1)	1(1)
O11	20(2)	12(2)	22(2)	1(1)	−6(1)	−1(1)
O12	27(2)	13(2)	22(2)	2(1)	−7(1)	−4(1)
O13	26(2)	19(2)	30(2)	2(1)	−1(1)	3(1)
O14	28(2)	13(2)	31(2)	3(1)	−12(1)	−2(1)
N11	17(2)	17(2)	22(2)	1(2)	−3(1)	−2(1)
C11	19(2)	13(2)	18(2)	2(2)	−6(2)	0(2)
C12	25(2)	14(2)	23(2)	1(2)	−1(2)	3(2)
C13	24(2)	17(2)	22(2)	−2(2)	4(2)	2(2)
C14	21(2)	14(2)	18(2)	1(2)	−2(2)	0(2)
C15	19(2)	13(2)	21(2)	2(2)	−3(2)	−3(2)
C16	37(3)	23(3)	27(2)	0(2)	12(2)	−5(2)
C17	69(4)	24(3)	33(3)	6(2)	21(3)	−9(3)
C18	44(3)	28(3)	51(3)	−5(3)	30(2)	−7(3)
C19	32(3)	36(3)	34(3)	−2(2)	11(2)	−15(2)
C20	18(2)	15(2)	26(2)	−2(2)	−5(2)	0(2)
S21	14(1)	17(1)	26(1)	2(1)	−8(1)	0(1)
F21	33(1)	21(2)	34(1)	−6(1)	−7(1)	−3(1)
F22	32(2)	18(1)	57(2)	1(1)	−16(1)	10(1)
F23	17(1)	26(2)	49(2)	−5(1)	−2(1)	4(1)
F24	27(2)	24(2)	44(2)	0(1)	−22(1)	2(1)
O21	21(2)	14(2)	27(2)	4(1)	−10(1)	−2(1)
O22	38(2)	14(2)	26(2)	2(1)	−15(1)	−6(1)
O23	20(2)	19(2)	33(2)	4(1)	−3(1)	5(1)
O24	18(2)	13(2)	26(2)	1(1)	−5(1)	−1(1)
N21	17(2)	16(2)	24(2)	1(2)	−6(1)	1(1)
C21	30(2)	12(2)	26(2)	1(2)	−15(2)	1(2)
C22	28(2)	15(2)	33(2)	−1(2)	−15(2)	4(2)
C23	18(2)	17(2)	39(3)	−1(2)	−10(2)	5(2)
C24	19(2)	13(2)	24(2)	−1(2)	−6(2)	1(2)
C25	22(2)	12(2)	23(2)	0(2)	−7(2)	1(2)
C26	15(2)	24(2)	32(2)	−1(2)	−3(2)	−5(2)
C27	34(3)	27(3)	40(3)	6(2)	0(2)	−9(2)

C28	22(2)	32(3)	40(2)	−1(2)	4(2)	−2(2)
C29	22(2)	33(3)	37(3)	−1(2)	−5(2)	−10(2)
C30	18(2)	15(2)	26(2)	−3(2)	−1(2)	−1(2)
S31	31(1)	15(1)	16(1)	2(1)	−3(1)	1(1)
F31	44(2)	21(1)	22(1)	−6(1)	−2(1)	−1(1)
F32	27(2)	19(1)	48(2)	1(1)	−1(1)	11(1)
F33	31(2)	24(2)	32(1)	−3(1)	7(1)	5(1)
F34	18(1)	20(1)	33(1)	−2(1)	−10(1)	3(1)
O31	19(2)	12(2)	22(2)	1(1)	−5(1)	0(1)
O32	33(2)	13(2)	21(2)	3(1)	−9(1)	−3(1)
O33	29(2)	18(2)	28(2)	4(1)	−3(1)	7(1)
O34	27(2)	13(2)	32(2)	2(1)	−16(1)	−4(1)
N31	23(2)	14(2)	16(2)	1(1)	−3(1)	−4(2)
C31	17(2)	12(2)	21(2)	1(2)	−7(2)	1(2)
C32	28(2)	12(2)	25(2)	−3(2)	−3(2)	7(2)
C33	23(2)	15(2)	26(2)	−2(2)	−6(2)	1(2)
C34	19(2)	12(2)	18(2)	−1(2)	−3(2)	0(2)
C35	17(2)	11(2)	19(2)	−1(2)	−2(2)	1(2)
C36	42(3)	20(2)	23(2)	−1(2)	5(2)	−3(2)
C37	59(4)	24(3)	36(3)	9(2)	9(3)	−4(3)
C38	47(3)	31(3)	32(2)	−2(3)	16(2)	−2(3)
C39	31(3)	29(3)	32(3)	−4(2)	5(2)	−10(2)
C40	16(2)	16(2)	27(2)	−1(2)	−7(2)	2(2)
S41	31(1)	14(1)	18(1)	2(1)	−9(1)	−1(1)
F41	48(2)	19(1)	21(1)	−8(1)	−7(1)	−4(2)
F42	31(2)	16(1)	42(2)	−1(1)	−2(1)	9(1)
F43	42(2)	21(2)	26(1)	−2(1)	6(1)	4(1)
F44	21(1)	19(1)	30(1)	−3(1)	−10(1)	1(1)
O41	18(1)	10(1)	22(1)	2(1)	−7(1)	−1(1)
O42	28(2)	12(2)	23(2)	2(1)	−12(1)	−5(1)
O43	27(2)	17(2)	27(2)	3(1)	−3(1)	4(1)
O44	29(2)	13(2)	36(2)	3(1)	−17(1)	−4(1)
N41	25(2)	13(2)	18(2)	1(1)	−9(1)	−1(2)
C41	25(2)	12(2)	21(2)	1(2)	−9(2)	1(2)
C42	24(2)	15(2)	28(2)	−2(2)	−3(2)	7(2)
C43	26(2)	17(2)	21(2)	−2(2)	−4(2)	5(2)
C44	24(2)	10(2)	18(2)	1(2)	−6(2)	0(2)
C45	21(2)	10(2)	22(2)	0(2)	−3(2)	−1(2)
C46	40(3)	18(2)	18(2)	0(2)	−5(2)	−1(2)
C47	54(3)	20(3)	29(2)	8(2)	−11(2)	−3(2)
C48	68(4)	27(3)	35(3)	3(3)	17(3)	−5(3)
C49	25(2)	30(3)	29(2)	3(2)	−4(2)	−6(2)
C50	22(2)	12(2)	28(2)	−1(2)	−3(2)	0(2)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	7717	−781	1596	32	1
H4	6251	2481	1017	37	1
H1	9640(40)	4320(50)	1430(20)	20	1
H1A	8870	979	2031	20	1
H4A	8324	2821	840	18	1
H5	8313	3010	1908	17	1
H7A	9124	7015	150	50	1
H7B	10231	7684	301	50	1
H7C	9249	7783	654	50	1
H8A	10762	4437	521	56	1
H8B	11289	5622	279	56	1
H8C	10180	5090	51	56	1
H9A	10194	6814	1404	50	1
H9B	11242	6952	1095	50	1
H9C	10947	5644	1327	50	1
H10A	6441	3329	1752	24	1
H10B	7120	4396	1505	24	1
H12	5832	−749	5571	32	1
H14	4427	2535	4913	37	1
H11	7730(40)	4280(50)	5500(20)	22	1
H11A	6799	1039	6077	20	1
H14A	6652	2841	4860	21	1
H15	6307	3066	5903	21	1
H17A	7705	7096	4226	62	1
H17B	8745	7738	4478	62	1
H17C	7635	7793	4744	62	1
H18A	9201	4461	4673	60	1
H18B	9703	5649	4421	60	1
H18C	8629	5046	4186	60	1
H19A	8412	6763	5528	50	1
H19B	9533	6897	5276	50	1
H19C	9165	5582	5476	50	1
H20A	4495	3422	5626	24	1
H20B	5257	4455	5408	24	1
H22	4056	−779	9474	39	1
H24	2664	2504	8850	29	1
H21	5940(40)	4300(50)	9470(20)	23	1
H21A	4988	964	10016	28	1
H24A	4927	2799	8807	23	1
H25	4537	3006	9848	23	1
H27A	5977	6969	8163	51	1
H27B	7046	7611	8385	51	1
H27C	5954	7766	8659	51	1
H28A	7527	4449	8697	46	1
H28B	8009	5602	8413	46	1
H28C	6970	4909	8186	46	1
H29A	6599	6878	9461	46	1
H29B	7767	6890	9249	46	1
H29C	7302	5644	9472	46	1
H30A	2742	3391	9568	24	1
H30B	3510	4419	9351	24	1
H32	2036	−706	3438	34	1
H34	643	2490	2899	37	1
H31	4040(40)	4370(50)	3350(20)	22	1
H31A	3199	960	3932	20	1
H34A	2811	2844	2741	20	1
H35	2686	2999	3803	19	1
H37A	3728	6979	2047	59	1
H37B	4789	7690	2238	59	1
H37C	3725	7804	2537	59	1
H38A	5448	4577	2582	55	1

H38B	5820	5713	2254	55	1
H38C	4791	4922	2079	55	1
H39A	4496	6976	3339	46	1
H39B	5625	7079	3091	46	1
H39C	5274	5805	3335	46	1
H40A	835	3367	3622	24	1
H40B	1527	4417	3371	24	1
H42	−184	−747	7541	32	1
H44	−1627	2498	7019	40	1
H41	1761	4230	7337	23	1
H41A	1058	961	7961	23	1
H44A	398	2835	6787	21	1
H45	525	2990	7857	21	1
H47A	1109	7000	6072	52	1
H47B	2234	7670	6181	52	1
H47C	1308	7808	6562	52	1
H48A	2921	4525	6468	64	1
H48B	3301	5697	6164	64	1
H48C	2219	4997	5996	64	1
H49A	2245	6923	7300	43	1
H49B	3294	7028	6989	43	1
H49C	3004	5747	7245	43	1
H50A	−1352	3335	7761	25	1
H50B	−709	4405	7496	25	1

Table 6. Torsion angles [°].

S1–N1–C4–C3	146.1(3)
S1–N1–C4–C5	–91.1(4)
F1–C2–C3–F3	–53.8(4)
F1–C2–C3–F4	–168.8(3)
F1–C2–C3–C4	71.0(4)
F2–C2–C3–F3	62.4(5)
F2–C2–C3–F4	–52.6(4)
F2–C2–C3–C4	–172.8(3)
F3–C3–C4–N1	–67.1(4)
F3–C3–C4–C5	168.4(3)
F4–C3–C4–N1	50.3(4)
F4–C3–C4–C5	–74.2(4)
O1–C1–C2–F1	–60.0(4)
O1–C1–C2–F2	–178.8(3)
O1–C1–C2–C3	59.9(4)
O1–C5–C10–O4	–65.6(4)
O2–C1–C2–F1	60.5(5)
O2–C1–C2–F2	–58.2(5)
O2–C1–C2–C3	–179.5(3)
O3–S1–N1–C4	101.9(3)
O3–S1–C6–C7	–64.9(4)
O3–S1–C6–C8	177.8(3)
O3–S1–C6–C9	54.3(4)
N1–S1–C6–C7	–176.8(3)
N1–S1–C6–C8	65.8(4)
N1–S1–C6–C9	–57.6(4)
N1–C4–C5–O1	–169.2(3)
N1–C4–C5–C10	74.3(4)
C1–O1–C5–C4	63.2(4)
C1–O1–C5–C10	–176.0(3)
C1–C2–C3–F3	–175.4(3)
C1–C2–C3–F4	69.6(4)
C1–C2–C3–C4	–50.6(5)
C2–C3–C4–N1	168.8(3)
C2–C3–C4–C5	44.3(5)
C3–C4–C5–O1	–48.6(4)
C3–C4–C5–C10	–165.1(3)
C4–C5–C10–O4	54.2(5)
C5–O1–C1–O2	168.5(3)
C5–O1–C1–C2	–68.4(4)
C6–S1–N1–C4	–149.6(3)
S11–N11–C14–C13	147.2(3)
S11–N11–C14–C15	–90.1(4)
F11–C12–C13–F13	–52.6(5)
F11–C12–C13–F14	–168.6(3)
F11–C12–C13–C14	71.1(5)
F12–C12–C13–F13	63.5(5)
F12–C12–C13–F14	–52.4(5)
F12–C12–C13–C14	–172.7(3)
F13–C13–C14–N11	–67.3(4)
F13–C13–C14–C15	167.7(3)
F14–C13–C14–N11	50.7(4)
F14–C13–C14–C15	–74.3(4)
O11–C11–C12–F11	–60.1(4)
O11–C11–C12–F12	–178.6(3)
O11–C11–C12–C13	60.1(4)
O11–C15–C20–O14	–63.6(4)
O12–C11–C12–F11	59.9(5)
O12–C11–C12–F12	–58.6(5)

O12–C11–C12–C13	−179.9(3)
O13–S11–N11–C14	102.1(4)
O13–S11–C16–C17	−61.6(4)
O13–S11–C16–C18	−178.9(4)
O13–S11–C16–C19	57.0(4)
N11–S11–C16–C17	−173.8(3)
N11–S11–C16–C18	68.9(4)
N11–S11–C16–C19	−55.1(4)
N11–C14–C15–O11	−169.6(3)
N11–C14–C15–C20	73.8(4)
C11–O11–C15–C14	64.0(4)
C11–O11–C15–C20	−175.2(3)
C11–C12–C13–F13	−174.6(4)
C11–C12–C13–F14	69.5(4)
C11–C12–C13–C14	−50.8(5)
C12–C13–C14–N11	169.5(4)
C12–C13–C14–C15	44.4(5)
C13–C14–C15–O11	−48.9(4)
C13–C14–C15–C20	−165.5(4)
C14–C15–C20–O14	56.3(5)
C15–O11–C11–O12	168.9(3)
C15–O11–C11–C12	−68.6(4)
C16–S11–N11–C14	−149.6(4)
S21–N21–C24–C23	145.6(3)
S21–N21–C24–C25	−92.2(4)
F21–C22–C23–F23	−52.5(5)
F21–C22–C23–F24	−167.8(4)
F21–C22–C23–C24	71.4(5)
F22–C22–C23–F23	63.5(5)
F22–C22–C23–F24	−51.8(5)
F22–C22–C23–C24	−172.6(4)
F23–C23–C24–N21	−66.6(5)
F23–C23–C24–C25	169.0(3)
F24–C23–C24–N21	51.1(5)
F24–C23–C24–C25	−73.3(5)
O21–C21–C22–F21	−61.9(4)
O21–C21–C22–F22	179.5(3)
O21–C21–C22–C23	58.3(4)
O21–C25–C30–O24	−61.9(4)
O22–C21–C22–F21	59.1(5)
O22–C21–C22–F22	−59.5(5)
O22–C21–C22–C23	179.3(3)
O23–S21–N21–C24	102.0(4)
O23–S21–C26–C27	−63.4(4)
O23–S21–C26–C28	179.3(3)
O23–S21–C26–C29	55.8(4)
N21–S21–C26–C27	−176.0(3)
N21–S21–C26–C28	66.7(4)
N21–S21–C26–C29	−56.8(4)
N21–C24–C25–O21	−171.2(3)
N21–C24–C25–C30	72.2(4)
C21–O21–C25–C24	64.9(4)
C21–O21–C25–C30	−174.1(4)
C21–C22–C23–F23	−174.0(3)
C21–C22–C23–F24	70.6(4)
C21–C22–C23–C24	−50.2(5)
C22–C23–C24–N21	170.2(4)
C22–C23–C24–C25	45.9(5)
C23–C24–C25–O21	−50.8(4)
C23–C24–C25–C30	−167.3(4)
C24–C25–C30–O24	57.3(5)

C25–O21–C21–O22	169.5(4)
C25–O21–C21–C22	–67.7(4)
C26–S21–N21–C24	–148.9(4)
S31–N31–C34–C33	144.0(3)
S31–N31–C34–C35	–94.2(4)
F31–C32–C33–F33	–53.8(5)
F31–C32–C33–F34	–169.0(3)
F31–C32–C33–C34	70.4(5)
F32–C32–C33–F33	64.0(5)
F32–C32–C33–F34	–51.2(5)
F32–C32–C33–C34	–171.8(3)
F33–C33–C34–N31	–66.2(4)
F33–C33–C34–C35	170.0(3)
F34–C33–C34–N31	51.3(5)
F34–C33–C34–C35	–72.5(4)
O31–C31–C32–F31	–61.7(4)
O31–C31–C32–F32	179.5(3)
O31–C31–C32–C33	58.8(4)
O31–C35–C40–O34	–61.9(4)
O32–C31–C32–F31	58.4(5)
O32–C31–C32–F32	–60.3(5)
O32–C31–C32–C33	178.9(3)
O33–S31–N31–C34	101.4(3)
O33–S31–C36–C37	–65.8(4)
O33–S31–C36–C38	176.2(3)
O33–S31–C36–C39	53.0(4)
N31–S31–C36–C37	–178.3(3)
N31–S31–C36–C38	63.6(4)
N31–S31–C36–C39	–59.6(4)
N31–C34–C35–O31	–170.9(3)
N31–C34–C35–C40	72.5(4)
C31–O31–C35–C34	64.8(4)
C31–O31–C35–C40	–174.2(3)
C31–C32–C33–F33	–175.2(3)
C31–C32–C33–F34	69.5(4)
C31–C32–C33–C34	–51.0(5)
C32–C33–C34–N31	170.4(4)
C32–C33–C34–C35	46.6(5)
C33–C34–C35–O31	–50.9(4)
C33–C34–C35–C40	–167.4(3)
C34–C35–C40–O34	57.4(5)
C35–O31–C31–O32	169.7(3)
C35–O31–C31–C32	–67.9(4)
C36–S31–N31–C34	–149.5(3)
S41–N41–C44–C43	144.8(3)
S41–N41–C44–C45	–92.9(4)
F41–C42–C43–F43	–53.7(5)
F41–C42–C43–F44	–168.4(3)
F41–C42–C43–C44	71.8(5)
F42–C42–C43–F43	62.0(5)
F42–C42–C43–F44	–52.6(5)
F42–C42–C43–C44	–172.5(3)
F43–C43–C44–N41	–65.7(4)
F43–C43–C44–C45	170.1(3)
F44–C43–C44–N41	51.1(5)
F44–C43–C44–C45	–73.1(5)
O41–C41–C42–F41	–60.9(4)
O41–C41–C42–F42	–179.7(3)
O41–C41–C42–C43	59.5(4)
O41–C45–C50–O44	–64.4(4)
O42–C41–C42–F41	59.7(5)

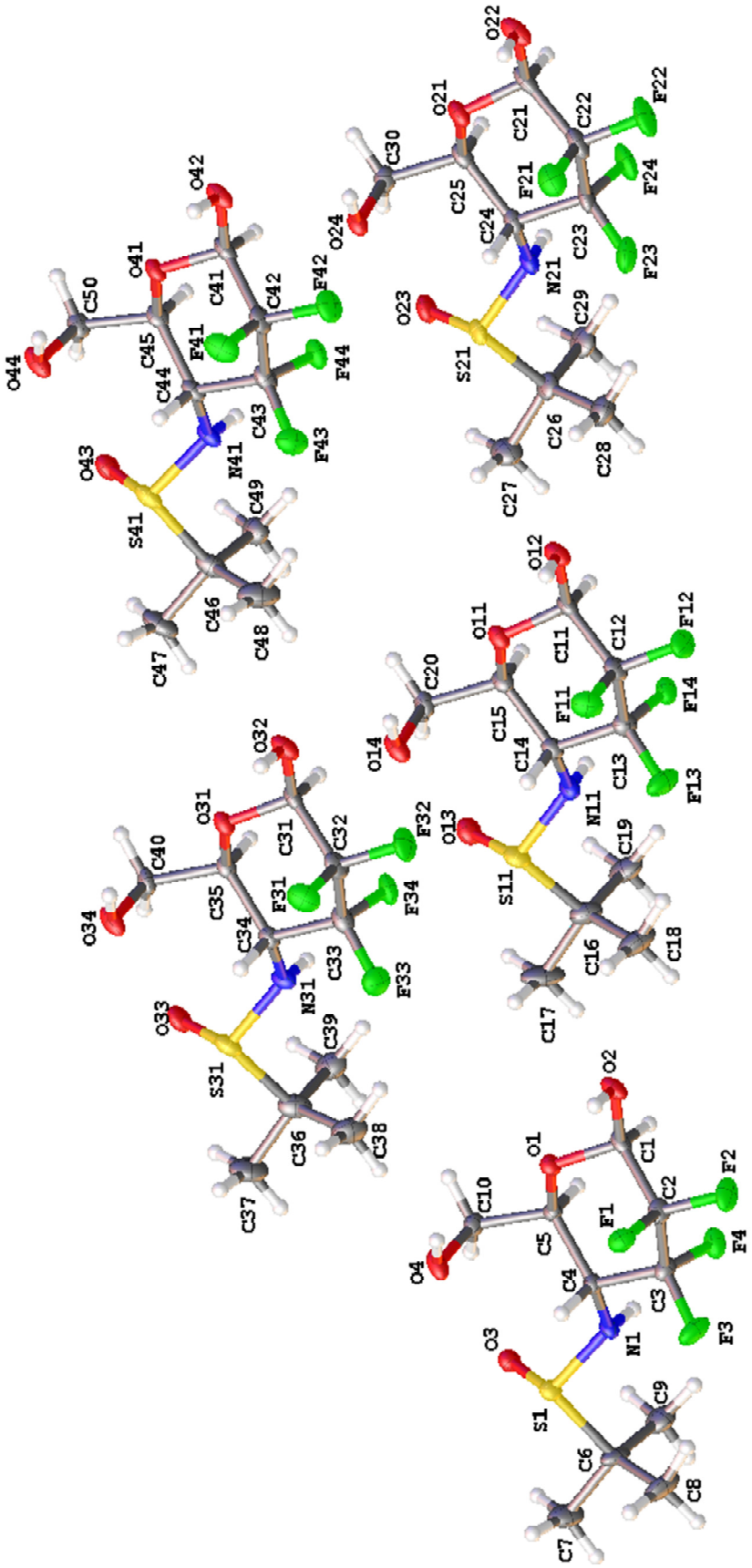
O42–C41–C42–F42	–59.0(5)
O42–C41–C42–C43	–179.8(3)
O43–S41–N41–C44	101.6(3)
O43–S41–C46–C47	–65.2(3)
O43–S41–C46–C48	175.7(3)
O43–S41–C46–C49	52.4(4)
N41–S41–C46–C47	–177.4(3)
N41–S41–C46–C48	63.5(4)
N41–S41–C46–C49	–59.8(4)
N41–C44–C45–O41	–170.3(3)
N41–C44–C45–C50	73.4(4)
C41–O41–C45–C44	65.0(4)
C41–O41–C45–C50	–174.1(3)
C41–C42–C43–F43	–176.0(3)
C41–C42–C43–F44	69.3(4)
C41–C42–C43–C44	–50.6(5)
C42–C43–C44–N41	169.4(3)
C42–C43–C44–C45	45.2(5)
C43–C44–C45–O41	–49.9(4)
C43–C44–C45–C50	–166.3(4)
C44–C45–C50–O44	54.8(5)
C45–O41–C41–O42	168.7(3)
C45–O41–C41–C42	–68.8(4)
C46–S41–N41–C44	–149.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H2···O24^{i}	0.84	1.81	2.630(4)	164.6
O4–H4···O23^{i}	0.84	1.90	2.690(5)	156.7
N1–H1···O42^{ii}	0.85(5)	2.15(5)	2.921(5)	151(5)
C1–H1A···O43^{i}	1.00	2.44	3.405(5)	161.1
C5–H5···O42^{ii}	1.00	2.58	3.390(5)	138.0
C9–H9B···F23^{iii}	0.98	2.48	3.276(6)	138.4
C10–H10B···S1	0.99	2.95	3.507(5)	116.9
C10–H10B···O3	0.99	2.51	3.387(6)	147.6
O12–H12···O14^{i}	0.84	1.81	2.631(4)	164.8
O14–H14···O13^{i}	0.84	1.87	2.691(5)	164.5
N11–H11···O32^{ii}	0.78(6)	2.20(6)	2.926(5)	155(5)
C11–H11A···O33^{i}	1.00	2.44	3.398(5)	160.4
C15–H15···O32^{ii}	1.00	2.49	3.307(5)	139.1
C17–H17A···F43^{ii}	0.98	2.49	3.355(6)	147.7
C19–H19B···F13^{iii}	0.98	2.58	3.411(6)	143.1
C20–H20B···S11	0.99	2.91	3.496(5)	118.7
C20–H20B···O13	0.99	2.50	3.395(6)	149.6
O22–H22···O4^{i}	0.84	1.81	2.630(5)	164.2
O24–H24···O3^{i}	0.84	1.87	2.700(4)	168.2
N21–H21···O22^{iv}	0.81(6)	2.15(6)	2.902(5)	155(5)
C21–H21A···O23^{v}	1.00	2.40	3.361(6)	160.1
C25–H25···O22^{iv}	1.00	2.47	3.277(5)	137.6
C27–H27A···F33^{ii}	0.98	2.55	3.491(6)	160.0
C28–H28C···F31^{ii}	0.98	2.64	3.463(6)	142.3
C29–H29B···F3^{iii}	0.98	2.61	3.465(6)	146.5
C30–H30B···S21	0.99	2.92	3.506(5)	118.5
C30–H30B···O23	0.99	2.49	3.375(6)	149.4
O32–H32···O44^{vi}	0.84	1.82	2.616(4)	158.3
O34–H34···O43^{vi}	0.84	1.89	2.700(5)	160.2
N31–H31···O12^{ii}	0.83(6)	2.19(6)	2.924(5)	146(5)
C31–H31A···O13^{i}	1.00	2.40	3.340(5)	156.9
C35–H35···O12^{ii}	1.00	2.53	3.338(5)	137.5
C37–H37A···F23^{ii}	0.98	2.63	3.541(7)	154.4
C38–H38C···F21^{ii}	0.98	2.61	3.380(6)	135.7
C40–H40B···S31	0.99	2.95	3.530(5)	118.1
C40–H40B···O33	0.99	2.49	3.375(6)	148.5
O42–H42···O34^{vi}	0.84	1.81	2.620(4)	161.1
O44–H44···O33^{vi}	0.84	1.91	2.690(5)	154.2
N41–H41···O2^{ii}	0.80	2.23	2.951(5)	151.2
C41–H41A···O3^{i}	1.00	2.40	3.350(5)	158.9
C45–H45···O2^{ii}	1.00	2.57	3.378(5)	138.2
C49–H49B···F33^{ii}	0.98	2.60	3.318(6)	130.5
C50–H50B···S41	0.99	2.97	3.522(5)	116.5
C50–H50B···O43	0.99	2.51	3.379(6)	146.9

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


O22
O21
C30
C21
C22
F22
C25
F21
F24
O24
C24
C23
F23
N21
O23
C29
S21
C26
C28
C27
O42
O41
C50
C41
C42
F42
C45
F41
F44
C44
C43
O44
F43
N41
O43
C49
S41
C46
C48
C47
O12
O11
C20
C11
C12
F12
C15
F11
F14
O14
C14
C13
F13
N11
O13
C19
S11
C16
C18
C17
O32
O31
C40
C31
C32
F32
C35
F31
F34
O34
C34
C33
F33
N31
O33
C39
S31
C36
C38
C37
O2
O1
C10
C1
C2
F2
C5
F1
F4
O4
C4
C3
F3
N1
O3
C9
S1
C6
C8
C7

Submitted by: **Fontenelle, C.**
Supervisor: **Linclau, B.**
Solved by: **Light, M.E.**
Sample ID: **CF300(R)Arc**

Crystal Data and Experimental

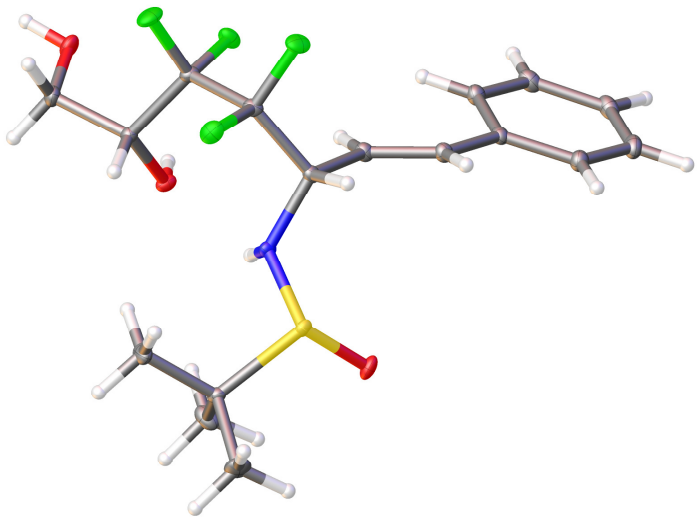


Figure 1. Thermal ellipsoids drawn at the 50 percent probability level.

Experimental. Single clear colourless fragment-shaped crystals of (**2014sot0044**) were recrystallised from TCM by slow evaporation. A suitable crystal (0.160 × 0.050 × 0.040 mm³) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{17}H_{23}F_4NO_3S$, M_r = 397.42, monoclinic, $P2_1$ (No. 4), a = 9.6650(2) Å, b = 10.3350(2) Å, c = 10.6040(2) Å, β = 116.754(3)°, α = γ = 90°, V = 945.82(4) Å³, T = 100(2) K, Z = 2, Z' = 1, μ (MoK$_\alpha$) = 0.225, 11733 reflections measured, 4649 unique (R_{int} = 0.0160) which were used in all calculations. The final wR_2 was 0.0667 (all data) and R_1 was 0.0255 (I > 2(I)).

Compound	**2014sot0044**
Formula	$C_{17}H_{23}F_4NO_3S$
$D_{calc.}$/ g cm^{-3}	1.395
μ/mm^{-1}	0.225
Formula Weight	397.42
Colour	clear colourless
Shape	fragment
Max Size/mm	0.160
Mid Size/mm	0.050
Min Size/mm	0.040
T/K	100(2)
Crystal System	monoclinic
Space Group	$P2_1$
a/Å	9.6650(2)
b/Å	10.3350(2)
c/Å	10.6040(2)
α/°	90
β/°	116.754(3)
γ/°	90
V/Å³	945.82(4)
Z	2
Z'	1
Θ_{min}/°	2.151
Θ_{max}/°	32.239
Measured Refl.	11733
Independent Refl.	4649
Reflections Used	4513
R_{int}	0.0160
Parameters	250
Restraints	1
Largest Peak	0.350
Deepest Hole	-0.253
GooF	1.043
wR_2 (all data)	0.0667
wR_2	0.0660
R_1 (all data)	0.0267
R_1	0.0255
Absolute structure	
Flack parameter	-0.03(3)
Hooft parameter	-0.02(2)

Experimental Extended. A clear colourless fragment-shaped crystal with dimensions 0.160 × 0.050 × 0.040 mm^3 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at $T = 100(2)$ K.

Data were measured using profile data from ω-scans of 1.0° per frame for 10.0 s using MoK_α radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieve resolution was $\Theta = 32.239$.

Cell parameters were retrieved using the **CrysAlisPro** (Agilent, V1.171.37.31, 2014) software and refined using **CrysAlisPro** (Agilent, V1.171.37.31, 2014) on 9576 reflections, 82 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Agilent, V1.171.37.31, 2014) software which corrects for Lorentz polarisation. The final completeness is 99.80 out to 32.239 in Θ. The absorption coefficient (MU) of this material is 0.225 and the minimum and maximum transmissions are 0.95152 and 1.00000.

The structure was solved by Direct Methods using the ShelXT (Sheldrick, 2008) structure solution program and refined by Least Squares using version of **ShelXL** (Sheldrick, 2008).

The structure was solved in the space group $P2_1$ (# 4). All non-hydrogen atoms were refined anisotropically. Hydrogens positions were calculated geometrically and refined using the riding model.

There is no entry for the cif item _refine_special_details

Citations

CrysAlisPro Software System, Agilent Technologies UK Ltd, Yarnton, Oxford, UK (2014).

CrystalClear, Rigaku, ?(?).

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

CRYSTAL STRUCTURE DETERMINATION OF **CF27Brc**

M. Sanselme and G. Coquerel
Unité de Croissance Cristalline et de Modélisation Moléculaire, UPRES EA 3233.
Institut de Recherche en Chimie Organique Fine.
Université de Rouen. 1 rue Lucien Tesnière, 76821 Mont-Saint-Aignan cedex, France

25/09/12

DATA COLLECTION

The crystal structure of CF27Brc [$C_{14}H_{25}F_2NO_5S$],H_2O has been determined from single crystal X-Ray diffraction. The chosen crystal was stuck on a glass fibre and mounted on the full three-circle goniometer of a Bruker SMART APEX diffractometer with a CCD area detector. Four sets of exposures (a total of 1315 frames) were recorded, corresponding to three ω scans (steps of 0.3°), for three different values of ϕ. The details of data collection are given in annexe 1.

The cell parameters and the orientation matrix of the crystal were preliminary determined by using SMART Software[1]. Data integration and global cell refinement were performed with SAINT Software[2]. Intensities were corrected for Lorentz, polarisation, decay and absorption effects (SAINT and SADABS Softwares) and reduced to F_O^2. The program package WinGX[3] was used for space group determination, structure solution and refinement.

DATA REFINEMENT

The standard space group $P2_1$ (n°4) was determined from systematic extinctions and relative F_O^2 of equivalent reflections. The structure was solved by direct methods[4]. Anisotropic displacement parameters were refined for all non-hydrogen atoms. Every Hydrogen atoms were located from subsequent difference Fourier syntheses and placed with geometrical constraints (SHELXL[5]). The final cycle of full-matrix least-square refinement on F^2 was based on 3726 observed reflections and 229 variable parameters and converged with unweighted and weighted agreement factors of:

R1 = 0.0497, wR2 = 0.1360 for 3487 reflections with $I>2\sigma I$ and R1 = 0.0524, wR2 = 0.1397 for all data.

The refinement data are given in annexe 1 table 2

CRYSTALLOGRAPHIC DATA AND STRUCTURAL DESCRIPTION

Crystallographic data

The crystal data are collected in Table 1. The full crystallographic parameters (atomic coordinates, bond length, angles and anisotropic displacements) are reported in annexe 2.

Table 1: Crystal data

Chemical Formula	C14 H27 F2 N O6 S
Molecular Weight / $g.mol^{1}$	375.43
Crystal System	Monoclinic
Space Group	$P2_1$ (n°4)
Z , Z' (asymmetric units per unit cell)	2, 1
a / *Å*	12.221(2)
b / *Å*	6.0654(11)
c / *Å*	13.752(2)
β / °	96.378(3)
V / $Å^3$	1013.1(3)
d_{calc} / $g.cm^{-3}$	1.231
F(000) / e^-	400
Absolute structure parameter	0.03(1)
Absorption coefficient μ (MoKα_1) / mm^{-1}	0.203

Structural description

The asymmetric unit is composed of one molecule of CF27Brc and one water molecule (Figures 1-2). Inside the packing, the water molecules ensure the cohesion between the molecules of CF27Brc by establishing Hydrogen bonds. There are three types of hydrogen bonds (Table 2). The first type bound a water molecule to the organic molecule; this H-bond is formed between the two entities of the asymmetric unit and generate a building unit (Figures 1-2). The second type of H-bond connects the building unit along b axis in single strand (Figure 3). Two adjacent strands are linked through the third type of H-bonds and thus give rise to molecular chains along *b* (Figures 4-5). The cohesion between the molecular chains are ensured by VdW interactions along *a* and *c* axis (Figures 6-7).

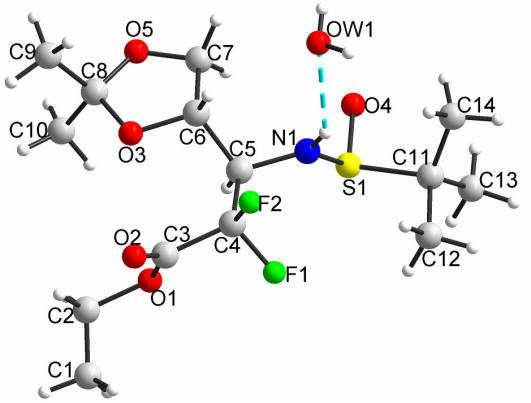


Figure 1: Asymmetric unit with atom labels. The hydrogen bond between the two entities is represented in dashed blue line.

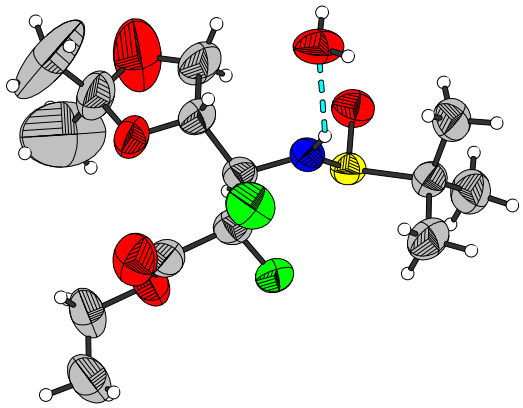


Figure 2: The asymmetric unit with thermal ellipsoid displacement (50% probability). The Hydrogen bond between the two entities is represented in dashed blue line.

Table 2: Hydrogen bonds

D-H...A	d(D-H) (Å)	d(H...A) (Å)	d(D...A) (Å)	<(DHA) (°)
First type : Building unit –dashed blue line				
N(1)-H(1)...OW1	0.86	2.13	2.825(3)	137.5
Second type : generating strands –dashed green line				
OW1-H(2O)...O(4)#1	0.91(5)	1.83(5)	2.735(4)	174(4)
Third type : Leading to molecular chains –dashed pink line				
OW1-H(1O)...O(4)#2	0.73(5)	2.08(5)	2.780(3)	161(6)
Symmetry transformations used to generate equivalent atoms: #1 x,y+1,z #2 -x+2,y+1/2,-z+1				

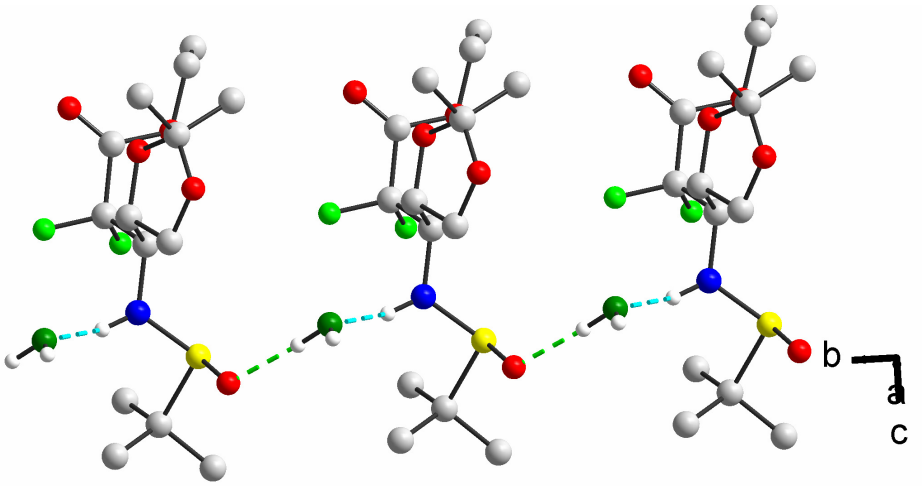


Figure 3: The building units are connected through the hydrogen bond (dashed green line) established between the water molecule (in green) and the sulfoxide moiety. These strands are spreading along *b* axis.

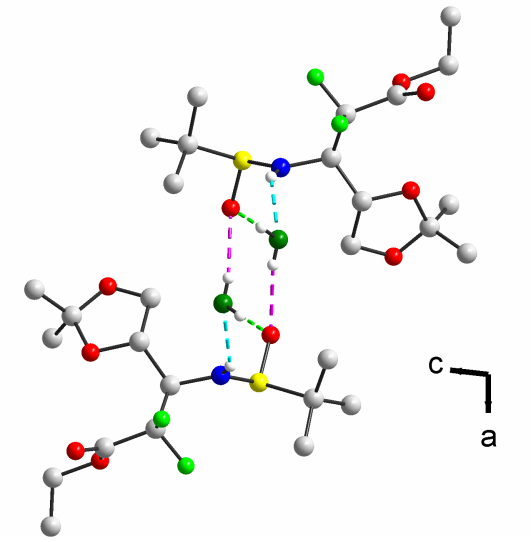


Figure 4: Two adjacent strands (along *a*) interact through a third type of hydrogen bonds (dashed pink line), and give rise to molecular chains spreading along *b*

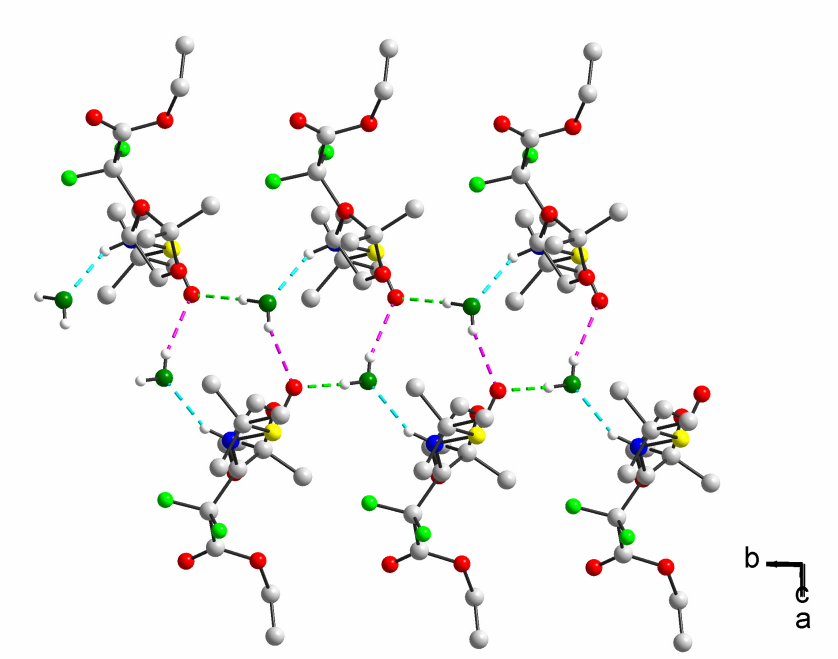


Figure 5: Two adjacent strands, through a third type of hydrogen bonds (dashed pink line), give rise to molecular chains spreading along *b*

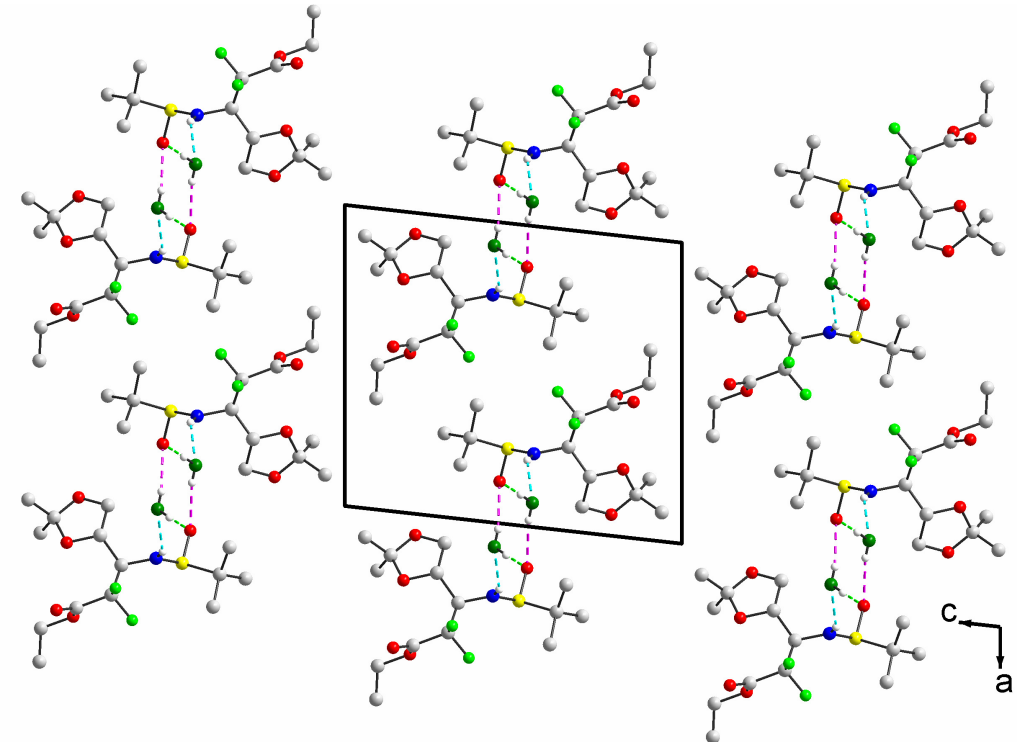


Figure 6: Packing of the structure, projection along *b* axis. The molecular chains are spreading along b, and interact through weak vdw interactions with adjacent ones along *a* and *c*.

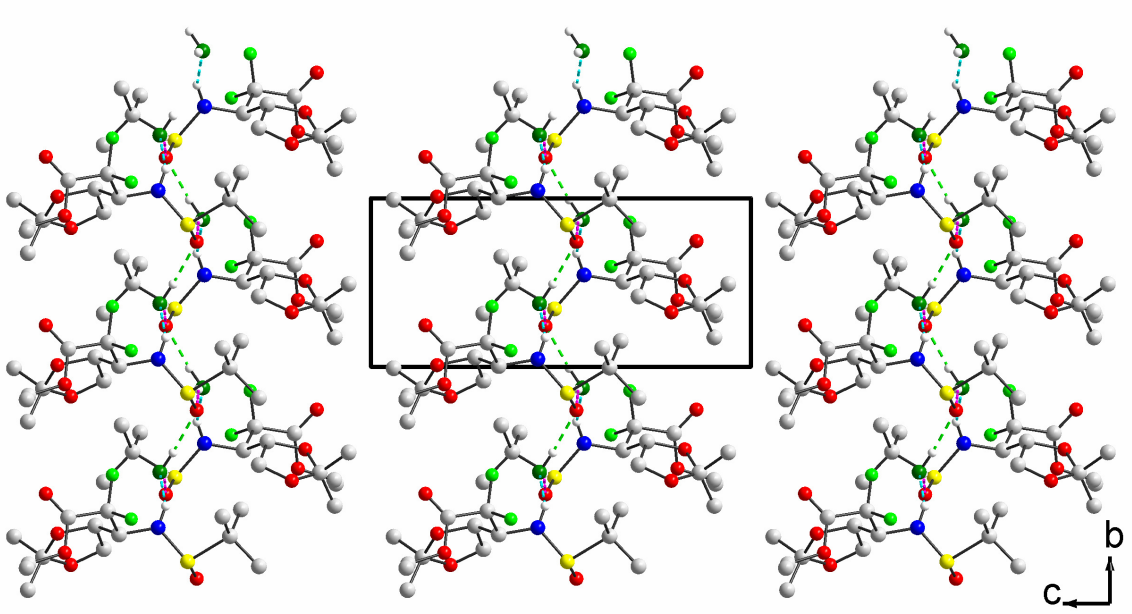


Figure 7: Projection along a. The molecular chains are spreading along *b* axis.

Sofwares :

(1)- SMART for WNT/2000 V5.622 (2001), Smart software reference manual, Bruker Advanced X Ray Solutions, Inc., Madison, Wisconsin, USA.

(2)- SAINT+ V6.02 (1999), Saint software reference manual, Bruker Advanced X Ray Solutions, Inc., Madison, Wisconsin, USA.

(3)-WinGX: Version 1.70.01: An integrated system of Windows Programs for the solution, refinement and analysis of Single Crystal X-Ray Diffraction Data, By LouisJ. Farrugia, Dept. of chemistry, University of Glasgow.

L. J. Farrugia (1999) J. Appl. Cryst. 32, 837-838.

(4)-include in WinGX suite : SIR 92: A. Altomare, G. Cascarano, & A. Gualardi (1993) J. Appl. Cryst. 26, 343-350; SHELXS-97: Sheldrick, G. M., (1990) Acta cryst, A46, 467.

(5)-include in WinGX suite: SHELXL-97 – a program for crystal structure refinement, G. M. .Sheldrick, University of Goettingen, Germany, 1997, release 97-2.

(6)-PowderCell for Windows (version 2.4) by Kraus W. & Nolze G., Federal institute for materials Research and testing, Rudower Chausse 5, 12489 Berlin Germany.

ANNEXE 1 :

- Table 1 : DATA COLLECTION FOR C14 H27 F2 N O6 S

Date	25/09/12
Temperature / *K*	RT
Radiation	Mo-Kα_1 (λ = 0.71073Å)
Monochromator	Graphite
Collimator / *mm*	0.5
Generator set	50 kV 40mA
Crystal-detector distance / *mm*	60
Detector 2θ angle / °	-28
ω oscillations / °	-0.3
ω scan 1 (600 frames)	χ = 54.7°, ϕ = 0°, -28° ≤ ω ≤ -208°
ω scan 2 (435)	χ = 54.7°, ϕ = 90°, -28° ≤ ω ≤ -158;5°
ω scan 3 (230 frames)	χ = 54.7°, ϕ = 180°, -28° ≤ ω ≤ -97°
ω scan 4 (50 frames)	χ = 54.7°, ϕ = 270°, -28° ≤ ω ≤ -43°
Time exposure / *s*	10
Total number of reflections	5889
Unique reflections [$F_o > 4.0\ \sigma(F_o)$]	3726 [3487]
θ range / °	1.68 to 26.37
hkl range	-15≤h≤15, -7≤k≤7, -17≤l≤12
$R_{int} = \Sigma[\lvert F_O^2 - F_O^2(mean)\rvert] / \Sigma[F_O^2]$	0.0186
Completeness to θ = 26.40 / %	98.7

- Table 2 : REFINEMENT DATA FOR C19H27NO3

Number of reflections (n) (with $F_O > 4.0\ \sigma(F_O)$)	3726 / 3487
Number of refined parameters (p) / restraints	229 / 1
Reflection / parameter ratio	
Final R indices [I>2sigma(I)]	R1 = 0.0497, wR2 = 0.1360
R indices (all data)	R1 = 0.0524, wR2 = 0.1397
Goodness of Fit indicator (Restrained GooF)	1.078
Maximum peak in Final Difference Map / $e^-Å^{-3}$	0.282
Maximum hole in Final Difference Map / $e^-Å^{-3}$	-0.175

$R_1 = \Sigma\ (||F_O|-|F_C||) / \Sigma\ |F_O|$

$wR_2 = [\ \Sigma\ [\ w\ (F_O^2 - F_C^2)^{\ 2}] / \Sigma\ [\ w\ (F_O^2)^2\ ]\ ]^{1/2}$

$GooF = [\Sigma\ [\ w\ (F_O^2 - F_C^2)^{\ 2}] / (n - p)\ ]^{1/2}$

ANNEXE 2 : CRYSTALLOGRAPHIC DATA

Table 1a: Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

	x	y	z	U(eq)
C(1)	3693(4)	3050(15)	926(3)	147(3)
C(2)	4809(4)	3279(15)	972(3)	126(2)
C(3)	5619(3)	6050(7)	2020(2)	73(1)
C(4)	6185(2)	6432(6)	3063(2)	64(1)
C(5)	7206(2)	5040(5)	3360(2)	54(1)
C(6)	8120(2)	5560(7)	2732(2)	71(1)
C(7)	9140(3)	4169(10)	2959(3)	110(2)
C(8)	8535(3)	3708(10)	1355(3)	93(1)
C(9)	9038(9)	4910(20)	594(7)	239(6)
C(10)	7977(9)	1738(18)	958(11)	261(7)
C(11)	7270(2)	4944(6)	6281(2)	63(1)
C(12)	6162(3)	6098(8)	6085(3)	87(1)
C(13)	7218(3)	3149(8)	7044(3)	85(1)
C(14)	8201(3)	6525(7)	6571(3)	83(1)
F(1)	5416(1)	5953(5)	3680(1)	85(1)
F(2)	6417(2)	8576(4)	3185(2)	92(1)
N(1)	7562(2)	5446(4)	4390(2)	56(1)
S(1)	7495(1)	3429(1)	5167(1)	54(1)
O(1)	5319(2)	3954(5)	1930(2)	92(1)
O(2)	5472(3)	7456(6)	1431(2)	103(1)
O(3)	7751(2)	5093(5)	1738(2)	83(1)
O(4)	8610(2)	2415(4)	5407(2)	70(1)
O(5)	9297(4)	3230(13)	2090(3)	215(3)
OW1	9200(2)	8742(5)	4435(2)	85(1)

Table 1b: Hydrogen coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

	x	y	z	U(eq)
H(1A)	3382	4356	1178	220
H(1B)	3522	1801	1310	220
H(1C)	3392	2833	258	220
H(2A)	4977	4364	492	152
H(2B)	5126	1886	800	152
H(5)	7009	3480	3277	65
H(6)	8316	7123	2800	85
H(7A)	9766	5074	3201	132
H(7B)	9029	3053	3444	132
H(9A)	9168	6409	796	359
H(9B)	8551	4879	-4	359
H(9C)	9724	4225	490	359
H(10A)	8508	593	899	392
H(10B)	7598	2060	325	392
H(10C)	7456	1260	1388	392
H(12A)	5949	6667	6687	130
H(12B)	5618	5065	5809	130
H(12C)	6220	7289	5634	130
H(13A)	7938	2526	7204	128
H(13B)	6717	2018	6789	128
H(13C)	6967	3769	7622	128
H(14A)	8165	7733	6118	124
H(14B)	8892	5772	6563	124
H(14C)	8141	7075	7218	124
H(1)	7803	6722	4585	67
H(2O)	8970(40)	9900(90)	4780(40)	102
H(1O)	9790(40)	8650(100)	4550(30)	102

Table 2: Bond lengths (Å)

C(1)-C(2)	1.365(7)	C(8)-C(9)	1.465(9)
C(1)-H(1A)	0.96	C(9)-H(9A)	0.96
C(1)-H(1B)	0.96	C(9)-H(9B)	0.96
C(1)-H(1C)	0.96	C(9)-H(9C)	0.96
C(2)-O(1)	1.452(4)	C(10)-H(10A)	0.96
C(2)-H(2A)	0.97	C(10)-H(10B)	0.96
C(2)-H(2B)	0.97	C(10)-H(10C)	0.96
C(3)-O(2)	1.177(5)	C(11)-C(14)	1.508(4)
C(3)-O(1)	1.324(5)	C(11)-C(13)	1.519(5)
C(3)-C(4)	1.539(5)	C(11)-C(12)	1.521(5)
C(4)-F(2)	1.337(4)	C(11)-S(1)	1.833(3)
C(4)-F(1)	1.366(4)	C(12)-H(12A)	0.96
C(4)-C(5)	1.524(4)	C(12)-H(12B)	0.96
C(5)-N(1)	1.455(3)	C(12)-H(12C)	0.96
C(5)-C(6)	1.520(4)	C(13)-H(13A)	0.96
C(5)-H(5)	0.98	C(13)-H(13B)	0.96
C(6)-O(3)	1.420(4)	C(13)-H(13C)	0.96
C(6)-C(7)	1.509(5)	C(14)-H(14A)	0.96
C(6)-H(6)	0.98	C(14)-H(14B)	0.96
C(7)-O(5)	1.356(6)	C(14)-H(14C)	0.96
C(7)-H(7A)	0.97	N(1)-S(1)	1.633(3)
C(7)-H(7B)	0.97	N(1)-H(1)	0.86
C(8)-O(5)	1.328(6)	S(1)-O(4)	1.498(2)
C(8)-O(3)	1.419(5)	OW1-H(2O)	0.91(5)
C(8)-C(10)	1.452(11)	OW1-H(1O)	0.73(5)

Table 3: Angles (°)

C(2)-C(1)-H(1A)	109.5	C(7)-C(6)-H(6)	109.5	C(13)-C(11)-S(1)	103.9(2)
C(2)-C(1)-H(1B)	109.5	C(5)-C(6)-H(6)	109.5	C(12)-C(11)-S(1)	107.2(2)
H(1A)-C(1)-H(1B)	109.5	O(5)-C(7)-C(6)	104.3(4)	C(11)-C(12)-H(12A)	109.5
C(2)-C(1)-H(1C)	109.5	O(5)-C(7)-H(7A)	110.9	C(11)-C(12)-H(12B)	109.5
H(1A)-C(1)-H(1C)	109.5	C(6)-C(7)-H(7A)	110.9	H(12A)-C(12)-H(12B)	109.5
H(1B)-C(1)-H(1C)	109.5	O(5)-C(7)-H(7B)	110.9	C(11)-C(12)-H(12C)	109.5
C(1)-C(2)-O(1)	113.4(4)	C(6)-C(7)-H(7B)	110.9	H(12A)-C(12)-H(12C)	109.5
C(1)-C(2)-H(2A)	108.9	H(7A)-C(7)-H(7B)	108.9	H(12B)-C(12)-H(12C)	109.5
O(1)-C(2)-H(2A)	108.9	O(5)-C(8)-O(3)	107.0(3)	C(11)-C(13)-H(13A)	109.5
C(1)-C(2)-H(2B)	108.9	O(5)-C(8)-C(10)	111.5(8)	C(11)-C(13)-H(13B)	109.5
O(1)-C(2)-H(2B)	108.9	O(3)-C(8)-C(10)	108.5(5)	H(13A)-C(13)-H(13B)	109.5
H(2A)-C(2)-H(2B)	107.7	O(5)-C(8)-C(9)	109.8(7)	C(11)-C(13)-H(13C)	109.5
O(2)-C(3)-O(1)	127.7(4)	O(3)-C(8)-C(9)	108.9(5)	H(13A)-C(13)-H(13C)	109.5
O(2)-C(3)-C(4)	123.4(4)	C(10)-C(8)-C(9)	110.9(8)	H(13B)-C(13)-H(13C)	109.5
O(1)-C(3)-C(4)	108.8(3)	C(8)-C(9)-H(9A)	109.5	C(11)-C(14)-H(14A)	109.5
F(2)-C(4)-F(1)	106.3(3)	C(8)-C(9)-H(9B)	109.5	C(11)-C(14)-H(14B)	109.5
F(2)-C(4)-C(5)	110.4(2)	H(9A)-C(9)-H(9B)	109.5	H(14A)-C(14)-H(14B)	109.5
F(1)-C(4)-C(5)	108.4(3)	C(8)-C(9)-H(9C)	109.5	C(11)-C(14)-H(14C)	109.5
F(2)-C(4)-C(3)	109.3(3)	H(9A)-C(9)-H(9C)	109.5	H(14A)-C(14)-H(14C)	109.5
F(1)-C(4)-C(3)	106.1(2)	H(9B)-C(9)-H(9C)	109.5	H(14B)-C(14)-H(14C)	109.5
C(5)-C(4)-C(3)	115.9(3)	C(8)-C(10)-H(10A)	109.5	C(5)-N(1)-S(1)	118.59(19)
N(1)-C(5)-C(6)	111.0(2)	C(8)-C(10)-H(10B)	109.5	C(5)-N(1)-H(1)	120.7
N(1)-C(5)-C(4)	108.4(2)	H(10A)-C(10)-H(10B)	109.5	S(1)-N(1)-H(1)	120.7
C(6)-C(5)-C(4)	111.4(3)	C(8)-C(10)-H(10C)	109.5	O(4)-S(1)-N(1)	109.95(12)
N(1)-C(5)-H(5)	108.7	H(10A)-C(10)-H(10C)	109.5	O(4)-S(1)-C(11)	103.87(13)
C(6)-C(5)-H(5)	108.7	H(10B)-C(10)-H(10C)	109.5	N(1)-S(1)-C(11)	101.20(14)
C(4)-C(5)-H(5)	108.7	C(14)-C(11)-C(13)	111.1(3)	C(3)-O(1)-C(2)	116.2(4)
O(3)-C(6)-C(7)	104.8(3)	C(14)-C(11)-C(12)	112.7(3)	C(8)-O(3)-C(6)	108.6(3)
O(3)-C(6)-C(5)	109.3(2)	C(13)-C(11)-C(12)	110.4(3)	C(8)-O(5)-C(7)	115.0(4)
C(7)-C(6)-C(5)	114.2(3)	C(14)-C(11)-S(1)	111.2(2)	H(2O)-OW1-H(1O)	108(5)
O(3)-C(6)-H(6)	109.5				

Table 4: Anisotropic displacement parameters (Å² x 10^3) The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
C(1)	120(4)	238(9)	76(3)	-5(4)	-13(2)	-71(5)
C(2)	121(3)	194(6)	60(2)	-19(3)	-6(2)	-44(4)
C(3)	60(2)	98(3)	61(2)	12(2)	6(1)	14(2)
C(4)	54(1)	68(2)	71(2)	-5(1)	7(1)	9(1)
C(5)	50(1)	57(2)	56(1)	-5(1)	5(1)	4(1)
C(6)	57(1)	91(2)	66(2)	-4(2)	14(1)	7(2)
C(7)	71(2)	176(6)	86(2)	-2(3)	21(2)	44(3)
C(8)	104(3)	103(3)	74(2)	-13(2)	28(2)	25(2)
C(9)	268(10)	259(12)	227(9)	85(9)	189(9)	111(10)
C(10)	200(9)	187(10)	404(19)	-166(12)	67(11)	-16(8)
C(11)	59(1)	70(2)	60(2)	-9(1)	13(1)	-6(1)
C(12)	76(2)	103(3)	85(2)	-10(2)	26(2)	17(2)
C(13)	94(2)	94(3)	69(2)	8(2)	14(2)	-11(2)
C(14)	92(2)	81(2)	76(2)	-26(2)	16(2)	-27(2)
F(1)	49(1)	139(2)	67(1)	-7(1)	11(1)	9(1)
F(2)	95(1)	65(1)	115(2)	-12(1)	1(1)	19(1)
N(1)	54(1)	57(1)	58(1)	-9(1)	7(1)	-9(1)
S(1)	47(1)	54(1)	61(1)	-6(1)	8(1)	-4(1)
O(1)	98(2)	117(3)	59(1)	2(1)	-7(1)	-35(2)
O(2)	118(2)	110(2)	79(2)	28(2)	5(2)	29(2)
O(3)	77(1)	115(2)	59(1)	-8(1)	17(1)	22(1)
O(4)	62(1)	64(1)	84(1)	-2(1)	6(1)	9(1)
O(5)	188(4)	333(9)	116(3)	-56(4)	-20(3)	181(5)
OW1	58(1)	72(2)	127(2)	-23(2)	15(1)	-12(1)

Table 5: Torsion angles (°)

O(2)-C(3)-C(4)-F(2)	3.0(5)	C(5)-N(1)-S(1)-O(4)	100.3(2)
O(1)-C(3)-C(4)-F(2)	-175.4(3)	C(5)-N(1)-S(1)-C(11)	-150.3(2)
O(2)-C(3)-C(4)-F(1)	117.2(4)	C(14)-C(11)-S(1)-O(4)	54.5(3)
O(1)-C(3)-C(4)-F(1)	-61.3(3)	C(13)-C(11)-S(1)-O(4)	-65.1(2)
O(2)-C(3)-C(4)-C(5)	-122.5(4)	C(12)-C(11)-S(1)-O(4)	178.1(3)
O(1)-C(3)-C(4)-C(5)	59.1(4)	C(14)-C(11)-S(1)-N(1)	-59.5(3)
F(2)-C(4)-C(5)-N(1)	60.9(3)	C(13)-C(11)-S(1)-N(1)	-179.1(2)
F(1)-C(4)-C(5)-N(1)	-55.1(3)	C(12)-C(11)-S(1)-N(1)	64.1(3)
C(3)-C(4)-C(5)-N(1)	-174.2(3)	O(2)-C(3)-O(1)-C(2)	4.0(6)
F(2)-C(4)-C(5)-C(6)	-61.5(3)	C(4)-C(3)-O(1)-C(2)	-177.6(3)
F(1)-C(4)-C(5)-C(6)	-177.5(3)	C(1)-C(2)-O(1)-C(3)	-103.4(7)
C(3)-C(4)-C(5)-C(6)	63.4(4)	O(5)-C(8)-O(3)-C(6)	4.1(6)
N(1)-C(5)-C(6)-O(3)	178.6(3)	C(10)-C(8)-O(3)-C(6)	124.6(7)
C(4)-C(5)-C(6)-O(3)	-60.6(4)	C(9)-C(8)-O(3)-C(6)	-114.5(7)
N(1)-C(5)-C(6)-C(7)	61.7(4)	C(7)-C(6)-O(3)-C(8)	-5.4(4)
C(4)-C(5)-C(6)-C(7)	-177.5(3)	C(5)-C(6)-O(3)-C(8)	-128.1(4)
O(3)-C(6)-C(7)-O(5)	4.7(6)	O(3)-C(8)-O(5)-C(7)	-0.9(9)
C(5)-C(6)-C(7)-O(5)	124.2(5)	C(10)-C(8)-O(5)-C(7)	-119.5(8)
C(6)-C(5)-N(1)-S(1)	-123.3(2)	C(9)-C(8)-O(5)-C(7)	117.1(8)
C(4)-C(5)-N(1)-S(1)	114.1(2)	C(6)-C(7)-O(5)-C(8)	-2.4(9)

Table 6: Calculated reflections from PowderCell*

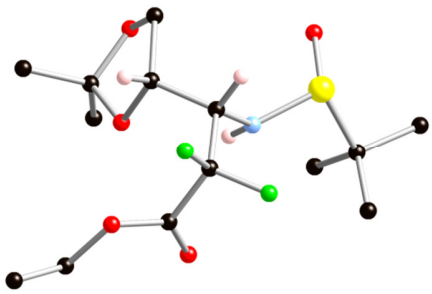
h	k	l	2θ/°	d/Å	I/rel.	|F(hkl)|
0	0	1	6.46	13.67	100.00	57.70
1	0	0	7.27	12.15	17.87	27.47
-1	0	1	9.18	9.63	73.39	70.36
1	0	1	10.26	8.62	13.39	33.62
2	0	0	14.57	6.07	6.69	33.92
-2	0	1	15.28	5.79	9.13	41.57
1	0	2	15.56	5.69	21.24	64.58
0	1	1	15.97	5.54	31.45	57.09
1	1	0	16.32	5.43	83.52	95.11
2	0	1	16.61	5.33	17.13	61.99
-1	1	1	17.27	5.13	16.05	44.16
1	1	1	17.87	4.96	15.74	45.31
-2	0	2	18.42	4.81	10.73	54.58
0	1	2	19.55	4.54	32.00	70.87
-1	1	2	20.37	4.36	4.10	26.45
2	1	0	20.68	4.29	20.27	59.78
-2	1	1	21.19	4.19	14.91	52.58
1	1	2	21.39	4.15	5.27	31.55
1	0	3	21.56	4.12	2.92	33.53
3	0	0	21.94	4.05	4.21	40.98
-3	0	1	22.18	4.00	12.03	70.03
-2	0	3	23.05	3.86	3.47	39.13
0	1	3	24.42	3.64	2.22	23.50
-1	1	3	24.87	3.58	18.29	68.83
-1	0	4	26.28	3.39	4.93	53.58
3	1	0	26.45	3.37	11.83	59.05
-2	1	3	27.39	3.25	2.19	26.35
-3	0	3	27.78	3.21	3.05	44.71
3	1	1	27.84	3.20	22.56	86.13
1	0	4	27.88	3.20	3.69	49.36
-3	1	2	28.42	3.14	4.52	39.39
0	2	0	29.43	3.03	2.92	46.46
2	1	3	29.67	3.01	3.18	34.59
0	1	4	29.99	2.98	2.56	31.44

Source: Cu-$K_{\alpha 1}$ (λ = 1.540598 Å)
Condition on reflections: I ≥ 2
Range (2θ): From 3° to 30°
*PowderCell for Windows (version 2.4) by Kraus W. & Nolze G., Federal institute for materials Research and testing, Rudower Chausse 5, 12489 Berlin Germany.

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2013sot0002** (CF145(R)A)
Empirical formula	$C_{14}H_{25}F_2NO_5S$
Formula weight	357.41
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.329(6) Å
	b = 9.292(7) Å
	c = 23.430(16) Å
Volume	1813(2) Å^3
Z	4
Density (calculated)	1.309 Mg / m^3
Absorption coefficient	0.219 mm^{-1}
$F(000)$	760
Crystal	Colourless Prism
Crystal size	0.210 × 0.190 × 0.150 mm^3
θ range for data collection	3.001 – 27.477°
Index ranges	$-10 \le h \le 7$, $-11 \le k \le 12$, $-30 \le l \le 30$
Reflections collected	11848
Independent reflections	4090 [R_{int} = 0.0396]
Completeness to θ = 27.500°	99.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4090 / 0 / 219
Goodness-of-fit on F^2	1.096
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0555, $wR2$ = 0.1230
R indices (all data)	$R1$ = 0.0632, $wR2$ = 0.1299
Absolute structure parameter	0.10(5)
Extinction coefficient	0.012(2)
Largest diff. peak and hole	0.293 and –0.480 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst.* **A64**, 112-122). **Structure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atom swere first identified in the difference map and then placed in calculated positions and refined using a riding model, except the NH which was freely refined.
Chirality: C5 = S, C6 = 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.*
S1	6714(1)	317(1)	1152(1)	31(1)	1
F1	11232(2)	3441(3)	1212(1)	40(1)	1
F2	9954(3)	2131(3)	1846(1)	42(1)	1
O1	7252(3)	4758(3)	742(1)	33(1)	1
O2	5937(4)	3844(4)	−8(1)	53(1)	1
O3	5644(3)	46(3)	656(1)	40(1)	1
O4	7973(4)	4457(3)	2066(1)	44(1)	1
O5	9844(3)	5694(3)	1564(1)	35(1)	1
N1	7181(4)	2043(4)	1210(1)	31(1)	1
C1	6757(9)	6371(6)	−42(2)	74(2)	1
C2	4543(6)	5453(6)	601(2)	56(1)	1
C3	6121(6)	5131(5)	313(2)	40(1)	1
C4	7442(5)	3129(5)	−24(2)	38(1)	1
C5	8343(5)	3712(4)	503(1)	32(1)	1
C6	8658(4)	2577(4)	964(1)	32(1)	1
C7	5414(4)	199(5)	1792(1)	32(1)	1
C8	6476(5)	408(5)	2319(1)	40(1)	1
C9	4071(5)	1289(5)	1765(2)	42(1)	1
C10	4746(5)	−1320(5)	1779(2)	42(1)	1
C11	9739(5)	3167(5)	1437(2)	34(1)	1
C12	9083(4)	4520(5)	1735(1)	33(1)	1
C13	9143(5)	7057(5)	1744(2)	42(1)	1
C14	10411(5)	8182(5)	1692(2)	45(1)	1

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

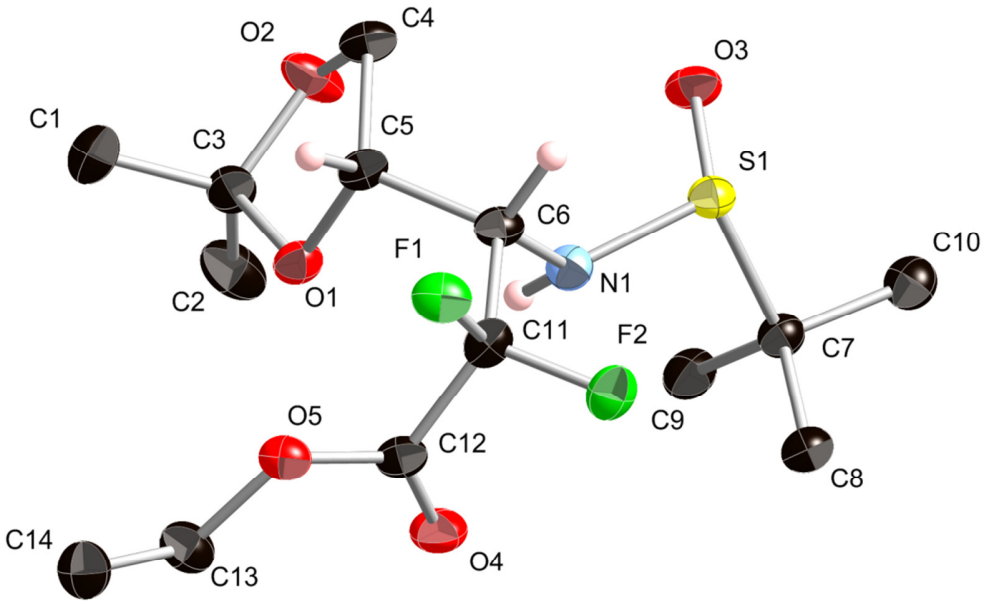
S1–O3	1.487(3)	N1–C6	1.446(5)
S1–N1	1.656(4)	C1–C3	1.515(6)
S1–C7	1.853(4)	C2–C3	1.507(6)
F1–C11	1.375(4)	C4–C5	1.543(5)
F2–C11	1.371(4)	C5–C6	1.533(5)
O1–C3	1.420(4)	C6–C11	1.529(5)
O1–C5	1.444(4)	C7–C9	1.510(6)
O2–C4	1.419(5)	C7–C10	1.518(6)
O2–C3	1.421(5)	C7–C8	1.531(5)
O4–C12	1.207(4)	C11–C12	1.539(6)
O5–C12	1.324(5)	C13–C14	1.491(6)
O5–C13	1.457(5)		
O3–S1–N1	111.61(17)	N1–C6–C5	111.8(3)
O3–S1–C7	105.86(16)	C11–C6–C5	111.4(3)
N1–S1–C7	97.38(17)	C9–C7–C10	110.6(4)
C3–O1–C5	107.9(3)	C9–C7–C8	112.2(3)
C4–O2–C3	108.3(3)	C10–C7–C8	110.2(3)
C12–O5–C13	115.9(3)	C9–C7–S1	111.0(3)
C6–N1–S1	120.0(3)	C10–C7–S1	104.6(3)
O1–C3–O2	103.9(3)	C8–C7–S1	107.9(3)
O1–C3–C2	108.1(3)	F2–C11–F1	106.3(3)
O2–C3–C2	108.0(4)	F2–C11–C6	109.4(3)
O1–C3–C1	110.0(4)	F1–C11–C6	108.7(3)
O2–C3–C1	112.9(3)	F2–C11–C12	107.6(3)
C2–C3–C1	113.5(5)	F1–C11–C12	110.1(3)
O2–C4–C5	104.0(3)	C6–C11–C12	114.4(3)
O1–C5–C6	107.3(3)	O4–C12–O5	126.9(4)
O1–C5–C4	104.0(3)	O4–C12–C11	121.6(4)
C6–C5–C4	114.0(3)	O5–C12–C11	111.5(3)
N1–C6–C11	109.6(3)	O5–C13–C14	107.6(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}
S1	29(1)	34(1)	28(1)	−3(1)	2(1)	1(1)
F1	24(1)	52(2)	44(1)	−7(1)	2(1)	2(1)
F2	41(1)	45(1)	40(1)	9(1)	−10(1)	5(1)
O1	35(1)	38(2)	26(1)	−1(1)	−5(1)	2(1)
O2	50(2)	55(2)	54(2)	−24(2)	−24(2)	8(2)
O3	40(2)	50(2)	28(1)	−5(1)	−5(1)	−7(2)
O4	49(2)	48(2)	34(1)	−7(1)	13(1)	−2(2)
O5	31(1)	40(2)	34(1)	−5(1)	2(1)	−2(1)
N1	26(2)	35(2)	32(2)	−1(2)	5(1)	0(2)
C1	125(5)	51(3)	44(2)	14(2)	−1(3)	10(4)
C2	51(3)	48(3)	69(3)	−19(3)	−15(2)	14(3)
C3	49(2)	37(2)	33(2)	−1(2)	−13(2)	2(2)
C4	36(2)	51(3)	26(2)	−6(2)	−3(2)	0(2)
C5	30(2)	41(2)	25(2)	0(2)	4(2)	0(2)
C6	29(2)	38(2)	27(2)	−5(2)	2(1)	1(2)
C7	29(2)	35(2)	30(2)	1(2)	1(1)	0(2)
C8	45(2)	44(2)	30(2)	0(2)	1(2)	0(2)
C9	35(2)	52(3)	37(2)	6(2)	9(2)	9(2)
C10	41(2)	41(2)	42(2)	3(2)	7(2)	−2(2)
C11	28(2)	42(2)	33(2)	5(2)	−1(2)	0(2)
C12	31(2)	42(2)	26(2)	−4(2)	−4(1)	0(2)
C13	41(2)	37(2)	48(2)	−8(2)	−3(2)	3(2)
C14	40(2)	44(3)	52(2)	2(2)	−2(2)	−5(2)

Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	6500(70)	2670(60)	1220(30)	80(20)	1
H1A	6958	7201	206	110	1
H1B	5964	6631	–333	110	1
H1C	7761	6082	–227	110	1
H2A	4216	4623	831	84	1
H2B	3724	5646	310	84	1
H2C	4663	6298	847	84	1
H4A	8029	3361	–380	45	1
H4B	7301	2073	1	45	1
H5	9370	4184	385	38	1
H6	9226	1748	781	38	1
H8A	6948	1374	2311	59	1
H8B	7336	–312	2318	59	1
H8C	5826	296	2665	59	1
H9A	3513	1202	1399	62	1
H9B	4517	2260	1802	62	1
H9C	3312	1112	2077	62	1
H10A	4107	–1491	2124	62	1
H10B	5635	–2011	1764	62	1
H10C	4066	–1440	1441	62	1
H13A	8767	6989	2143	51	1
H13B	8215	7302	1498	51	1
H14A	11250	8007	1977	68	1
H14B	9935	9133	1757	68	1
H14C	10882	8146	1309	68	1

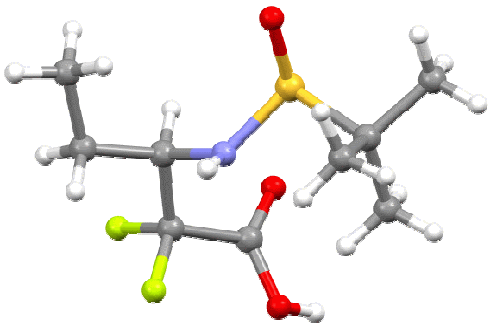


Thermal ellipsoids drawn at the 35% probability level, selected hydrogens omitted for clarity.

UNIVERSITY OF Southampton

Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
Contact: Dr Mark Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2013sot0098** (CF317(S)rc)
Empirical formula	$C_9H_{17}F_2NO_3S$
Formula weight	257.29
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.742(4) Å
b = 17.689(11) Å	β = 100.655(14)°
c = 6.193(4) Å	
Volume	618.1(7) Å^3
Z	2
Density (calculated)	1.382 Mg / m^3
Absorption coefficient	0.280 mm^{-1}
F(000)	272
Crystal	Prism; Colourless
Crystal size	0.120 × 0.070 × 0.020 mm^3
θ range for data collection	3.540 – 27.420°
Index ranges	$-7 \le h \le 7$, $-22 \le k \le 14$, $-8 \le l \le 7$
Reflections collected	5534
Independent reflections	2056 [R_{int} = 0.0360]
Completeness to θ = 25.242°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.694
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2056 / 3 / 155
Goodness-of-fit on F^2	1.032
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0244, $wR2$ = 0.0659
R indices (all data)	$R1$ = 0.0246, $wR2$ = 0.0662
Absolute structure parameter	0.02(4)
Largest diff. peak and hole	0.317 and –0.207 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst.* **A64**, 112-122). **Structure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogens were located in the difference map; those attached to carbon were placed in calculated positions and refined using a riding model, those attached to oxygen and nitrogen were refined using distance restraints and a thermal parameter 1.2 times that of the parent.

Chirality: C3 = R

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.*
S1	5516(1)	5701(1)	4024(1)	13(1)	1
F1	9975(2)	7841(1)	7182(2)	25(1)	1
F2	11810(2)	7149(1)	5094(2)	25(1)	1
O1	12385(3)	6233(1)	8315(2)	20(1)	1
O2	8769(3)	6471(1)	9092(2)	21(1)	1
O3	3362(2)	5705(1)	2212(2)	20(1)	1
N1	7561(3)	6302(1)	3570(3)	14(1)	1
C1	10317(3)	6560(1)	8031(3)	15(1)	1
C2	9934(3)	7148(1)	6158(3)	15(1)	1
C3	7614(3)	7064(1)	4524(3)	13(1)	1
C4	7405(4)	7696(1)	2801(3)	17(1)	1
C5	5027(4)	7707(2)	1227(4)	24(1)	1
C6	7030(3)	4805(1)	3633(3)	15(1)	1
C7	7574(4)	4753(1)	1314(3)	22(1)	1
C8	5255(4)	4194(1)	4011(4)	23(1)	1
C9	9263(4)	4762(1)	5391(4)	21(1)	1

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

S1–O3	1.5090(14)	C1–C2	1.544(3)
S1–N1	1.646(2)	C2–C3	1.524(3)
S1–C6	1.845(2)	C3–C4	1.535(3)
F1–C2	1.377(3)	C4–C5	1.524(3)
F2–C2	1.363(2)	C6–C9	1.523(3)
O1–C1	1.303(3)	C6–C7	1.528(3)
O2–C1	1.209(3)	C6–C8	1.533(3)
N1–C3	1.470(3)		
O3–S1–N1	112.47(9)	C3–C2–C1	114.71(16)
O3–S1–C6	104.34(10)	N1–C3–C2	107.95(16)
N1–S1–C6	99.45(11)	N1–C3–C4	113.27(16)
C3–N1–S1	119.07(14)	C2–C3–C4	109.67(16)
O2–C1–O1	127.8(2)	C5–C4–C3	113.60(17)
O2–C1–C2	118.58(18)	C9–C6–C7	112.18(18)
O1–C1–C2	113.60(17)	C9–C6–C8	110.57(18)
F2–C2–F1	105.89(16)	C7–C6–C8	111.03(18)
F2–C2–C3	110.54(15)	C9–C6–S1	107.67(14)
F1–C2–C3	109.37(16)	C7–C6–S1	110.97(15)
F2–C2–C1	110.40(17)	C8–C6–S1	104.06(15)
F1–C2–C1	105.44(15)		

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}
S1	12(1)	13(1)	14(1)	2(1)	2(1)	0(1)
F1	32(1)	16(1)	24(1)	–4(1)	–5(1)	–5(1)
F2	14(1)	39(1)	23(1)	9(1)	6(1)	–3(1)
O1	14(1)	24(1)	20(1)	2(1)	1(1)	3(1)
O2	18(1)	28(1)	18(1)	5(1)	5(1)	2(1)
O3	13(1)	21(1)	22(1)	4(1)	–5(1)	–2(1)
N1	16(1)	13(1)	15(1)	0(1)	6(1)	–2(1)
C1	15(1)	16(1)	12(1)	–4(1)	–1(1)	–2(1)
C2	12(1)	17(1)	17(1)	1(1)	3(1)	–2(1)
C3	12(1)	13(1)	14(1)	0(1)	1(1)	0(1)
C4	19(1)	14(1)	17(1)	2(1)	0(1)	–1(1)
C5	24(1)	24(1)	22(1)	6(1)	–2(1)	0(1)
C6	16(1)	13(1)	17(1)	0(1)	4(1)	1(1)
C7	28(1)	20(1)	21(1)	–3(1)	10(1)	–2(1)
C8	24(1)	14(1)	32(1)	0(1)	10(1)	–3(1)
C9	18(1)	20(1)	25(1)	3(1)	2(1)	6(1)

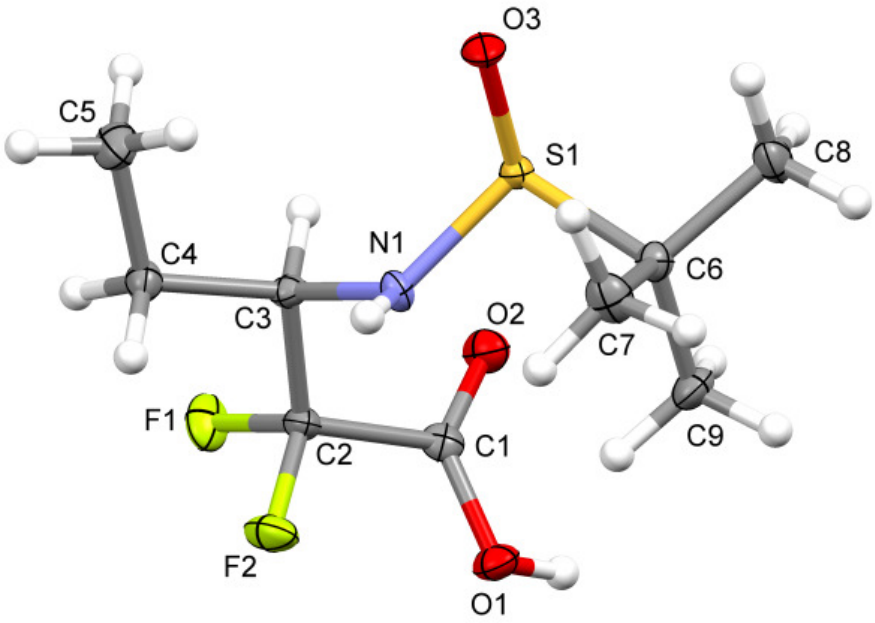
Table 5. Hydrogen coordinates [× 10⁴] and isotropic displacement parameters [Å² × 10³].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H902	12620(50)	6001(15)	9560(40)	25	1
H901	8010(40)	6273(16)	2320(30)	17	1
H3	6269	7111	5336	16	1
H4A	7645	8189	3565	20	1
H4B	8683	7633	1939	20	1
H5A	3750	7777	2063	36	1
H5B	4797	7227	425	36	1
H5C	5004	8124	182	36	1
H7A	8165	4246	1075	34	1
H7B	8780	5129	1142	34	1
H7C	6127	4851	238	34	1
H8A	4840	4263	5464	34	1
H8B	5969	3694	3933	34	1
H8C	3823	4234	2878	34	1
H9A	9935	4252	5414	32	1
H9B	8867	4876	6829	32	1
H9C	10424	5130	5061	32	1

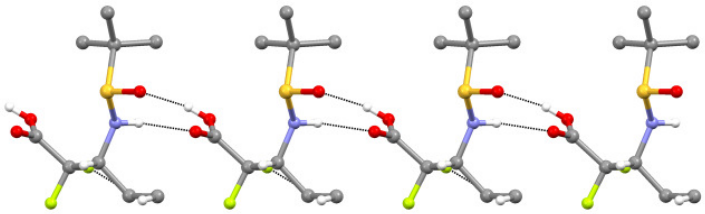
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
C3–H3···F2^{i}	1.00	2.54	3.419(3)	146.8
N1–H901···O2^{ii}	0.859(18)	2.15(2)	2.995(3)	166(3)
O1–H902···S1^{iii}	0.861(19)	3.00(2)	3.777(3)	151(2)
O1–H902···O3^{iii}	0.861(19)	1.70(2)	2.551(2)	169(3)

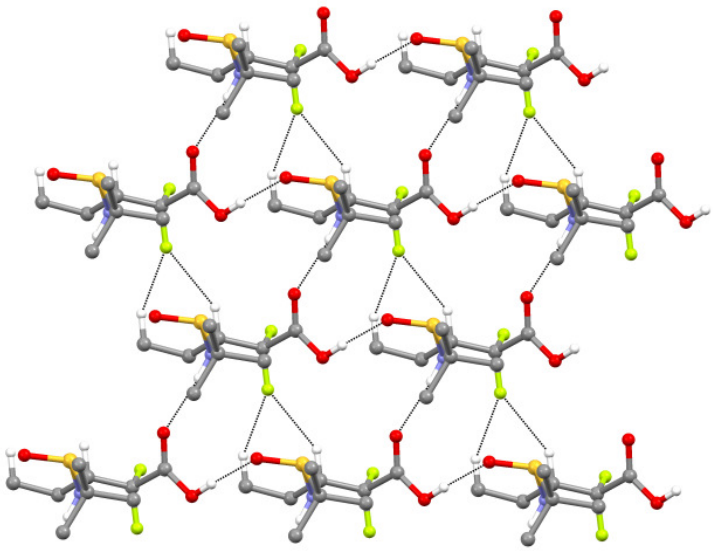
Symmetry transformations used to generate equivalent atoms:
(i) x−1,y,z (ii) x,y,z−1 (iii) x+1,y,z+1



Thermal ellipsoids drawn at the 50% probability level.



Hydrogen bonded sheets viewed down a



Hydrogen bonded sheets viewed down b

JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Stereoselectivity of the Honda–Reformatsky Reaction in Reactions with Ethyl Bromodifluoroacetate with α-Oxygenated Sulfinylimines

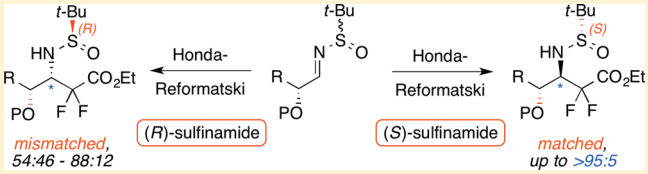
Clément Q. Fontenelle,[†] Matthew Conroy,[†] Mark Light,[†] Thomas Poisson,*[,‡] Xavier Pannecoucke,[‡] and Bruno Linclau*[,†]

[†]Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom

[‡]Normandie University, COBRA, UMR 6014 and FR 3038; University of Rouen, INSA Rouen, CNRS, 1 rue Tesnière, 76821 Mont Saint-Aignan Cedex, France

Supporting Information

ABSTRACT: The Reformatsky reaction of ethyl bromodifluoroacetate to α-oxygenated sulfinylimines is described. Using Honda–Reformatsky conditions, the reaction proceeds with double diastereodifferentiation, with the configuration of the sulfinyl group determining the stereochemical course of the reaction. Excellent diastereoselectivities (>94:6) are obtained for the matched cases. In contrast, reaction with sulfinylimines derived from unsubstituted alkanals proceeded with virtually no diastereoselectivity.



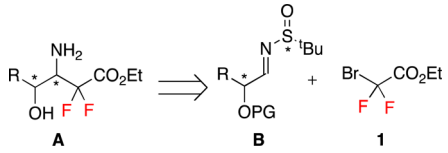
The introduction of fluorine in molecules of interest to modulate their properties is a major strategy in many application areas.[1−3] These include the pharmaceutical and agrochemical industries, around 20% of the commercially available pharmaceuticals and 30% of agrochemicals are fluorinated,[4] and performance materials, such as liquid crystals.[5] Given the abundance of amine-containing bioactive compounds, their fluorination has received great attention.[6−9] The β-position of amino groups is often considered for fluorination given the resulting effect on their $pK_{a(H)}$ value and lipophilicity.[10,11] Fluorination will also have an impact on the amine hydrogen-bonding properties and will induce potentially strong conformational effects.[12]

The conformational properties and biological activities of β-amino acids have received great attention, including the corresponding α,α-difluoro-β-amino acids.[13−16] Their synthesis using direct C−C bond formations with fluorinated building blocks usually involve Reformatsky reaction of $BrCF_2COOEt$ (**1**) to imine derivatives (or their equivalents).[13] The synthesis of enantioenriched α,α-difluoro-β-amino acid derivatives using the Reformatsky reaction has been reported with imines derived from chiral amines, such as the *tert*-butyl- and *p*-toluenesulfinylimines[7,17−21] and imines derived from (*R*)-phenylglycinol.[13,22−26] Excellent diastereoselectivities are obtained with imines derived from aromatic aldehydes, while imines derived from aliphatic substrates generally give lower selectivities.

The β-amino alcohol moiety is a well-known pharmacophore in bioactive compounds, and the corresponding γ,γ-difluoro-β-amino alcohols are thus of interest. Whereas nucleophilic addition to sulfinylimines that contain an α-oxygenated chiral center is a popular method for the diastereoselective synthesis of β-amino alcohols,[19] we are not aware of examples of Reformatsky reactions (either with **1** or with $BrCH_2COOEt$) on these types of sulfinylimines. Only a few examples were found where **1** was reacted with imines derived from achiral amines and α-oxygenated aldehydes: the benzyl imine derived from glyceraldehyde acetonide was reported to react with a ∼4:1 *syn*-selectivity,[27,28] while a complex C-glycosyl-derived imine gave complete *syn*-selectivity.[29]

We were interested in investigating a short synthesis of the motif **A** (Scheme 1), a versatile intermediate for the synthesis of

Scheme 1. Retrosynthetic Analysis Featuring a Reformatsky Reaction



complex α,α-difluoro-β-amino acids and of 2,2-difluoro-3-amino carbohydrate analogues, via a Reformatsky reaction as shown in Scheme 1. The sulfinylimine auxiliaries were selected, given they are accessible in both enantiomeric forms, and because of the absence of concomitant β-lactam formation upon addition reaction. Addition reactions to substrates **B** using various organometallic derivatives have been described to occur with various levels of double diastereoselection, in which the chirality of the auxiliary is usually dominant.[20] Furthermore, Ellman has recently described the addition of a benzyl zinc reagent to either diastereomer of the *tert*-butanesulfinylimine derived from (*R*)-glyceraldehyde acetonide, which for the matched case proceeded with virtually complete stereoselectivity.[30] Herein we describe a study of the Reformatsky reaction using **1** with

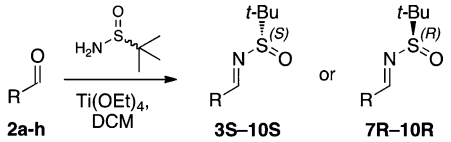
Received: February 20, 2014

   dx.doi.org/10.1021/jo500396p | J. Org. Chem. XXXX, XXX, XXX−XXX

α-oxygenated sulfinylimines **B**, in which the anticipated double diastereoselection was investigated by combining both enantiomeric sulfinylimine auxiliaries with all chiral aldehydes employed.

The imines were synthesized from the corresponding aldehydes in good yields mainly using the $Ti(OEt)_4$ procedure (Table 1).[31,32] As expected,[33] no epimerization of the

Table 1. Synthesis of the *tert*-Butanesulfinylimines



2a-h **3S–10S** **7R–10R**

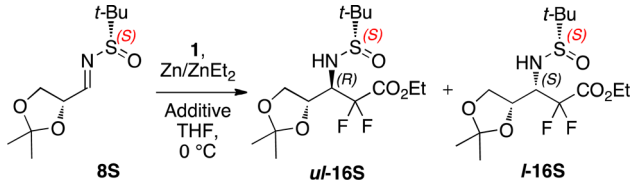
entry	R	product	yield[a] (%)
1	Et	**3S**	72
2	$C_{11}H_{23}$	**4S**	87
3	BnO	**5S**	88
4	BnO	**6S**	79
5[b]		**7S**	82
6[b]	BnO	**7R**	71
7		**8S**	80
8		**8R**	86
9		**9S**	89
10		**9R**	88
11[b]	BnO	**10S**	83
12[b]		**10R**	85

[a]Isolated yield. [b]Enantiomers were synthesized. See the Supporting Information.

α-stereocenter was observed with chiral aldehydes. Imines **3**–**6** were synthesized as model compounds to enable comparison with the stereoinduction exerted by the chiral auxiliaries without the additional bias of an α-oxygenated substituent.

The Reformatsky reaction was first investigated by a short optimization effort using sulfiminine **8S**, which was predicted to proceed with matched double diastereoselection.[30] Promotion by indium[34] (Table 2, entry 1) gave no reaction, even at 60 °C. The use of zinc was successful, and the desired product was obtained in 46% yield and a 72:28 diastereoisomeric ratio (dr) (entry 2). Modification of the stoichiometry afforded an improved 61% yield and 85:15 dr (entry 3). The use of activated zinc (dil HCl), and DCM as cosolvent enhanced the yield, but proceeded with slightly lower dr (entry 4). The use of Et_2O or toluene as cosolvent gave similar results (not shown). Zn

Table 2. Optimisation of the Reaction[a]



8S ***ul*-16S** ***l*-16S**

entry	**1** (equiv)	metal (equiv)	additive (equiv)	d.r[b]	yields (%)[c]
1	2	In (2)	-	-	NR
2	4	Zn (3)	-	72:28	46
3	5	Zn (4)	-	85:15	61
4	5	Zn[d] (4)	-[e]	75:25	78
5	5	Zn[f] (4)	-	-	<5
6	1.5	Et_2Zn (1.5)	$RhCl(PPh_3)_3$ (3)	>95:5	45
7	3	Et_2Zn (2)	$RhCl(PPh_3)_3$ (3)	>95:5	61
8	1.5	Et_2Zn (1.5)	$NiCl_2(PPh_3)_2$ (5)	-	NR
9	1.1	Me_2Zn (3)	$RhCl(PPh_3)_3$ (3)	-	NR

[a]The prefix *l* (like) indicates that the sulfinyl group and the newly formed amine stereocenter have the same absolute configuration (and otherwise for *ul* (unlike)). The suffix R or S in the numbering refers to the absolute configuration of the sulfinylimine auxiliary. [b]Determined by ^{19}F NMR (crude reaction mixture) [c]Isolated yield. [d]Dilute aq HCl activation. [e]DCM was used as cosolvent. [f]DMSO/TMSCl activation.

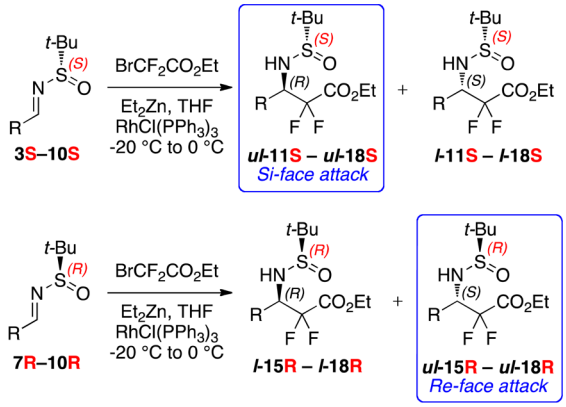
activation by DMSO/TMSCl[35] failed to induce reaction (entry 5). Pleasingly, using Et_2Zn under Honda–Reformatsky conditions, which employ the Wilkinson catalyst to promote Zn insertion,[36,37] a single diastereoisomer was obtained in 45% yield (entry 6), which could be increased to 61% upon doubling the amount of **1** (entry 7). Replacement of the Wilkinson catalyst by $NiCl_2(PPh_3)_2$ (entry 8)[38] or of Et_2Zn by Me_2Zn (entry 9) was not possible.

Next, the Reformatsky reaction was investigated on a range of sulfinylimines (Table 3).

Reaction with the aliphatic sulfinylimines **3S** and **4S** was not diastereoselective under the Honda–Reformaksky conditions (entries 1 and 2). We also observed slight variations in diastereoselectivity depending on the age of the Et_2Zn and rate of its addition (53:47 to 60:40), but always with the same major diastereomer. The low dr was surprising, given the much higher values obtained by Staas[18] and Soloshonok (up to 86:14 even in refluxing THF, using Zn)[17] for similar sulfinylimines derived from linear aliphatic aldehydes. However, Reformatsky reaction of **5S**, which has an α-benzyloxy substituent, proceeded with much increased diastereoselectivity (entry 3). Interestingly, the sterically hindered substrate **6S** was unreactive under the conditions used (entry 4). Pleasingly, the Reformatsky reaction of substrate **7S** (entry 5), derived from (*R*)-lactaldehyde and the (*S*)-configured chiral auxiliary, proceeded with enhanced diastereoselectivity compared to the benzyloxymethyl-derived sulfinylimine **5S**. In contrast, when the enantiomeric chiral

dx.doi.org/10.1021/jo500396p | J. Org. Chem. XXXX, XXX, XXX–XXX

Table 3. Scope of the Reaction[a]



entry	R	imine	major product	yield[b] (%)	d.r. (*ul*:*l*)
1	Et	**3S**	***ul*-11S**	64	53:47
2	$C_{11}H_{23}$	**4S**	***ul*-12S**	58	53:47
3	BnO	**5S**	***ul*-13S**	46	88:12
4	BnO	**6S**	-	NR	-
5[c]	BnO	**7S**	***ul*-15S**	57	94:6
6[c]		**7R**	***ul*-15R**	46	54:46
7	O O	**8S**	***ul*-16S**	62	>95:5
8		**8R**	***ul*-16R**	59	88:12
9	O O	**9S**	***ul*-17S**	52	>95:5
10		**9R**	***ul*-17R**	56	81:19
11[c]	BnO O O	**10S**	***ul*-18S**	62 (67)	>95:5
12[c]		**10R**	***ul*-18R**	48	60:40

[a]See Footnote a, Table 2. [b]Isolated yield. [c]Enantiomers were synthesized. Shown as is to facilitate stereochemical analysis.

auxiliary was used (**7R**, entry 6), the diastereoselectivity was much reduced, evidencing a double diastereodifferentiation effect. This was also observed for the other chiral aldehydes derived from glyceraldehyde and threose, for which the matched cases proceeded with excellent diastereoselectivity (entries 7, 9, and 11).

The relative configuration of the major diastereomers obtained from reaction of the aliphatic-derived **3S** and the α-alkoxy-derived **8S** and **8R** could be determined by X-ray crystallographic analysis (see the Supporting Information). In all cases, the *ul*-relative configuration was confirmed. Both products ***ul*-16S** and ***ul*-16R** are derived from the same glyceraldehyde enantiomer but with differently configured chiral auxiliaries, and the different configuration of the formed amine stereocenter clearly proved that the diastereoselection was determined by the configuration of the auxiliary and not by the α-stereocenter. On that basis, the stereochemistry of the other major and minor isomers was assigned.

The relative stereochemistry determined for ***ul*-11S** was most unexpected, given the precedence of both Staas and Soloshonok, who reported the other diastereomer as the major product of the Reformatsky reaction on alkyl-derived sulfinylimines. However, these Reformatsky reactions were performed under different conditions (Zn, THF, reflux or room temperature, versus $ZnEt_2$/$RhCl(PPh_3)_3$, THF, 0 °C in our case), and it should be remembered that the dr in our case was very low. On the other hand, our results correspond to the stereoinduction determined previously by Ellman for reactions of sulfinylimines derived both from aliphatic aldehydes, and from (*R*)-glyceraldehyde acetonide, with benzylzinc reagents, including the matched/mismatched stereoinduction.[30] Their benzylzinc reagent was synthesized from the corresponding benzyl chloride using $ZnCl_2$/Mg/LiCl (Knochel conditions[39]).

The stereoinduction by the α-oxygenated chiral center for **8S** can be deduced from the Cornforth-Evans (CE)/polar Felkin-Anh (PFA) models **TS-1** and **TS-2** (Figure 1),[40] which both predict the observed *Si*-face attack. In contrast, the cyclic "Cram model" **TS-3**,[41] involving coordination of the imine nitrogen and the α-alkoxy group, predicts *Re*-face attack.

Several models have been proposed to rationalize the induction by the sulfinylimine auxiliary.[19−21] The cyclic Ellman transition state **TS-4** has been suggested for the Reformatsky reaction (Zn, refluxing THF) of **1** to sulfinylimines derived from aromatic and aliphatic aldehydes[17] and which successfully explains the Staas and Soloshonok results[17,18] (as well as for Reformatsky reactions using $BrCH_2COOEt$).[42,43] However, given that it predicts *Re*-face attack (for an (*S*)-configured sulfinylimine), it is not consistent with our findings. Equally, **TS-5**,[44,45] involving a Zn-enolate, predicts the wrong facial selectivity. However, this model correctly explained the facial selectivity of addition with allyl zinc to an aryl sulfinylimine (in THF).[43] In contrast, the Barrow chelation model **TS-6**,[46] involving chelation with both the S═O and the α-alkoxy groups and a rapid sulfinyl imine *E*/*Z* isomerization, predicts the correct stereochemical outcome, including the double diastereodifferentiation (though now due to the avoidance of a sterically unfavorable interaction with the sulfinyl group as opposed to involvement of **TS-1**/**TS-2**). The transition state **TS-7** proposed by Marek, also for reaction with allyl zinc derivatives in THF, correctly predicts *Si*-face attack as well.[47] This model differs from **TS-5** in that chelation is only involving the imine nitrogen atom, with the S═O dipole oriented antiperiplanar to the imine lone pair. Both **TS-7** and **TS-5** (which predict opposing facial selectivity) have been successfully used to explain the outcome of additions of allylzinc to sulfinylimines,[43,47] which shows that the exact conditions, especially the amount of coordinating species in solution, can influence the facial selectivity. However, for a Reformatsky reaction the additional pseudo-axial OEt-substituent could disfavor **TS-7**. Finally, an open transition state **TS-8** proposed by Davis[48] also predicts the observed *Si*-facial attack. This model was used by Ellman to explain the stereochemical outcome of the aforementioned addition of benzylzinc reagents to both aryl- and (*R*)-glyceraldehyde-derived sulfinylimines (involving excess of coordinating ions and a coordinating solvent).[30]

The much-increased selectivities for substrates **5** and **7**−**10** compared to **3** and **4** suggest a chelation role of the α-oxygen-containing substituent, which points to the Barrow transition state **TS-6**. For the alkyl sulfinylimines **3** and **4**, it is unlikely that the

dx.doi.org/10.1021/jo500396p | J. Org. Chem. XXXX, XXX, XXX−XXX

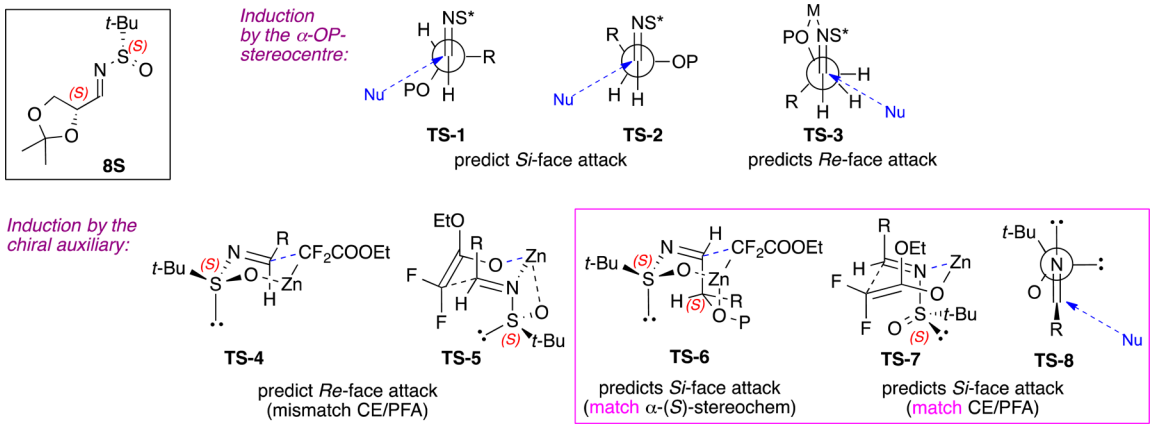


Figure 1. Models to explain the stereoinduction/double diastereodifferentiation.

required E/Z isomerization is occurring/complete, given there is no chelating α-substituent to drive this process.

CONCLUSIONS

The Reformatsky reaction involving ethyl bromodifluoroacetate was investigated both with sulfinylimines derived from aldehydes with a chiral α-oxygenated substituent as well as from aliphatic aldehydes. Reformatsky reaction of the former proceeds with double diastereodifferentiation, with the configuration of the chiral auxiliary determining the stereoinduction. The stereochemical outcome is consistent with the Barrow model.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of *tert*-Butanesulfinylimines (Table 1).[30] To a mixture of aldehyde (1 equiv) and sulfinamide (1.05 equiv) in CH_2Cl_2 was added $Ti(OEt)_4$ (3−5 equiv). After the mixture was stirred at rt overnight, water was added. Stirring for a further 15 min was followed by filtration over a pad of $MgSO_4$ and Celite. The filter cake was washed with EtOAc and the filtrate concentrated under reduced pressure. The residue was purified via filtration over a pad of silica to afford pure sulfinylimine (pale yellow oils).

*(S_S,E)-N-(Propylidene)-2-methyl-2-propanesulfinamide (**3S**).*[49]

Propionaldehyde (0.100 g, 1.72 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.219 g, 1.81 mmol) and $Ti(OEt)_4$ (1.18 g, 5.17 mmol) yielded **3S** (0.201 g, 1.25 mmol, 72%) as a pale yellow oil: R_f 0.27 (hexane/EtOAc 75:25); $[\alpha]_D$ +338.4 (*c* 0.12, $CHCl_3$, 26 °C) [lit.[49] (***ent*-3S**) $[\alpha]_D$ −328.5 (*c* 1.0, $CHCl_3$, 23 °C)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (t, $^3J_{HH}$ = 4.3 Hz, 1H), 2.55 (dq, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 4.3 Hz, 2H), 1.20 (s, 9H), 1.20 (t, $^3J_{HH}$ = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 56.5, 29.5, 22.3 (3C), 9.6 ppm. NMR spectra correspond to the reported data for ***ent*-3S**.[49]

*(S_S,E)-N-(Dodecylidene)-2-methyl-2-propanesulfinamide (**4S**).*

Dodecanal (0.30 mL, 0.249 g, 1.34 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.170 g, 1.41 mmol), and $Ti(OEt)_4$ (1.53 g, 6.70 mmol) yielded **4S** (0.366 g, 1.17 mmol, 87%) as a pale yellow oil: R_f 0.47 (hexane/EtOAc 75:25); $[\alpha]_D$ +166.0 (*c* 0.21, $CHCl_3$, 28 °C); IR (neat) 2923 (s), 2854 (m), 1622 (m), 1457 (w), 1363 (w), 1087 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (t, $^3J_{HH}$ = 4.7 Hz, 1H), 2.52 (dt, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 4.7 Hz, 2H), 1.70−1.60 (m, 2H), 1.51−1.24 (m, 16H), 1.20 (s, 9H), 0.89 (t, $^3J_{HH}$ = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 56.5, 36.1, 31.9, 29.6 (2C), 29.5, 29.3 (2C), 29.2, 25.5, 22.7, 22.3 (3C), 14.1 ppm; HRMS (MS+) for $C_{16}H_{34}NOS$ $(M + H)^+$ calcd 288.2356, found 288.2356.

*(S_S,E)-N-(2-Benzyloxyethylidene)-2-methyl-2-propanesulfinamide (**5S**).*

To benzyloxyacetaldehyde[50] (0.250 g, 1.67 mmol) in CH_2Cl_2 (3.5 mL) were added (*S*)-2-methyl-2-propanesulfinamide (0.212 g, 1.75 mmol) and $CuSO_4$ (0.558 g, 3.50 mmol). The resultant mixture was stirred at rt for 15 h and then filtered over Celite to afford the desired crude product. Purification over a short pad of silica eluting with PE/EtOAc 75:25 yielded **5S** (0.371 g, 1.46 mmol, 88%) as a pale yellow oil: R_f 0.21 (hexane/ethyl acetate 70:30); $[\alpha]_D$ +161.6 (*c* 0.09, $CHCl_3$, 26 °C) [lit.[51] (***ent*-5S**) $[\alpha]_D$ −212 (*c* 1.0, $CHCl_3$, 23 °C)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (t, $^3J_{HH}$ 3.2 Hz, 1H), 7.40−7.29 (m, 5H), 4.65 (s, 2H), 4.45 (dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 3.2 Hz, 1H), 4.39 (dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 3.2 Hz, 1H), 1.23 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 137.2, 128.5, 128.0, 127.9, 73.3, 71.3, 57.0, 22.4 ppm. NMR spectra correspond to the reported data for ***ent*-5S**.[51]

*(S_S,E)-N-[2-(Benzyloxy)-2-methylpropylidene]-2-methyl-2-propanesulfinamide (**6S**).*

2-Benzyloxy-2-methylpropanal[52] (0.120 g, 0.673 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.086 g, 0.707 mmol), and $Ti(OEt)_4$ (0.768 g, 3.37 mmol) yielded **6S** (0.149 g, 0.529 mmol, 79%) as a pale yellow oil: R_f 0.47 (PE/Et_2O 60:40); $[\alpha]_D$ +210.6 (*c* 0.50, $CHCl_3$, 22 °C); IR (neat) 2979 (w), 1622 (w), 1160 (m), 1087 (s), 1059 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.40−7.23 (m, 5H), 4.48 (d, $^2J_{HH}$ = 11.1 Hz, 1H), 4.45 (d, $^2J_{HH}$ = 11.1 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H), 1.23 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 138.4, 128.4, 127.5, 127.6, 78.1, 66.4, 56.9, 24.4, 24.0, 22.5 ppm; HRMS (MS+) for $C_{15}H_{23}NNaO_2S$ $(M + Na)^+$ calcd 304.1342, found 304.1338.

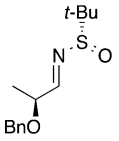
*(R_S,E)-N-[(2S)-2-(Benzyloxy)propylidene]-2-methyl-2-propanesulfinamide (**ent-7S**).*[33]

(2*S*)-2-Benzyloxypropanal[52] (0.150 g, 0.914 mmol), (*R*)-2-methyl-2-propanesulfinamide (0.122 g, 1.01 mmol), and $Ti(OEt)_4$ (0.625 g, 2.74 mmol) yielded ***ent*-7S** (0.200 g, 0.748 mmol, 82%) as a pale

dx.doi.org/10.1021/jo500396p | J. Org. Chem. XXXX, XXX, XXX−XXX

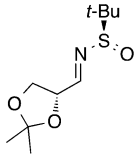
yellow oil: R_f 0.60 (hexane/EtOAc 50:50). $[\alpha]_D$ −222 (*c* 0.52, EtOH, 22 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$ = 4.6 Hz, 1H), 7.41−7.23 (m, 5H), 4.66 (d, $^2J_{HH}$ = 11.7 Hz, 1H), 4.54 (d, $^2J_{HH}$ = 11.7 Hz, 1H), 4.35 (dq, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 1.41 (d, $^3J_{HH}$ = 6.7 Hz, 3H), 1.22 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 137.6, 128.5, 127.9, 127.8, 76.3, 71.6, 56.9, 22.4, 18.7 ppm. NMR spectra correspond to the reported data.[33]

*(S$_S$,E)-N-[(2S)-2-(Benzyloxy)propylidene]-2-methyl-2-propanesulfinamide (**ent-7R**).*



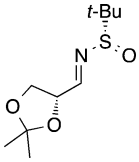
(2*S*)-2-Benzyloxypropanal[52] (0.150 g, 0.914 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.116 g, 0.959 mmol), and $Ti(OEt)_4$ (0.833 g, 3.65 mmol) yielded ***ent*-7R** (0.173 g, 0.647 mmol, 71%) as a pale yellow oil: R_f 0.40 (hexane/EtOAc 50:50); $[\alpha]_D$ +67.3 (*c* 0.53, EtOH, 22 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, $^3J_{HH}$ = 4.5 Hz, 1H), 7.43−7.28 (m, 5H), 4.67 (d, $^2J_{HH}$ = 11.6 Hz, 1H), 4.50 (d, $^2J_{HH}$ = 11.6 Hz, 1H), 4.34 (dq, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 1.43 (d, $^3J_{HH}$ = 6.6 Hz, 3H), 1.24 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 137.7, 128.5, 127.9, 127.8, 76.2, 71.5, 56.8, 22.5, 18.5 ppm; NMR spectra correspond to the reported data.[33]

*(R$_S$,E)-N-[(2S)-2,3-(Isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**8R**).*



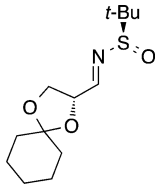
2,3-*O*,*O*-Isopropylidene-D-glyceraldehyde[53] (0.500 g, 3.84 mmol), (*R*)-2-methyl-2-propanesulfinamide (0.489 g, 4.03 mmol), and $Ti(OEt)_4$ (4.38 g, 19.2 mmol) yielded **8R** (0.771 g, 3.30 mmol, 86%) as a pale yellow oil: R_f 0.21 (hexane/EtOAc 70:30); $[\alpha]_D$ −198.6 (*c* 0.84, $CHCl_3$, 26 °C); IR (neat) 2984 (m), 2873 (m), 1626 (s), 1060 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, $^3J_{HH}$ = 4.5 Hz, 1H), 4.83 (ddd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 4.25 (dd, $^2J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 7.6 Hz, 1H), 4.00 (dd, $^2J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.20 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 111.0, 76.7, 67.1, 57.2, 26.4, 25.4, 22.3 ppm; HRMS (MS+) for $C_{10}H_{19}NNaO_3S$ $(M + Na)^+$ calcd 256.0983, found 256.0978. NMR spectra correspond to the reported data.[30]

*(S$_S$,E)-N-[(2S)-2,3-(Isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**8S**).*



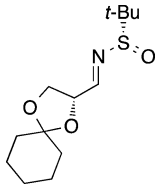
2,3-*O*,*O*-Isopropylidene-D-glyceraldehyde[53] (1.05 g, 8.07 mmol), (*S*)-2-methyl-2-propanesulfinamide (1.03 g, 8.47 mmol), and $Ti(OEt)_4$ (7.36 g, 32.3 mmol) yielded **8S** (1.50 g, 6.43 mmol, 80%) as a pale yellow oil: R_f 0.6 (PE/EtOAc 50:50); $[\alpha]_D$ +248 (*c* 0.49, EtOH, 23 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$ = 4.1 Hz, 1H), 4.85 (ddd, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 4.1 Hz, 1H), 4.23 (dd, $^2J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 4.05 (dd, $^2J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 5.1 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.21 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 110.8, 76.9, 67.2, 57.0, 26.4, 25.4, 22.3 ppm. NMR spectra correspond to the reported data.[30]

*(R$_S$,E)-N-[(2S)-2,3-Cyclohexylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**9R**).*



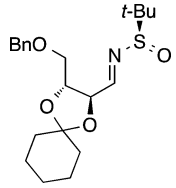
2,3-*O*,*O*-Cyclohexylidene-D-glyceraldehyde[54] (1.00 g, 5.88 mmol), (*R*)-2-methyl-2-propanesulfinamide (0.748 g, 6.17 mmol), and $Ti(OEt)_4$ (6.70 g, 29.4 mmol) yielded **9R** (1.41 g, 5.16 mmol, 88%) as a pale yellow oil: R_f 0.29 (hexane/EtOAc 70:30); $[\alpha]_D$ −216.6 (*c* 0.49, $CHCl_3$, 20 °C); IR (neat) 2934 (m), 2863 (m), 1625 (s), 1084 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, $^3J_{HH}$ = 4.5 Hz, 1H), 4.83 (ddd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 4.24 (dd, $^2J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 4.01 (dd, $^2J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 1.77−1.53 (m, 8H), 1.48−1.34 (m, 2H), 1.21 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 111.6, 76.5, 66.8, 57.2, 36.0, 35.0, 25.0, 23.83, 23.80, 22.4 ppm; HRMS (MS+) for $C_{13}H_{23}NNaO_3S$ $(M + Na)^+$ calcd 296.1291, found 296.1296.

*(S$_S$,E)-N-[(2S)-2,3-Cyclohexylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (**9S**).*



2,3-*O*,*O*-Cyclohexylidene-D-glyceraldehyde[54] (1.00 g, 5.88 mmol), (*S*)-2-methyl-2-propanesulfinamide (0.748 g, 6.17 mmol), and $Ti(OEt)_4$ (6.70 g, 29.4 mmol) yielded **9S** (1.43 g, 5.23 mmol, 89%) as a pale yellow oil: R_f 0.53 (PE/EtOAc 60:40); $[\alpha]_D$ +193 (*c* 0.53, EtOH, 22 °C). IR (neat) 2934 (m), 2359 (s), 1625 (m), 1364 (m), 1088 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, $^3J_{HH}$ = 4.2 Hz, 1H), 4.84 (ddd, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 4.22 (dd, $^2J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.7 Hz, 1H), 4.04 (dd, $^2J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 5.1 Hz, 1H), 1.73−1.54 (m, 8H), 1.48−1.37 (m, 2H), 1.20 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 111.5, 76.7, 67.0, 57.1, 36.1, 35.0, 25.0, 23.9, 23.9, 22.4 ppm; MS (ESI+) (*m*/*z*) 274 $(M + H)^+$; HRMS (MS+) for $C_{13}H_{23}NNaO_3S$ $(M + Na)^+$ calcd 296.1291, found 296.1297.

*(R$_S$,E)-N-[(2R,3R)-4-(Benzyloxy)-2,3-(cyclohexylidenedioxy)-butylidene]-2-methyl-2-propanesulfinamide (**ent-10S**).*



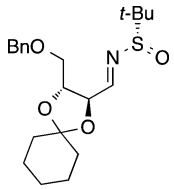
SO_3·pyridine (3.27 g, 20.5 mmol, 3.0 equiv), Et_3N (3.34 mL, 23.9 mmol, 3.5 equiv), DMSO (8 mL), and CH_2Cl_2 (17 mL) were combined and stirred at −20 °C for 0.5 h. The corresponding alcohol ($[\alpha]_D$ −4.02 (*c* 1.3, $CHCl_3$, 21 °C) [lit.[55] +0.90 (*c* 1.3, $CHCl_3$, 24 °C, enantiomer)] (2.00 g, 6.84 mmol, 1 equiv), DMSO (8 mL), and DCM were stirred at −20 °C in a separate flask, and to this solution was added dropwise via cannula the solution of SO_3. The resultant mixture was allowed to stir below −10 °C for 1 h then at rt for 3 h. Quenching with saturated aqueous NH_4Cl solution and extraction with EtOAc (2 × 15 mL) and Et_2O (2 × 15 mL) was followed by drying over $MgSO_4$ and concentration in vacuo to afford a bright yellow oil. Column chromatography (PE/EtOAc 75:25 to 70:30) afforded 1.63 g (5.61 mmol, 82%) of the pure aldehyde **2h** as a colorless oil: R_f 0.31 (PE/EtOAc 75:25); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, $^3J_{HH}$ = 1.6 Hz, 1H), 7.40−7.28 (m, 5H), 4.62 (s, 2H), 4.32−4.22 (m, 2H), 3.67 (dd, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 1.1 Hz, 2H), 1.75−1.54 (m, 8H),

dx.doi.org/10.1021/jo500396p | J. Org. Chem. XXXX, XXX, XXX−XXX

1.49−1.34 (m, 2H) ppm. The aldehyde was used immediately after purification.

4-*O*-Benzyl-2,3-*O*,*O*-cyclohexylidene-D-threose **2h** obtained as described above (800 mg, 2.76 mmol), (*R*)-2-methyl-2-propanesulfinamide (367 mg, 3.03 mmol), and $Ti(OEt)_4$ (3.14 g, 13.8 mmol) yielded ***ent*-10S** (900 mg, 2.29 mmol, 83%) as a pale yellow oil: R_f 0.7 (PE/EtOAc 50:50); $[\alpha]_D$ −104 (*c* 0.67, EtOH, 23 °C); IR (neat) 2933 (m), 2861 (m), 2359 (m), 2342 (m), 1084 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, $^3J_{HH}$ = 4.7 Hz, 1H), 7.39−7.28 (m, 5H), 4.67−4.55 (m, 3H), 4.22 (ddd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 4.4 Hz, 1H), 3.68 (dd, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 4.4 Hz, 1H), 3.64 (dd, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 5.6 Hz, 1H), 1.74−1.57 (m, 8H), 1.52−1.31 (m, 2H), 1.14 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 137.7, 128.4 (2C), 127.8 (3C), 112.0, 79.0, 77.9, 73.6, 69.8, 57.1, 36.5, 36.1, 25.0, 23.9, 23.7, 22.3 (3C) ppm; MS (ESI+) (*m*/*z*) 416 (M + Na)$^+$; HRMS (MS+) for $C_{21}H_{31}NNaO_4S$ (M + Na)$^+$ calcd 416.1866, found 416.1873.

*(S_S,*E*)-N-[(2R,3R)-4-(Benzyloxy)-2,3-(cyclohexylidenedioxy)-butylidene]-2-methyl-2-propanesulfinamide (**ent-10R**).*

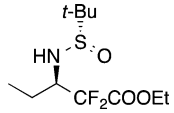


4-*O*-Benzyl-2,3-*O*,*O*-cyclohexylidene-D-threose **2h** obtained as described above (900 mg, 3.1 mmol), (*S*)-2-methyl-2-propanesulfinamide (394 mg, 3.26 mmol), and $Ti(OEt)_4$ (3.54 g, 15.5 mmol) yielded ***ent*-10R** (1.03 g, 2.63 mmol, 85%) as a pale yellow oil: R_f 0.7 (PE/EtOAc 50:50); $[\alpha]_D$ +156 (*c* 0.47, EtOH, 23 °C); IR (neat) 2934 (m), 2862 (m), 2359 (m), 2342 (m), 1087 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, $^3J_{HH}$ = 4.2 Hz, 1H), 7.39−7.28 (m, 5H), 4.67−4.59 (m, 3H), 4.28 (ddd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 5.2 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 3.72 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 3.68 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.2 Hz, 1H), 1.76−1.57 (m, 8H), 1.48−1.35 (m, 2H), 1.20 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 137.9, 128.4 (2C), 127.7 (3C), 111.9, 78.7, 77.8, 73.6, 69.7, 57.2, 36.5, 36.0, 25.0, 23.9, 23.7, 22.4 (3C) ppm; MS (ESI+) (*m*/*z*) 416 (M + Na)$^+$; HRMS (MS+) for $C_{21}H_{31}NNaO_4S$ (M + Na)$^+$ calcd 416.1866, found 416.1864.

General Procedure for the Honda−Reformatski Reaction (Table 3). A mixture of sulfinylimine (1 equiv) and $RhCl(PPh_3)_3$ (3 mol %) in THF (7.5 mL/mmol) was cooled to −20 °C. Compound **1** (3 equiv) was added immediately followed by dropwise addition of Et_2Zn (1.0 M in hexane, 2 equiv). The mixture was allowed to warm to 0 °C over 30 min, and stirring was continued for 1 h. Quenching with satd NH_4Cl was followed by extraction with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography gave the products as pale yellow oils unless mentioned otherwise.

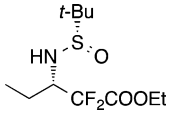
Reaction with sulfinylimine **3S** (100 mg, 0.620 mmol) yielded **11S** (53:47 dr). Chromatography (PE/EtOAc 70:30) afforded an inseparable mixture of diastereoisomers (114 mg, 0.400 mmol, 64%). Analytical samples of pure diastereoisomers were obtained by HPLC (hexane/EtOAc 70:30).

*Major Isomer: (3R,SS)-Ethyl 3-(tert-Butylsulfinamino)-2,2-difluoropentanoate (**ul-11S**).*



Pale yellow oil: R_f 0.20 (hexane/EtOAc 70:30); $[\alpha]_D$ +62.9 (*c* 0.19, $CHCl_3$, 21 °C); IR (in $CDCl_3$) 3207 (br), 2982 (m), 1773(s), 1062 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (dq, $^2J_{HH}$ = 10.7, $^3J_{HH}$ = 7.2 Hz, 1H), 4.29 (dq, $^2J_{HH}$ = 10.7, $^3J_{HH}$ = 7.1 Hz, 1H), 3.81−3.66 (m, 1H), 3.15 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 1.98−1.86 (m, 1H), 1.65−1.52 (m, 1H), 1.36 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.20 (s, 9H), 1.14 (t, $^3J_{HH}$ = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$ = 32.3 Hz), 114.8 (t, $^1J_{CF}$ = 255.7 Hz), 62.8, 60.8 (dd, $^2J_{CF}$ = 25.7, 24.2 Hz), 56.5, 22.6, 22.4 (3C), 13.8, 10.0 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.4 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 7.5 Hz), −119.1 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; MS (ESI+) (*m*/*z*) 349 (M + Na + MeCN)$^+$; HRMS (MS+) for $C_{11}H_{21}F_2NNaO_3S$ (M + Na)$^+$ calcd 308.1102, found 308.1106.

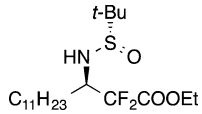
*Minor Isomer: (3S,SS)-Ethyl 3-(tert-Butylsulfinamino)-2,2-difluoropentanoate (**l-11S**).*



Pale yellow oil: R_f 0.23 (hexane/EtOAc 70:30); $[\alpha]_D$ +26.6 (*c* 0.51, $CHCl_3$, 19 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 3.80−3.66 (m, 1H), 3.57 (d, $^3J_{HH}$ = 9.3 Hz, 1H), 1.91−1.78 (m, 1H), 1.66−1.52 (m, 1H), 1.38 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.24 (s, 9H), 1.06 (t, $^3J_{HH}$ = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$ = 31.9 Hz), 114.7 (t, $^1J_{CF}$ = 256.4 Hz), 63.3, 60.4 (dd, $^2J_{CF}$ = 25.3, 23.8 Hz), 56.9, 22.7 (3C), 22.3, 13.8, 10.3 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.9 (dd, $^2J_{FF}$ = 264.3, $^3J_{HF}$ = 7.5 Hz),−118.4 (dd, $^2J_{FF}$ = 264.3 Hz, $^3J_{HF}$ = 15.6 Hz) ppm; MS (ESI+) (*m*/*z*) 308 (M + Na)$^+$; HRMS (MS+) for $C_{11}H_{21}F_2NNaO_3S$ (M + Na)$^+$ calcd 308.1102, found 308.1106.

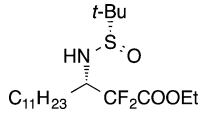
Reaction with sulfinylimine **4S** (150 mg, 0.522 mmol) yielded **12S** (53:47 dr). Chromatography (hexane/EtOAc 90:10→65:35) afforded an inseparable mixture of diastereoisomers (125 mg, 0.304 mmol, 58%). Analytical samples of pure diastereoisomers were obtained by HPLC (hexane/EtOAc 75:25).

*Major Isomer: (3R,S_S)-Ethyl 3-(tert-Butylsulfinamino)-2,2-difluorotetradecanoate (**ul-12S**).*



Pale yellow oil: R_f 0.19 (hexane/EtOAc 75:25); $[\alpha]_D$ +43.9 (*c* 0.54, $CHCl_3$, 21 °C); IR (in $CDCl_3$) 3206 (br w), 2924 (s), 2854 (s), 1774 (s), 1057 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (dq, $^2J_{HH}$ = 10.9, $^3J_{HH}$ = 7.2 Hz, 1H), 4.29 (dq, $^2J_{HH}$ = 10.9, $^3J_{HH}$ = 7.2 Hz, 1H), 3.79 (ddddd app. as dddt, $^3J_{HF}$ = 16.1, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 8.6, $^3J_{HH}$ = 8.6, $^3J_{HH}$ = 3.8 Hz, 1H), 3.10 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 1.87−1.76 (m, 1H), 1.73−1.59 (m, 1H), 1.59−1.22 (m, 18H), 1.36 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.20 (s, 9H), 0.88 (t, $^3J_{HH}$ = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (t, $^2J_{CF}$ = 33.0 Hz), 114.9 (t, $^1J_{CF}$ = 255.4 Hz), 62.9, 59.4 (dd, $^2J_{CF}$ = 26.3 Hz, $^2J_{CF}$ = 23.4 Hz), 56.6, 31.9, 29.6 (4C), 29.3, 29.3 (2C), 25.2, 22.7, 22.5 (3C), 14.1, 13.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.8 (dd, $^2J_{FF}$ = 261.1 Hz, $^3J_{HF}$ = 8.6 Hz), −118.8 (dd, $^2J_{FF}$ = 261.1 Hz, $^3J_{HF}$ = 16.1 Hz) ppm; MS (ESI+) (*m*/*z*) 475 (M + Na + MeCN)$^+$; HRMS (MS+) for $C_{20}H_{39}F_2NNaO_3S$ (M + Na)$^+$ calcd 434.2511, found 434.2516.

*Minor Isomer: (3S,S_S)-Ethyl 3-(tert-Butylsulfinamino)-2,2-difluorotetradecanoate (**l-12S**).*

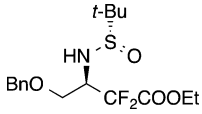


Pale yellow oil: R_f 0.17 (hexane/EtOAc 70:30); $[\alpha]_D$ +61.9 (*c* 0.59, $CHCl_3$, 23 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 3.86−3.72 (m, 1H), 3.56 (d, $^3J_{HH}$ = 9.5 Hz, 1H), 1.80−1.68 (m, 1H), 1.63−1.49 (m, 2H), 1.41−1.24 (m, 17H), 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.23 (s, 9H), 0.89 (t, $^3J_{HH}$ = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (t, $^2J_{CF}$ = 32.2 Hz), 114.7 (t, $^1J_{CF}$ = 256.1 Hz), 63.3, 58.9 (t, $^2J_{CF}$ = 24.9 Hz), 56.9, 31.9, 29.6 (2C), 29.5, 29.3 (2C), 29.1, 28.9, 25.4, 22.7 (3C), 22.7, 14.1, 13.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.1 (dd, $^2J_{FF}$ = 264.3, $^3J_{HF}$ = 7.5 Hz, 1F), −118.3 (dd, $^2J_{FF}$ = 264.3, $^3J_{HF}$ = 16.1 Hz, 1F) ppm; MS (ESI+) (*m*/*z*) 475 (M + Na + MeCN)$^+$; HRMS (MS+) for $C_{20}H_{39}F_2NNaO_3S$ (M + Na)$^+$ calcd 434.2511, found 434.2513.

dx.doi.org/10.1021/jo500396p | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Reaction with sulfinylimine **5S** (100 mg, 0.395 mmol) yielded **13S** (88:12 dr). Chromatography (hexane/EtOAc 75:25→65:35) afforded an inseparable mixture of diastereoisomers (68 mg, 0.180 mmol, 46%).

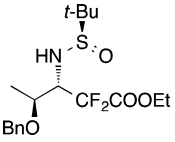
*Analytically Pure Sample of the Major Diastereoisomer (3R,S$_S$)-Ethyl 4-(Benzyloxy)-3-(tert-butylsulfinamino)-2,2-difluorobutanoate (**ul-13S**).*



Pale yellow oil obtained by HPLC (hexane/EtOAc 70:30): R_f 0.31 (hexane/EtOAc 40:60); $[\alpha]_D$ +33.1 (*c* 0.62, $CHCl_3$, 19 °C); IR (neat) 3209 (br w), 2982 (br w), 2871 (br w), 1771 (s), 1077 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.56 (d, $^2J_{HH}$ = 11.6 Hz, 1H), 4.49 (d, $^2J_{HH}$ = 11.6 Hz, 1H), 4.15 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 4.08−3.95 (m, 2H), 3.92−3.86 (m, 1H), 3.80−3.73 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ162.9 (t, $^2J_{CF}$ = 32.2 Hz), 137.2, 128.4 (2C), 127.84, 127.79 (2C), 113.8 (t, $^1J_{CF}$ = 256.1 Hz), 73.6, 67.6, 62.9, 58.6 (t, $^2J_{CF}$ = 24.9 Hz), 56.7, 22.4 (3C), 13.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ−112.7 (dd, $^2J_{FF}$ = 261.8 Hz, $^3J_{HF}$ 8.7 Hz), −115.7 (dd, $^2J_{FF}$ = 261.8 Hz, $^3J_{HF}$ = 13.0 Hz) ppm; MS (ESI+) (*m*/*z*) 400 (M + Na)$^+$; HRMS (MS+) for $C_{17}H_{25}F_2NNaO_4S$ (M + Na)$^+$ calcd 400.1365, found 400.1364.

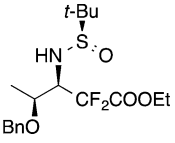
Reaction with sulfinylimine ***ent*-7S** (100 mg, 0.374 mmol) yielded ***ent*-15S** (94:6 *dr*). Chromatography (PE/Et_2O 40:60→20:80) afforded ***ent-ul*-15S** (80 mg, 0.204 mmol, 54%) as a white solid and ***ent-l*-15S** (4 mg, 0.010 mmol, 3%) as a pale yellow oil.

*Major isomer: (3S,4S,R$_S$)-ethyl 4-(benzyloxy)-3-(tert-butylsulfinamino)-2,2-difluoropentanoate (**ent-ul-15S**):*



R_f 0.10 (PE/Et_2O 40:60); mp 109−111 °C; $[\alpha]_D$ −4.2 (*c* 0.14, $CHCl_3$, 23 °C); IR (neat) 3213 (w, br), 2982 (w), 1771 (s), 1099 (s), 1054 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 4.57 (d, $^2J_{HH}$ = 11.1 Hz, 1H), 4.38 (d, $^2J_{HH}$ = 11.1 Hz, 1H), 4.05−3.85 (m, 3H), 3.80 (dq app. as quin, $^3J_{HH}$ = 6.3 Hz, 1H), 3.71 (d, $^3J_{HH}$ = 9.5 Hz, 1H), 1.44 (d, $^3J_{HH}$ = 6.3 Hz, 3H), 1.24 (s, 9H), 1.16 (t, $^3J_{HH}$ = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0 (t, $^2J_{CF}$ = 32.2 Hz), 137.4, 128.3 (2C), 128.2 (2C), 127.9, 114.2 (t, $^1J_{CF}$ = 254.7 Hz), 74.9, 71.4, 63.3 (t, $^2J_{CF}$ = 23.4 Hz), 62.6, 57.0, 22.5 (3C), 16.4, 13.7 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.0 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 8.6 Hz), −115.2 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 12.9 Hz). MS (ESI+) (*m*/*z*) 414 (M + Na)$^+$; HRMS (MS+) for $C_{18}H_{27}F_2NNaO_4S$ (M + Na)$^+$ calcd 414.1521, found 414.1525.

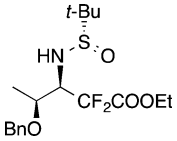
*Minor isomer: (3R,4S,R$_S$)-ethyl-4-(benzyloxy)-3-(tert-butylsulfinamino)-2,2-difluoropentanoate (**ent-l-15S**):*



R_f 0.20 (PE/Et_2O 40:60); $[\alpha]_D$ −33.5 (*c* 0.07, $CHCl_3$, 23 °C); IR (neat) 2980 (w), 1770 (m), 1108 (s), 1082 (s), 1026 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.56 (d, $^2J_{HH}$ = 11.1 Hz, 1H), 4.36 (d, $^2J_{HH}$ = 11.1 Hz, 1H), 4.31 (d, $^3J_{HH}$ = 10.5 Hz, 1H), 4.09 (qd, $^3J_{HH}$ = 7.1 Hz, $^2J_{HH}$ = 6.7 Hz, 1H), 4.07 (qd, $^3J_{HH}$ = 7.1 Hz, $^2J_{HH}$ = 6.7 Hz, 1H), 4.00 (qt, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 1.7 Hz, 1H), 3.74 (dddd, $^3J_{HF}$=12.4 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HF}$ = 8.7 Hz, $^3J_{HH}$ = 1.8 Hz, 1H), 1.29 (d, $^3J_{HH}$ = 6.3 Hz, 3H), 1.27 (s, 9H), 1.20 (t, $^3J_{HH}$ = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 128.3 (2C), 127.8 (3C), 113.6 (t, $^1J_{CF}$ = 257.6 Hz), 72.1 (d, $^3J_{CF}$ = 2.9 Hz), 71.1, 63.0 (t, $^2J_{CF}$ = 24.9 Hz), 63.0, 57.2, 22.9 (3C), 16.6, 13.7 ppm (The C═O signal was not observed). ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.0 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 8.7 Hz), −114.6 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 12.4 Hz) ppm; MS (ESI) (*m*/*z*) 455 (M + Na + MeCN)$^+$; HRMS (ESI) for $C_{18}H_{27}F_2NNaO_4S$ (M + Na)$^+$ calcd 414.1521, found 414.1509.

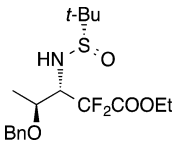
Reaction with sulfinylimine ***ent*-7R** (100 mg, 0.374 mmol) yielded ***ent*-15R** (54:46 *dr*). Chromatography (PE/Et_2O 40:60→20:80) afforded ***ent-ul*-15R** (37 mg, 0.095 mmol, 25%) and ***ent-l*-15R** (31 mg, 0.079 mmol, 21%).

*Major Isomer: (3R,4S,S$_S$)-Ethyl 4-(Benzyloxy)-3-(tert-butylsulfinamino)-2,2-difluoropentanoate (**ent-ul-15R**).*



Pale yellow oil: R_f 0.38 (PE/Et_2O 20:80); $[\alpha]_D$ +30.0 (*c* 0.62, $CHCl_3$, 23 °C); IR (neat) 3353 (w, br), 2979 (w), 1765 (m), 1079 (s), 1021 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.60 (d, $^2J_{HH}$ = 11.0 Hz, 1H), 4.33 (d, $^2J_{HH}$ = 11.0 Hz, 1H), 4.30 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 4.09−3.98 (m, 3H), 3.66 (dddd, $^3J_{HF}$=12.8, $^3J_{HH}$ = 9.1 Hz, $^3J_{HF}$ = 8.9 Hz, $^3J_{HH}$ = 0.9 Hz, 1H), 1.42 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.24 (s, 9H), 1.16 (t, $^3J_{HH}$ = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (dd, $^2J_{CF}$ = 33.7, 30.7 Hz), 137.5, 128.3 (2C), 127.8 (2C), 127.7, 113.8 (t, $^1J_{CF}$ = 255.4 Hz), 70.7, 70.4 (d, $^3J_{CF}$ = 2.9 Hz), 64.1 (dd, $^2J_{CF}$ = 27.8 Hz, $^2J_{CF}$ = 23.4 Hz), 62.7, 56.8, 22.5 (3C), 16.6, 13.7 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.9 (dd, $^2J_{FF}$ = 257.9 Hz, $^3J_{HF}$ = 8.9 Hz), −114.7 (dd, $^2J_{FF}$ = 257.9 Hz, $^3J_{HF}$ = 12.8 Hz) ppm; MS (ESI+) (*m*/*z*) 414 (M + Na)$^+$; HRMS (MS+) for $C_{18}H_{27}F_2NNaO_4S$ (M + Na)$^+$ calcd 414.1521, found 414.1526.

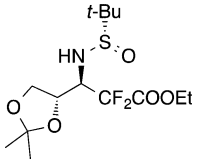
*Minor Isomer: (3S,4S,S$_S$)-Ethyl 4-(Benzyloxy)-3-(t-butylsulfinamino)-2,2-difluoropentanoate (**ent-l-15R**).*



Pale yellow oil: R_f 0.22 (PE/Et_2O 20:80); $[\alpha]_D$ +37.7 (*c* 0.53, $CHCl_3$, 23 °C); IR (neat) 3213 (w, br), 2981 (w), 1770 (m), 1097 (s), 1055 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 4.51 (d, $^2J_{HH}$ = 11.2 Hz, 1H), 4.39 (d, $^2J_{HH}$ = 11.2 Hz, 1H), 4.08−3.92 (m, 3H), 3.76−3.68 (m, 1H), 3.68 (d, $^3J_{HH}$ = 9.3 Hz, 1H), 1.32 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 1.24 (s, 9H), 1.18 (t, $^3J_{HH}$ = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (dd, $^2J_{CF}$ = 32.2 Hz, $^2J_{CF}$ = 30.7 Hz), 137.4, 128.3 (2C), 128.0 (2C), 127.8, 113.8 (t, $^1J_{CF}$ = 254.7 Hz), 73.9, 71.0, 62.8, 62.7 (dd, $^2J_{CF}$ = 23.4 Hz, $^2J_{CF}$ = 22.0 Hz), 57.1, 22.7 (3C), 16.6, 13.7 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.6 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 8.6 Hz), −117.3 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; MS (ESI) (*m*/*z*) 455 (M + Na + MeCN)$^+$; HRMS (MS+) for $C_{18}H_{27}F_2NNaO_4S$ (M + Na)$^+$ calcd 414.1521, found 414.1524.

Reaction with sulfinylimine **8S** (109 mg, 0.467 mmol) yielded ***ul*-16S** as a single diastereoisomer. Chromatography (PE/EtOAc 70:30→50:50) afforded ***ul*-16S** (103 mg, 0.288 mmol, 62%) as a white solid.

*Major isomer: (3R,4S,S$_S$)-ethyl 4,5-isopropylidenedioxy-3-(tert-butylsulfinylamino)-2,2-difluoropentanoate (**ul-16S**):*

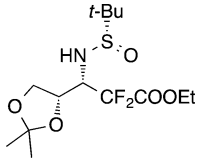


R_f 0.26 (PE/EtOAc 50:50); mp 88−90 °C; $[\alpha]_D$ +30.3 (*c* 0.29, $CHCl_3$, 23 °C); IR (neat) 3194 (w), 2986 (w), 1777 (m), 1761 (m), 1053 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 4.38−4.11 (m, 5H), 3.96 (dddd, $^3J_{HF}$=17.4 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HF}$ = 8.2 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 3.54 (d, $^3J_{HH}$ = 8.7 Hz, 1H), 1.39 (s, 3H), 1.34 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.29 (s, 3H), 1.21 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (t, $^2J_{CF}$ = 30.8 Hz), 113.8 (dd, $^1J_{CF}$ = 256.4 Hz, $^1J_{CF}$ = 252.5 Hz), 110.6, 73.6, 66.8, 63.0, 61.1 (dd, $^2J_{CF}$ = 22.6 Hz, $^2J_{CF}$ = 21.5 Hz), 57.1, 25.9, 24.9, 22.4 (3C), 13.7 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.0 (dd, $^2J_{FF}$ = 262.6 Hz, $^3J_{HF}$ = 8.2 Hz), −119.4 (dd, $^2J_{FF}$ = 262.6 Hz,

dx.doi.org/10.1021/jo500396p | J. Org. Chem. XXXX, XXX, XXX−XXX

$^3J_{HF}$ = 17.4 Hz) ppm; MS (ESI+) (*m*/*z*) 421 (M + Na + MeCN)$^+$; HRMS (MS+) for $C_{14}H_{25}F_2NNaO_5S$ (M + Na)$^+$ calcd 380.1314, found 380.1312.

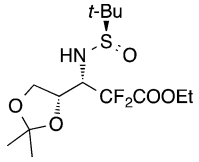
*Minor Isomer: (3S,4S,S_S)-Ethyl 4,5-Isopropylidenedioxy-3-(tert-butylsulfinylamino)-2,2-difluoropentanoate (**l-16S**).*



Isolated from an unselective reaction, pale yellow oil: $[\alpha]_D$ +6.2 (*c* 0.17, $CHCl_3$, 23 °C); IR (neat) 2991 (w), 1770 (s), 1137 (s), 1123 (s), 1107 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (ddd, $^3J_{HH}$ = 7.1 Hz, $^3J_{HH}$ = 6.1 Hz, $^3J_{HH}$ = 2.2 Hz, 1H), 4.45−4.32 (m, 2H), 4.11 (dd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 7.1 Hz, 1H), 4.14 (d, $^3J_{HH}$ = 10.4 Hz, 1H), 3.85 (dddd, $^3J_{HF}$ = 16.3 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HF}$ = 6.1 Hz, $^3J_{HH}$ = 2.2 Hz, 1H), 3.80 (dd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 6.1 Hz, 1H), 1.44 (s, 3H), 1.38 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.33 (s, 3H), 1.26 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$ = 31.4 Hz), 113.5 (dd, $^1J_{CF}$ = 261 Hz, $^1J_{CF}$ = 256 Hz), 110.2, 72.1 (d, $^3J_{CF}$ = 3.3 Hz), 66.1, 63.5, 59.4 (t, $^2J_{CF}$ = 24.8 Hz), 57.3, 26.1, 24.4, 22.6 (3C), 13.7 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.0 (dd, $^2J_{FF}$ = 265.7 Hz, $^3J_{HF}$ = 6.1 Hz), −117.9 (dd, $^2J_{FF}$ = 265.7 Hz, $^3J_{HF}$ = 16.3 Hz) ppm; HRMS (MS+) for $C_{14}H_{25}F_2NNaO_5S$ (M + Na)$^+$ calcd 380.1314, found 380.1305.

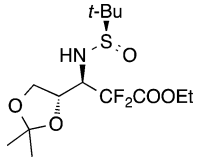
Reaction with sulfinylimine **8R** (150 mg, 0.643 mmol) yielded **16R** (88:12 dr). Chromatography (PE/EtOAc 75:25→70:30) afforded ***ul*-16R** (120 mg, 0.336 mmol, 52%) and ***l*-16R** (15 mg, 0.042 mmol, 7%) as white solids.

*Major isomer: (3S,4S,R_S)-ethyl 4,5-isopropylidenedioxy-3-(tert-butylsulfinylamino)-2,2-difluoropentanoate (**ul-16R**):*



R_f 0.50 (hexane/EtOAc 50:50); mp 84−86 °C; $[\alpha]_D$ −62.5 (*c* 0.81, $CHCl_3$, 21 °C); IR (neat) 3313 (br w), 2985 (br m), 1771 (s), 1077 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54−4.40 (m, 1H), 4.38−4.25 (m, 3H), 4.15 (dd, $^2J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 7.8 Hz, 1H), 4.10 (dd, $^2J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.6 Hz, 1H), 3.91−3.77 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.36 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.24 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$ = 30.7 Hz), 113.9 (dd, $^1J_{CF}$ = 259.1 Hz, $^1J_{CF}$ = 254.7 Hz), 110.4, 70.8 (d, $^3J_{CF}$ = 2.9 Hz), 66.2, 63.0, 57.9 (t, $^2J_{CF}$ = 25.6 Hz), 56.7, 26.2, 25.6, 22.5 (3C), 13.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.9 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 8.6 Hz), −118.1 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; MS (ESI+) (*m*/*z*) 421 ((M + Na + MeCN)$^+$; HRMS (MS+) for $C_{14}H_{26}F_2NO_5S$ (M + H)$^+$ calcd 358.1500, found 358.1494.

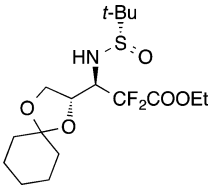
*Minor isomer: (3R,4S,R_S)-ethyl 4,5-isopropylidenedioxy-3-(tert-butylsulfinylamino)-2,2-difluoropentanoate (**l-16R**):*



R_f 0.32 (hexane/EtOAc 50:50); mp 86−88 °C; $[\alpha]_D$ −22.6 (*c* 0.06, $CHCl_3$, 22 °C); IR (neat) 3205 (br w), 2986 (br m), 1775 (s), 1065 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43−4.22 (m, 3H), 4.14 (dd, $^2J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 6.4 Hz, 1H), 4.07−3.94 (m, 1H), 3.88 (dd, $^2J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 6.3 Hz, 1H), 3.65 (d, $^3J_{HH}$ = 9.0 Hz, 1H), 1.39 (s, 3H), 1.38 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.33 (s, 3H), 1.25 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (t, $^2J_{CF}$ = 30.8 Hz), 113.6 (dd, $^1J_{CF}$ = 257.5, 253.8 Hz), 110.5, 73.7 (d, $^3J_{CF}$ = 2.9 Hz), 67.1, 63.3, 61.0 (t, $^2J_{CF}$ = 22.0 Hz), 57.2, 26.1, 25.1, 22.6 (3C), 13.8 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.1 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ 8.6 Hz), −118.1 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 12.9 Hz) ppm; MS (ESI+) (*m*/*z*) 421 ((M + Na + MeCN)$^+$, 100). HRMS (MS+) for $C_{14}H_{26}F_2NO_5S$ (M + H)$^+$ calcd 358.1500, found 358.1498.

Reaction with sulfinylimine **9S** (100 mg, 0.366 mmol) yielded ***ul*-17S** (single diastereoisomer). Chromatography (PE/EtOAc 65:35→50:50) afforded ***ul*-17S** (75 mg, 0.189 mmol, 52%).

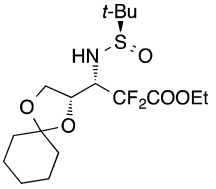
*(3R,4S,S_S)-Ethyl 4,5-cyclohexylidenedioxy-3-(tert-butylsulfinylamino)-2,2-difluoropentanoate (**ul-17S**).*



White solid: R_f 0.23 (PE 40−60 °C/EtOAc 50:50); mp 112−116 °C; $[\alpha]_D$ +28.3 (*c* 0.56, $CHCl_3$, 23 °C); IR (neat) 3203 (br, w), 2937 (m), 1761 (m), 1092 (m), 1050 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37−4.06 (m, 5H), 3.96 (dddd, $^3J_{HF}$=17.2 Hz, $^3J_{HF}$ = 8.6 Hz, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 7.3 Hz, 1H), 3.54 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 1.70−1.45 (m, 8H), 1.44−1.28 (m, 2H), 1.35 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.21 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$ = 30.7 Hz), 113.9 (dd, $^1J_{CF}$ = 256.1 Hz, $^1J_{CF}$ = 251.8 Hz), 111.3, 73.2, 66.5, 62.9, 61.1 (t, $^2J_{CF}$ = 22.0 Hz), 57.1, 35.6, 34.2, 24.9, 23.8, 23.6, 22.4 (3C), 13.8 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.5 (dd, $^2J_{FF}$ = 264.3 Hz, $^3J_{HF}$ = 8.6 Hz), −118.9 (dd, $^2J_{FF}$ = 264.3 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; MS (ESI+) (*m*/*z*) 461 (M + Na + MeCN)$^+$; HRMS (MS+) for $C_{17}H_{30}F_2NO_5S$ (M + H)$^+$ calcd 398.1807, found 398.1804.

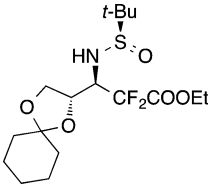
Reaction with sulfinylimine **9R** (100 mg, 0.366 mmol) yielded **17R** (81:19 dr). Chromatography (PE/EtOAc 80:20→65:35) afforded ***ul*-17R** (70 mg, 0.176 mmol, 48%) and ***l*-17R** (12 mg, 0.030 mmol, 8%) as white solids.

*Major isomer: (3S,4S,R_S)-ethyl 4,5-cyclohexylidenedioxy-3-(t-butylsulfinylamino)-2,2-difluoropentanoate (**ul-17R**):*



R_f 0.21 (PE/EtOAc 65:35); mp 72−75 °C; $[\alpha]_D$ −29.9 (*c* 0.68, $CHCl_3$, 21 °C); IR (neat) 3311 (br w), 2935 (m), 1770 (s), 1075 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (t, $^3J_{HH}$ = 7.2 Hz, 1H), 4.39−4.24 (m, 3H), 4.16−4.07 (m, 2H), 3.90−3.76 (m, 1H), 1.70−1.51 (m, 8H), 1.46−1.33 (m, 2H), 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.25 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (t, $^2J_{CF}$ = 30.7 Hz), 113.9 (t, $^1J_{CF}$ = 259.1 Hz), 111.0, 70.5 (d, $^3J_{CF}$ = 2.9 Hz), 65.9, 63.0, 58.0 (t, $^2J_{CF}$ = 26.3 Hz), 56.7, 35.7, 35.4, 25.0, 23.9, 23.7, 22.5 (3C), 13.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.9 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 8.6 Hz), −117.8 (dd, $^2J_{FF}$ = 262.2 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; MS (ESI+) (*m*/*z*) 461 (M + Na + MeCN)$^+$; HRMS (MS+) for $C_{17}H_{30}F_2NO_5S$ (M + H)$^+$ calcd 398.1807, found 398.1808.

*Minor isomer: (3R,4S,R_S)-ethyl 4,5-cyclohexylidenedioxy-3-(tert-butylsulfinylamino)-2,2-difluoropentanoate (**l-17R**):*



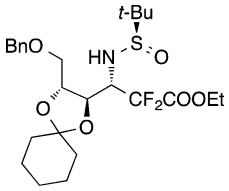
R_f 0.12 (PE/EtOAc 65:35); mp 122−124 °C; $[\alpha]_D$ −39.0 (*c* 0.50, $CHCl_3$, 19 °C); IR (neat) 3204 (br w), 2937 (m), 1762 (s), 1053 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (dq, $^2J_{HH}$ = 10.7, $^3J_{HH}$ = 7.2 Hz, 1H), 4.30 (dq, $^2J_{HH}$ = 10.7, $^3J_{HH}$ = 7.2 Hz, 1H), 4.25−4.18 (m, 1H), 4.15−4.08 (m, 1H), 3.98 (dddd app. ddt, $^3J_{HF}$ = 16.1, $^3J_{HH}$ = 9.1, $^3J_{HF}$ =^{3} J_{HH} = 8.6 Hz, 1H), 3.83 (dd, $^3J_{HH}$ = 8.6, 6.3 Hz, 1H), 3.67 (d,

dx.doi.org/10.1021/jo500396p | J. Org. Chem. XXXX, XXX, XXX−XXX

$^3J_{HH}$ = 9.1 Hz, 1H), 1.63−1.48 (m, 8H), 1.43−1.31 (m, 2H), 1.36 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.23 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (t, $^2J_{CF}$ = 30.7 Hz), 113.7 (dd, $^1J_{CF}$ = 256.1 Hz, $^1J_{CF}$ 253.2 Hz), 111.2, 73.2 (br. s), 66.8, 63.2, 61.1 (t, $^2J_{CF}$ = 22.0 Hz), 57.1, 35.8, 34.4, 24.9, 23.8, 23.6, 22.6 (3C), 13.8 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.6 (dd, $^2J_{FF}$ = 262.8, $^3J_{HF}$ = 8.6 Hz), −118.3 (d, $^2J_{FF}$ = 262.2, $^3J_{HF}$ = 16.1 Hz) ppm; MS (ESI+) (m/z) 461 (M + Na + MeCN; HRMS (MS+) for $C_{17}H_{30}F_2NO_5S$ (M + H)$^+$ calcd 398.1807, found 398.1814.

Reaction with sulfinylimine ***ent*-10S** (2.06 g, 5.24 mmol) yielded ***ent-ul*-18S** (single diastereoisomer). Chromatography (PE/EtOAc 75:25→60:40) afforded ***ent-ul*-18S** (1.81 g, 3.50 mmol, 67%).

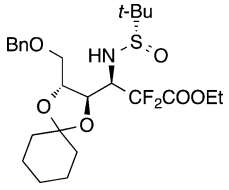
*(3S,4R,5R,R_S)-Ethyl [6-(Benzyloxy)-3-(tert-butylsulfinylamino)-4,5-(cyclohexylidenedioxy)-2,2-difluorohexanoate (**ent-ul-18S**).*



Pale yellow oil: R_f 0.35 (PE/EtOAc 50:50); $[\alpha]_D$ +43.2 (c 0.35, $CHCl_3$, 22 °C); IR (neat) 3244 (w), 2936 (m), 2360 (m), 1774 (m), 1759 (m), 1060 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 4.62 (d, $^3J_{HH}$ = 6.4 Hz, 1H), 4.56 (s, 2H), 4.49 (ddd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 4.4 Hz, 1H), 4.32 (dq, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 7.1 Hz, 1H), 4.28 (dq, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 7.1 Hz, 1H), 4.13 (dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 3.99 (dddd, $^3J_{HF}$ = 17.2 Hz, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 7.5 Hz, $^3J_{HH}$ = 6.4 Hz, 1H), 3.88 (dd, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 4.4 Hz, 1H), 3.38 (dd app. t, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 8.8 Hz, 1H), 1.74−1.61 (m, 1H), 1.61−1.45 (m, 7H), 1.36 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.44−1.26 (m, 2H), 1.08 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (t, $^2J_{CF}$ = 30.7 Hz), 136.9, 128.6 (2C), 128.1 (3C), 114.0 (dd, $^1J_{CF}$ = 257.6 Hz, $^1J_{CF}$ = 251.8 Hz), 111.6, 76.5, 76.2, 73.9, 71.1, 62.8, 61.7 (t, $^2J_{CF}$ = 22.0 Hz), 56.4, 36.3, 35.7, 24.9, 23.7, 23.6, 22.5 (3C), 13.8 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.8 (dd, $^2J_{FF}$ = 260.0 Hz, $^3J_{HF}$ = 7.5 Hz), −121.4 (dd, $^2J_{FF}$ = 260.0 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; MS (ESI+) (m/z) 540 (M + Na)$^+$; HRMS (MS+) for $C_{25}H_{38}F_2NO_6S$ (M + H)$^+$ calcd 518.2382, found 518.2377.

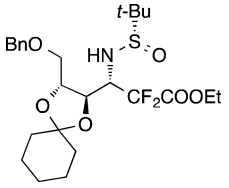
Reaction with sulfinylimine ***ent*-10R** (100 mg, 0.254 mmol) yielded ***ent*-18R** (60:40 dr). Chromatography (PE/EtOAc 75:25→70:30) afforded ***ent-ul*-18R** (41 mg, 0.079 mmol, 31%) and ***ent-l*-18R** (22 mg, 0.043 mmol, 17%).

*Major Isomer: (3R,4R,5R,S_S)-Ethyl-6-(Benzyloxy)-3-(tert-butylsulfinylamino)-4,5- (cyclohexylidenedioxy)-2,2-difluorohexanoate (**ent-ul-18R**).*



Pale yellow oil: R_f 0.37 (PE/EtOAc 70:30); $[\alpha]_D$ +50.8 (c 0.53, $CHCl_3$, 20 °C); IR (neat) 2936 (s), 2863 (w), 1773 (m), 1760 (m), 1073 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 4.63 (d, $^2J_{HH}$ = 12.1 Hz, 1H), 4.59 (d, $^2J_{HH}$ = 12.1 Hz, 1H), 4.51−4.44 (m, 2H), 4.30 (dq, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 4.26 (dq, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 4.20 (d, $^3J_{HH}$ = 8.7 Hz, 1H), 4.05 (ddd, $^3J_{HF}$ = 17.2 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 7.5 Hz, 1H), 3.78 (dd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 3.62 (dd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 6.4 Hz, 1H), 1.77−1.47 (m, 8H), 1.44−1.30 (m, 2H), 1.33 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.24 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$ = 33.7 Hz), 137.9, 128.3 (2C), 127.6 (3C), 114.0 (dd, $^1J_{CF}$ = 259.1 Hz, $^1J_{CF}$ = 254.7 Hz), 110.8, 74.3, 74.2 (d, $^3J_{CF}$ = 2.9 Hz), 73.6, 69.5, 62.9, 57.7 (t, $^2J_{CF}$ = 24.9 Hz), 56.7, 36.6, 36.1, 24.9, 23.8, 23.7, 22.5 (3C), 13.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.1 (dd, $^2J_{FF}$ = 257.9 Hz, $^3J_{HF}$ = 7.5 Hz), −117.9 (dd, $^2J_{FF}$ = 257.9 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; MS (ESI+) (m/z) 540 (M + Na)$^+$;HRMS (MS+) for $C_{25}H_{38}F_2NO_6S$ (M + H)$^+$ calcd 518.2382, found 518.2378.

*Minor Isomer: (3S,4R,5R,S_S)-Ethyl 6-(Benzyloxy)-3-(tert-butylsulfinylamino)-4,5- (cyclohexylidenedioxy)-2,2-difluorohexanoate (**ent-l-18R**).*



Pale yellow oil: R_f 0.18 (PE/EtOAc 70:30); $[\alpha]_D$ +28.3 (c 0.72, $CHCl_3$, 20 °C); IR (neat) 2936 (s), 2863 (w), 1773 (m), 1760 (m), 1057 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 4.57 (s, 2H), 4.36 (dq, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 4.31 (dq, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 4.30−4.23 (m, 1H), 4.09−3.95 (m, 2H), 3.83 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 3.63 (dd, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 3.58 (dd, $^2J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 4.9 Hz, 1H), 1.68−1.47 (m, 8H), 1.41−1.32 (m, 2H), 1.36 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.15 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (t, $^2J_{CF}$ = 31.1 Hz), 137.6, 128.5 (2C), 128.0 (2C), 127.9, 113.8 (dd, $^1J_{CF}$ = 256.5 Hz, $^1J_{CF}$ = 255.0 Hz), 111.4, 77.5, 76.0 (t, $^3J_{CF}$ = 2.6 Hz), 73.7, 71.1, 63.2, 60.7 (t, $^2J_{CF}$ = 22.7 Hz), 57.2, 36.4, 36.3, 25.0, 23.8, 23.7, 22.5 (3C), 13.8 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.4 (d, $^2J_{FF}$ = 262.2 Hz), −116.8 (d, $^2J_{FF}$ = 262.2 Hz) ppm; MS (ESI+) (m/z) 540 (M + Na)$^+$; HRMS (MS+) for $C_{25}H_{37}F_2NNaO_6S$ (M + Na)$^+$ calcd 540.2202, found 540.2192.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for known compounds, copies of ^{19}F NMR spectra of the crude Honda−Reformatsky reaction mixtures, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Fax: +44 23 8059 7574. E-mail: thomas.poisson@insa-rouen.fr.
*E-mail: bruno.linclau@soton.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The European Community (INTERREG IVa Channel Programme, IS:CE-Chem, project 4061) is thanked for financial support.

■ REFERENCES

(1) Kirsch, P. In *Modern Fluororganic Chemistry*; Wiley-VCH: Weinheim, 2004.
(2) J.-P. Bégué, D. Bonnet-Delpon In *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc.: Hoboken, NJ, 2008.
(3) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.
(4) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071−1081.
(5) Bremer, M.; Kirsch, P.; Klasen-Memmer, M.; Tarumi, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8880−8896.
(6) Acena, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. *Synthesis* **2012**, *44*, 1591−1602.
(7) Sorochinsky, A. E.; Soloshonok, V. A. *J. Fluorine Chem.* **2010**, *131*, 127−139.
(8) Fustero, S.; Sanz-Cervera, F. F.; Acena, J. L.; Sanchez-Rosello, M. *Synlett* **2009**, 525−549.
(9) Salwicek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koksch, B. *Chem. Soc. Rev.* **2012**, *41*, 2135−2171.

(10) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643.
(11) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100−1115.
(12) Lankin, D. C.; Chandrakumar, N. S.; Rao, S. N.; Spangler, D. P.; Snyder, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 3356−3357.
(13) March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. *Chem. Biodiversity* **2012**, *9*, 2410−2440.
(14) Mikami, K.; Fustero, S.; Sanchez-Rosello, M.; Acena, J. L.; Soloshonok, V.; Sorochinsky, A. *Synthesis* **2011**, 3045−3079.
(15) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, 3261−3278.
(16) Yoshinari, T.; Gessier, F.; Noti, C.; Beck, A. K.; Seebach, D. *Helv. Chem. Acta* **2011**, *94*, 1908−1942.
(17) Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, *43*, 5445−5448.
(18) Staas, D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276−8279.
(19) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869−8905.
(20) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600−3740.
(21) Choppin, S.; Ferreiro-Medeiros, L.; Barbarotto, M.; Colobert, F. *Chem. Soc. Rev.* **2013**, *42*, 937−949.
(22) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461−8464.
(23) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634−1645.
(24) Niida, A.; Tomita, K.; Mizumono, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.-I.; Fuji, N. *Org. Lett.* **2006**, *8*, 613−616.
(25) Tarui, A.; Kondo, K.; Taira, H.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Heterocycles* **2007**, *73*, 203−208.
(26) March, T. L.; Johnston, M. R.; Duggan, P. J. *Org. Lett.* **2012**, *14*, 182−185.
(27) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5291−5294.
(28) Baldwin, J. E.; Lynch, G. P.; Schofield, C. *Tetrahedron* **1992**, *48*, 9085−9100.
(29) Dondoni, A.; Massi, A.; Sabbatini, S. *Chem.—Eur. J.* **2005**, *11*, 7110−7125.
(30) Buesking, A. W.; Baguley, T. D.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 964−967.
(31) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284.
(32) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403−1406.
(33) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948−9957.
(34) Poisson, T.; Belhomme, M.-C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277−9285.
(35) Ivashkin, I.; Couve- Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 2270−2273.
(36) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549−2551.
(37) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307−308.
(38) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143−2150.
(39) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665−4668.
(40) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920−2930.
(41) (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835. (b) Reetz, M. T.; Huellmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477−480.
(42) Brinner, K.; Doughan, B.; Poon, D. J. *Synlett* **2009**, 991−993.
(43) Fustero, S.; Herrera, L.; Lazaro, R.; Rodriguez, E.; Maestro, M. A.; Mateu, N.; Barrio, P. *Chem.—Eur. J.* **2013**, *19*, 11776−11785.
(44) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387−6389.
(45) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12−13.
(46) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051−2054.
(47) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291−9294.
(48) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396−3397.
(49) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914.
(50) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887−2896.
(51) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772−8778.
(52) Enders, D.; Berg, S. V.; Jandeleit, B. *Org. Synth.* **2002**, *78*, 177.
(53) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6−13.
(54) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585−587.
(55) Sishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Heterocycles* **1988**, *27*, 495−508.

dx.doi.org/10.1021/jo500396p | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Journal of Fluorine Chemistry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

The synthesis of tetrafluorinated aminosugars

Clément Q. Fontenelle, Graham J. Tizzard, Bruno Linclau *

Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom

ARTICLE INFO

Article history:
Received 12 June 2014
Received in revised form 14 July 2014
Accepted 21 July 2014
Available online xxx

Keywords:
Fluorine
Carbohydrate
Fluorosugar
Fluorination
Aminosugar

ABSTRACT

The synthesis of two tetrafluorinated 4-aminosugars, 4-amino-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-*erythro*-hexopyranose hydrochloride (**7•HCl**) and 4-amino-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-*threo*-hexopyranose hydrochloride (**8•HCl**), is described. The amino group in α-position of a $CF_2(CF_2)$ group is proposed as a mimic for the hydrogen bond accepting capacity of an alcohol group in an unfluorinated sugar. The synthesis of the two sugars was achieved in 4 steps each from the sulfinylimine diastereoisomers of D-glyceraldehyde.

1. Introduction

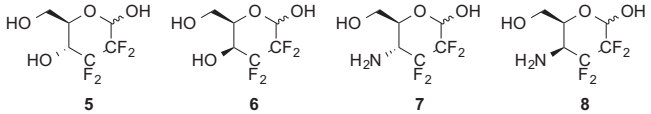
Fluorination of carbohydrates is a popular strategy to investigate carbohydrate binding epitopes [1] and enzyme mechanism [2], or to stabilize glycosidic bonds [2,3], and indeed a vast number of fluorinated carbohydrates and their glycosides have been synthesized for these purposes [4]. While the replacement of CHOH with CHF (or CF_2) has as main consequence that the hydrogen bond donating capacity at that position is lost, the electronic properties of the remaining hydroxyl groups can also undergo substantial changes. With respect to protein binding, the change in hydrogen bond donating and accepting properties of these alcohol groups could have significant additional effects. While these properties are influenced by the fluorine electronegativity, there are other factors that play a role, such as intramolecular hydrogen bonding of the OH group with the fluorine atom and hyperconjugation effects, both of which depend on relative stereochemistry [5].

With regard to alcohol hydrogen bond acceptor capacity, it is instructive to compare a relevant parameter, pK_{BHX}, which refers to the equilibrium of the acceptor with a standard hydrogen bond donor (*p*-fluorophenol) [6]. Clearly, the hydrogen bond acceptor capacity of the alcohol group in trifluoroethanol **2** is reduced compared to that of ethanol **1** to such an extent that it cannot be considered a hydrogen bond acceptor any more (Table 1). A similar decrease is seen by comparing ethylamine **3** and 2,2,2-trifluoroethylamine **4**. Nevertheless, the pK_{BHX} value for **4** is relatively close to that of **1**, so it can be proposed that a β-trifluorinated (or difluorinated) amine is a reasonable mimic for a regular alcohol, if hydrogen bond acceptor properties are concerned.

The design of carbohydrate-based analogues with greater affinity to carbohydrate-processing proteins is of interest for use as probes or therapeutics [7]. We have an interest in investigating polyfluorination of carbohydrates as a strategy for increasing the typically low protein-carbohydrate binding affinities. Polyfluorination introduces a hydrophobic moiety, thus causing beneficial hydrophobic desolvation upon binding [8], yet the individual polar

Table 1
Influence of trifluoromethylation on alcohol and amine hydrogen bond acceptor capacity.

	pK_{BHX}		pK_{BHX}
CH_3CH_2OH (**1**)	1.02	$CH_3CH_2NH_2$ (**3**)	2.17
CF_3CH_2OH (**2**)	−0.28	$CF_3CH_2NH_2$ (**4**)	0.71

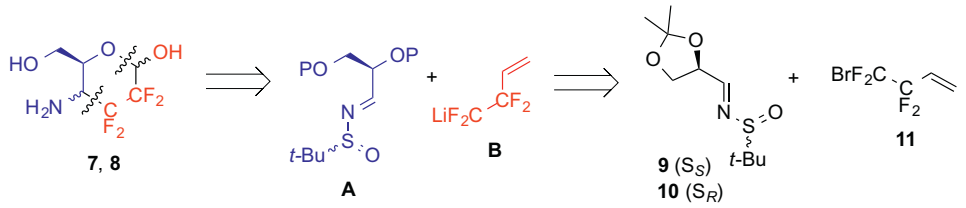


5 6 7 8

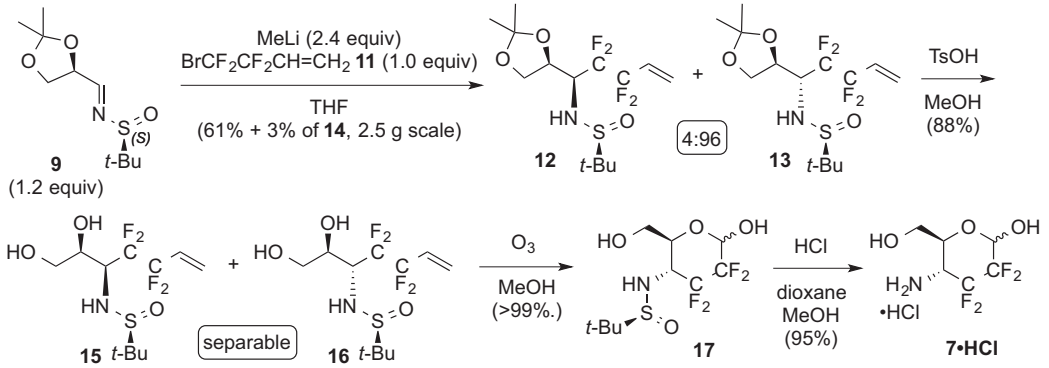
Fig. 1. Tetrafluorinated sugars with the proposed aminosugar analogues.

* Corresponding author. Tel.: +44 2380593816.
E-mail address: bruno.linclau@soton.ac.uk (B. Linclau).

http://dx.doi.org/10.1016/j.jfluchem.2014.07.015
0022-1139/



Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of the glucose analogue **7**.

C–F bonds retain the capacity for attractive interactions with electropositive protein residues [9]. The combination of these effects has been coined "polar hydrophobicity" [10]. In order to retain chiral alcohol groups in the carbohydrate ring, which were deemed important for binding selectivity, we have focused on the synthesis of sugars containing a medium-size hydrophobic moiety such as 2,3-dideoxy-2,2,3,3-tetrafluorinated carbohydrates, including "tetrafluorinated glucose" (2,3-dideoxy-2,2,3,3-tetrafluoro-D-*erythro*-hexopyranose) **5** (Fig. 1) and—galactose (2,3-dideoxy-2,2,3,3-tetrafluoro-D-*threo*-hexopyranose) **6** [11]. It was shown that these structures retain the conventional carbohydrate shape [12], and **6** was found to be a weak substrate of the enzyme galactose oxidase [13]. A successful inhibitor of the mycobacterial enzyme UDP-Gal mutase, based on a tetrafluorinated galactofuranose sugar, has been recently reported [14].

With the above discussion in mind, the hydrogen bond acceptor capacity of the 4-OH groups in **5** and **6** will be very low, and hence the corresponding tetrafluorinated aminosugars **7**, a glucose analogue, and **8**, a galactose analogue, became a focus for their synthesis and investigations. In addition, a further interest in their synthesis stems from the known interesting biological activities of aminosugars and their derivatives [15], with only a small number of fluorinated aminosugar derivatives reported [16].

Herein we report the synthesis of **7** and **8**.

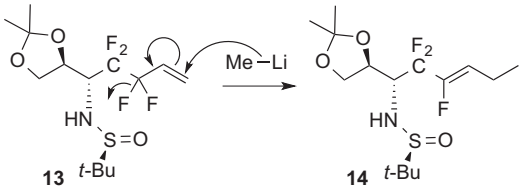
2. Results and discussion

The synthesis of the 4-aminosugars was envisaged by reaction of the lithiated fluorinated building block **B** with a chiral glyceraldehyde derived sulfinylimine **A**. The absolute configuration of the auxiliary was expected to control the configuration of the newly formed chiral centre [17,18]. The corresponding reactants **9**/**10** and **11** are known [18] or commercially available. After the addition reaction, diol deprotection and alkene ozonolysis would give the fluorinated aminosugar (Scheme 1).

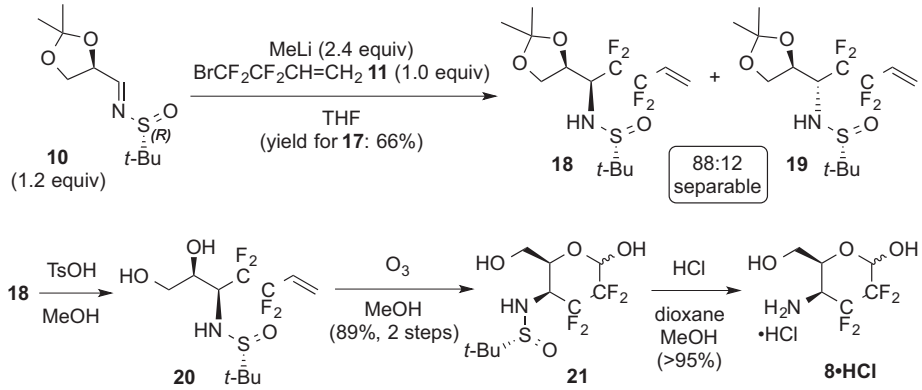
The plan benefitted from important literature precedence, in that Konno had not only demonstrated that reagent **B** could be formed and cleanly reacted with electrophiles, but that it also reacted with the sulfinylimine derived from benzaldehyde (a 9:1 diastereomeric ratio was reported) [19]. The ozonolysis/pyranose ring formation had also been demonstrated in an efficient synthesis of 2,3-dideoxy-2,2,3,3-tetrafluorinated glucose **5** and galactose **6** by the same group [20].

The synthesis of **7** is shown in Scheme 2. Following Konno's conditions, using the (*S*)-configured sulfinylimine auxiliary, a 78% yield was achieved for the coupling reaction as a 92:8 mixture of diastereoisomers. However, under these conditions, the limiting reagent is bromotetrafluorobutene **11**, with no less than 2.4 equiv of sulfinylimine used. Given 3 steps are used to obtain the sulfinylimines, we chose to reduce the relative amount of this substrate, in order to increase the isolated quantity of adducts **12**/**13**. Hence, reducing the number of equivalents of **9** to 1.2, a reduced 61% (isolated) yield was obtained for **12**/**13**, in a 4:96 ratio of diastereoisomers, but in a larger absolute quantity than would have been obtained under Konno's conditions. Interestingly, under these modified conditions the formation of a minor byproduct was observed which, despite isolation in pure form was not possible, could be assigned as **14** (~3%, Scheme 3). The presence of the terminal methyl group and the alkene C–H were clearly observed in the ^{1}H NMR spectrum, and the $^{3}J_{H-F}$ value of 36.5 Hz indicated a *Z*-substituted fluoroalkene. The ^{19}F NMR spectrum showed three resonances, including one geminal CF_2 group as obvious from a large coupling constant. This type of byproduct, not reported by Konno, presumably arose from nucleophilic attack of MeLi to the alkene moiety in **12**/**13** *via* S_N2' fashion as shown [21].

High-yielding acetonide hydrolysis allowed separation of the diastereoisomers, leading to the desired product as a single diastereoisomer **16** in 88% isolated yield. Ozonolysis and amine



Scheme 3. Proposed identity and formation of the byproduct **14**.



Scheme 4. Synthesis of the galactose analogue **8**.

auxiliary removal gave the 4-deoxy-4-amino glucose derivative **7** in high yield, as the hydrochloric acid salt. Interestingly, the precipitated salt was obtained as pure α anomer.

The similar synthesis of the corresponding galactose isomer is shown in Scheme 4. Now the (*R*)-configured sulfinylimine auxiliary is used for the reaction with lithiated 1,1,2,2-tetrafluorobutene, leading to a separable mixture of adducts **18** and **19**. The MeLi S_N2' adduct was again observed as minor isomer (not shown). Diol deprotection and ozonolysis led to the pyranose **21** in excellent yield. The removal of the auxiliary proved cumbersome, in that for this compound, precipitation as the hydrochloride salt was not possible. This resulted in an incomplete separation from the sulfinate ester byproduct. Any attempt of purification by chromatography proved unsuccessful, leading to a complex mixture. Protection of the 4-amino and 6-hydroxy groups as Cbz allowed the purification but subsequent hydrogenolysis resulted in obtaining a similar complex mixture. As methyl *tert*-butanesulfinate is somewhat volatile (52 °C/16 torr), purification was attempted by co-evaporating with MeOH carefully keeping the temperature below 40 °C to avoid apparition of impurities. This proved only partially successful, but after dissolving the salt in water, the impurity could largely be removed by extraction with Et_2O. Hence, **8•HCl** was obtained in excellent yield.

The relative stereochemistry of the obtained products could be deduced from X-ray crystallographic analysis of **17** (Fig. 2). With the S_S-configuration of the auxiliary and the C5 configuration from the starting material retained in the product, the gluco configuration at C4 is evident, as is the $^4C_1$ conformation. This was also confirmed in solution by ^{13}C NMR analysis, in that the $^2J_{C4\text{-}F}$ values were 19 Hz for both fluorine atoms (for both anomers), indicating

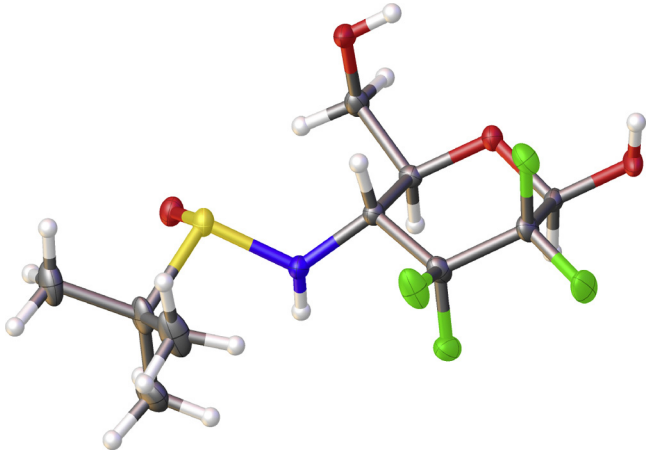


Fig. 2. X-ray crystallographic analysis of ***β*-17**.

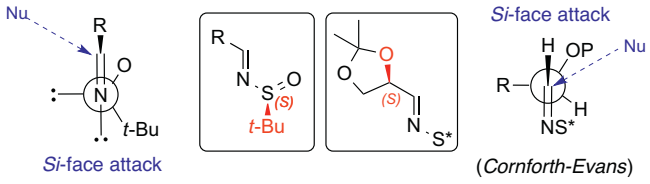


Fig. 3. Explanation for the diastereoselectivity of the addition reactions.

that the electronegative substituent at the 4-position is equatorial [22]. While we have not been able to crystallise **21**, a similar NMR analysis showed $^2J_{C4\text{-}F}$ values of around 30 and 19 Hz (for both anomers), indicating an axial electronegative substituent at C4. The ^{13}C NMR of the fully deprotected aminosugars **7** and **8** showed similar values.

The $^2J_{C4\text{-}F}$ values mentioned above for both the gluco and galacto configured structures also indicated that they existed in the pyranose form in solution. This was unambiguously shown by HMBC analysis of the aminosugars **7** and **8** (see supporting information). Irradiation of the anomeric proton led to a cross peak to C5 (and not to C4, which would represent the possible iminosugar isomer).

Interestingly, **7•HCl** solidified as the pure α-anomer, though no crystals suitable for X-ray crystallography could be obtained. The anomeric equilibrium in CD_3OD consisted of a 75:25 α/β mixture of anomers. The anomeric equilibrium for the galacto configured **8•HCl** in CD_3OD was 54:46 α/β.

The observed stereochemical outcome of the addition reactions to give **12**/**13** and **18**/**19** clearly demonstrated that the absolute configuration of the sulfinylimine auxiliary determined the stereochemical course of the reaction. The formation of the major isomers is consistent with an open transition state as shown in Fig. 3, left.[1] The difference in stereoselectivity of the addition of **11** to **9** or **10** can be explained by the additional influence of the glyceraldehyde stereogenic centre.

According to the Cornforth-Evans model of stereoselection [23] (or the polar Felkin Anh model [24], not shown), the *S*-glyceraldehyde configuration induces *Si*-face attack (Fig. 3, right). This is also the imine face that the *S*-configured sulfinylimine auxiliary makes available for reaction, according to the open transition state shown. Hence, in the (S,S_S) combination (**9**), both stereoelements lead to a matched stereoinduction, resulting in a 96:4 ratio of products. In contrast, the stereoinduction in the (S,R_S) combination (**10**) shows a mismatch, leading to a reduced 88:12 ratio of products[2].

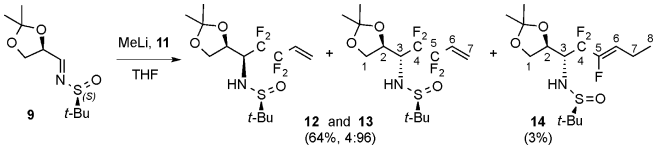
[1] This is in contrast with the stereoselection as assumed in Ref [19].
[2] Other recent examples of double diastereodifferentiation, see Refs. [17,18].

3. Conclusion

The β,β-difluorinated amino moiety is proposed as a mimic for alcohol groups with regard to hydrogen bond accepting capacity. This led to tetrafluorinated aminosugars **7** and **8** as analogues of interest in the context of our investigations involving polyfluorinated carbohydrates. A short synthesis of these aminosugars is described with the addition of a lithiated tetrafluorobutene building block to a glyceraldehyde sulfinylimine as key step.

4. Experimental

4.1. (2S,3S,S_S)-1,2-Isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene (**12**) and (2S,3R,S_S)-1,2-isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene (**13**)

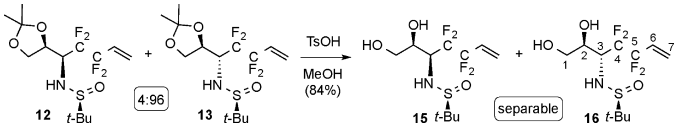


To a solution of sulfinylimine **9** (2.5 g, 10.7 mmol, 1.2 equiv) in THF (40 mL) at −78 °C was added bromotetrafluorobutene **11** (1.14 mL, 8.93 mmol, 1.0 equiv). After 10 min, MeLi (1.6 M in Et_2O, 13.4 mL, 21.4 mmol, 2.4 equiv) was added dropwise over 30 min and the reaction mixture was stirred for another 1.5 h. The reaction was quenched with saturated NH_4Cl aq. (25 mL), diluted with H_2O (15 mL) and extracted with Et_2O (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude mixture of diastereoisomers (*dr* 97:3). Purification *via* column chromatography (petroleum ether/EtOAc 60:40 to 50:50) afforded 1.96 g (5.43 mmol, 61%) of a mixture of diastereoisomers **12**/**13** along with 0.098 g (0.27 mmol, 3%) of **14** as an off-white solid. R_f 0.23 (petroleum ether 40–60 °C/EtOAc 60:40). IR (neat) 3219 (w, br), 2985 (m), 1371 (m), 1112 (s), 1056 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.14–5.80 (m, 4*H*, H-7_{trans} + H-6, major and minor), 5.71 (d, $^3J_{HH}$ = 10.6 Hz, 1*H*, H-7_{cis}, major), 5.70 (d, $^3J_{HH}$ = 10.9 Hz, 1*H*, H-7_{cis}, minor), 4.61–4.54 (m, 2*H*, H-2, major and minor), 4.20–4.08 (m, 1*H*, H-3, major), 4.08–3.99 (m, 3*H*, H-1_{a+b}, major and H-1_a, minor), 3.95 (d, $^3J_{HH}$ = 10.2 Hz, 1*H*, NH, minor), 3.78 (dd, $^2J_{HH}$ = 8.2, $^3J_{HH}$ = 6.1 Hz, 1*H*, H-1_b, minor), 3.82–3.70 (m, 1*H*, H-3, minor), 3.68 (d, $^3J_{HH}$ = 5.4 Hz, 1*H*, NH, major), 1.55 (s, 3*H*, $CH_{3,iPr}$, major), 1.45 (s, 3*H*, $CH_{3,iPr}$, minor), 1.32 (s, 6*H*, $CH_{3,iPr}$, major and minor), 1.24 (s, 9*H*, $CH_{3,tBu}$, minor), 1.22 (s, 9*H*, $CH_{3,tBu}$, major) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 126.4 (t, $^2J_{CF}$ = 24.2 Hz, C-6, minor), 126.0 (t, $^2J_{CF}$ = 24.2 Hz, C-6, major), 124.5 (t, $^3J_{CF}$ = 9.5 Hz, C-7, major), 124.3 (t, $^3J_{CF}$ = 9.5 Hz, C-7, minor), 115.9 (tt, $^1J_{CF}$ = 256.1, $^2J_{CF}$ = 36.6 Hz, CF_2, major), 115.5 (tt, $^1J_{CF}$ = 248.8, $^2J_{CF}$ = 35.1 Hz, CF_2, major), 110.1 ($C_{q,iPr}$, minor), 109.7 ($C_{q,iPr}$, major), 72.7 (C-2, minor), 72.6 (C-2, major), 66.5 (C-1, minor), 64.6 (d, $^4J_{CF}$ = 4.4 Hz, C-1, major), 58.4 (t, $^2J_{CF}$ = 23.4 Hz, C-3, minor), 57.8 (t, $^2J_{CF}$ = 21.3 Hz, C-3, major), 57.6 ($C_{q,tBu}$, minor), 56.7 ($C_{q,tBu}$, major), 26.2 ($CH_{3,iPr}$, minor), 25.8 ($CH_{3,iPr}$, major), 24.34 ($CH_{3,iPr}$, major), 24.25 ($CH_{3,iPr}$, minor), 22.5 ($CH_{3,tBu}$, minor), 22.3 ($CH_{3,tBu}$, major) ppm (2 × CF_2, minor not visible). ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.8 (dd, $^2J_{FF}$ = 279.2, *J* = 8.6 Hz, 1F, minor), −111.8 to −112.8 (m, 1F, major), −112.4 to −113.5 (m, 1F, major), −113.1 to −114.2 (m, 1F, major), −118. 7 (ddd, $^2J_{FF}$ = 279.4, *J* = 17.2, $^3J_{FF}$ = 4.4 Hz, 1F, minor), −120.1 (app. ddt, $^2J_{FF}$ = 281.5, *J* = 16.1, 7.5 Hz, 1F, major) ppm (2 × F, minor overlap with major). MS (ESI+) (*m*/*z*) 425 $(M + Na + MeCN)^+$. HRMS (MS+) for $C_{14}H_{23}F_4NNaO_3S$ $(M + Na)^+$ calcd 384.1227, found 384.1233.

4.1.1. Selected data for the MeLi S_N2' byproduct (2S,3R,S_S,Z)-1,2-isopropylidenedioxy-3-(tert-butylsulfinylamino)-4,4,5-trifluorooct-5-ene (**14**)

^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (dt, $^3J_{HF,trans}$ = 36.5, $^3J_{HH}$ = 7.6 Hz, 1*H*, H-6), 2.28–2.15 (m, 2*H*, H-7), 1.03 (t, $^3J_{HH}$ = 7.5 Hz, 3*H*, H-8) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.8 (d, $^4J_{CF}$ = 4.4 Hz, C-7), 13.1 (s, C-8) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.1 (dddt, $^2J_{FF}$ = 265.0, $^3J_{FF}$ = 14.8, *J* = 10.8, 2.2 Hz, 1F, F-4), −110.8 (app. dt, $^2J_{FF}$ = 265.0, *J* = 13.3 Hz, 1F, F-4′), −132.0 to −132.2 (m, 1F, F-5) ppm. MS (ESI +) (*m*/*z*) 358 $(M + H)^+$. HRMS (MS +) for $C_{15}H_{27}F_3NO_3S$ $(M + H)^+$ calcd 358.1658, found 358.1663. The C3 stereochemistry is assumed.

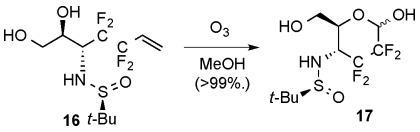
4.2. (2S,3S,S_S)-3-(tert-Butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene-1,2-diol (**15**) and (2S,3R,S_S)-3-(tert-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene-1,2-diol (**16**)



The 4:96 mixture of **12**/**13** (2.06 g, 5.70 mmol, 1 equiv) was dissolved in MeOH (60 mL). PTSA (196 mg, 1.14 mmol, 0.2 equiv) was added, and the solution stirred for 23 h, and then quenched with sat. aq. $NaHCO_3$ (30 mL). H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 120 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification *via* column chromatography (petroleum ether/acetone 70:30 to 50:50) afforded 1.607 g (5.00 mmol, 88%) of the pure major diasteroisomer **16** as a yellow syrup. R_f 0.51 (petroleum ether 40–60 °C/acetone 60:40). $[\alpha]_D$ +68.3 (c 0.204, $CHCl_3$, 25 °C). IR (neat) 3362 (m, br), 3243 (m, br), 2962 (w), 1102 (s), 1068 (s), 1039 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.12–5.83 (m, 2*H*, H-6 + H-7_{trans}), 5.73 (d, $^3J_{HH}$ = 10.6 Hz, 1*H*, H-7_{cis}), 5.57 (d, $^3J_{HH}$ = 9.5 Hz, 1*H*, NH), 4.83 (d, $^3J_{HH}$ = 10.3 Hz, 1*H*, OH-2), 4.21–4.07 (m, 1*H*, H-3), 4.07–3.91 (m, 3*H*, H-1_{a+b}, H-2), 3.48–3.35 (m, 1*H*, OH-1), 1.27 (s, 9*H*, $CH_{3,tBu}$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 126.3 (t, $^2J_{CF}$ = 24.4 Hz, C-6), 124.3 (t, $^3J_{CF}$ = 9.5 Hz, C-7), 66.1 (C-2), 65.0 (C-1), 62.8 (t, $^2J_{CF}$ = 22.6 Hz, C-3), 56.7 ($C_{q,tBu}$), 22.6 ($CH_{3,tBu}$) ppm (2 × CF_2 not visible). ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.7 (dd, $^2J_{FF}$ = 264.0, J_{HF} = 11.3 Hz, 1F), −113.9 (dd, $^2J_{FF}$ = 264.0, J_{HF} = 11.3 Hz, 1F), −118.9 (dd, $^2J_{FF}$ = 277.4, J_{HF} = 13.0 Hz, 1F), −119.7 (dd, $^2J_{FF}$ = 277.4, J_{HF} = 15.6 Hz, 1F) ppm. MS (ESI +) (*m*/*z*) 385 $(M + Na + MeCN)^+$. HRMS (MS+) for $C_{11}H_{19}F_4NNaO_3S$ $(M + Na)^+$ calcd 344.0914, found 344.0915.

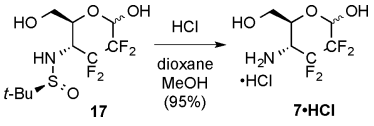
A sample was purified by HPLC to obtain the minor isomer **15** in pure form (hexane/acetone 70:30). R_f 0.31 (petroleum ether 40–60 °C/acetone 60:40). $[\alpha]_D$ −0.866 (c 0.289, $CHCl_3$, 25 °C). IR (neat) 3368 (m), 3280 (m), 1107 (s), 1053 (s), 1036 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.13–5.98 (m, 1*H*, H-6), 5.94–5.87 (m, 1*H*, H-7_{trans}), 5.74 (d, $^3J_{HH}$ = 10.9 Hz, 1*H*, H-7_{cis}), 4.36 (d, $^3J_{HH}$ = 9.0 Hz, 1*H*, NH), 4.28 (qd, *J* = 5.8, 2.9 Hz, 1*H*, H-2), 4.08–3.96 (m, 1*H*, H-3), 3.71 (dd, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 6.0 Hz, 1*H*, H-1_a), 3.65 (dd, $^2J_{HH}$ = 11.6, $^3J_{HH}$ = 6.4 Hz, 1*H*, H-1_b), 3.13 (d, $^3J_{HH}$ = 5.3 Hz, 1*H*, OH-2), 3.02 (t, $^3J_{HH}$ = 6.6 Hz, 1*H*, OH-1), 1.26 ppm (s, 9*H*, $CH_{3,tBu}$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 126.3 (t, $^2J_{CF}$ = 24.5 Hz, C-6), 124.4 (t, $^3J_{CF}$ = 9.5 Hz, C-7), 115.8 (tt, $^1J_{CF}$ = 249.6, $^2J_{CF}$ = 35.9 Hz, CF_2), 116.7 (tt, $^1J_{CF}$ = 256.1, $^2J_{CF}$ = 35.5 Hz, CF_2), 68.6 (C-2), 63.1 (C-1), 57.7 ($C_{q,tBu}$), 54.7 (t, $^2J_{CF}$ = 22.7 Hz, C-3), 22.4 ($CH_{3,tBu}$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ −110.4 (dd, $^1J_{FF}$ = 279.4, *J* = 10.7 Hz, 1F, C<u>F</u>F), −112.7 (d, *J* = 11.8 Hz, 2F, CF_2), −117.0 (dd, $^1J_{FF}$ = 279.4, *J* = 16.1 Hz, 1F, CF<u>F</u>) ppm.

*4.3. (S_S)-4-(*tert*-Butylsulfinylamino)-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-erythro-hexopyranose (**17**)*



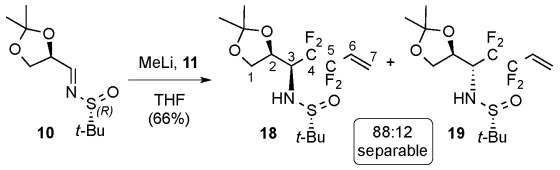
Ozone was bubbled through a solution of **16** (1.60 g, 4.98 mmol) in MeOH (50 mL) until TLC showed complete consumption of the starting material (15 min). O_2 was bubbled through to remove excess ozone (10 min) and then, Me_2S (1.83 mL, 24.9 mmol, 5 equiv) was added and the reaction mixture was allowed to warm to rt and concentrated to afford 1.56 g (4.83 mmol, 97%) of the pure aminosugar derivative **17**, which solidified as the pure β–anomer. At equilibrium in CD_3OD, a 60:40 α/β mixture of anomers is obtained. R_f 0.23 (petroleum ether 40–60 °C/acetone 60:40). $[\alpha]_D$ +97.6 (c 0.469, CH_3OH, 26 °C, at anomeric equilibrium). IR (neat) 3245 (m), 2985 (w), 1303 (m), 1151 (m), 1037 (s) cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 5.23 (dd, $^3J_{HF}$ = 7.8, 5.5 Hz, 1*H*, H-1α), 4.90 (dd, $^3J_{HF}$ = 15.5, J_{HF} = 2.9 Hz, 1*H*, H-1β), 4.29–4.18 (m, 1*H*, H-5α), 3.98–3.76 (m, 6*H*, H-4α, H-4β, 2 × H-6α, 2 × H-6β), 3.76–3.69 (m, 1*H*, H-5β), 1.26 (s, 18H, $CH_{3,tBu}$,α + $CH_{3,tBu}$,β) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ 92.9 (ddd, $^2J_{CF}$ = 26.4, $^2J_{CF}$ = 19.4, $^3J_{CF}$ = 2.6 Hz, C-1β), 92.8 (dd, $^2J_{CF}$ = 36.6, $^2J_{CF}$ = 26.3 Hz, C-1α), 75.2 (d, J_{CF} = 2.9 Hz, C-5β), 70.6 (d, J_{CF} = 4.4 Hz, C-5α), 61.4 (C-6β), 61.3 (C-6α), 59.2 (t, $^2J_{CF}$ = 18.7 Hz, C-4β), 59.0 (t, $^2J_{CF}$ = 17.6 Hz, C-4α), 58.6 (2 × $C_{q,tBu}$), 23.2 ($CH_{3,tBu}$,α), 23.2 ($CH_{3,tBu}$,β) ppm (2 × CF_2, α + β not visible). ^{19}F NMR (376 MHz, CD_3OD) δ −121.3 to −122.3 (m, 1F, Fα), −125.2 (dddd, $^2J_{FF}$ = 258.4, J = 21.7, 15.6, 6.9 Hz, 1F, Fα), −125.9 to −126.8 (m, 1F, Fα), −128.2 (dt, $^2J_{FF}$ = 259.2, J = 16.5 Hz, 1F, Fβ), −129.1 (dq, $^2J_{FF}$ = 259.2, J = 10.4 Hz, 1F, Fβ), −135.8 (ddd, $^2J_{FF}$ = 265.3, J = 15.2, 11.7 Hz, 1F, Fα), −138.5 (dt, $^2J_{FF}$ = 257.5, 12.6 Hz, 1F, Fβ), −140.8 to −141.7 (m, 1F, Fβ) ppm. MS (ESI+) (*m*/*z*) 387 (M + Na + MeCN)$^+$. HRMS (MS+) for $C_{10}H_{17}F_4NNaO_4S$ (M + Na)$^+$ calcd 346.0707, found 346.0706.

*4.4. 4-Amino-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-erythro-hexopyranose hydrochloride (**7•HCl**)*



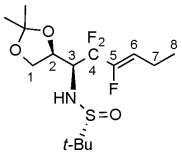
A solution of **17** (700 mg, 2.17 mmol, 1 equiv) in MeOH (1.65 mL) and 4 M HCl in dioxane (1.1 mL, 4.33 mmol, 2 equiv) was stirred at rt for 1 h then evaporated *in vacuo* to near dryness. Et_2O (10 mL) was added in order to precipitate the hydrochloride salt and the supernatant was removed. The solid was washed once more with Et_2O (10 mL) then dried under vacuum to yield 525 mg (2.05 mmol, 95%) of the **7•HCl** as a white solid consisting only of α-anomer. At equilibrium in CD_3OD, a 75:25 α/β mixture of anomers is obtained. $[\alpha]_D$ +52.7 (c 0.430, CH_3OH, 26 °C, at anomeric equilibrium). IR (neat) 3343 (m, br), 2888 (m, br), 1153 (s), 1111 (s), 1059 (s) cm^{-1}. Data for the α anomer: ^1H NMR (400 MHz, CD_3OD) δ 5.33 (dd, J_{HF} = 7.3, 4.3 Hz, 1*H*, H-1), 4.38 (dt, J = 10.3, 3.5 Hz, 1*H*, H-5), 4.07–3.93 (m, 1*H*, H-4), 3.85 (dd, $^2J_{HH}$ = 12.5, $^3J_{HH}$ = 4.3 Hz, 1*H*, H-6_a), 3.80 (dd, $^2J_{HH}$ = 12.5, $^3J_{HH}$ = 3.7 Hz, 1*H*, H-6_b) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ 117.9–108.8 (2 × CF_2), 92.6 (dd, $^2J_{CF}$ = 35.6, 26.0 Hz, C-1), 67.9 (d, J_{CF} = 2.2 Hz, C-5), 61.7 (C-6), 52.5 (t, $^2J_{CF}$ = 19.1 Hz, C-4) ppm. ^{19}F NMR (376 MHz, CD_3OD) δ −121.4 to −122.5 (m, 1F), −124.0 to −125.8 (m, 2F), −137.1 (dt, $^2J_{FF}$ = 267.6, J = 12.4 Hz, 1F) ppm. Unambiguous resonances for the β anomer: 1*H* NMR (400 MHz, CD_3OD) δ 5.06 (d, J_{HF} = 14.3 Hz, 1*H*, H-1). ^{13}C NMR (101 MHz, CD_3OD) δ 72.4 (s, C-5), 61.8 (s, C-6). ^{19}F NMR (376 MHz, CD_3OD) δ −127.8 (t, J = 12.1 Hz, 2F), −139.6 (dt, $^2J_{FF}$ = 260.1, J = 11.3 Hz, 1F), −140.8 (dd, $^2J_{FF}$ = 260.1, J = 13.9 Hz, 1F) ppm. MS (ESI+) (*m*/*z*) 261 (M + H + MeCN)$^+$. HRMS (MS+) for $C_6H_{10}F_4NO_3$ (M + H)$^+$ calcd 220.0591, found 220.0590.

*4.5. ($2S,3S,R_S$)-1,2-Isopropylidenedioxy-3-(*tert*-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene (**18**)*



To a solution of sulfinylimine **10** (0.52 g, 2.23 mmol, 1.2 equiv) in THF at −78 °C was added bromotetrafluorobutene (0.236 mL, 1.86 mmol, 1.0 equiv). After 10 min, MeLi (1.6 M in Et_2O, 2.8 mL, 4.46 mmol, 2.4 equiv) was added over 45 min and the reaction mixture was stirred for another 1.5 h. The reaction was quenched with saturated NH_4Cl aq. (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude mixture of diastereoisomers **18** and **19** (*dr* 88:12). Purification *via* column chromatography (petroleum ether/EtOAc 75:25) afforded 442 mg (1.22 mmol, 66%) of pure **18** as a white solid. R_f 0.29 (petroleum Ether 40–60 °C/EtOAc 70:30). $[\alpha]_D$ −77.6 (c 0.502, $CHCl_3$, 19 °C). IR (neat) 3347 (w), 2982 (w), 1189 (m), 1109 (s), 1073 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddd, $^3J_{HF}$ = 22.6, $^3J_{HH,trans}$ = 17.3, $^3J_{HH,cis}$ = 10.9 Hz, 1*H*, H-6), 5.90–5.81 (m, 1*H*, H-7_{trans}), 5.69 (d, $^3J_{HH,cis}$ = 10.9 Hz, 1H, H-7_{cis}), 4.54 (t, J = 6.9 Hz, 1*H*, H-2), 4.31 (d, J = 7.3 Hz, 1*H*, NH), 4.17 (app. t, J = 8.2 Hz, 1*H*, H-1_a), 4.07 (dd, $^2J_{HH}$ = 8.5, $^3J_{HH}$ = 6.7 Hz, 1*H*, H-1_b), 3.82 (td, J = 12.9, 7.6 Hz, 1*H*, H-3), 1.46 (s, 3*H*, $CH_{3,iPr}$), 1.37 (s, 3*H*, $CH_{3,iPr}$), 1.25 ppm (s, 9*H*, $CH_{3,tBu}$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 126.5 (t, $^2J_{CF}$ = 24.2 Hz, C-6), 124.0 (t, $^3J_{CF}$ = 9.5 Hz, C-7), 115.7 (tt, $^1J_{CF}$ = 256.1, $^2J_{CF}$ = 35.1 Hz, CF_2), 115.5 (tt, $^1J_{CF}$ = 250.3, $^2J_{CF}$ = 35.1 Hz, CF_2), 110.2 ($C_{q,iPr}$), 71.3 (C-5), 66.2 (C-1), 56.7 ($C_{q,tBu}$), 56.1 (t, $^2J_{CF}$ = 23.4 Hz, C-3), 26.2 ($CH_{3,iPr}$), 25.3 ($CH_{3,iPr}$), 22.6 ($CH_{3,tBu}$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.3 (dd, $^2J_{FF}$ = 265.3, J = 11.3 Hz, 1F), −113.1 (dd, $^2J_{FF}$ = 265.3, J = 11.3 Hz, 1F), −117.2 (dd, $^2J_{FF}$ = 277.4, J = 13.9 Hz, 1F), −118.3 (ddd, $^2J_{FF}$ = 277.4, J = 12.1, 3.5 Hz, 1F) ppm. MS (ESI+) (*m*/*z*) 425 (M + Na + MeCN)$^+$. HRMS (MS+) for $C_{14}H_{23}F_4NNaO_3S$ (M + Na)$^+$ calcd 384.1227, found 384.1230.

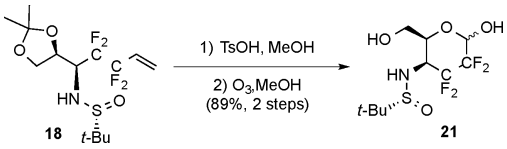
The minor isomer ($2S,3R,R_S$)-1,2-isopropylidenedioxy-3-(*tert*-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene **19** could be isolated along with the MeLi S_N2' byproduct and some unknown impurity (53 mg, 76:9:15 ratio). Selected characterization data: R_f 0.17 (petroleum ether 40–60 °C/EtOAc 70:30). ^1H NMR (400 MHz, $CDCl_3$) δ 6.14–5.98 (m, 1*H*, H-6), 5.93–5.85 (m, $^3J_{HH,trans}$ = 17.5 Hz, 1H, H-7_{trans}), 5.73 (d, $^3J_{HH,cis}$ = 10.9 Hz, 1*H*, H-7_{cis}), 4.50–4.43 (m, 1*H*, H-2), 4.24–4.12 (m, 1*H*, H-3), 3.98 (app. t, J = 7.5 Hz, 1*H*, H-1_a), 3.79 (app. t, J = 7.8 Hz, 1*H*, H-1_b), 3.73 (d, $^3J_{HH}$ = 7.6 Hz, 1*H*, NH), 1.40 (s, 3*H*, $CH_{3,iPr}$), 1.32 (s, 3*H*, $CH_{3,iPr}$), 1.24 (s, 9*H*, $CH_{3,tBu}$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 125.9 (t, $^2J_{CF}$ = 24.2 Hz, C-6), 124.9 (t, $^3J_{CF}$ = 9.5 Hz, C-7), 115.7 (tt, $^1J_{CF}$ = 256.4, $^2J_{CF}$ = 35.6 Hz, CF_2), 115.6 (tt, $^1J_{CF}$ = 249.4, $^2J_{CF}$ = 33.7 Hz, CF_2), 109.0 ($C_{q,iPr}$), 73.3 (C-2), 64.8 (C-1), 57.5 (t, $^2J_{CF}$ = 23.1 Hz, C-3), 57.0 ($C_{q,tBu}$), 26.0 ($CH_{3,iPr}$), 24.6 ($CH_{3,iPr}$), 22.5 ($CH_{3,tBu}$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.3 (m, $^2J_{FF}$ = 264.9 Hz, 1F), −113.3 (ddt, $^2J_{FF}$ = 264.9, J = 12.1, 6.5 Hz, 1F), −114.6 (ddt, $^2J_{FF}$ = 278.5, J = 12.6, 5.6 Hz, 1F), −117.4 (ddt, $^2J_{FF}$ = 278.5, J = 14.5, 6.1 Hz, 1F) ppm.



*4.5.1. Selected data for the MeLi S_N2' byproduct (2S,3S,R_S,Z)-1,2-isopropylidenedioxy-3-(*tert*-butylsulfinylamino)-4,4,5-trifluorooct-5-ene*

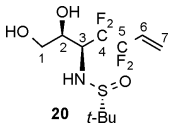
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (dt, $^3J_{HF,trans}$ = 35.9, $^3J_{HH}$ = 7.6 Hz, 1*H*, H-6), 2.28–2.15 (m, 2*H*, H-7), 1.05 (t, $^3J_{HH}$ = 7.5 Hz, 3*H*, H-8) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.7 (d, $^4J_{CF}$ = 4.0 Hz, C-7), 13.0 (C-8) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.2 (app. dt, $^2J_{FF}$ = 264.4, *J* = 13.9 Hz, 1F, F-4), −112.8 (app. dt, $^2J_{FF}$ = 264.4, *J* = 13.9 Hz, 1F, F-4′), −130.8 (app. dt, $^3J_{HF,trans}$ = 35.5, *J* = 14.7 Hz, 1F, F-3) ppm. The stereochemistry at C3 is presumed.

*4.6. (R_S)-4-(tert-Butylsulfinylamino)-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-threo-hexopyranose (**21**)*



18 **21**

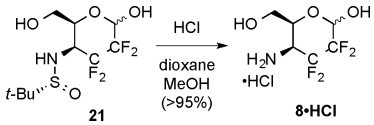
A mixture of sulfinamine **18** (435 mg, 1.20 mmol, 1 equiv) and PTSA (41 mg, 0.24 mmol, 0.2 equiv) in MeOH (10 mL) was stirred for 13.5 h then quenched with sat. aq. $NaHCO_3$ (3 mL). H_2O (12 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), filtered and concentrated to afford 383 mg of the crude product **20**. The latter was dissolved in MeOH (15 mL) and ozone was bubbled through the solution until blue colour appeared (15 min). O_2 was bubbled through to remove excess ozone (10 min) and then, Me_2S (0.44 mL, 6.0 mmol, 5 equiv) was added and the reaction mixture was allowed to warm to rt and concentrated. Purification *via* column chromatography (petroleum ether/acetone 70:30 to 60:40) afforded 348 mg (1.01 mmol, 89%) of the pure aminosugar derivative **21,** as a white solid enriched in β-anomer. At equilibrium in both acetone-d_6 and CD_3OD, a 50:50 α/β mixture of anomers was obtained. R_f 0.19 (petroleum ether 40–60 °C/acetone 60:40). $[\alpha]_D$ +20.0 (c 0.627, CH_3OH, 26 °C, at anomeric equilibrium). IR (neat) 3487 (w), 3287 (m), 2975 (w), 1041 (s), 1005 (s) cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6) δ 5.36 (dd, *J* = 9.3, 6.4 Hz, 1*H*, H-1α), 5.11 (ddd, *J* = 14.7, 3.9, 0.7 Hz, 1*H*, H-1β), 4.61–4.53 (m, 1*H*, H-5α), 4.51–4.41 (m, 2*H*, NHα, NHβ), 4.35–4.16 (m, 2*H*, 2 × OH-6), 4.16–4.03 (m, 3*H*, H-4α, H-4β, H-5β), 3.82–3.64 (m, 4*H*, 2 × H-6α, 2 × H-6β), 1.26 (s, 9*H*, tBu,β), 1.25 (s, 9*H*, tBu,α) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 93.2 (ddd, $^2J_{CF}$ = 27.1, 19.8, $^3J_{CF}$ = 3.7 Hz, C-1β), 92.7 (dd, $^2J_{CF}$ = 36.6, 26.3 Hz, C-1α), 73.6 (d, $^3J_{CF}$ = 4.4 Hz, C-5β), 68.4 (d, $^3J_{CF}$ = 2.9 Hz, C-5α), 60.5 (C-6α), 60.2 (C-6β), 59.8 (dd, $^2J_{CF}$ = 30.7, 19.0 Hz, C-4α), 59.5 (dd, $^2J_{CF}$ = 29.3, 17.6 Hz, C-4β), 57.4 ($C_{q,tBu}$,β), 57.4 ($C_{q,tBu}$,α), 22.8 (6 × $CH_{3,tBu}$,α + β) ppm (2 × CF_2, α + β not visible). ^{19}F NMR (376 MHz, CD_3OD) δ −116.6 (ddtd, $^2J_{FF}$ = 260.5, *J* = 15.2, 9.1, 2.2 Hz, Fα), −118.2 (m, $^2J_{FF}$ = 261.8 Hz, Fβ), −119.1 (dddd, $^2J_{FF}$ = 269.6, *J* = 19.5, 9.5, 9.1 Hz, Fα), −126.3 (m, $^2J_{FF}$ = 260.5 Hz, Fα), −128.9 (m, $^2J_{FF}$ = 261.8 Hz, Fβ), −134.6 (dddd, $^2J_{FF}$ = 269.6, *J* = 16.0, 11.3, 5.2 Hz, Fα), −137.4 (m, $^2J_{FF}$ = 263.1 Hz, Fβ), −138.5 (dddd, $^2J_{FF}$ = 263.1, *J* = 17.8, 14.3, 6.9 Hz, Fβ) ppm. MS (ESI+) (*m/z*) 387 (M + Na + MeCN)$^+$. HRMS (MS+) for $C_{10}H_{17}F_4NNaO_4S$ (M + Na)$^+$ calcd 346.0707, found 346.0713.



20

Analytical sample of the pure diol (2*S*,3*S*,R_S)-3-(*tert*-butylsulfinylamino)-4,4,5,5-tetrafluorohept-6-ene-1,2-diol (**20**) was obtained by column chromatography (petroleum ether 40–60 °C/acetone 70:30). R_f 0.25 (petroleum ether 40–60 °C/acetone 60:40). $[\alpha]_D$ −44.8 (c 0.532, $CHCl_3$, 21 °C). IR (neat) 3299 (m), 2963 (w), 1237 (m), 1116 (s), 1028 (s) cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.19–6.03 (m, 1*H*, H-6), 5.87 (dt, $^3J_{HH,trans}$ = 17.3, $^4J_{HF}$ = 2.3 Hz, 1*H*, H-7$_{trans}$), 5.77 (d, $^3J_{HH,cis}$ = 11.1 Hz, 1*H*, H-7$_{cis}$), 4.15 (dd, $^3J_{HH}$ = 8.5, 5.9 Hz, 1*H*, H-2), 4.03 (t, $^3J_{HF}$ = 13.6 Hz, 1*H*, H-3), 3.62 (dd, $^2J_{HH}$ = 10.9, $^3J_{HH}$ = 8.5 Hz, 1*H*, H-1$_a$), 3.54 (dd, $^2J_{HH}$ = 10.9, $^3J_{HH}$ = 5.9 Hz, 1*H*, H-1$_b$), 1.26 (s, 9*H*). ^{13}C NMR (101 MHz, CD_3OD) δ 128.5 (t, $^2J_{CF}$ = 24.2 Hz, C-6), 124.8 (t, $^3J_{CF}$ = 9.5 Hz, C-7), 118.1 (tt, $^1J_{CF}$ = 255.4, $^2J_{CF}$ = 33.7 Hz, CF_2), 117.2 (tt, $^1J_{CF}$ = 248.8, $^2J_{CF}$ = 34.4 Hz, CF_2), 68.4 (C-2), 63.2 (C-1), 58.6 (t, $^2J_{CF}$ = 22.7 Hz, C-3), 58.3 ($C_{q,tBu}$), 23.1 ($CH_{3,tBu}$) ppm. ^{19}F NMR (282 MHz, CD_3OD) δ −112.8 (dd, $^2J_{FF}$ = 265.7, 11.8 Hz, 1F), −113.8 (dd, $^2J_{FF}$ = 265.7, 10.7 Hz, 1F), −117.2 (dd, $^2J_{FF}$ = 274.0, 14.0 Hz, 1F), −119.3 (dd, $^2J_{FF}$ = 274.0, 12.9 Hz, 1F) ppm. MS (ESI +) (*m/z*) 385 (M + Na + MeCN)$^+$. HRMS (MS+) for $C_{11}H_{19}F_4NNaO_3S$ (M + Na)$^+$ calcd 344.0914, found 344.0909.

*4.7. 4-Amino-2,3,4-trideoxy-2,2,3,3-tetrafluoro-D-threo-hexopyranose hydrochloride (**8•HCl**)*



21 **8•HCl**

A solution of sulfinamide **21** (190 mg, 0.588 mmol, 1 equiv) in MeOH (1.2 mL) and 4 M HCl in dioxane (0.60 mL, 2.35 mmol, 4 equiv) was stirred at rt for 0.5 h then evaporated *in vacuo*. The residue was coevaporated with MeOH (10 × 20 mL) then diluted in H_2O (15 mL), washed with Et_2O (2 × 5 mL) and concentrated to afford 153 mg of the amine hydrochloride **8•HCl** along with less than 3% of impurities as a colourless oil. Anomeric ratio at equilibrium in CD_3OD: 54:46 α/β. Approximated yield >95%. IR (neat) 3210 (m, br), 2886 (m), 1526 (m), 1109 (s), 1029 (s) cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 5.39 (dd, *J* = 8.5, 7.1 Hz, 1*H*, H-1α), 5.12 (dd, *J* = 15.0, 3.1 Hz, 1*H*, H-1β), 4.66–4.57 (m, 1*H*, H-5α), 4.34–4.20 (m, 2*H*, H-4α, H-4β), 4.19–4.10 (m, 1*H*, H-5β), 3.96–3.71 ppm (m, 4*H*, 2 × H-6α, 2 × H-6β) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ 117.5–108.7 (2 × CF_2, α + β), 93.5 (ddd, $^2J_{CF}$ = 26.4, 19.0, $^3J_{CF}$ = 3.4 Hz, C-1β), 92.9 (dd, $^2J_{CF}$ = 36.7, 24.9 Hz, C-1α), 72.0 (d, J_{CF} = 4.4 Hz, C-5β), 66.7 (d, J_{CF} = 3.7 Hz, C-5α), 60.9 (C-6α), 60.7 (C-6β), 54.3 (dd, $^2J_{CF}$ = 33.4, 19.4 Hz, C-4α), 53.9 (dd, $^2J_{CF}$ = 32.6, 19.4 Hz, C-4β) ppm. ^{19}F NMR (376 MHz, CD_3OD) δ −116.9 (app. ddt, $^2J_{FF}$ = 274.0, *J* = 15.9, 9.2, Hz, Fα), −118.1 to −118.9 (m, Fβ), −119.5 (ddt, $^2J_{FF}$ = 273.8, $^3J_{FF}$ = 17.5, $^3J_{FF}$ = 8.7, J_{HF} = 8.7 Hz, Fα), −125.3 to −126.3 (m, Fα), −127.8 to −128.7 (m, Fβ), −136.0 (dddd, $^2J_{FF}$ = 273.8, $^3J_{FF}$ = 16.2, $^3J_{FF}$ = 10.3, J_{HF} = 4.2 Hz, Fα), −137.9 (app. dtd, $^2J_{FF}$ = 267.5, *J* = 15.4, 6.6 Hz, Fβ), −139.2 (m, $^2J_{FF}$ = 267.5 Hz, Fβ) ppm. {^{1}H} ^{19}F NMR (376 MHz, CD_3OD) δ −116.8 (ddd, $^2J_{FF}$ = 274.0, $^3J_{FF}$ = 16.1, $^3J_{FF}$ = 8.6 Hz, Fα), −118.5 (ddd, $^2J_{FF}$ = 275.0, $^3J_{FF}$ = 13.4, $^3J_{FF}$ = 6.4 Hz, Fβ), −119.4 (ddd, $^2J_{FF}$ = 273.9, $^3J_{FF}$ = 17.3, $^3J_{FF}$ = 8.5 Hz, Fα), −125.8 (ddd, $^2J_{FF}$ = 274.0, $^3J_{FF}$ = 17.3, $^3J_{FF}$ = 10.3 Hz, Fα), −128.3 (ddd, $^2J_{FF}$ = 275.2, $^3J_{FF}$ = 15.6, $^3J_{FF}$ = 10.5 Hz, Fβ), −136.0 (ddd, $^2J_{FF}$ = 273.8, $^3J_{FF}$ = 16.1, $^3J_{FF}$ = 10.3 Hz, Fα), −138.3 to −137.5 (m, Fβ), −139.2 (ddd, $^2J_{FF}$ = 267.5, $^3J_{FF}$ = 13.4, $^3J_{FF}$ = 10.5 Hz, Fβ) ppm. MS

(ESI+) (m/z) 220 $(M + H)^+$. HRMS (MS+) for $C_6H_{10}F_4NO_3$ $(M + H)^+$ calcd 220.0591, found 220.0596.

Acknowledgements

The European Community (INTERREG IVa Channel Programme, IS:CE-Chem, project 4061) is thanked for financial support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.07.015.

References

[1] (a) C.P. Glaudemans, J. Chem. Rev. 91 (1991) 25–33;
(b) R.U. Lemieux, Chem. Soc. Rev. 18 (1989) 347–374.
[2] (a) J.-H. Kim, R. Resende, T. Wennekes, H.-M. Chen, N. Bance, S. Buchini, A.G. Watts, P. Pilling, V.A. Streltsov, M. Petric, R. Liggins, S. Barrett, J.L. McKimm-Breschkin, M. Niikura, S.G. Withers, Science 340 (2013) 71–75;
(b) D. Vocadlo, G.J. Davies, R. Laine, S.G. Withers, Nature 421 (2001) 835–838;
(c) Reviews: D.L. Zechel, S.G. Withers, Acc. Chem. Res. 33 (2000) 11–18;
(d) R. Pongdee, H.-W. Liu, Bioorg. Chem. 32 (2004) 393–437.
[3] S. Wagner, C. Mersch, A. Hoffmann-Röder, Chem. Eur. J. 16 (2010) 7319–7330.
[4] (a) Reviews: Y. Cheng, A.-L. Guo, D.-S. Guo, Curr. Org. Chem. 14 (2010) 977–999;
(b) M. Hein, R. Miethchen, Adv. Org. Synth. 2 (2006) 381–429;
(c) R. Miethchen, J. Fluorine Chem. 125 (2004) 895–901;
(d) K. Dax, M. Albert, J. Ortner, B.J. Paul, Carbohydr. Res. 327 (2000) 47–86;
(e) K. Dax, M. Albert, J. Ortner, B.J. Paul, Curr. Org. Chem. 3 (1999) 287–307;
(f) T. Tsuchiya, Adv. Carbohydr. Chem. Biochem. 48 (1990) 91–277;
(g) P.J. Card, J. Carbohydr. Chem. 4 (1985) 451–487;
(h) A.A.E. Penglis, Adv. Carbohydr. Chem. Biochem. 38 (1981) 195–285.
[5] J. Graton, Z. Wang, A.-M. Brossard, D. Goncalves Monteiro, J.-Y. Le Questel, B. Linclau, Angew. Chem. Int. Ed. 51 (2012) 6176–6180.
[6] C. Laurence, K.A. Brameld, J. Graton, J.-Y. Le Questel, E. Renault, J. Med. Chem. 52 (2009) 4073–4086.
[7] (a) A. Bernardi, J. Jiménez-Barbero, A. Casnati, C. De Castro, T. Darbre, F. Fieschi, J. Finne, H. Funken, K.-E. Jaeger, M. Lahmann, T.K. Lindhorst, M. Marradi, P. Messner, A. Molinaro, P.V. Murphy, C. Nativi, S. Oscarson, S. Penadés, F. Peri, R.J. Pieters, O. Renaudet, J.-L. Reymond, B. Richichi, J. Rojo, F. Sansone, C. Schäffer, W.B. Turnbull, T. Velasco-Torrijos, S. Vidal, S. Vincent, T. Wennekes, H. Zuilhof, A. Imberty, Chem. Soc. Rev. 42 (2013) 4709–4727;
(b) B. Ernst, J.L. Magnani, Nat. Rev. Drug Discovery 8 (2009) 661–677;
(c) D.C. Koester, A. Holkenbrink, D.B. Werz, Synthesis (2010) 3217–3242;
(d) P. Sears, C.-H. Wong, Angew. Chem. Int. Ed. 38 (1999) 2300–2324.
[8] (a) V.H. Dalvi, P.J. Rossky, Proc. Nat. Acad. Sci. U.S.A. 107 (2010) 13603–13607;
(b) J. Mecinovic, P.W. Snyder, K.A. Mirica, S. Bai, E.T. Mack, R.L. Kwant, D.T. Moustakas, A. Heroux, G.M. Whitesides, J. Am. Chem. Soc. 133 (2011) 14017–14026.
[9] (a) K. Müller, C. Faeh, F. Diederich, Science 317 (2007) 1881–1886;
(b) M. Zürcher, F. Diederich, J. Org. Chem. 73 (2008) 4345–4361.
[10] (a) H.W. Kim, P. Rossi, R.K. Schoemaker, S.G. DiMagno, J. Am. Chem. Soc. 120 (1998) 9082–9083;
(b) J.C. Biffinger, H.W. Kim, S.G. DiMagno, ChemBioChem 5 (2004) 622–627.
[11] R.S. Timofte, B. Linclau, Org. Lett. 10 (2008) 3673–3676.
[12] (a) B. Linclau, S. Golten, M. Light, M. Sebban, H. Oulyadi, Carbohydr. Res. 346 (2011) 1129–1139;
(b) B. Linclau, S. Golten, M. Light, J. Carbohydrate Chem. 60 (2011) 618–625.
[13] A. Ioannou, E. Cini, R.S. Timofte, S.L. Flitsch, N.J. Turner, B. Linclau, Chem. Commun. 47 (2011) 11228–11230.
[14] I. N'Go, S. Golten, A. Arda, J. Canada, J. Jimenez-Barbero, B. Linclau, S. Vincent, Chem. Eur. J. 20 (2014) 106–112.
[15] (a) Reviews: F. Pfrengle, H.-U. Reissig, Chem. Soc. Rev. 39 (2010) 549–557;
(b) R. Rai, I. McAlexander, C.-W.T. Chang, Org. Prep. Proc. Int. 37 (2005) 337–375.
[16] (a) Examples: C. Albler, W. Schmid, Eur. J. Org. Chem. (2014) 2451–2459;
(b) E. Poirot, A.H.C. Chang, D. Horton, P. Kovac, Carbohydr. Res. 334 (2001) 195–205.
[17] M.T. Robak, M.A. Herbage, J.A. Ellman, Chem. Rev. 110 (2010) 3600–3740; Review:
[18] (a) Examples: A.W. Buesking, T.D. Baguley, J.A. Ellman, Org. Lett. 13 (2011) 964–967;
(b) C.Q. Fontenelle, M. Conroy, M. Light, T. Poisson, X. Pannecoucke, B. Linclau, J. Org. Chem. 79 (2014) 4186–4195.
[19] T. Konno, S. Takano, Y. Takahashi, H. Konishi, Y. Tanaka, T. Ishihara, Synthesis (2011) 33–44.
[20] T. Konno, T. Hoshino, T. Kida, S. Takano, T. Ishihara, J. Fluorine Chem. 152 (2013) 106–113.
[21] M. Bergeron, T. Johnson, J.-F. Paquin, Angew. Chem. Int. Ed. 50 (2011) 11112–11116.
[22] V. Wray, J. Chem. Soc., Perkin Trans. 2 (1976) 1598–1605.
[23] (a) D.A. Evans, S.J. Siska, V.J. Cee, Angew. Chem. Int. Ed. 42 (2003) 1761–1765;
(b) V.J. Cee, C.J. Cramer, D.A. Evans, J. Am. Chem. Soc. 128 (2006) 2920–2930.
[24] (a) M. Cherest, H. Felkin, N. Prudent, Tetrahedron Lett. 9 (1968) 2199–2204;
(b) N.T. Anh, O. Eisenstein, Nouv. J. Chim. 1 (1977) 61–70.