University of Southampton
School of Chemistry
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The Enantioselective Synthesis of 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Galactose and 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Glucose

Roxana Sidonia Timofte

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

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THE ENANTIOSELECTIVE SYNTHESIS OF 2,3-DIDEOXY-2,2,3,3-TETRAFLUORO-GALACTOSE AND 2,3-DIDEOXY-2,2,3,3-TETRAFLUORO-GLUCOSE

By Roxana Sidonia Timofte

Protein-carbohydrate interactions are at the basis of cell-cell and cell-external agent interactions and therefore play a major role in the biological events in the body. However, protein-carbohydrate interactions are characterized by low binding constants and the scientific community is searching for methods for increasing the rate of binding of carbohydrates to proteins. One proposed method for increasing the binding in protein-carbohydrate interactions is the fluorination of carbohydrates. Pioneering work of DiMagno, who synthesized a racemic hexafluorinated hexose and tested its capacity of trasmembrane transport, has shown that the haxafluorinated hexose crosses the erythrocyte membrane ten fold faster than glucose. It was postulated that this is because of the enhanced affinity in the protein-carbohydrate interactions, instilled by the increased hydrophobicity of the carbohydrate. This thesis describes the successful enantioselective synthesis of 2,3-dideoxy-2,2,3,3-tetrafluoro -galactose and 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose and a preliminary investigation of the glycosylation of 2,3-dideoxy-2,2,3,3-tetrafluoro-galactose. A tetrafluorinated building block approach was considered for the synthesis of 2,3-dideoxy-2,2,3,3-tetarfluoro-galactose and 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose. Key steps in the synthesis of galactose and glucose were the β- and α-SAD reactions for the formation of the respective diols and also for introducing the enantioselctivity in the synthesis. The pentose rings were formed by the anionic cyclization reactions, methodology which was previously developed in our group. The glycosylation was achieved via an anomeric alkylation strategy.

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Abbreviations

α	Alpha
Å	Armstrong
Ac	Acetyl
AD	Asymmetric Dihydroxylation
Alk	Alkaloid
All	Allyl
app	Apparent
aq	Aqueous
AQN	Antraquinone linker
18-C-6	18-Crown-6 (1,4,7.10,13,16-hexaoxacyclooctadecane)
β	Beta
Bn	Benzyl
Bz	Benzoyl
CA	Cinchona Alkaloid
CE	Crown Ether
CI	Chemical Ionization
COSY	Correlated Spectroscopy
Cp	Cyclopentadienyl
CRD	Carbohydrate Recognition Domain
d	Doublet
DAST	(Diethylamino)sulfur trifluoride
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-5-ene
DCC	N,N'-dicyclohexylcarbodiimide
DEPT	Distortionless Enhancement by Polarization Transfer
DHQ	Dihydroquinine
DHQD	Dihydroquinidine

DIAD	Diisopropyl azodicarbohylate
DIC	Diisopropylcarbodiimide
DIPCl	B-chlorodiisopinocampheylborane
DMAP	4-(Dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DPP	Diphenyl pyrazinopyridazine linker
EDCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EI	Electron Impact
equiv	Equivalent
ES	Electrospray
Et	Ethyl
Fmoc	9-Fluorenylmethoxycarbonyl
g	Gram
h	Hour
HMBC	Heteronuclear Multiple Bond Connectivity
HMQC	Heteronuclear Multiple Quantum Connectivity
HPLC	High Performance Liquid Chromatography
HR	High Resolution
Hz	Hertz
IPA	2-Propoanol
IR	Infra Red
J	Coupling constant
L	Ligand
LR	Low Resolution
m	Multiplet
M	Molar
Me	Methyl
mg	Miligram
mL	Mililiter

mmol	Milimole
mp	Melting point
MS	Mass Spectrometry
Ms	Methanesulfonyl
MW	Molecular Weight
NaHMDS	Sodium hexamethyldisilane
NE	North-Est
NMO	4-methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
NW	North-West
p	Para
PC	Protein-Carbohydrate
PHAL	Phthalazine linker
PMB	*p*-Methoxybenzyl
Py	Pyridine
PYR	Diphenylpyrimidine linker
q	Quartet
rac	Racemic
R_f	Retention factor
RT	Room Temperature
s	Singlet
SAD	Sharpless Asymmetric Dihydroxylation
SE	South-Est
SET	Single Electron Transfer
SW	South-West
T	Temperature
t	Time, triplet
TBAB	Tetrabuthyl ammonium bromide
TBAF	Tetrabuthyl ammonium fluoride
TBAI	Tetrabuthyl ammonium iodide
^{t}Bu	Tertiary butyl
Tf	Trifluoromethanesulfonyl

THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMSOTf	Trimethylsilyl triflate
Ts	Tosyl (*p*-toluenesulfonyl)

Chapter 1. Introduction

1.1. Protein-Carbohydrate Interactions

1.1.1. Introduction

Protein-carbohydrate interactions (PC interactions) are at the basis of cell-cell and cell-external agent recognition.[1,2,3] Hence, the biological action of carbohydrate-containing drugs is based on PC interactions. The formation of PC complexes often forms the initial step in a cascade of further receptor –ligand interactions, leading to biological events.[2] Favourable stereospecific interactions occur between the hydroxyl groups of the carbohydrate (and the ring oxygen) and the amino acid functionalities of the proteins. The active sites of proteins in protein-carbohydrate interactions are called *CRD*(s) (*carbohydrate recognition domain*).[2] The active hydroxyls in the PC interactions form the *epitope* and they are usually from different carbohydrate units.[4] Protein-carbohydrate interactions are mediated by hydrogen bonds, hydrophobic interactions, metal coordination, van der Waals forces, dipole-dipole, ionic, π-π interactions, lipophilicity and shape complementarity.[5,6]

Metal coordination arises between vicinal hydroxyl groups on the sugar and Ca^{2+} or Mg^{2+}. *Ionic interactions* are observed in the complexation of proteins or nucleic acids with charged or derivatized sugars.[5] The relative contribution of each of these factors is still poorly known, although the binding must be based on the interplay amongst them. Hydrogen-bonding and hydrophobic interactions are the predominant factors in binding.

1.1.2. Hydrogen-Bonding

Hydrogen-bonds usually occur between the carbonyl groups and the NH groups of the protein backbone and the sugar hydroxyl groups.[5] Not all hydroxyl groups present in a carbohydrate unit are active in binding: few OH groups make H-bonding with the protein being H donors (those are the key polar groups);[7] fewer OH groups are H-bonded to the periphery of the binding site and they act as H acceptors and the remaining ones stay in full

contact with water. *"Cooperative" H- bonds* are those resulting from the simultaneous participation of a sugar hydroxyl as donor and acceptor of H-bonds.[8,9] When each of two adjacent hydroxyls of the same carbohydrate unit interacts with different atoms of the same amino acid, they form *bidentate H-bonds.*[8,9]

Approaches towards quantifying the contribution of H-bonding in ligand-receptor interactions were reported.[6] It was determined that a neutral-neutral H-bond leads to a 2- to 15-fold increase in affinity and that a charged H-bond leads to up to a 3000-fold increase in affinity.[6]

1.1.3. Hydrophobic Interactions

Hydrophobic interactions could be defined as the "tendency of relatively apolar molecules to stick together in aqueous solution".[10] Hydrophobic interactions could occur between the hydrophobic parts of the protein and the carbohydrate. Although sugars are highly polar molecules, the steric disposition of the hydroxyl groups leads to the formation of hydrophobic patches on their surfaces.[5]

Davis and Teague[6] reviewed the role of the hydrogen-bonds and hydrophobic interactions in PC interactions. They examined a database of modified substrates, with the hydrophobic patch increased through appending of a hydrocarbon moiety or of hydrophobic atoms. They concluded that the hydrophobic interactions contribute a minimum of 3.2-fold increase in binding per Me group. In some cases, where the complementarity between the drug's hydrophobic surface and the receptor is particularly high, the contribution can be greater than this.[6]

Whitesides *et al.*[11] have demonstrated that the hydrophobic surface area, rather than details of the structure of the hydrophobic group, is the dominant factor in determining the strength of hydrophobic binding. He revealed that for a given class of compounds, binding constants of hydrocarbons and fluorocarbons having the same surface area are very similar. Fluorocarbons seem to be more hydrophobic than hydrocarbons of the same carbon number because they have larger areas of hydrophobic surface. After the correction of the

differences in the surface area, the hydrophobicity of hydrocarbon and fluorocarbon surfaces is similar.

1.1.4. Affinity and Selectivity in PC Interactions

It is believed that hydrophobic interactions constitute the major driving force for association and that the formation of hydrogen-bonds provide the specificity.[12] The reason for the high selectivity provided by the formation of H-bonds in PC interactions is of energetic origin. The H- bonds are highly directional and hence, only those carbohydrates that perfectly fit in the active site will generate enough compensation to offset the desolvation energy.[13]

Davis and Teague[6] reported that increased affinity has been observed in analogues where hydrophobic interactions have been optimised, even at the expense of the possible hydrogen bonds. However, the hydrophobic interactions are not selective.

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1.1.5. Role of Water in PC Interactions

Protein-carbohydrate binding events are complicated by the highly participatory nature of water.[4,7,13]

The *hydrophilic carbohydrates* are extensively hydrated in aqueous solution and desolvation is required before binding to the receptor. Similarly, the bonded water in the receptor has to be removed. Together, this constitutes an energetic penalty and this is thought to be the reason for the low binding constants associated with the PC interactions. The energetic compensation is partly provided by the establishment of interactions between the carbohydrate and the receptor and between the released water and the bulk water. The increase in entropy also provides energetic compensation.[4,7,13] Therefore, the binding energy expressed results partially from enthalpic differences due to different H-bond geometries but mainly from the increase in entropy associated with water release from the active site and the ligand into bulk water.[12] It can be concluded that if all desolvation interactions are replaced upon binding, it is the energy achieved during desolvation which

drives the formation of the complex. In their studies towards the understanding of the energetics of protein-carbohydrate binding in water, Toone *et al.*[14] suggested that 25-100% of the net measured enthalpy of binding is accounted for by solvent reorganization.

Hydrophobic hydration is a high-energy situation, due to the tendency of the water molecules to "order" around the hydrophobic part of the solute.[15] In this case, the desolvation is entropically more favourable than desolvation of the hydrophilic carbohydrates. Hence, it can be hypothesised that the PC interactions are energetically more favourable in the case of the carbohydrates with increased hydrophobic area. Thus, one strategy to increase the binding affinities in PC interactions is to increase the hydrophobic area of the carbohydrates.

1.2. Effects of Fluorine Substitution on Biological Activity

Amazingly, the most abundant halogen in the earth's crust, fluorine, has been identified as a component of only 13 products found in Nature.[16] The exploitation of fluorinated compounds as drugs lie on the physical-chemistry changes and biological activity impairing caused by the fluorine atom.[17] These effects can be direct by the interaction of fluorine with the protein or can be indirect by the modulation of the activity of other groups which interact with the protein. The effects of fluorine substitution on biological activity are caused by many factors such as the alteration in affinity, pKa, liphophilicity, bioavailability and metabolic stability.[18]

Fluorination always increases hydrogen bond acidity of the adjacent groups and consequently, their H bond donating capability. This, together with the increase of the hydrophobic path of the molecule, leads to an increase in affinity. It is known that strong basic compounds have a limited ability to pass through membranes. Hence, it can be considered that the decrease of basicity caused by the electron withdrawing capability of fluorine results in increased bioavailability.[18] Quite often, a change in the pKa of a molecule has an effect on both affinity for binding and bioavailability.[18] Fluorination usually increases liphophilicity[19] and this results in an increased (but non-specific) affinity

for the protein[18] and increased bioavaialability.[20] Lipophilicity also controls absorption, transport and receptor binding.[21]

Metabolic stability is one of the most important factors in determining the bioavailability of a compound. Rapid oxidative metabolism by the liver enzymes is often found to limit the bioavailability. A commonly used strategy to surmount this problem is to block the reactive site by the introduction of a fluorine atom.[18] The strong C-F bond (116 kcal/mol) has an increased oxidative and thermal stability compared with the carbon-hydrogen bond (C-H=99 kcal/mol).[22]
Hydrolytic metabolism could be impaired as well, because of the destabilisation of cationic species by the electron withdrawing character of the fluorinated group.[23]

Fluorine substitution could result in a change in chemical reactivity because of the electron withdrawing character of fluorine or because of a possible loss of fluoride anion or HF. This could lead to a modification of the course of reactions in biological process.[17,24]

Examples of the fluorine –containing molecules with altered biological activity can be found in reviews.[25]

1.3. Fluorine as Substitution for the Ring-Hydroxyl in Carbohydrates

1.3.1. Deoxyfluoro Sugars

Just one fluorine-containing carbohydrate derivative has been isolated from an organism-the 4'-fluoro-5'-O-sulfamoyladenoside (Figure 1.1).[26]

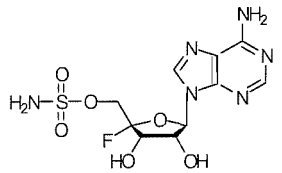


Figure 1.1

However, numerous man-made fluorinated sugars are synthesized, especially because of their utility for biological purposes. There are three types of ring-containing fluorine carbohydrates: glycosyl fluorides, [26,27] gem-difluorocarba-sugars[26,28] and deoxyfluoro-sugars.[26,29] Glycosyl fluorides are used as modern glycosyl donors, because of the good combination of their
stability and reactivity.[21] Gem-difluorocarba-sugars are synthesized in the light of their utilization for probing the role of endocyclic oxygen atoms of carbohydrates in PC interactions.[28] Considerable efforts has been expanded in the recent years in the synthesis of deoxyfluoro-sugars, especially for the synthesis of 2-deoxy-fluoro- and 2-dideoxy-2,2-difluoro-carbohydrates.[26,29] The interest in such analogues lies on their use as probes of enzyme active sites, as tools for probing the biosynthesis of glycoproteins, as *in vivo* imaging agents for carbohydrate metabolism and carriers of ^{18}F for positron emission topographic (PET) studies.[30] Also, fluorine-containing nucleosides and ^{18}F-labelled carbohydrates play important roles in medical applications including studies of pathophysiological processes.[21]

Furthermore, the presence of one or two fluorine atoms close to the anomeric centre make the oxocarbenium ion intermediates unstable, making hydrolytic reactions of fluorinated glycosides more difficult[11] and resulting in useful inhibition of glycosydases and glycosyltransferases. This makes the deoxyfluoro-carbohydrates very useful in identifying key interactions between the receptors and saccharide ligands.[31] For example, Withers *et al.*[32] has used 2-deoxy-2,2-difluorosugar derivatives (for example, the molecule depicted in Figure 1.2) to identify the active site of an α-glycosidase enzyme.

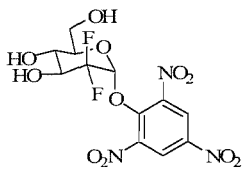


Figure 1.2

Lately, research centered on the utilisation of fluorinated carbohydrates as potential enhancers of affinity in PC interactions. The reasons for the potential affinity enhancement of fluorinated sugars are as follows:

- Increased hydrophobic path and therefore increased possibility of hydrophobic interactions (Section 1.1.3.);
- PC interactions are energetically more favourable in the case of carbohydrates with increased hydrophobic paths than in the case of hydrophilic carbohydrates (Section 1.1.5.);
- The possibility of dipole-dipole interaction (Section 1.3.4.) and H-bonding (Section 1.3.3.);
- Changes in bioavailability, metabolic stability, liphophilicity and pKa of the molecule (Section 1.2.).

1.3.2. Steric Size of Fluorine

From the steric point of view, fluorine is the smallest element after hydrogen. Fluorine can mimic a hydrogen atom or a hydroxyl group in a bioactive compound with respect to the steric requirements at the receptor site.[22] However, the length of C-F bond (1.35 Å) is more similar to that of a hydroxyl group (1.43 Å) and to that of a C=O group (1.23 Å) (Table 1.1).[15a]

Element X	Bond Length (CH_2X, Å)	Van der Waals radius (Å)
C-H	1.09	1.20
C-F	1.35	1.47
C-OH	1.43	1.52
C=O	1.23	1.50

Table 1.1

DiMagno stated that on purely steric grounds, the gem-difluoro group should be superior to CFH as a substituent for CHOH. Although the angular orientation is slightly different, the spatial extent of the two groups is very similar (Figure 1.3).[15]

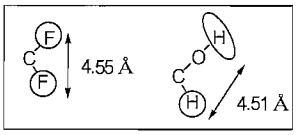


Figure 1.3

1.3.3. The Hydrogen-Bond Accepting Capability of Fluorine

Fluorine cannot possibly act as a hydrogen-bond donor but can indeed act as a weak acceptor, as has been suggested by X-ray data.[33] It must be specified that the F···H interaction could be observed only in structures which lack other heteroatoms which could compete for the H -bond, *i.e.* in the gas and solid phase.[19,15] The gas-phase data indicate that C-F dipolar interactions can be significant when competing heteroatoms are absent.[15a] From the crystallographic data of the compounds containing C-F bonds, it was concluded that the C-F···H bond could form in solid state only in structures with an excess of proton donors over acceptors.[15a] The H-bonding of C-F dipoles is generally not observed in solvents which can compete for the H-bond (*i.e.* alcohols, amines and water).[15a] However, it was reported that when the C-F···H is formed, the strength of F···H bond (1.9 Å) is 2.38 kcal/mol, much weaker than the corresponding O···H bond (5 kcal/mol).[17] The reason for the low accepting H-bond accepting capability of C-F bonds is that the high electronegativity of fluorine favours bonding, but since the electrons to be shared are held tightly to the fluorine nucleus, the resultant hydrogen bonds are weak.[34] The C-F···H-C is the preponderant F···H interaction; although not very common,[34] discrete C-F···H-O and C-F···H-N bonds were reported.

A rationale for the possible alteration of the affinity of fluorine-containing carbohydrates in PC interactions as a consequence of different H-bonding capability of C-F bond was done by Withers *et al.*and is as follows.[12] If the enzyme donates an H bond to the sugar, then F

can accept that bond and the affinity should not be lost. If the enzyme normally accepts a hydrogen bond at that position, thus cannot interact favourably with the carbohydrate and the affinity is altered substantially.[12]

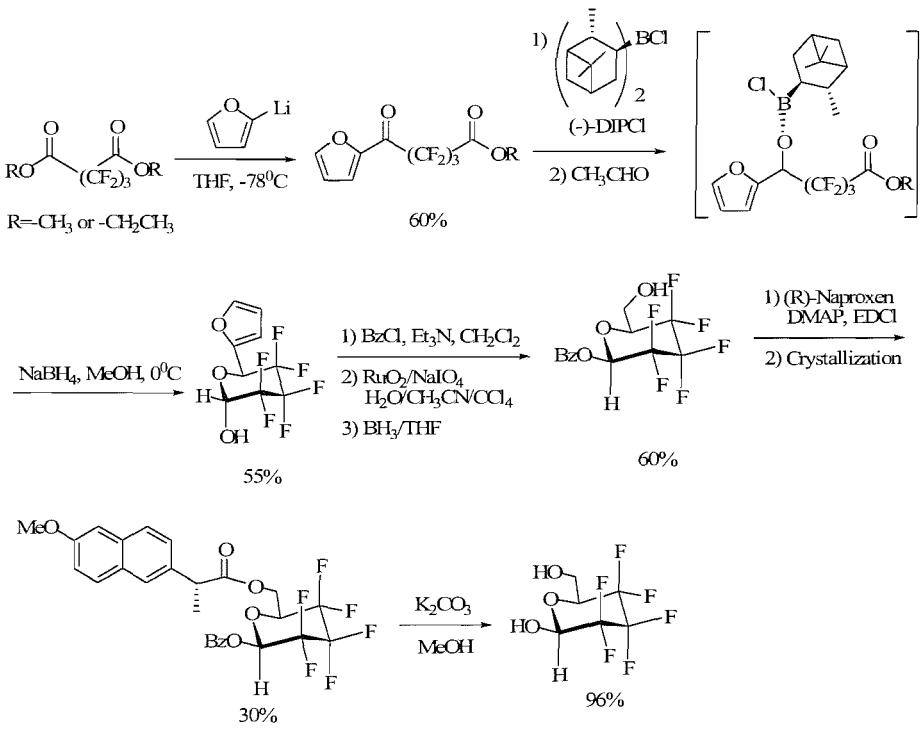
1.3.4. The "Polar Hydrophobicity" Concept [15a]

DiMagno *et. al.* introduced the "polar hydrophobicity" concept.[15a] The following characteristics instilled by the fluorine substitution in a molecule are supporting the "polar hydrophobicity" concept:

a) the increase of the hydrophobic patch of a molecule by fluorination and the subsequent increase of the affinity and of the binding energy of the carbohydrate-containing fluorine in PC interactions;
b) the capacity of C-F bonds to accept H-bonds in systems where competition for the H-bonds is not possible;
c) the capacity to engage in dipole-dipole interactions, in spite of the low polarizability of C-F bond.

Nevertheless, DiMagno's concept is based especially on the following to points: "1) the energies of electrostatic interactions of the C-F bond dipole with positive ions or dipoles can be substantial in appropriately organised systems, and 2) these same interactions are of minimal importance in polar heteroatom solvents".[15a]

In order to support and empirically test the "polar hydrophobicity" theory, DiMagno *et al.* synthesized a hexafluorinated hexose (Scheme 1.1). Since the hydrophobic effect is cooperative, DiMagno has chosen to synthesise a polyfluorinated carbohydrate.[15]



Scheme 1.1

Transport studies of 1-, 2-, 3-, 4-, and 6-monodeoxyfluoro-D-glucose across the RBC (Red Blood Cell) membrane have been performed to probe the binding for transmembrane transport.[15a] It was reported that the 2- and 3-deoxy-fluoro-derivatives cross the erythrocyte membrane at rates very similar to that of glucose, while the values for the 4- and 6-fluorinated derivatives are approximatively halved.[15a] Alteration of a single hydroxyl group on the ring has major effect; for example, galactose is transported tenfold slower than glucose.[15a] It can be concluded that the active site is sterically discriminating and different affinities could be observed even in the case of epimeric or regioisomeric sugars of fluorinated sugars.

The transmembrane transport studies of DiMagno's hexafluorinated hexose have shown that the racemic hexafluorinated hexose crosses the erythrocyte membrane ten times the rate glucose itself and it is postulated that this is because of the increased protein-carbohydrate affinity through enhanced polar hydrophobicity.
However, the results are not absolute and further investigation in this field is required.

1.4. Aims of the Project

1.4.1. 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Carbohydrates

The synthesis of polyfluorinated carbohydrates is not very common. Apart from DiMagno's hexafluorinated hexose, the only polyfluorinated carbohydrate published to date is a tetrafluorinated pentose synthesised by Linclau *et. al* (Figure 1.4).[35]

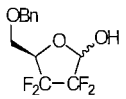
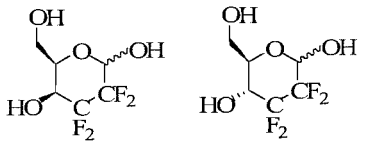


Figure 1.4

Although it is postulated that the extensive fluorination of carbohydrates increases the affinity of carbohydrates in PC interactions, the PC interactions are specific and through extensive polyfluorination the specificity may be lost. For example, DiMagno's hexafluorinated hexose has an increased hydrophobic area and an increase in affinity is expected. However, in this case, the possibility of H-bond formation is reduced, since the key hydroxyl groups (*i.e.* the hydroxyls at C2, C3 and C4), which could form hydrogen-bonds, are replaced by the CF_2 groups. It could be supposed that if all the hydroxyls replaced by the -CF_2 groups were hydrogen–bond acceptors, the specificity would not have major alterations. However, this situation is generally unlikely and the loss of specificity could be a drawback of extensive fluorination of carbohydrates.

The synthesis of 2,3-dideoxy-2,2,3,3-tetrafluoro-galactose and 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose is proposed. It is aimed not only at increasing the affinity, but also the selectivity of PC interactions, by exploiting inherent physico-chemical characteristics instilled by the fluorine substitution.



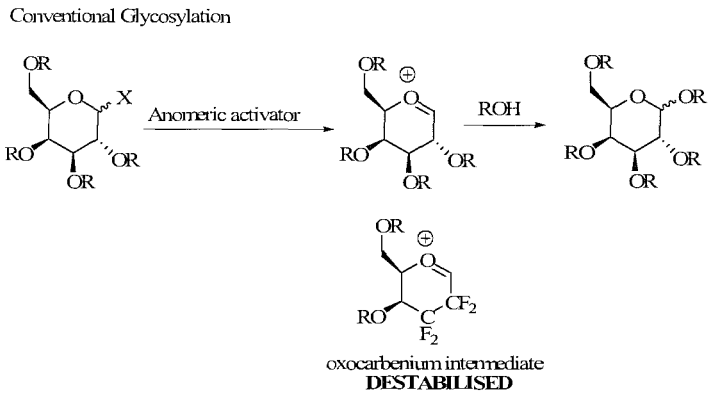
1.1 **1.2**

Figure 1.5

Positions 2 and 4 of the ring are significant, as they distinguish glucose, mannose and galactose, which are major components of biological saccharides. Our proposed targets still have the OH group at C4 unaltered. The selectivity of binding could be influenced by C4 stereochemistry if that OH group is involved in hydrogen bonding with the protein. An adjacent tetrafluorinated moiety, as in **1.1/1.2**, will decrease the pKa value of the OH group, resulting in stronger hydrogen bond donating capability. Hence, it is believed that in addition of the increase in affinity, a higher directionality in PC interactions may be achieved for carbohydrates **1.1** and **1.2**. Details for the retrosynthetic analysis of the tetrafluorinated carbohydrates **1.1** and **1.2** are presented in Section **1.5.2**. The ultimate goal of this project is to test the potential of the 2,3-dideoxy-2,2,3,3-tetrafluoro-galactose **1.1** and 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose **1.2** to bind to proteins.

1.4.2. Anomeric Alkylation

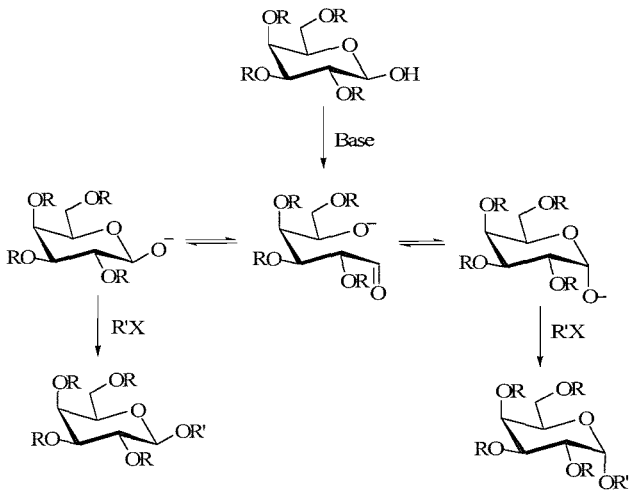
Conventional glycosylation of carbohydrates involves an oxocarbenium ion intermediate, [36] as depicted in Scheme 1.2. The CF_2 group at C2 would destabilize the oxocarbenium ion intermediate[37] and therefore the glycosylation would not be possible.



Scheme 1.2

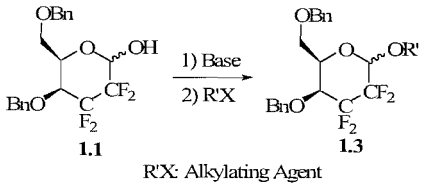
Few examples of glycosylation of 2-deoxy-2,2-difluoro-carbohydrates by the non-conventional methods were reported. However, to our knowledge, a methodology for the glycosylation of 2-deoxy-2,2-difluoro-carbohydrates has not been developed to date.

Hence, it is proposed that a non-conventional glycosylation method, anomeric alkylation, would be envisaged for the glycosylation of fluorinated sugars. As can be observed from the general scheme of anomeric alkylation (Scheme 1.3), the method involves the deprotonation of the anomeric hydroxyl, followed by the nucleophilic substitution by the alkylating agent.[36,38]



Scheme 1.3

The scheme of anomeric alkylation of fluorinated sugars is presented in Scheme 1.4. The anomeric alkylation reaction is presented in Chapter 5.

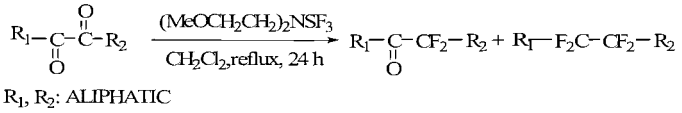


Scheme 1.4

1.5. Retrosynthetic Analysis of 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Carbohydrates

1.5.1. Building Block Approach *vs.* Fluorination

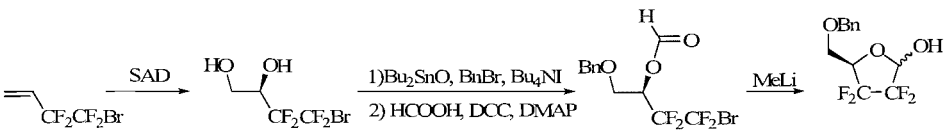
Electrophilic and nucleophilic fluorination methods have been applied to the synthesis of deoxy-fluorosugars[39]and deoxy-difluorosugars.[32,40] Glycal fluorination typifies the former approach, while transformations of hydroxyl or ketonic carbonyl with DAST accounts for the latter. The fluorination or difluorination of carbohydrates with DAST usually leads to complications *i.e.* neighbouring group participation, 1,2-group shifts and elimination reactions.[41] With the difficulties encountered during the difluorination of a ring ketone of a carbohydrate, the synthesis of a tetrafluorinated moiety starting from a diketone-containing sugar derivative is not a viable route. Even with an acyclic system, the tetrafluorination of a 1,2-diketone is not successful. Attempts towards the synthesis of 1,2 –tetrafluorinated moieties from the 1,2-diketons (with R_1 and R_2 aliphatic) with Deoxofluor lead to a mixture of both difluorianted and tetrafluorinated compounds, in low yields (Scheme 1.5).[42]



Scheme 1.5

Hence, an attractive approach for the synthesis of tetrafluoroethylene-containing molecules is the utilization of a tetrafluorinated building block, with the condition that the building block is available and inexpensive.

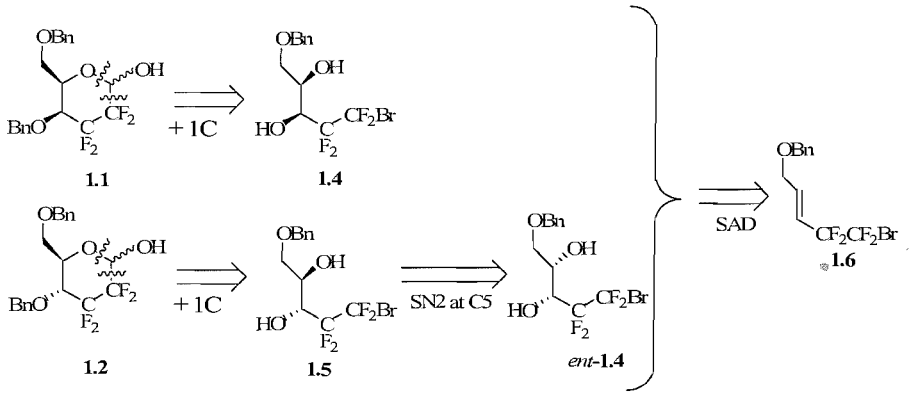
Both DiMagno's hexafluorinated hexose[15] and Linclau's tetrafluorinated pentose[35] were synthesised *via* a building block approach, the first one starting from a hexafluorinated moiety and the second one from a tetrafluorinated moiety. The tetrafluorinated pentose previously synthesised by Linclau *et al.*[35] was synthesised from the commercially available tetrafluorinated olefin shown in Scheme 1.6. The ring-formation step was an anionic cyclisation reaction.



Scheme 1.6

1.5.2. Retrosynthesis of 1.1 and 1.2

It was envisaged that for the synthesis of galactose **1.1** and glucose **1.2**, a tetrafluorinated building block would be used. The synthesis of both **1.1** and **1.2** would start from the same precursor **1.6**. The synthesis of tetrafluorinated olefin **1.6** comprises a radical addition reaction of ICF_2CF_2Br to allyl benzyl ether, followed by the dehydroiodination of the addition product. The synthesis of olefin **1.6** is described in Chapter 2.



Scheme 1.7

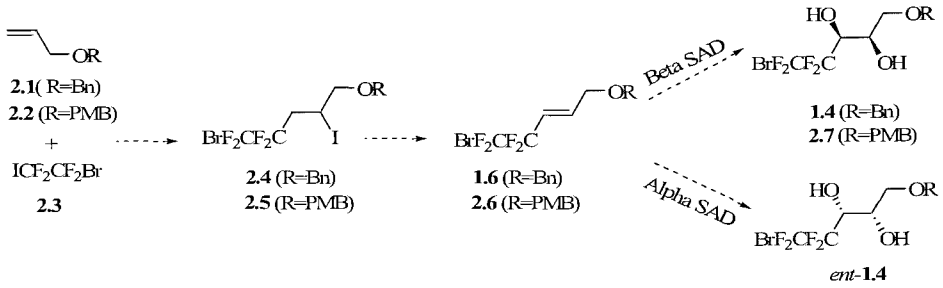
Syn diols **1.4** and *ent*-**1.4** are synthesized from olefin **1.6** via β- and α-SAD, respectively. As can be observed from Scheme 1.7, galactose and glucose are epimers at C4. Hence, *syn* diol **1.4** would be utilized as precursor for the synthesis of galactose **1.1** and the *anti* diol **1.5** would be used for the synthesis of glucose **1.2**. The *anti* diol **1.5** would be synthesized from *ent*-diol **1.4** via a S_N2 reaction at C2. The S_N2 reaction is expected to be regioseletcive (C2 over C3), as it is known that generally the S_N2 reactions at a Cα to a perfluroalkyl group are difficult to undertake.[43] Hence, the *anti* diol **1.5** could be synthesized only from the *ent*-**1.4**, not from **1.4**. A list of the possible routes for the inversion at C2 of *ent*-diol **1.4** is presented in Chapter 4.

In Chapter 3 is presented the synthesis of galactose **1.1** and in Chapter 4 is presented the synthesis of glucose **1.2**. Starting from the suitable diols, the synthesis of **1.1** and **1.2** would follow the same route: the selective Bn monoprotection at the hydroxyl α to the fluorinated moiety followed by the formic ester formation at the unprotected hydroxyl and finally, anionic cyclisation to give the carbohydrates.

Chapter 2. The Enantioselective Synthesis of the 1,2-Diol Intermediates

2.1. The Proposed Synthesis

The synthesis of diols **1.4** and *ent*-**1.4** starts with the radical addition of 1-bromo-2-iodo-tetrafluoroethane **2.3** to allyl benzyl ether **2.1**. The subsequent step is dehydroiodination to form the alkene **1.6**, followed by either the β- or the α-Sharpless asymmetric dihydroxylation (SAD) reaction. It was demonstrated that in the case of various allylic alcohols, the dihydroxylation of the corresponding PMB-protected substrates leads to the formation of products with higher *ee* values than the *ee* values of the Bn-protected substrates.[44] Hence, the PMB-protected allyl alcohol **2.2** was considered as one of the starting materials for the synthesis.



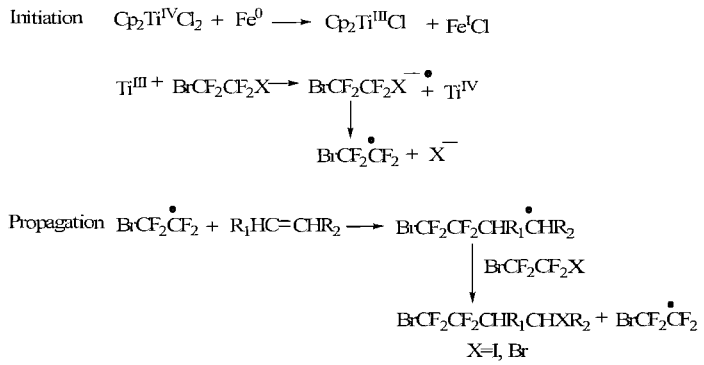
Scheme 2.1

2.2. Radical Addition Reaction

2.2.1. Radical Addition Reaction Initiated by Fe(0)/Cp_2TiCl_2

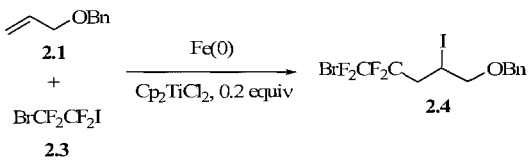
The radical addition of perfluoroalkyl halides to olefins constitutes a successful manner of introducing the perfluoroalkyl moiety in molecules.[45] Hu *et al.*[46] investigated the addition of R_FX to alkenes in the presence of redox systems such as iron powder /Cp_2TiCl_2. It has been demonstrated that the addition of $I(CF_2)_2X$ (X=I, Br) to allylic systems initiated by iron powder /Cp_2TiCl_2 leads to high yields of the addition product.[46a] The active species is

Cp_2TiCl, formed *in situ*. The mechanism is a radical chain mechanism and also involves a single electron transfer (SET) process (Scheme 2.2).



Scheme 2.2

Following a literature procedure, allyl benzyl ether **2.1** was synthesised in 77% yield from allyl alcohol and benzyl bromide.[47] The synthesis of **2.4** from allyl benzyl ether **2.1** and 1-bromo-2-iodo-tetrafluoroethane **2.3** under Hu conditions is presented in Table 2.1.



Scheme 2.3

Entry	2.3 (equiv)	Fe(0) (equiv)	Solvent	T (°C)	Time (h)	Yield 2.4 (%)
1	2.5	0.3[a]	MeOH	65	23	19
2	2.5	0.3[a]	EtOH	78	21	20
3	3.75	1.5[a]	EtOH	50-70	20	40
4	**3.75**	**1.5[a]**	**THF**	**50-70**	**20**	**80**
5	3.75	1.5[b]	THF	65	15.5	33
6	3.75	1.5[c]	THF	65	47	40

a) Iron powder; b): soluble Fe(0): $Fe_3(CO)_{12}$; c) soluble Fe(0): $Fe_2(CO)_9$

Table 2.1

The parameters varied during the reactions were the number of equivalents of **2.3** and of iron powder and the solvent. The utilization of 2.5 equiv of **2.3** and 0.3 equiv of iron powder in a protic solvent leads to the formation of **2.4** in low yields (Table 2.1, entries 1 and 2). An improved yield (40%) was obtained when the number of equiv of **2.3** and of iron powder were increased (Table 2.1, entry 3). When EtOH was replaced with THF, the yield raised significantly (80%) (Table 2.1, entry 3 *vs.* entry 4). These results are in agreement with Hu's findings that the utilization of protic solvents in the radical addition reactions is not leading to high yields.[46b]

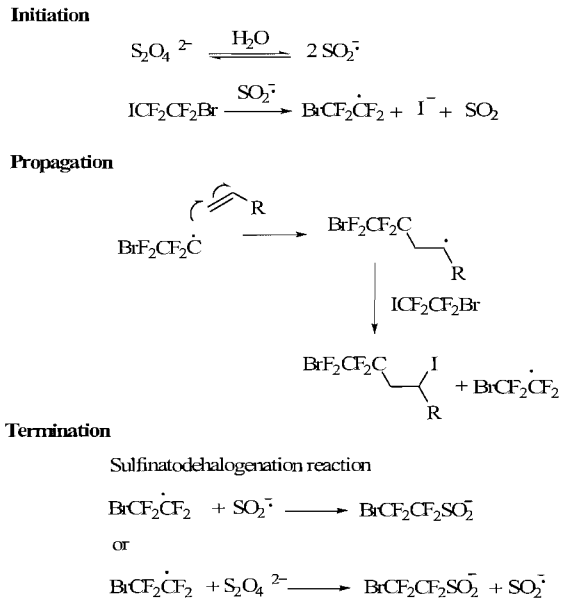
During the first attempts there was a practical problem with the utilisation of iron powder, as the iron powder "stuck" on the stirring bar. Hence, it was decided that the stirring bar should be omitted and to allow diffusion within the reaction vessel by simply using a stirring plate, causing the Fe(0) powder to swirl around. This practical inconvenience affected the large scale reaction and soluble sources of Fe(0) such as $Fe_3(CO)_{12}$ or $Fe_2(CO)_9$ were tested.[48] Their utilisation did not lead to high yields of the desired product **2.4** (Table 2.1, entries 5 and 6) and it was concluded that an alternative initiator must be found.

2.2.2. Radical addition reaction initiated by $Na_2S_2O_4$

Huang discovered the first sulfinatodeiodination reaction, in which perfluroalkyl iodides were converted to sodium perfluoroalkanesulfinates in the presence of sodium sulfite.[49] Since then, it has been shown that sulfinatodehalogenation reagents can be used as valuable initiators in radical addition reactions.[50,51] Fluoroalkyl radicals appear as transient species and in the presence of an unsaturated compound are able to begin the classical radical chain reaction resulting in the addition product. In this way, the sulfinatodehalogenation reaction is suppressed to the advantage of the radical chain process.[50,51,52]

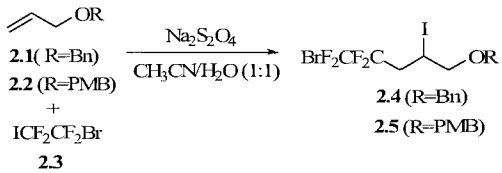
The mechanism of radical addition of perfluoroalkyl halogens to olefins initiated by $Na_2S_2O_4$ is depicted in Scheme 2.4. Homolytic S-S bond cleavage of $Na_2S_2O_4$ leads to the formation of $SO_2^{\cdot-}$ which subsequently initiates a single electron transfer to the perfluroalkyl iodide. This gives rise to the formation of the perfluroalkyl radical, which

then adds to the double bond. Iodine atom transfer occurs at the propagation step. The sulfinatodehalogenation reaction is one of the possible ways for the termination of the reaction.



Scheme 2.4

The optimization of the $Na_2S_2O_4$-initiated radical addition of **2.3** to **2.1** is presented in Table 2.2.



Scheme 2.5

Entry	2.3 (equiv)	$Na_2S_2O_4$ (equiv)	T (°C)	Time (h)	Yield 2.4 (%)	Recovered 2.1 (%)
1	1.05	1	RT	40	42	7
2	1.05	0.5	RT	40	14	36
3	1.05	1	-10 to 15	15	41	4
4	1.05	0.5	-10 to 15	15	55	12
5	0.77	1	RT	40	10	36
6	1.25	1	RT	40	50	5
7	**1.25**	**0.5**	**4-6**	**17.5**	**88**	**-**
8	**1.25**	**1.5**	**4-6**	**17.5**	**88**	**-**
9[a]	**1.25**	**1.5**	**4-6**	**17.5**	**100**	**-**
10	2.5	1	RT	0.25	96	-
11[b]	1.25	1.5	5-6	15	94	-

[a] A 7.57 g (**2.1**) scale reaction; [b] The synthesis of **2.5**.

Table 2.2

The parameters which were optimised for the synthesis of **2.4** in a high yield were the temperature, the equiv of **2.3** and of $Na_2S_2O_4$ and the reaction time.

In spite of the long reaction time, the yields were modest when 1.05 equiv of **2.3** were used, at RT (entries 1 and 2). The yield obtained upon the utilization of 1 equiv initiator, 42%, dropped to 14% when only 0.5 equiv of the initiator were used. Literature precedent revealed that the utilization of as little as 0.25 equivalents of $Na_2S_2O_4$ to initiate the reaction affords similar, high yields of products as with an equivalent amount of the initiator.[53] The possible explanation for the very low yield obtained with 0.5 equiv initiator (entry 2) could be that under these conditions, the chain mechanism was interrupted at some stage. The reduction of the temperature from RT to -10 to 15°C, led to moderate yields also (entries 3 and 4). The yield obtained with 0.5 equiv initiator at -10 to 15°C was higher than the yield obtained with 1 equiv initiator at the same temperature (entry 4 *vs.* entry 3). Literature precedent revealed that the utilization of a smaller amount of $Na_2S_2O_4$ reduces the possibility of sulfinate and by-product formation.[52] Although there was no evidence for the sulfinate formation, the sulfinate formation and consequently the termination of the chain reaction could explain the lower yield obtained with 1 equiv initiator (entry 3). It is known that upon the utilization of an excess of alkene, the bis addition product could form.[52] When the reaction was done with an excess of **2.1** rather than an excess of **2.3**, a low yield of the monoaddition product was obtained (entry 5). However, no bis addition product was

isolated in this case, as for all other experiments. The structure of the bis addition product which could have formed is presented in Figure 2.1.

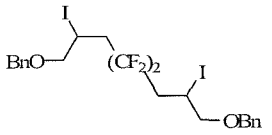


Figure 2.1

It was decided that an increase of the amount of **2.3** is necessary. The utilization of 1.25 equiv of **2.3** at RT led to only 50% yield of **2.4** (entry 6). However, when the temperature was lowered from RT to 4-6 °C, **2.4** was synthesised in 88% yield after 17.5 h (entries 7 and 8). It must be noted that at this temperature, the same yield, 88%, was obtained when 0.5 equiv or 1.5 equiv initiator were used (entries 7 and 8). It appears that only at a particular temperature (4-6 °C) the yields obtained after the reaction are similar, regardless of the amount of the initiator used (0.5 or 1.5 equiv). Upon the utilization of a large excess of **2.3** (2.5 equiv), the yield increased dramatically, even at RT and in a short reaction time (entry 10). The high yield of the addition product obtained in a short reaction time made us consider that the low yields obtained after a longer reaction time could be accounted for by the formation of byproducts, which were not isolated or observed. However, this hypothesis was eliminated, since on a 7.57 g (**2.1**) scale, the reaction was quantitative, after 17.5 h (entry 9).

Consequently, it can be considered that the utilization of a large excess of $I(CF_2)_2Br$ is the most important parameter in obtaining high yields of **2.4**. However, the utilization of a large excess of **2.3** such as 2.5 equivalents is expensive, given its cost, and it was considered that the synthesis of **2.4** in 88% yield (on a small scale) after the utilization of 1.25 equiv of **2.3** (entry 8) is a pertinent approach for the synthesis of **2.4**.

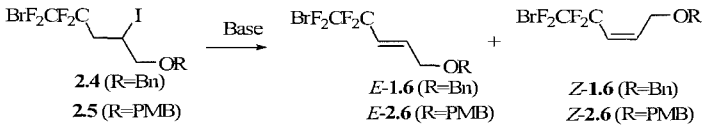
Following a literature procedure, **2.2** was synthesised in 91% yield from *p*-methoxy benzyl alcohol and benzyl bromide.[54] The utilization of 1.25 equiv of **2.3** and 1.5 equiv of the initiator at 5-6 °C lead to the formation of **2.5** in 94% yield, after 15 h (entry 11). The

product partially decomposed during column chromatography and traces of the impurity could be observed in ^{1}H, ^{13}C and ^{19}F NMR.

2.3. The Elimination Reaction

2.3.1. Results and Discussion

The dehydrohalogenation of halogeno perfluoroalkyl alkanes is described in the literature for a few substrates, using bases such as DBU, [55] DBN, [56] KOH, [57] TBAF, [58] NaH, [58] K_2CO_3 [58] or ethanolamine.[59] Geometrically pure *E* alkene is necessary for the SAD reaction and the optimization of the elimination reaction was focused on discovering the conditions for the synthesis of the geometrically pure *E* alkene. Bases such as DBU, KOH, TBAF and a variety of solvents and temperatures were tested. The results are presented in Table 2.3.



2.4 (R=Bn)
2.5 (R=PMB)

E-**1.6** (R=Bn)
E-**2.6** (R=PMB)

Z-**1.6** (R=Bn)
Z-**2.6** (R=PMB)

Scheme 2.6

Entry	Base (equiv)	Solvent	Time (h)	T (°C)	Yield 1.6 (%)	*E/Z* ratio
1	KOH (1.5)	MeOH	16.5	50	91	77/23
2	KOH (1.2)	DMF	2	50	77	83/17
3	TBAF (1.2)	THF	16.5	- 78 to RT	67	90/10
4	DBN (3)	DMF	0.25	0	94	93/7
5	DBU (3)	CH_2Cl_2	18	- 70 to 15	93	97/3
6	DBU (3)	THF	0.25	- 10	92	95/5
7	DBU (3)	Et_2O	0.25	RT	85	93/7
8	DBU (1)	Et_2O	2.5	0 to RT	28	94/6
9	DBU (3)	Et_2O	0.6	- 60	58	95/5
10	DBU (3)	DMF	1	RT	85	95/5
11	DBU (3)	DMF	0.25	0	89	96/4
12	DBU (3)	DMF	0.25	- 10	94	96/4
13	**DBU(3)**	**DMF**	**0.5**	**- 50**	**95**	**98/2**
14[a]	**DBU(3)**	**DMF**	**0.5**	**- 50**	**98**	**98/2**
15[b]	DBU (3)	DMF	1	- 50	97	>99

[a] A 23.15 g scale reaction; [b] The synthesis of **2.6**

Table 2.3

The elimination reaction performed with an alcoholic solution of KOH at 50 °C led to the formation of **1.6** with an *E/Z* ratio of 77/33 (entry 1). A smaller *Z* ratio, *E/Z*: 83/17, was obtained when using DMF (entry 2). With TBAF in THF at -78 °C to RT an *E/Z* ratio of 90/10 was obtained (entry 3). A higher *E* ratio (*E/Z*: 93/7) was obtained when using DBN in DMF at 0°C (entry 4). The utilization of DBU in CH_2Cl_2 at -70 to 15 °C led to an *E/Z* of 93/7 (entry 5).The E/Z ratio obtained in the presence of DBU was the highest amongst the E/Z ratios obtained with the bases tested. Consequently, it was concluded that DBU would be used in the further investigations, in the search for the conditions which could lead to the formation of the geometrically pure *E*-**1.6**. The optimization of the solvent and of the temperature was envisaged. With THF as the reaction solvent, at -10°C, the *E/Z* ratio observed was 95/5 (entry 6). When using Et_2O as the solvent for the reaction, the temperature was lowered from RT (entry 7) to 0-RT (entry 8) to -60 °C (entry 9). Comparing the *E/Z* ratios, it can be noted that a slightly higher *E* ratio was obtained at the lowest temperature (*E/Z*: 95/5 (entry 9) *vs.* 94/6 (entry 8) *vs.* 93/7 (entry 7)). When using a stoechiometric amount of the base rather than an excess (entry 8 *vs.* entry 7), the yield decreased dramatically. It was observed that when DMF was used as the solvent and the temperature was lowered from RT to 0, to -10 °C, to -50 °C, the *E* ratio increased with the

lowering of the temperature (entries 10-13). The highest *E* ratio (*E*/*Z*: 98/2) and a high yield (95%) were obtained at -50 °C, after 0.5 h (entry 13). On a 23.15 g scale (**2.4**), the yield increased to 98% (entry 14).

It can be observed that the highest rates of the *E* isomer are formed at the lower temperatures (entries 9 and 13). High yields were obtained with all the bases tested and generally the reaction was very fast: 77-91 % of **1.6** were obtained with KOH after 2 or 16.5 h (entries 1 and 2), 67% with TBAF after 16.5 h (entry 3), 94% with DBN after 0.25 h (entry 4) and yields between 58-98% with DBU, generally after 0.25-0.5 h (entries 5-13).

Although the low temperature usually favors nucleophilic substitution at the expense of the elimination, the substitution product was not isolated after any of the experiments.

Alternative ways of increasing the *E* % in the *E*/*Z* mixture were approached. Trials for the isomerisation of the *Z* into the *E* isomer from a mixture of *E* and *Z* isomers were done with I_2. The reaction was done under irradiation or without irradiation, but the isomerisation was not successful in either case. The separation of the isomers via column chromatography was difficult to accomplish, since the isomers have very similar R_f values. However, on a large scale pure fractions of the *E* isomer could be obtained, with the remaining fractions containing a mixture of both *E* and *Z* isomers. A pure sample of the *Z* isomer could not be isolated. Nevertheless, having an *E*/*Z* ratio of 98/2 and a yield of 95%, it was considered that no further optimization of the elimination reaction would be necessary.

The treatment of **2.5** with DBU in DMF at -50 °C led to the formation of **2.6** in 97% yield, after 1 h (entry 15). The product had >99% *E* purity. However, the product partially decomposed during column chromatography and traces of the impurity could be observed in the ^{1}H, ^{13}C and ^{19}F NMR of **2.6**.

For the next step, the SAD reaction, geometrically pure *E* alkene **1.6** or *E*/*Z* mixtures (95/5, 96/4 or 98/2) of **1.6** were used.

2.3.2. Assignment of the *E* and *Z* isomers

The assignment as *E* or Z of perfluorinated alkenes can be accomplished by the ^{19}F NMR or ^{1}H NMR. It is known that the -CF_2- group α to the double bond exhibits higher δ values in ^{19}F NMR for the *E* isomer than for the *Z* isomer.[57,59] The *E* and *Z* isomers could be identified also via ^{1}H NMR, since the olefinic protons of *E* and *Z* alkenes have different *J* values (12-18 Hz for the *E* alkene, 7-11 Hz for the Z alkene).

The *E*/*Z* ratios of **1.6** were determined by the integration of the protons in ^{1}H NMR of the crude reactions. In Figure 2.2 are presented sections of the ^{1}H and ^{19}F NMR of alkene **1.6** with an *E*/*Z*: ratio of 77/23. The peaks corresponding to the two isomers are distinct in both ^{1}H and ^{19}F NMR.

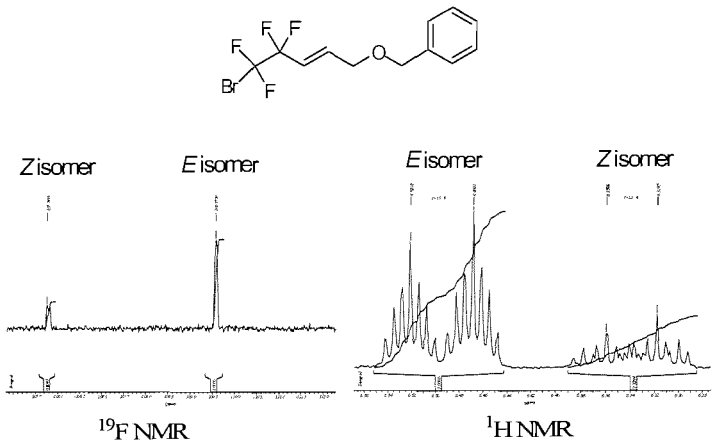


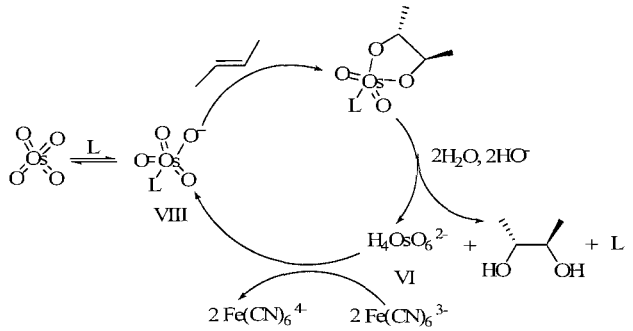
Figure 2.2

2.4. The Enantioselective Synthesis of the 1,2-Diol Intermediates

2.4.1. Sharpless Asymmetric Dihydroxylation

In 1980 Sharpless *et al.*[60] introduced the asymmetric dihydroxylation of alkenes and since then the reaction has become one of the most useful reactions in the toolbox of organic chemistry. The Sharpless asymmetric dihydroxylation represents a powerful method of

introducing chirality in a molecule, particularly in the light of the possibility of synthesising both enantiomeric forms of a compound from the same prochiral olefin. The general reaction scheme is depicted in Scheme 2.8.[61]



Scheme 2.8

Criegee introduced the stoichiometric reaction of OsO_4 with olefins.[62] However, cost considerations make the stoechiometric osmylation uneconomical. Catalytic utilization of Os was possible by using cheap inorganic cooxidants for reoxidation of Os(VI) glycolate products.[61] Since the discovery of the asymmetric variant of the reaction by Sharpless, ample research was focused on finding the most appropriate cooxidant (to circumvent over-oxidation), solvent and chiral catalyst for the reaction.[61] This reaction has been performed on numerous substrates and virtually every type of olefin can be dihydroxylated by a proper choice of the reagent and reaction conditions, though not necessarily all with a very high enantioslectivity.[61]

Sharpless *et al.*[63] discovered that chincona alkaloid derivatives are successful chiral catalysts for inducing enantioselectivity in AD (Figure 2.3).

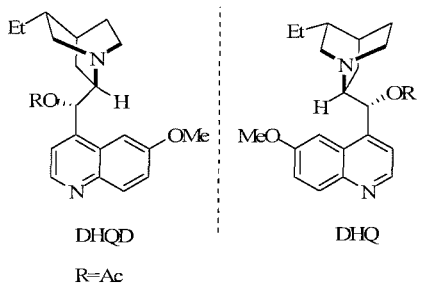


Figure 2.3

In the view of the staking interactions between the ligand and substrate, Sharpless [61] proposed a mnemonic for prediction the enantiofacial selectivity of the reaction (Figure 2.4), which was later refined by Norrby.[64]

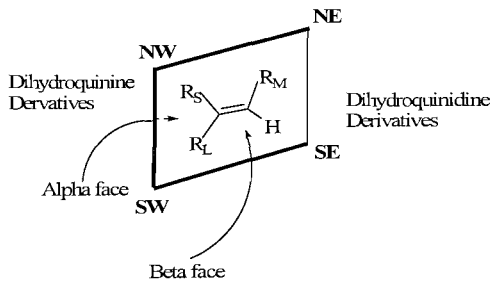


Figure 2.4

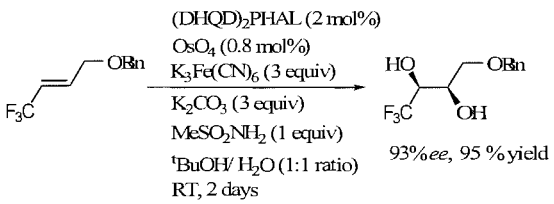
The south-east quadrant and to a much lesser extent the nort-west quadrant present steric barriers, whereas nort-east quadrant is relatively open for olefin substituients of moderate size. The south-west quadrant is regarded as being an attractive area, especially well suited to accommodate flat, aromatic substituients or, in their absence, "large" aliphatic groups. Amberg, Xu and Sharpless[65] discovered that the hydrolysis of the osmium (VI) glycolate can be accelerated considerably by $MeSO_2NH_2$. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at RT, which normally has a positive influence on the selectivity. Hence, with the exception of terminal alkenes, which appear to react slightly slower in the presence of $MeSO_2NH_2$, one equiv of $MeSO_2NH_2$ can be added to the reaction.

The use of $K_2OsO_2(OH)_4$ as a non-volatile Os source in combination with the inorganic oxidant $[K_3Fe(CN)_6]$ allowed Sharpless to formulate a commercially available premix containing all reagents, including the ligand.[61]

2.4.2. Sharpless Asymmetric Dihydroxylation of Fluorinated Substrates

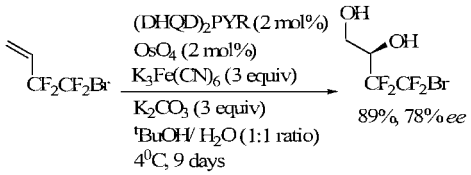
It was known that dihydroxylation of fluorinated alkenes require modified reaction conditions in order to achieve high yields.[66] The *ee* values obtained with fluorinated alkenes are usually different compared to the corresponding nonfluorinated alkenes.[66] The strong inductive effect of the fluorine in the α position to the double bond in alkenes makes the alkene less reactive towards dihydroxylation. The recommended modification for reducing the reaction time is to increase the amount of Os used. The typically used 0.2-0.4 mol % of Os and 1 mol% of ligand can be increased up to 2 mol% of Os and 5 mol% of ligand.[66]

After increasing the amount of Os to 0.8 mol% and the amount of ligand to 2 mol%, Qing *et al.* have obtained high enantioselectivity (93% *ee*) and a high yield after 2 days at RT (Scheme 2.9).[68c]



Scheme 2.9

Linclau *et al.* have used 2 mol% Os and 2 mol % ligand for the asymmetric dihydroxylation of a tetrafluoroethylene containing-terminal alkene.[35] A high yield was obtained only after 9 days (89%); the low *ee* obtained is accounted for the fact that the alkene is terminal (Scheme 2.10).



Scheme 2.10

From Qing's and Linclau's examples of asymmetric dihydroxylation of perfluoroalkyl olefins, it can be concluded that the longer the perfluoroalkyl chain, the longer reaction time is necessary for achieving a high yield, even when the amounts the Os and ligand are increased.

2.4.3. Results and Discussion

2.4.3.1. Synthesis of diols 1.4, *ent*-1.4 and 2.9

Sharpless asymmetric dihydroxylation is the step in which the chirality is introduced in the synthesis of tetrafluorinated carbohydrates **1.1** and **1.2**. Our principal goal was the synthesis of diols with high *ee* values.

1,2-(*E*)-Disubstituted olefins appear to be the best substrates for the AD reaction with *ee* values normally >90%.[61,67] The recommended ligands for this class of olefin are PHAL, AQN, DPP. [61, 67] The ligands tested with **1.6** were PHAL, AQN and PYR (Figure 2.5); PHAL was tested with **2.6**.

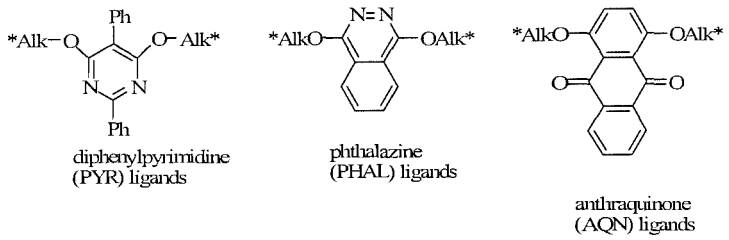
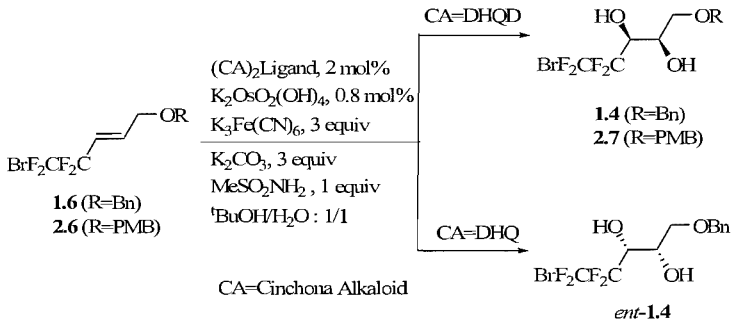


Figure 2.5

With R_L=-$(CF_2)_2Br$, R_M=-CH_2OR (for **1.6**, R=-Bn and for **2.6**, R=PMB) and R_S=-H, it was considered that olefins **1.6** and **2.6** follow the mnemonic predicted by Sharpless (Figure 2.4). It was envisaged that DHQD would be used for the synthesis of diols **1.4** and **2.7** and DHQ for the synthesis of *ent*-**1.4**.

Given the similarity of **1.6** (Scheme 2.11) with Qing's substrate (Scheme 2.9), the amounts of Os and ligand used in the SAD reaction of **1.6** were equal to the amounts used by Qing (0.8 mol% Os and 2 mol% ligand). The results for the synthesis of diols **1.4**, *ent*-**1.4** and **2.7** are presented in Table 2.4.



Scheme 2.11

Entry	Alkene (*E*/*Z* ratio)	$(CA)_2L$	T (°C)	Time (days)	Diol	Yield (%)	ee (%)
1	**1.6** (*E*/*Z*:98/2)	$(DHQD)_2PYR$	4 -6	8	**1.4**	81	88
2	**1.6** (*E*/*Z*:98/2)	$(DHQD)_2AQN$	4 -6	11	**1.4**	36[a]	88
3	**1.6** (*E*/*Z*:94/6)	$(DHQD)_2AQN$	0	8	**1.4**	67	90
4	**1.6** (*E*)	$(DHQD)_2PHAL$	RT	4	**1.4**	75	84
5	**1.6** (*E*)	**$(DHQD)_2PHAL$**	**4 -6**	**8**	**1.4**	**77**	**90**
6[b]	**1.6** (*E*/*Z*: 98/2)	**$(DHQD)_2PHAL$**	**4 -6**	**8**	**1.4**	**83**	/
7	**1.6** (*E*/*Z*:96/4)	$(DHQ)_2PHAL$	5-6	10	*ent*-**1.4**	86	83
8[c]	**1.6** (*E*/*Z*:98/2)	$(DHQ)_2PHAL$	5-6	11	*ent*-**1.4**	84	/
9	**2.6** (>99% *E*)	$(DHQD)_2PHAL$	4 -6	8	**2.7**	67	90

[a] A part of the crude was lost during workup;

[b] A 8.0 g scale reaction; the *ee* value was not determined.;

[c] A 5.7 g scale reaction; the *ee* value was not determined.

CA=Cinchona Alkaloid; L=Ligand

Table 2.4

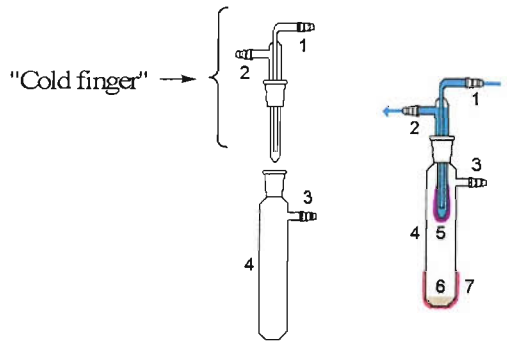
Reasonable yields (67-81%) of **1.4** were obtained after 8-11 days at low temperatures (entries 1-5). On a 8.0 g scale, the yield increased to 83% (entry 6).

Both PYR and AQN lead to an 88% *ee* at 4-6 °C (entries 1 and 2). When AQN was used as the ligand and the temperature was lowered from 4-6 to 0°C, the *ee* value (88% *vs.* 90%) did not increase significantly (entry 2 *vs.* entry 3). However, when PHAL was used as the ligand and the temperature was decreased from RT to 4-6, a considerable higher *ee* value (84% *vs.* 90%) was obtained (entry 4 *vs.* 5). Since the *ee* value did not increase with the lowering of the temperature from 4-6 to 0 °C when using AQN, the utilization of the PHAL at 0°C was not tested. Amongst the ligands screened at 4-6 °C, the utilization of PHAL led to the highest *ee* value, 90% (entry 1 (PYR) *vs.* entry 2 (AQN) *vs.* entry 5 (PHAL)). Given that a higher *ee* value than 90% *ee* was not obtained with any of the ligands and the temperatures screened, the increase of the *ee* value via recrystallization was envisaged. The attempts towards recrystallization of diol **1.4** were unsuccessful. Hence, the 90% *ee* value and 77% yield after 8 days at 4-6°C were considered acceptable for the enantioselctive synthesis of diol **1.4** and no further optimization was undertaken.

Diol *ent*-**1.4** was synthesised in a good yield (86%) and an average *ee* (83% *ee*), after 10 days at 5-6°C, using $(DHQ)_2PHAL$ (entry 7). The yield was 84 % on a 5.7 g scale (entry 8).

Literature precedent[44] reported that a number of PMB protected substrates had higher *ee* values of the products after the AD reaction than the Bn protected substrates. The possible explanation could be that favorable interactions occur between the PMB-containing substrate and the π-systems of the catalyst leading to an increase in the *ee* value of the diol. However, diols **1.4** (Bn containing) and **2.7** (PMB conatining) had the same *ee* value (90%) after similar reaction conditions (entry 5 *vs.* entry 9). Diol **2.7** was synthesized in 67% yield after 8 days at 4-6°C (entry 9). Since the PMB protecting group did not display a major influence in the AD enantioselectivity, diol **1.4** rather than diol **2.7** was considered as the precursor for the syntheses of 2,3-dideoxy-2,2,3,3-tetrafluorinated galactose **1.1** and glucose **1.2**.

The recrystallization of diol **1.4** via sublimation made possible the single crystal X-ray analysis. The recrystallization via sublimation was achieved by using an oil bath at 92 ^{0}C, *in vacuo*, for 72 h. The apparatus used for the recrystallization via sublimation is presented in Figure 2.6.



1. Cooling water in; 2. Cooling water out; 3. Vacuum/gas inlet; 4. Sublimation chamber; 5. Sublimed compound; 6. Crude material; 7. Heating.

Figure 2.6

The X-ray analysis of diol **1.4** (Figure 2.7) have proven that the hydroxyl groups are *syn* one to another.

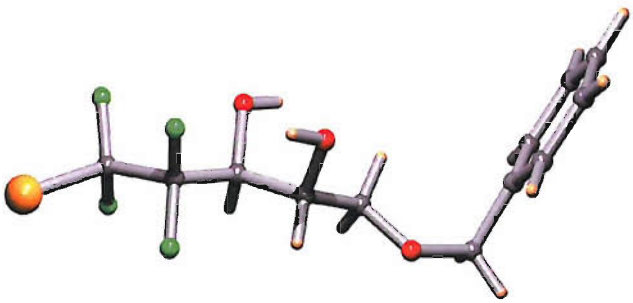


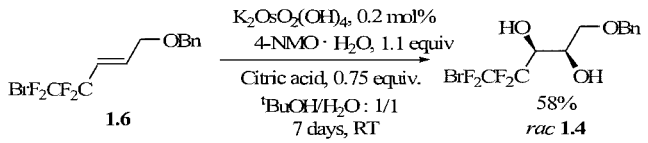
Figure 2.7

The alkenes used as starting materials for the AD reactions were either geometrically pure *E* alkenes or mixture of *E* and *Z* alkenes (98/2 or 96/4) (Table 2.4). It is known[61] that the *Z* alkenes react slowly in the AD reactions. *Anti* diol **1.5**, which could be formed after the AD reaction of the *Z* alkene, was not isolated in any of the experiments described in Table 2.6.

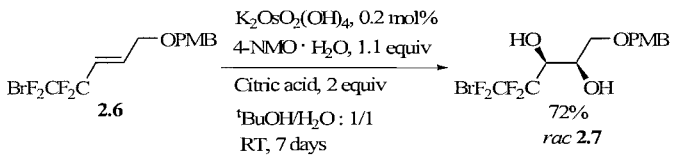
2.4.3.2. Determination of the Enantioselectivity

Racemic diols **1.4** and **2.7** were used for finding the resolution conditions on the chiral HPLC.

Sharpless *et al.* discovered that olefins bearing electron withdrawing groups benefit from the addition of the citric acid to the reaction.[70] However, the syntheses of both racemic diols **1.4** (Scheme 2.12) and **2.7** (Scheme 2.13) proceeded with in average yields after 7 days at RT, even in the presence of citric acid.

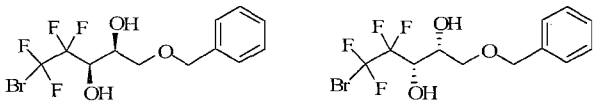


Scheme 2.12



Scheme 2.13

The *ee* of the diols **1.4** and **2.7** could be determined using analytical HPLC with chiral column Chiralcel OD-H. The conditions for resolution of diols **1.4** and *ent*-**1.4** on chiral column Chiralcel OD-H were 8% IPA in hexane at 254 nm, using samples with concentrations of 2 mg/ mL. The injection volume was 3 μL and the flow 1 mL/min. The retention times were 10.270 min for (*2S, 3S*) -1-benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentane-2,3-diol and 11.597 min for (*R,R*)- 1-benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentane-2,3-diol. The chromatogram for the *rac*-**1.4** is presented in Figure 2.8 and the chromatogram of the diol **1.4** with the *ee* value of 90% is presented in Figure 2.9.



(*2S,3S*)-**1.4**
(**1.4**)

(*2R,3R*)-**1.4**
(*ent*-**1.4**)

Scheme 2.14

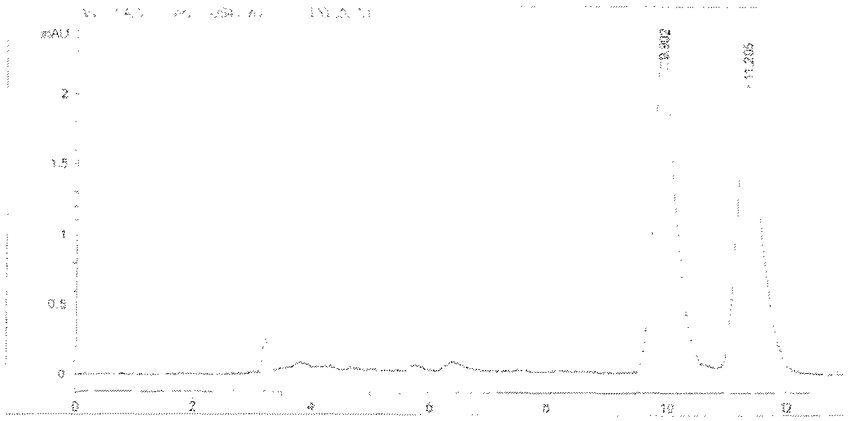


Figure 2.8

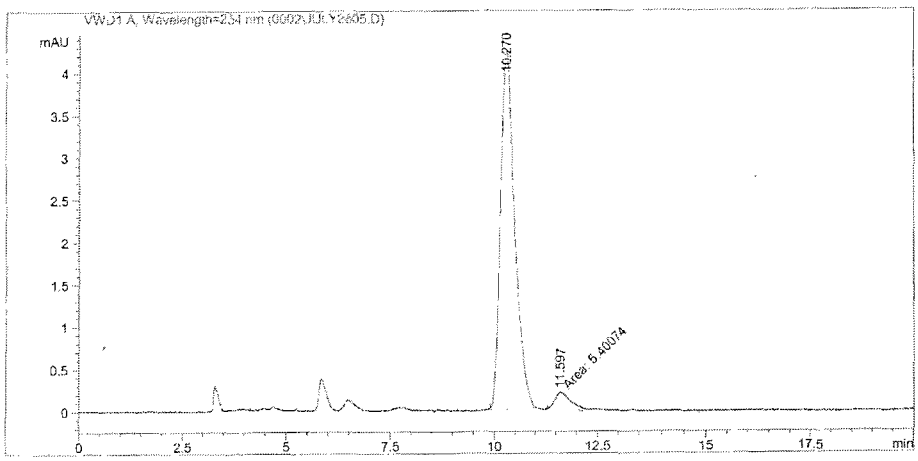
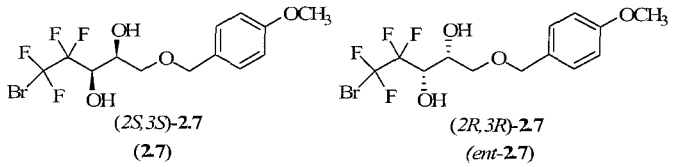


Figure 2.9

The conditions for resolution of diol **2.7** on chiral column Chiralcel OD-H were 10% IPA in hexane at 254 nm, using samples with concentrations of 1 mg/mL and the flow 1 mL/min. The injection volume was 3 μL. The retention times were 10.159 min for (*2S, 3S)*

-5-Bromo-4,4,5,5-tetrafluoro-1-(4-methoxy-benzyloxy)-pentane-2,3-diol and 12.376 min for *(2R, 3R)* -5-Bromo-4,4,5,5-tetrafluoro-1-(4-methoxy-benzyloxy)-pentane-2,3-diol. The chromatogram for the *rac*-**2.7** is presented in Figure 2.10 and the chromatogram of the diol **2.7** with the *ee* value of 90% is presented in Figure 2.11.



Scheme 2.15

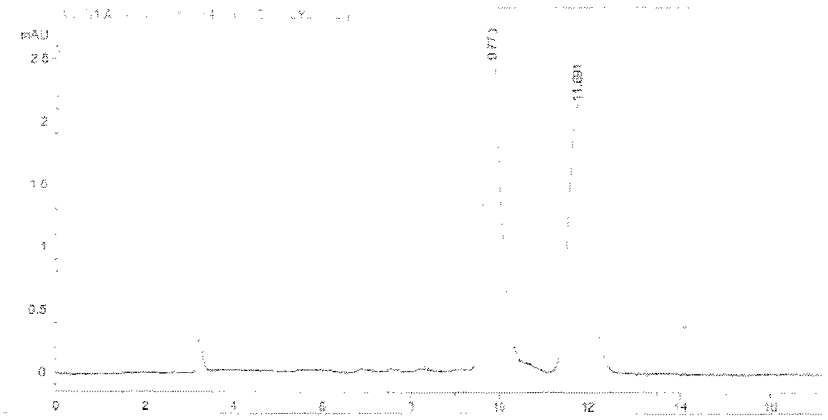


Figure 2.10

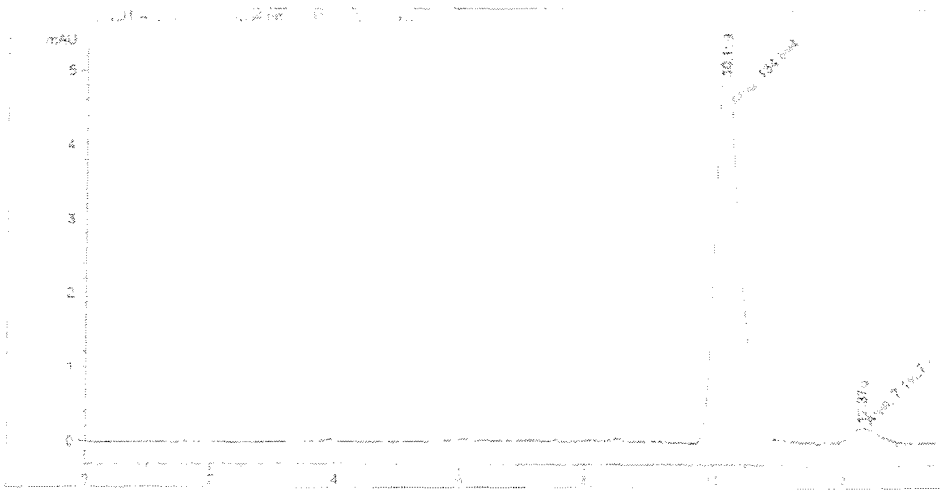


Figure 2.11

2.5. Summary

The syntheses of **1.4** (precursor of tetrafluorinated galactose **1.1**) and *ent*-**1.4** (precursor of tetrafluorinated glucose **1.2**), was accomplished. Diols **1.4** and *ent*-**1.4** were synthesized in 67% overall yield (81.3% yield on a larger scale) and 71.9 % overall yield (82.3% yield on a larger scale), respectively, from allyl benzyl ether **2.1**, after 3 steps. Diol **2.7** was synthesised in 61.1 % overall yield from PMB-protected allyl alcohol **2.2**, after 3 steps. The structure of diol **1.4** has been proven by X-ray analysis.

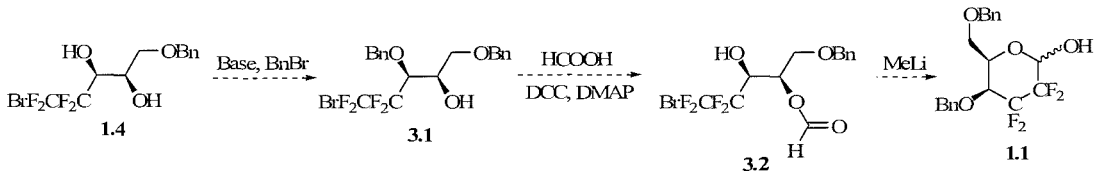
The ligands tested for the enantioselective synthesis of **1.4** were AQN, PYR and PHAL. The utilization of PHAL led to the highest *ee* value obtained for the diol **1.4**, 90% *ee*. Diols *ent*-**1.4** and **2.7** have *ee* values of 83% *ee* and 90% *ee*, respectively.

After similar AD reaction conditions, the PMB and Bn protected diols had the same *ee* value (90%). Since the PMB-protected diol (**2.7**) did not have higher *ee* value than the Bn-protected diol (**1.4**), it was considered that the further transformations towards the synthesis of tetrafluorinated galactose **1.1** woul be undertaken with diol **1.4**.

Chapter 3. The Enantioselective Synthesis of 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Galactose

3.1. The Proposed Synthesis

The first step envisaged for the synthesis of the tetrafluorinated galactose **1.1** from the diol **1.4** was the selective benzyl monoprotection of the diol **1.4** at the hydroxyl in the α position to the
$-(CF_2)_2Br$ group. The next step would be the synthesis of the formic ester **3.2**, followed by the anionic cyclisation to give **1.1** (Scheme 3.1).



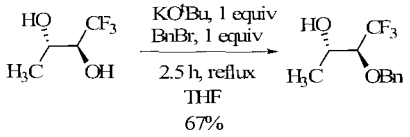
Scheme 3.1

3.2. Selective Monoprotection of Diol 1.4

3.2.1. Introduction

Monobenzylation of the 1,2-diols flanked by the perfluoroalkyl groups under basic conditions is regioselective. The monobenzylation occurring at the hydroxyl group α to the perfluoroalkyl group is the testimony of the increased acidity instilled by the adjacent electron withdrawing perfluoroalkyl group.[35,71,72]

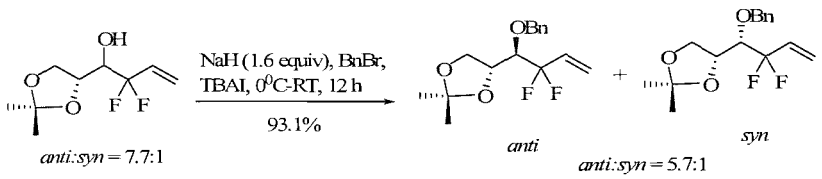
The selective monobenzylation of fluorinated 1, 2-diols was demonstrated by Manitto *et al.* (Scheme 3.2).[72]



Scheme 3.2

Qing *et al.* have shown that the benzylation in the presence of NaH of a hydroxyl group α to a $-CF_2$ group occurred with epimerisation of the product when an excess of base was used.[68a]

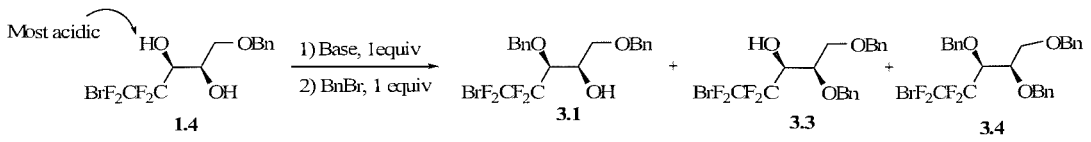
The epimerisation process occurs because of the acidity of the proton in –C*H*OBn, instilled by the electron withdrawing character of the $-CF_2$ group α to –C*H*OBn group (Scheme 3.3).[68a] Qing stated that the epimerization of the product occurred after the product was formed. The explanation is that if epimerization would have occurred before the product would have been formed, then a deprotonation would have to occur at -C*H*O$^-$ and this process in not probable, due to the instability of the product. The epimerisation did not occur upon the utilization of 1.0 equiv NaH or less.



Scheme 3.3

3.2.2. Results and Discussion

The general reaction scheme for the synthesis of **3.1** from **1.4** is presented in Scheme 3.4. It was envisaged that the amount of the base used would be 1 equivalent, in order to diminish the possibility of epimerisation and dibenzylation.



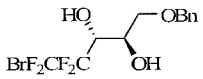
Scheme 3.4

Entry	Diol	Base (equiv)	Time (h)	Yield 3.1 (%)	Yield 3.3 (%)	Yield 3.4 (%)	Yield 1.5 (%)
1	*rac*-**1.4**	KO^{t}Bu (1)	4	50	-	-	-
2	*rac*-**1.4**	KO^{t}Bu (1)	15.5	58	1.1	3.7	-
3	**1.4**	KO^{t}Bu (1)	16.5	75	1.24	2.8	2.22
4	**1.4**	**NaH (1)**	**17**	**71**	**-**	**4.5**	**-**
5[a,b]	**1.4**	**NaH (1)**	**18.5**	**77**	**-**	/	**-**

[a] A 7.27 g scale reaction; [b] The yield of **3.4** could not be quoted.

Table 3.1

The reaction in the presence of KO^{t}Bu is selective towards the formation of **3.1**, which was synthesised in 50 % yield as the only product after 4h (entry 1). High yields of **3.1** and moderate yields of **3.3** and **3.4** were obtained after the over night reactions with KO^{t}Bu (entry 2-3). *Anti* diol **1.5** (Figure 3.1) was isolated from the reaction done with the chiral nonracemic **1.4**, in the presence of 1 equiv KO^{t}Bu (entry 3). The reason for the formation of **1.5** could be the epimerisation of **1.4** during the reaction.



anti diol **1.5**

Figure 3.1

When the reaction was done in the presence of NaH, only **3.1** (71% yield) and **3.4** (4.5 % yield) were isolated (entry 4). Since the reaction in the presence of NaH led to the synthesis of **3.1** in a high yield and of only one undesired product, it was considered that the utilization of NaH in the selective benzylation of **1.4** is more appropriate than the utilization of KO^{t}Bu. On a 7.27 g scale, **3.1** was synthesised on 77% yield (entry 5).

The prospect of epimerisation in the presence of 1 equiv KO^{t}Bu had to be further investigated. The nonracemic diol **1.4** used for the monobenzylation reactions was synthesised from the alkene **1.6** with an *E*/*Z* ratio of 95/5 (for the KO^{t}Bu experiment) and 98/2 (for the NaH experiment). Although the *anti* diol **1.5** was not isolated from the SAD reaction, it is probable that the small % of the *Z* alkene reacted in the SAD reaction, leading to the formation of the *anti* diol **1.5**. Consequently, it is possible that the *syn* diol **1.4** used for the monobenzylation reaction was contaminated with the *anti* diol **1.5**, which was detected only after the column chromatography of the monobenzylation reaction with KO^{t}Bu.

The structure of diol **1.5** was proven by X-ray analysis of a single crystal of **1.5** (Figure 3.2). It is evident that the two hydroxyl groups are *anti* one to another. Diol **1.5** was synthesized also at some stage in the synthesis of 2,3-dideoxy-2,2,3,3-tetrafluorinated glucose **1.2** and the data collected on the product isolated after the selective monobenzylation of **1.4** matched perfectly the data acquired on **1.5** synthesized during the glucose synthesis (see Chapter 4).

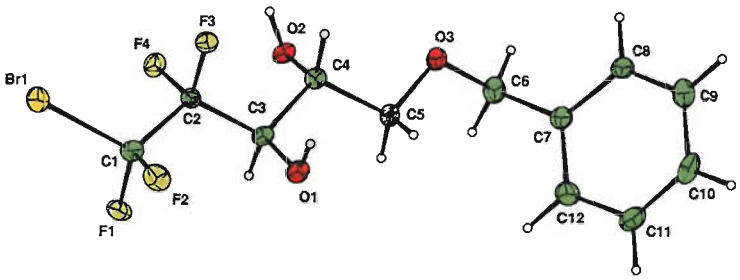


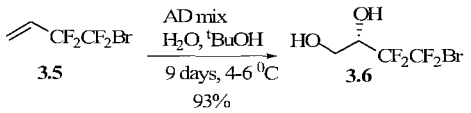
Figure 3.2

Given that the separation of **1.5** after the monobenzylation reaction could have two origins, it was envisaged that the control experiments with a model compound are necessary.

3.2.3. Control Experiments for Epimerization

A terminal 1,2-diol flanked by a tetrafluoroethylene moiety was chosen for the epimerization experiments (**3.6**, Scheme 3.5). If epimerization occurs in the monobenzylation reaction of **3.6**, it could be monitored by HPLC, by comparison of the *ee* values of the starting material and of the product.

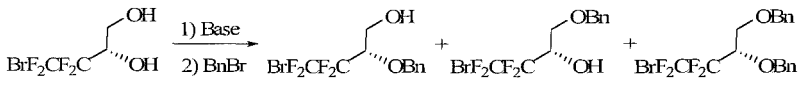
Diol **3.6** was synthesized in 93% yield after 9 days, following a procedure previously developed in our group (Scheme 3.5).[35]



3.5 3.6

Scheme 3.5

The selective monobenzylation of terminal diol **3.6** was investigated, using bases such as NaH, ^{t}BuOK and Na_2CO_3. The reaction conditions for the selective monoprotection of diol **3.6** in the presence of NaH or ^{t}BuOK were similar to the reaction conditions for the selective monoprotection of diol **1.4**. The conditions for the reaction of the diol **3.6** with Na_2CO_3/BnBr were previously developed by Linclau *et al.*.[73] The general reaction scheme is presented in Scheme 3.6 and the results for the selective monobenzylation of the diol **3.6** are presented in Table 3.2.



3.6 3.7 3.8 3.9

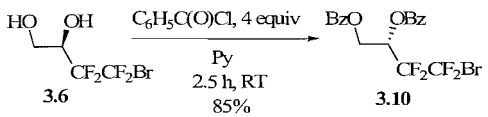
Scheme 3.6

Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield 3.7 (%)	Yield 3.8 (%)	Yield 3.9 (%)
1	KO^tBu (1)	THF	65	16	51	4	11
2	NaH (1)	THF	0-RT	16	6.6	0.8	traces
3	Na_2CO_3 (27)	H_2O	RT	18	56	2	traces

Table 3.2

The selective monoprotection reaction of **3.6** in the presence of KO^tBu and Na_2CO_3 gave monoprotected diol **3.7** in satisfactory yields (51% and 56%, respectively) and **3.8** and **3.9** in small quantities (entry 1 and entry 3). The reaction in the presence of NaH led to a small yield of **3.7** (6.6%) and traces of **3.8** and **3.9** (entry 2); the experiment in the presence of NaH was repeated and the results were similar.

For monitoring the occurrence of the epimerization, the *ee* value of **3.7** was compared against the *ee* value of the starting material **3.6**. Given that the diol **3.6** does not have UV active groups for the detection on the HPLC, the bis benzoate **3.10** was synthesized (Scheme 3.6). Bis benzoate **3.10** was synthesized in 85% yield from **3.6**; no starting material was recovered. The *ee* value of the bis benzoate **3.10** was considered the *ee* value of the diol **3.6**.



Scheme 3.6

In Table 3.3 is presented a comparison between the *ee* values for the bis benzoate **3.10** and the monoprotected diol **3.7**.

Entry	3.10/3.7 (base)	*ee* (%)
1	**3.10**	83
2	**3.7**(Na_2CO_3)	85
3	**3.7** (KO^tBu)	79
4	**3.7 (NaH)**	**58 and 62**[a]

[a] The reaction was done twice,
to verify the consistency of the *ee* value.

Table 3.3

Th *ee* of the bis benzoate **3.10** was 83%. The difference in the *ee* values of **3.10** (83%, entry 1) and of **3.7** after the reaction with Na_2CO_3 (85%, entry 2) is in the experimental error range. It can be concluded that the epimerization did not occur in the presence of Na_2CO_3, which is a weak base (entry 1 *vs.* entry 2). The *ee* value obtained after the reaction with ^{t}BuOK (79%, entry 3) was not significantly altered in comparison with the *ee* value of the starting material (83%, entry 1). Hence, it can be concluded that little or no epimerization occurred in the presence of this base (entry 3 *vs.* entry 1). In order to confirm the accuracy of the *ee* value, two experiments in similar reaction conditions were done for the monobenzylation reaction of **3.6** in the presence of NaH. The products obtained after the reactions had 58 and 62% *ee*, respectively (entry 4). Since the *ee* values obtained after the reactions in the presence of NaH (58 and 62%, entry 4) are much lower than the *ee* value of the starting material (83%, entry 1), it was concluded that with the substrate **3.6** epimerization occurred in the presence of 1 equiv NaH. The epimerization of **3.6** in the presence of only 1 equiv of NaH is not in agreement with Qing's finding[68a] that his substrate epimerizes only when an excess of NaH is used. The control experiments with **3.6** revealed that the epimerization in the monobenzylation reaction of the vicinal diols flanked by a tetrafluoroethylene moiety is probable, depending on the base used. However, **3.6** epimerized in the presence of NaH and not in the presence of ^{t}BuOK, while it is probable that the internal 1,2-diol **1.4** epimerized in the presence of ^{t}BuOK; diol **1.4** did not epimerize in the presence of NaH. A plausible explanation for this phenomenon could not be found and further experiments are envisaged.

The *ee* values of **3.10** and **3.7** were obtained on chiral HPLC with an OJ column. The eluent used for the resolution of **3.7** was 12% IPA in hexane and the concentration of the samples was 2 mg/ mL. The injection volume was 10 μL and the flow 1 mL/min. The retention times were 5.834 min for (*S*)-**3.7** and 6.737 min for (*R*)-**3.7**. The chromatogram for *rac*-**3.7** is presented in Figure 3.4 and the chromatogram of **3.7** with an *ee* value of 58% is presented in Figure 3.5.

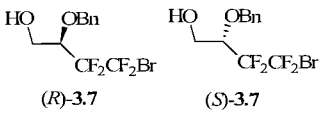


Figure 3.3

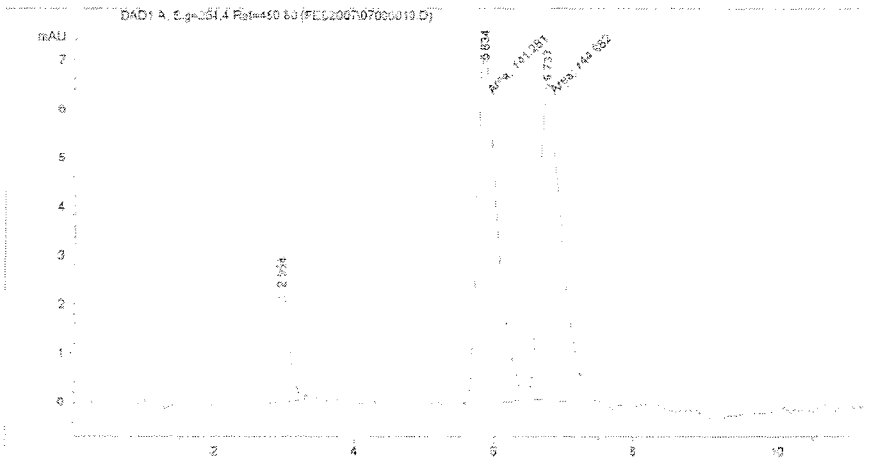


Figure 3.4

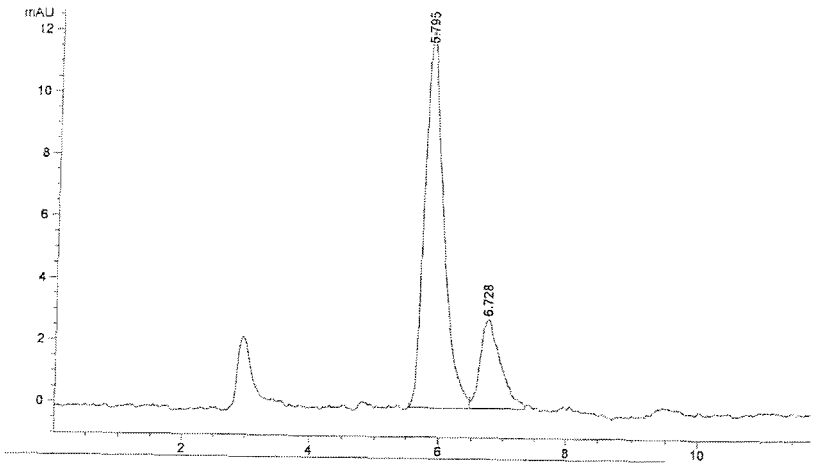
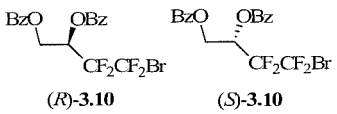


Figure 3.5

The eluent used for the resolution of **3.10** was 10% IPA in hexane and the concentration of the samples were 2 mg/mL. The injection volume was 10 μL and the flow 0.5 mL/min. The retention times were 13.534 for (*R*)-**3.10** and 15.496 for (*S*)-**3.10**. The chromatogram of **3.10** with an *ee* value of 83% is presented in Figure 3.7.



(*R*)-**3.10** (*S*)-**3.10**

Figure 3.6

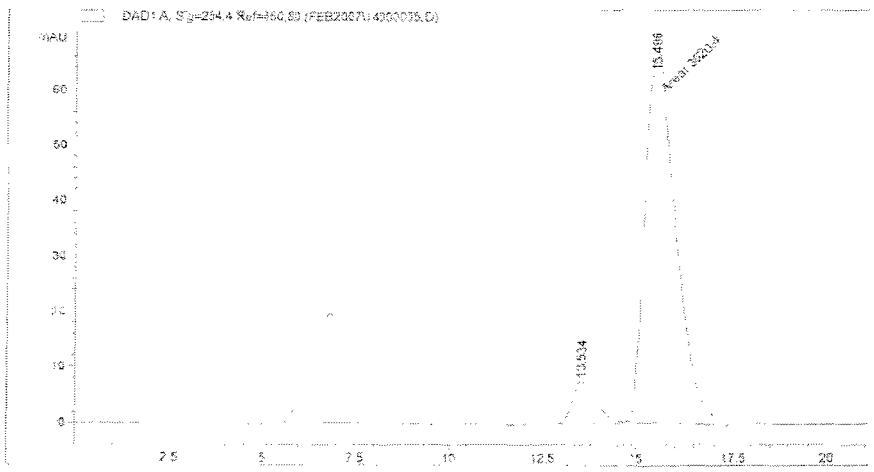


Figure 3.7

3.3. The Formic Ester Formation Reaction

The monoprotected diol **3.1** was treated with formic acid and a coupling reagent for the synthesis of formic ester **3.2**.[35] The general scheme for the synthesis of **3.2** from **3.1** is depicted in Scheme 3.7 and the results for the optimization of the reaction are presented in Table 3.4.

3.1 3.2

Scheme 3.7

Entry	Formic acid (equiv)	Coupling reagent (equiv)	DMAP (equiv)	Time (h)	Yield (%)
1	1.1	DCC, 1.1	0.1	16	56
2	1.2	DCC, 1.2	0.2	48	77
3	**1.2**	**DIC, 1.2**	**0.2**	**21**	**81**
4[a]	**1.2**	**DIC, 1.2**	**0.2**	**25**	**96**

[a] A 7.03 g scale reaction.

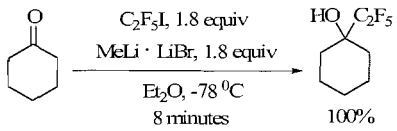
Table 3.4

An average yield (56%) was obtained after 16 h at RT, when using 1.1 equiv DCC, 0.1 equiv DMAP and 1.1 equiv formic acid (entry 1). A higher yield, 77%, was achieved when using slightly higher number of equiv of DCC, DMAP and formic acid and after a longer reaction time (entry 1 *vs.* entry 2). The yield increased to 81% when DCC was replaced by DIC (entry 2 *vs.* entry 3) and it was considered that the further optimization of the reaction was not necessary. The yield increased to 96% on a 7.03 g scale (entry 4).

3.4. Synthesis of 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Galactose 3.14

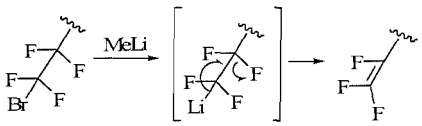
3.4.1. Anionc Cyclisation

The *intermolecular reaction* of various perfluoroalkyllithium species with different aldehydes at -78 °C is well described in the literature.[74,75,76] Perfluoroalkyl-substituted secondary or tertiary carbinols could be synthesized by this method (Scheme 3.8).[75]



Scheme 3.8

The reaction involves a halogen-lithium exchange process and it was proven that the X-Li exchange occurs considerably faster than the reaction between the RLi and the aldehyde functionality.[77] The instability and the short half-life (5 to 10 minutes at -78 °C) of the perfluoroalkyllithium species are ascribed to the rapid β-elimination of lithium fluoride (Scheme 3.9).[74]



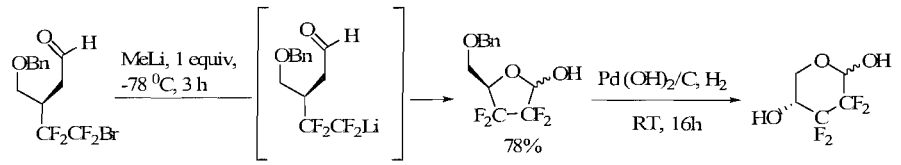
Scheme 3.9

The β-fluoride elimination competes with the reaction between the perfluoroalkyllithium species and the aldehyde functionality. However, the possibility of β-elimination can be surmounted by the formation of the perfluoroalkyllithium in the presence of an appropriate substrate.[77]

The *intramolecular reaction* between the perfluoroalkyllithium and an aldehyde functionality was first reported by Linclau *et al.* (Scheme 3.10).[35,73] The reaction is an anionic cyclization. Amongst all the organometallic reagents screened, MeLi furnished the highest yield of the cyclization product.[77] Linclau *et al.* [35,73] reported that the most successful reaction conditions for the anionic cyclization reaction are the utilization of 1

equiv of MeLi, at -78 °C. Under these conditions, the elimination is outstripped by the cyclization and the elimination product is formed in less than 5% yield.

The pyranosic form of Linclau's tetrafluoro-pentose was obtained after the deprotection of the benzyl group at C6 (Scheme 3.10).[35]

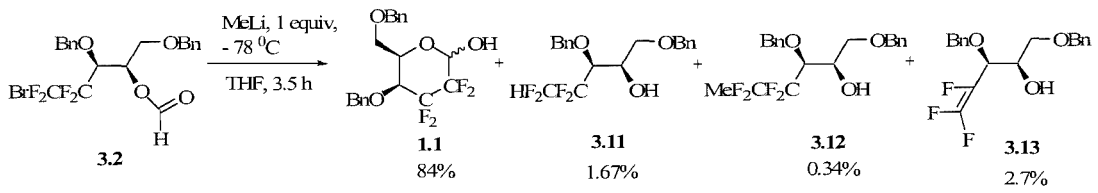


Scheme 3.10

3.4.2. Synthesis of 2,3-dideoxy-2,2,3,3-tetrafluoro-galactose 3.14

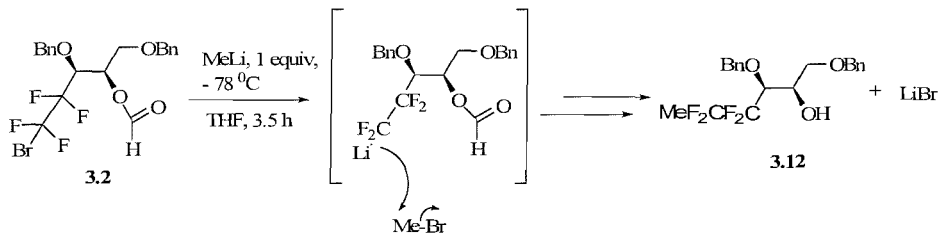
3.4.2.1. Results and Discussion

4,6-Dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-galactose **1.1** was synthesized via anionic cylization from formic ester **3.2**, using 1 equiv of MeLi at -78 °C (Scheme 3.11).



Scheme 3.11

The 4,6-dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-galactose **1.1** was synthesized in 84 % yield after 3.5h; on a 7.084 g scale, the yield increased to 90%. The β-fluoride elimination led to the formation of 2.7% yield of the elimination product **3.13**. It was supposed that the product **3.11** has been synthesized from the perfluoroalkyllithium species in the presence of moisture; the proposed mechanism for the formation of product **3.12** is depicted in Scheme 3.12. Product **3.12** could have been formed after the reaction between the anionic intermediate and the MeBr byproduct.

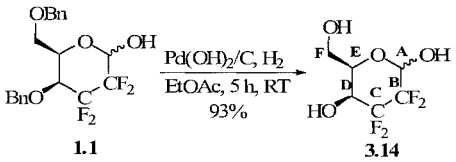


Scheme 3.12

The proposed structure of **3.11** was confirmed by the *J* value between the proton and fluorine in

$-CF_2H$ moiety ($^2J_{H\text{-}F}$=53.0 Hz). The proposed structure of **3.12** was confirmed by the *J* value between the protons of the methyl group and fluorine in $-CF_2CH_3$ moiety ($^3J_{H\text{-}F}$=19.3 Hz).

The attempts for the separation of α and β anomers of **1.1** failed (eluents for HPLC: Hexane/Acetone: 80/20, Hexane/EtOAc: 75/25 and 80/20). The anomeric ratio in the anomeric mixture was determined by the ratio of the integrals of protons and fluorine atoms in ^{1}H NMR and ^{19}F NMR respectively. The anomeric ratio in the anomeric mixture was α/β: 1.14/1 by ^{1}H NMR ($CDCl_3$, 400 MHz) and α/β: 1.6/1 by ^{19}F NMR ($CDCl_3$, 282 MHz). Deprotection of **1.1** with H_2, $Pd(OH)_2/C$ led to the synthesis of **3.14** in 93% yield (Scheme 3.13).



Scheme 3.13

Separation of α and β anomers of deprotected galactose **3.14** failed (eluent for HPLC: neat EtOAc). The anomeric ratio was determined by the ratio of the integrals of protons and fluorine atoms in ^{1}H NMR and ^{19}F NMR respectively. The α/β anomeric ratio of the anomeric mixture was 1/1.5 by ^{1}H NMR (D_2O, 400 MHz) and 1/1.15 by ^{19}F NMR (D_2O, 282 MHz).

An HMBC experiment of **3.14** has proven that **3.14** is the pyranosic form of the carbohydrate (Figure 3.9). In Scheme Figure 3.8 are presented the pyranosic form (**3.14**) and the furanosic form of 2,3-dideoxy-2,2,3,3-tetrafluoro-galactose.

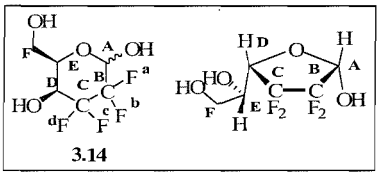


Figure 3.8

Cross peaks between $H_{A\alpha}$ (δ 5.52) and $C_{E\alpha}$ (δ 68.03) and $H_{E\beta}$ (δ 4.06) and $C_{A\beta}$ (δ 89.43-90.20, overlapping with $C_{A\alpha}$) have been observed in the HMBC spectrum. This proves a long range correlation in the carbohydrate ring, between positions A and E of the ring. If **3.14** would have been the furanosic form of the carbohydrate, a long range correlation would have not been possible, since C_E is not in the ring in the furanosic form of the carbohydrate. Hence, with the aid of the HMBC experiment, it was demonstrated that **3.14** is the pyranosic form of the carbohydrate.

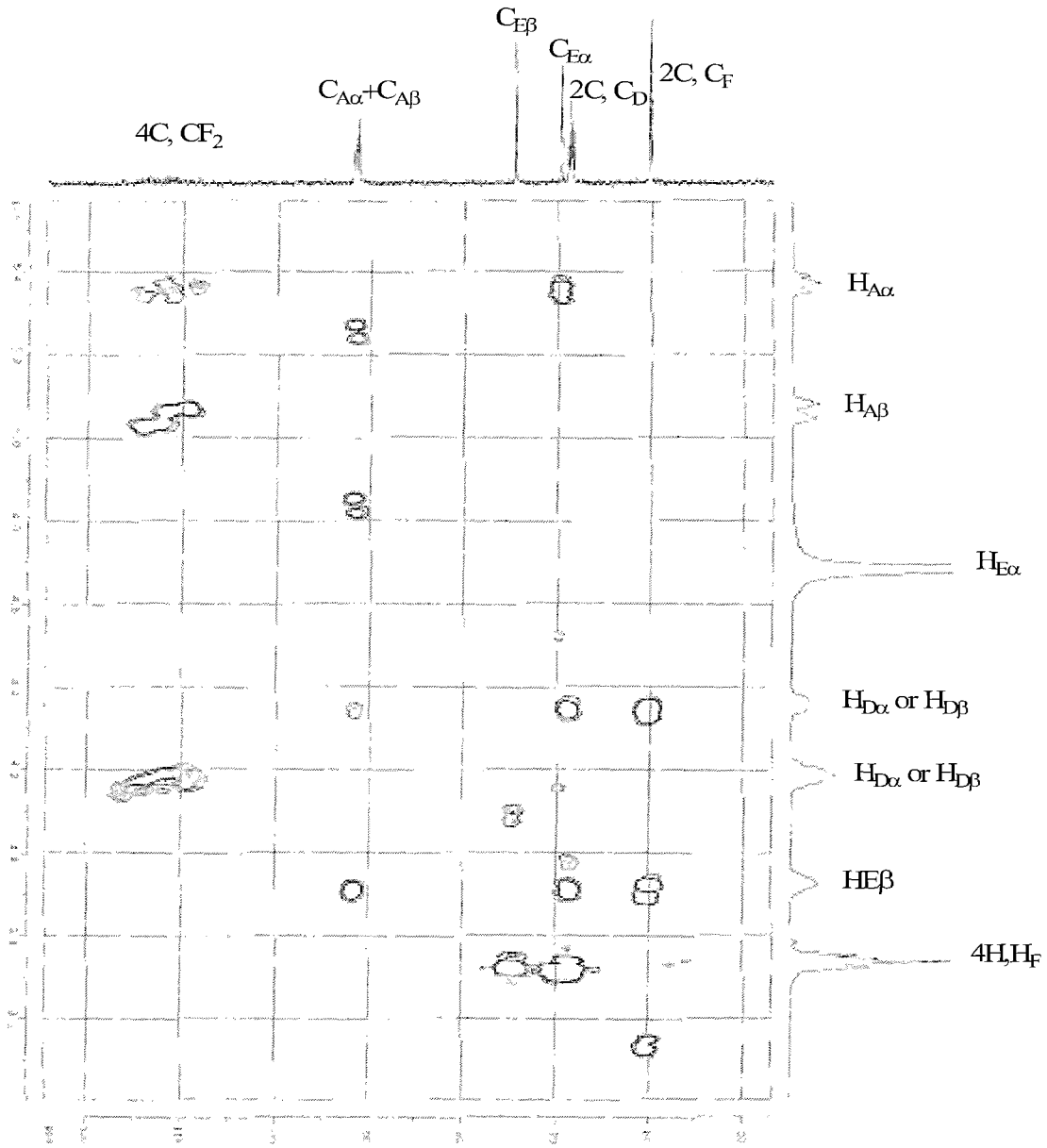


Figure 3.9

2,3-dideoxy-2,2,3,3-tetrafluoro-galactose **3.14** was synthesized in 45% overall yield (61 % on a larger scale) from diol **1.4** and in 30% overall yield (50 % on a larger scale) from allyl benzyl ether **2.1**.

3.4.2.2. Assignment of α and β anomers of 1.1 and 3.14

The parameters used for the assignment of α and β anomers were the chemical shift of the anomeric proton and the $^3J_{H\text{-}F}$ values of the anomeric protons. It is known that for pyranoses, the anomeric proton of the α anomer has a higher chemical shift than the β anomeric proton.[78] The $^3J_{H\text{-}F}$ of the anomeric proton in the α anomer of 2-deoxy-2,2-difluorinated pyranoses is reported to be 6.3 Hz, while the reported value for the β anomer is 15.2 Hz.[41c]

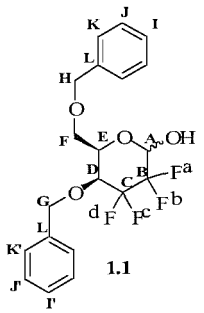
For **1.1**, the proton at δ 5.18 was assigned as the anomeric proton for the α anomer and the proton at δ 4.78 was assigned as the anomeric proton for the β anomer (400 MHz, $CDCl_3$). A $^3J_{H\text{-}F}$ = 5.9 Hz was found for the α anomer, which is in agreement with the literature data.[41c] For the β anomer, the $^3J_{H\text{-}F}$ value in the ^1H ($CDCl_3$, 400 MHz) and ^{19}F NMR ($CDCl_3$, 282 MHz,) did not match very well one with another, although both values were close to the literature data.[41c]

For **3.14**, the anomer with the anomeric proton at δ 5.52 was assigned as the α anomer, while the anomer with the anomeric proton at δ 5.21 was assigned as the β anomer (400 MHz, D_2O). A $^3J_{H\text{-}F}$ = 6.3 Hz was found for the α anomer, which is in agreement with the literature data.[41c] For the β anomer, the $^3J_{H\text{-}F}$ values in ^1H and ^{19}F NMR did not match very well one with another, although both values were close to the literature data.[41c]

The assignment of the fluorine atoms in the anomeric mixtures of both **1.1** and **3.14** as belonging to the α or to the β anomer and as $F_{a/b}$ or $F_{c/d}$ was aided by H-F correlation (Figure 3.11 for **1.1**).

The α- and β-protons have been assigned by COSY and HMQC and hence the cross peaks between the fluorine atoms and the protons assisted the assignment of the fluorine atoms in the anomeric mixture. Cross peaks have been observed between $H_{A\alpha}$ (δ 5.18) and $F_{\alpha\,(a/b)}$ (δ -119.54) and $F_{\alpha\,(b/a)}$ (δ-129.23) and between $H_{D\alpha}$ (δ 3.78) and $F_{\alpha\,(c/d)}$ (δ -134.21) and $F_{\alpha\,(d/c)}$ (δ -115.49), proving that the fluorine atoms are the fluorine atoms of the α-anomer as well as establishing the assignment of the fluorine atoms as $F_{\alpha\,(a/b)}$ and $F_{\alpha\,(c/d)}$. For the β-anomer, cross peaks have been observed between $H_{A\beta}$ (δ 4.78) and $F_{\beta\,(a/b)}$ (δ -138.53) and between $H_{D\beta}$ (δ 3.85-3.89, overlaps with $H_{E\beta}$) and $F_{\alpha\,(c/d)}$ (δ -130.81), $F_{\beta\,(c/d)}$ (δ -136.38) and $F_{\alpha\,(a/b)}$ (δ

-117.07). These cross peaks have supported the assignment of the fluorine atoms of the β-anomer.



1.1

Figure 3.10

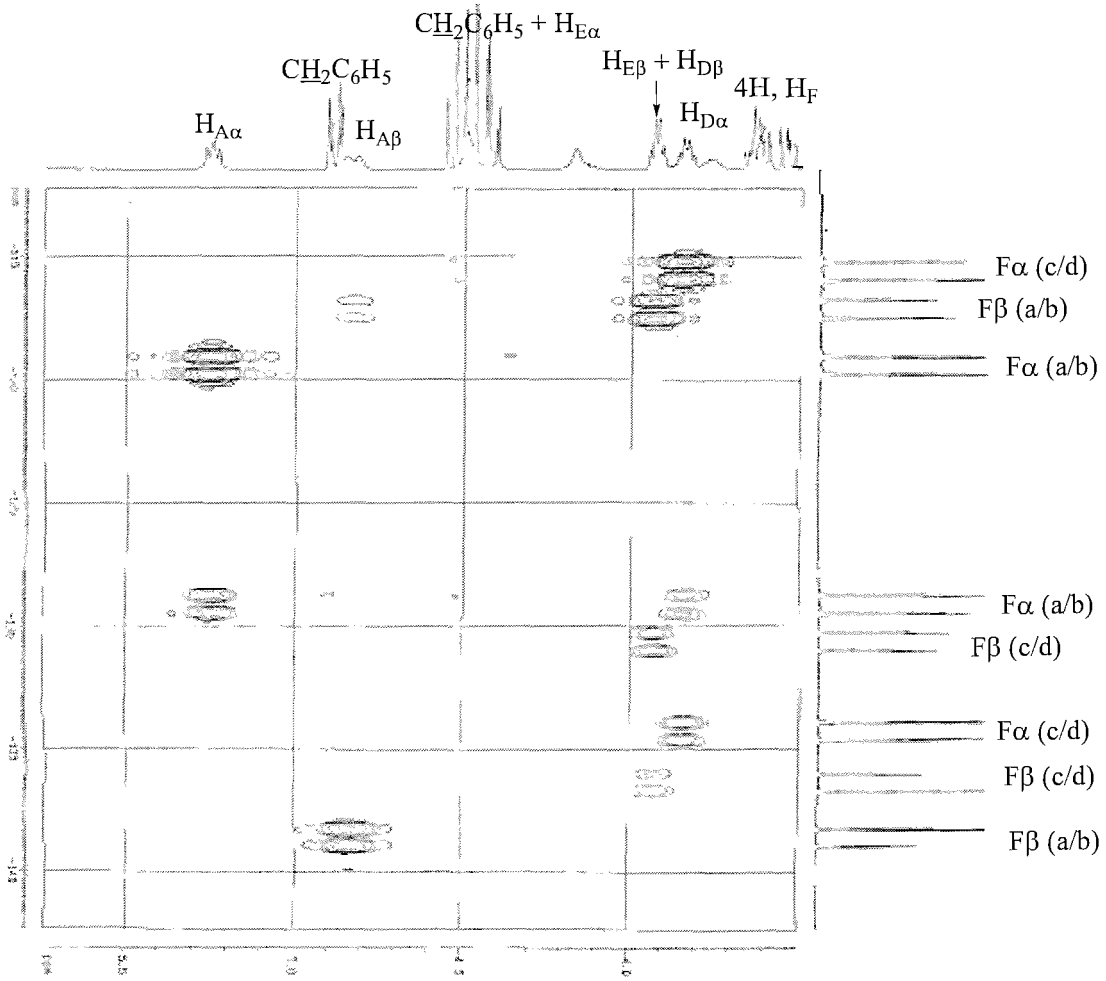


Figure 3.11

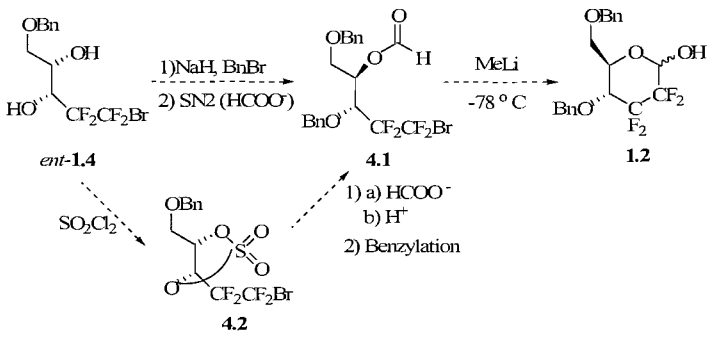
3.5. Summary

2,3-Dideoxy-2,2,3,3-tetrafluoro-galactose **3.14** was successfully synthesized from the diol **1.4**. Key steps involved the selective monobenzylation of the 1,2-diol moiety, and the anionic cyclization to give the pyranose ring. The synthesis was successfully carried out on a large scale. The formation of three side products was observed in the cyclization reaction, arising from the β-fluoride elimination, protonation and the reaction of the anionic intermediate with the MeBr byproduct. However, all these side products were isolated in <5 % yield, demonstrating the synthetic usefulness of the cyclization step.

Chapter 4. The Enantioselective Synthesis of 2,3-dideoxy-2,2,3,3-Tetrafluoro-Glucose

4.1. The Proposed Synthesis

As explained in the Introduction, the glucose synthesis required an inversion step at C5. The synthesis of **1.2** from *ent*-**1.4** was envisaged, as shown in Scheme 4.1. The first step in the synthesis would be the selective benzyl monoprotection at the hydroxyl at C3, followed by the S_N2 reaction at C2, to give **4.1**. An alternative route for the synthesis of **4.1** would be the S_N2 reaction with a formate at the C2 of the cyclic sulfate **4.2**, followed by the monobenzylation of the hydroxyl at C3. Anionic cyclization of **4.1** with MeLi would lead to the synthesis of **1.2**.

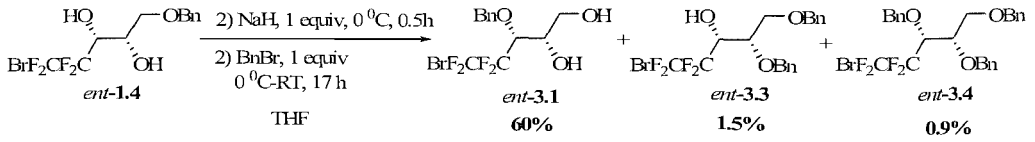


Scheme 4.1

4.2 Towards the Synthesis of 4.1

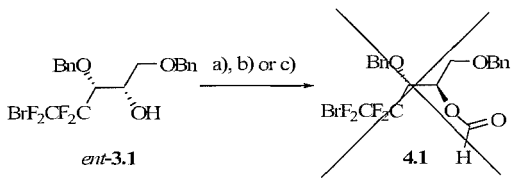
4.2.1 Mitsunobu Reaction

The selective benzyl monoprotection of diol **1.4** was presented in detail in Chapter 3. The best reaction conditions for the selective benzyl monoprotection of **1.4** were applied to the diol *ent*-**1.4**. The selective monoprotection of diol *ent*-**1.4** was accomplished with NaH/BnBr (Scheme 4.2). The desired product, *ent*-**3.1**, was synthesized in 60% yield.



Scheme 4.2

The attempts for the synthesis of **4.1** via the Mitsunobu reaction[79] failed. The parameters changed during the attempts were the solvent, the temperature and the order of addition of the reagents to the reaction (Scheme 4.3). The reaction time was between 18-69.5 h. However, even after such long reaction times, only the starting material was isolated after the reactions.



a)
1) DIAD (1.5 equiv) was added to PPh_3 (1.5 equiv) in THF, 0 °C, 0.5 h
2) Add ROH (1 equiv), HCOOH (3.0 equiv) at 0°C
3) Reaction at RT, 69.5 h.

b)
1) DIAD (2 equiv) in THF, was added to a solution of (*ent*-**3.1** (1 equiv), PPh_3 (2 equiv), HCOOH (3 equiv) in THF), RT
2) Reaction at RT for 18 h

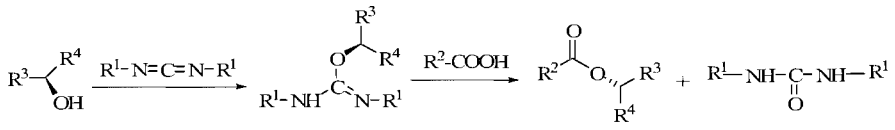
c)
1) DIAD (2 equiv) in toluene was added to a solution of (*ent*-**3.1** (1 equiv), HCOOH (2 equiv), PPh_3 (2 equiv) in toluene), 0 °C
2) 0 °C- RT, 68 h

Scheme 4.3

4.2.2. The Isourea Mediated S_N2

4.2.2.1. Introduction

Mathias [80] developed the isourea mediated ester formation, which occurs with inversion (Scheme 4.4).

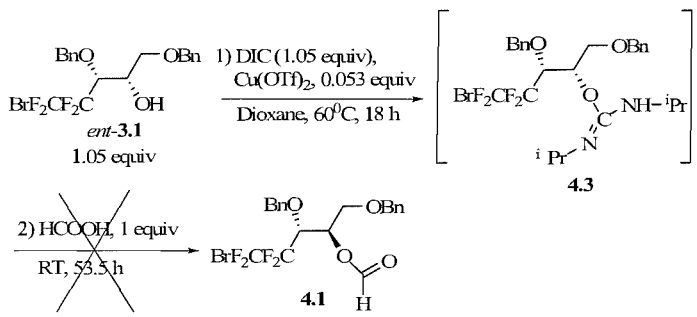


Scheme 4.4

The reaction involves two steps: the isourea formation and the reaction of the isourea with the acid. *O*-Alkylisoureas are easily formed by the addition of an alcohol to a dialkylcarbodiimide under copper catalysis (CuX or CuX_2).[80] Literature precedent revealed that the synthesis of formates mediated by DCC/ CuCl[81] or DIC/ $Cu(OTf)_2$[82] leads to high yields of the desired products.

4.2.2.2. Results and Discussion

The attempted synthesis of **4.1** is depicted in Scheme 4.5. The monoprotected diol *ent*-**3.1** was reacted with DIC and $Cu(OTf)_2$ in dioxane at 60 °C for 18 h. The formation of the isourea **4.3** after the first step was proven by the appearance of the isourea peak in the IR spectrum (1655 cm^{-1}) and by the disappearance of the carbodiimide peak (2110 cm^{-1}). The isourea was not isolated and was treated immediately with HCOOH. After 53.5 h at RT, ^1H NMR proved that the crude reaction was mainly the starting material *ent*-**3.1**. It was hypothesized that the isourea has been hydrolyzed by the moisture, to give the starting material.

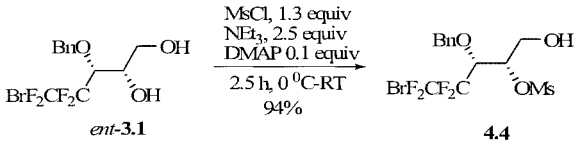


Scheme 4.5

Given that the synthesis of the formic ester **4.1** by DIC/$Cu(OTf)_2$ method was difficult to control, it was decided to investigate the typical S_N2 reaction at C2 of *ent*-**3.1**.

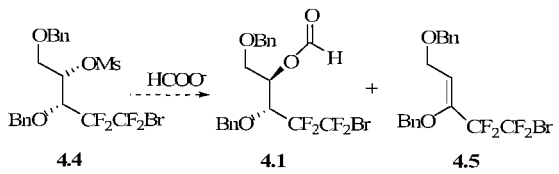
4.2.3. Inversion via the Mesylate

In order to transform the hydroxyl at C2 of *ent*-**3.1** to a better leaving group for the S_N2 reaction, mesylate **4.4** was synthesized (Scheme 4.6). The reaction of *ent*-**3.1** with 1.3 equiv of MsCl in the presence of NEt_3 and DMAP gave **4.4** in 94% yield.[83]



Scheme 4.6

The reaction of **4.4** with various formates is presented in Table 4.1. Apart from the synthesis of the nucleophilic substitution product (**4.1**), low yields of the elimination product (**4.5**) were expected (Scheme 4.7).



Scheme 4.7

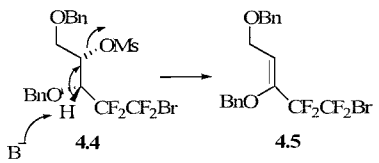
Entry	Nucleofile (equiv)	Additives (equiv)	Solvent	Temp (°C)	Time (h)	Yield 4.5 (%)	Yield 4.4[a] (%)
1	$HCOONH_4$ (2)	/	DMF	80	23.5	--	60
2	HCOONa (2)	18-C-6 (1)	DMF	50	18	14	59
3	HCOOCs (5)	/	DMF	80	16.5	40	20
4	HCOOCs (5)	DMAP(0.5)	Toluene	Reflux	16	50	0
5	HCOOH (3)	CsF (3)	DMF	50	19	14	60

[a] Recovered **4.4** after the reaction.

Table 4.1

The reaction of **4.4** with $HCOONH_4$ at 80 °C for 23.5 h led only to the recovery of the starting material (entry 1). Previous research has shown that for a variety of substrates the S_N2 reaction outstrips the elimination in the reaction of mesylates with carboxylates and 18-C-6 at high temperature.[84] However, the reaction of **4.4** with HCOONa and 18-C-6 in DMF at 50°C gave only the elimination product **4.5** (14% yield) and the unreacted starting material **4.4** (59%), after 18 h (entry 2). It is known that the S_N2 reactions with cesium salts are more efficient than the reactions with other metal salts.[85] The "cesium effect" is attributed to the better solubilities of the cesium salts and the generation of highly reactive "naked anions".[86] However, the reaction of **4.4** with HCOOCs in DMF at 80 °C gave only the elimination product (40%) and the unreacted starting material (20%) after 16.5 h (entry 3). In spite of the fact that it was reported that cesium formate in the presence of DMAP in toluene is less reactive that other cesium carboxylates, [87] these reaction conditions were tested with substrate **4.4**. The reaction of **4.4** with HCOOCs and DMAP in refluxing toluene gave 50% of the elimination product **4.5** after 16 h (entry 4). Otera *et al.* have demonstrated that the S_N2 reaction of activated alcohols with carboxylic acids in the presence of CsF in DMF proceeds with clean inversion.[88] Nevertheless, with substrate **4.4**, only the elimination product (14% yield) and the unreacted starting material (60%) were isolated after 19h (entry 5).

Since the S_N2 reaction did not occur under the conditions shown in Table 4.1, it was concluded that with substrate **4.4**, the elimination is favored over the substitution. It is proposed that the reaction is an E2 elimination reaction (Scheme 4.8).



Scheme 4.8

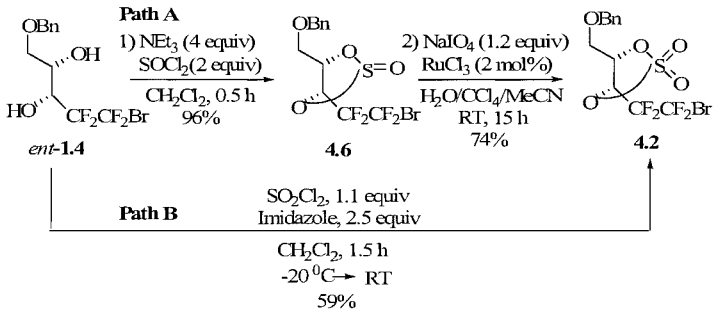
The elimination reaction could be favored over the substitution reaction at C2 of **4.4** because C2 is hindered and because the proton at C3 has an increased acidity, instilled by the electron withdrawing character of the $-(CF_2)_2Br$ group.

4.2.4. The S_N2 Reaction of the Cyclic Sulfate 4.2

4.2.4.1. Synthesis of the Cyclic Sulfate 4.2

The two most popular ways of synthesizing cyclic sulfates are the synthesis of a cyclic sulfites followed by oxidation to the cyclic sulfates and the direct synthesis of the cyclic sulfates from vicinal diols.[89]

Two stereoisomeric cyclic sulfites **4.6** were synthesized in the reaction of *ent*-**1.4** with thionyl chloride (Scheme 4.9, path A). The two stereoisomeric sulfites **4.6** had similar R_f values and their separation by column chromatography was not achieved. Hence, the ratio between the stereoisomers was not determined, although analytically pure samples were obtained for both stereoisomers. The oxidation of the cyclic sulfite **4.6** (mixture of stereoisomers) with $RuCl_3/NaIO_4$ to the cyclic sulfate **4.2** proceeded in 74% yield. Cyclic sulfate **4.2** was synthesized in 71% overall yield from *ent*-**1.4** (Scheme 4.9, path A). Further optimization for the synthesis of **4.2** by this route was not attempted.



Scheme 4.9

The one-step synthesis of **4.2** from *ent*-**1.4** and sulfuryl chloride was attained in 59% yield (Scheme 4.9, path B).[89] One byproduct was observed, presumably as a result of the

substitution reaction with chlorine. Time has not been spent for the purification and characterization of this
compound.

4.2.4.2. The S_N2 Reaction of the Cyclic Sulfate 4.2

4.2.4.2.1. Introduction

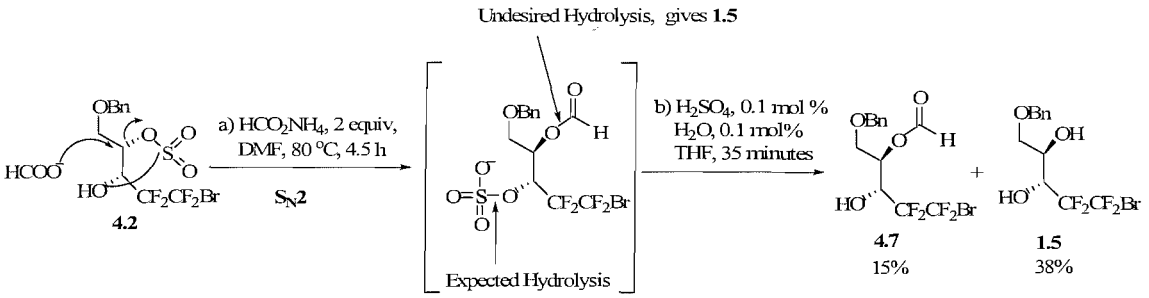
The reaction of cyclic sulfates with nucleophiles involves two steps: the S_N2 reaction, followed by the hydrolysis of the sulfate ester intermediate. The general hydrolysis conditions are 20% aqueous H_2SO_4 in Et_2O, while for substrates containing acid labile groups the hydrolysis could be undertaken with a catalytic amount of concentrated H_2SO_4 and 0.5-1.0 equivalents of H_2O in THF, with the acid labile functional groups found intact after the reaction.[90] The S_N2 reaction with cyclic sulfates generally leads to the formation of two regioisomeric products.

Sharpless[91] and Qing[68 b,c] have reported that the S_N2 reaction of cyclic sulfates containing perfluoroalkyl groups adjacent to the cyclic sulfate functionality occurs regioselectively at the Cβ to the perfluoroalkyl groups. The reason for the regioselectivity is that generally S_N2 reactions do not occur at a Cα to perfluorolakyl groups, testimony of the stereoelectronic effects of the perfluoroalkyl group.[43] However, examples of the S_N2 reaction occurring at Cα to perfluorolakyl groups could be found, for example for perfluoroalkyl-containing mesylates.[92] The S_N2 reaction of perfluoroalkyl group-containing cyclic sulfates was developed with a range of nucleophiles, including carboxylates.[68b,c] To our knowledge, the S_N2 reaction of cyclic sulfates with formates has not been published to date.

4.2.4.2.2. Results and Discussion

Following Qing's procedure of S_N2 reaction of CF_3-containing cyclic sulfates with benzoates, [68b, c] cyclic sulfate **4.2** was treated with 2 equiv ammonium formate at 80 °C. The hydrolysis of the sulfate ester intermediate was undertaken with 0.1 mol% H_2SO_4, 0.1 mol% H_2O in THF. The inversion occurred regioselectively at C2 of **4.2**. The products

isolated after the reaction were the desired product **4.7** (15% yield) and **1.5** (38%) (Scheme 4.10). It was hypothesized that during the hydrolysis step the formate functionality **4.7** was hydrolyzed to give **1.5**.



Scheme 4.10

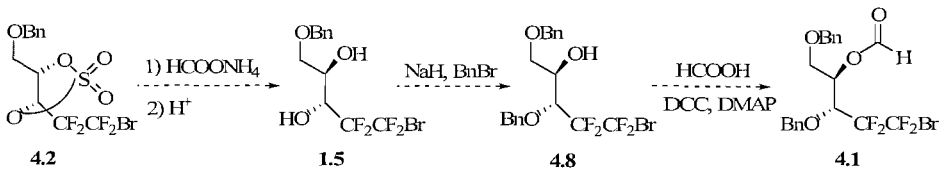
A shorter hydrolysis time (13 minutes *vs.* 35 minutes, Scheme 4.10) gave 22% of **4.7**. Diol **1.5** was not isolated under these conditions and the balance for the missing material was accounted for the unhydrolysed sulfate ester intermediate. Further optimization for the synthesis of **4.7** by this route was not undertaken.

4.3. Synthesis of 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Glucose 4.13

4.3.1. Revised Route for the Synthesis of 4.1

Since the synthesis of **4.1** by all the attempted methods was unsuccessful, it was considered that a modification of the route for the synthesis of **4.1** was necessary. The proposed alternative route for the synthesis of **4.1** is shown in Scheme 4.11.

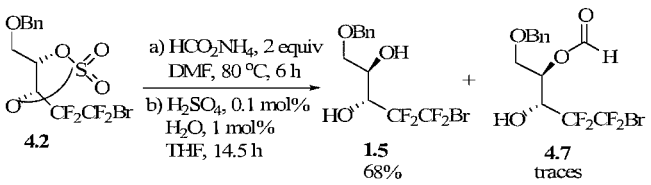
Diol **1.5** could be a precursor for **4.1** and the optimization of the synthesis of diol **1.5** by the S_N2 reaction of the cyclic sulfate **4.2** was envisaged. The following step would be the selective benzyl monoprotection of the hydroxyl in the α-position to the perfluoroalkyl group in **1.5**, followed by the formic ester formation at C2 of **4.8**.



Scheme 4.11

4.3.2. The Synthesis of *Anti* Diol 1.5

It was envisaged that for the synthesis of **1.5** from **4.2**, the optimization of the hydrolysis step is necessary. The optimization of the hydrolysis conditions for the hydrolysis of both the sulfate ester and the formate functionality was aimed. Sharpless stated that in the hydrolysis of sulfate esters containing acid labile functionality groups, the use of the minimum amount of water is crucial to achieve the desired chemoselectivity.[91] Consequently, since the hydrolysis of both the sulfate ester and the formate functionality was desired, the amount of H_2O used in the hydrolysis step was increased ten-fold (Scheme 4.12).



Scheme 4.12

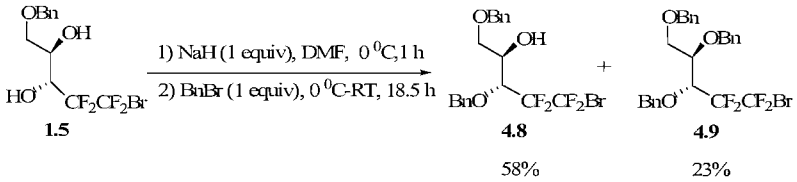
Under these conditions, after 14.5 h for hydrolysis, **1.5** was synthesized in 68% yield and only traces of **4.7** were isolated. Since *anti* diol **1.5** was synthesized in 68% yield, time has not been spent in further optimization of this reaction.

4.3.3. Synthesis of 2,3-Dideoxy-2,2,3,3-Tetrafluoro-Glucose 4.13

The next steps for the 2,3-dideoxy-2,2,3,3-tetrafluorinated glucose synthesis would be the selective benzyl monoprotection at C3 of **1.5**, followed by the formic ester formation at C2

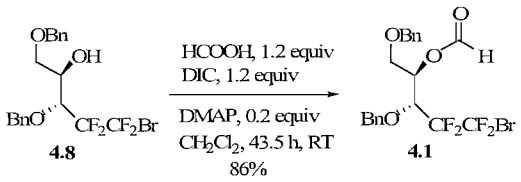
of **4.8** and anionic cyclization. These steps were presented in detail in Chapter 3 and no further details are presented here.

The selective benzyl monoprotection of **1.5** proceeded in 58% yield after 18.5 h with NaH, BnBr. The dibenzyl protected diol was synthesized in 23% yield (Scheme 4.13).



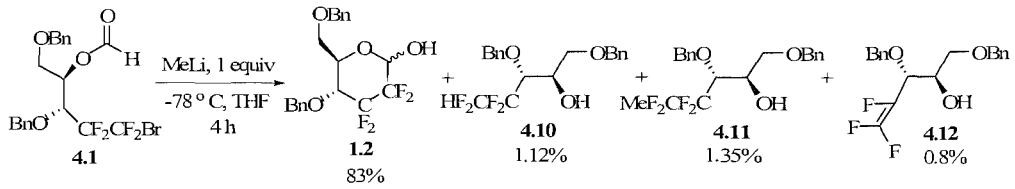
Scheme 4.13

Formic ester **4.1** was synthesized in 86% yield, after 43.5 h (Scheme 4.14).



Scheme 4.14

Anionic cyclisation of formate **4.1** with 1 equiv MeLi at -78°C led to 83% of the expected 4,6-dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-glucose **1.2** and low yields of the byproducts **4.10**, **4.11** and **4.12**. The byproducts are diastereoisomeric isomers of the byproducts obtained in the synthesis of 4,6-dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-galactose **1.1** and their formation was discussed in Chapter 3.

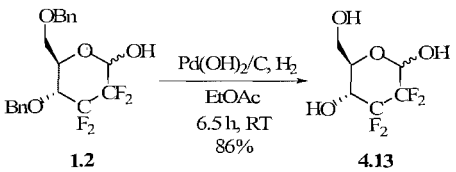


Scheme 4.15

As in the case of the side products synthesised in the synthesis of **1.1** (Chapter 3), the proposed structure of **4.10** was confirmed by the *J* value between the proton and the fluorine atoms in the $-CF_2H$ moiety ($^2J_{HF}$=53.5 Hz). The proposed structure of **4.11** was confirmed by the *J* value between the protons of the methyl group and the fluorine atoms in the $-CF_2CH_3$ moiety (^3J=19.3 Hz).

The attempted separation of the α-and the β-anomers of **1.2** failed (eluent for the HPLC: Hexane/EtOAc: 80/20). The anomeric ratio was determined by the ratio of the integrals of protons and fluorine atoms in ^{1}H NMR and ^{19}F NMR respectively. The α/β anomeric ratio in the anomeric mixture was 1/1.06 by ^{1}H NMR (Acetone, 400 MHz), and 1/1.07 by ^{19}F NMR ($CDCl_3$, 282 MHz).

Deprotection of **1.2** with H_2, $Pd(OH)_2/C$ gave 2,3-dideoxy-2,2,3,3-tetarfluro-glucose **4.13** in 86% yield (Scheme 4.16).



Scheme 4.16

The separation of the α- and β-anomers of **4.13** failed (eluent for HPLC: neat EtOAc). The anomeric ratio was determined by the ratio of the integrals of protons and fluorine atoms in ^{1}H NMR and ^{19}F NMR respectively. The anomeric ratio in the anomeric mixture was α/β: 1/1.09 by ^{1}H NMR (D_2O, 400 MHz) and α/β: 1/1.02 by ^{19}F NMR (D_2O, 282 MHz).

2,3-dideoxy-2,2,3,3-tetrafluoro-glucose **4.13** was synthesized in 14.3 % overall yield from diol *ent*-**1.4** and in 12% overall yield from allyl benzyl ether **2.1**.

4.3.4 Assignment of the α and β Anomers of 1.2 and 4.13

The theoretical background for the assignment of the α- and β-anomers was presented in Chapter 3.

For **1.2**, the proton at δ 5.40 was assigned as the anomeric proton for the α anomer and the proton at δ 5.08 was assigned as the anomeric proton for the β anomer (400 MHz, Acetone). The $^{3}J_{H\text{-}F}$ value in the ^{1}H (400 MHz, Acetone) and ^{19}F NMR (282 MHz, $CDCl_3$) for the α anomer did not match very well one with another, although they were close to the value stated in the literature for the $^{3}J_{H\text{-}F}$ of the α anomer of 2-deoxy-2,2-difluorocarbohydrates.[41c] A $^{3}J_{H\text{-}F}$ = 15.3 Hz was found for the β anomer, which is in agreement with the literature data.[41c]

For **4.13**, the anomer with the anomeric proton at δ 5.48 was assigned as the α anomer, while the anomer with the anomeric proton at δ 5.20 was assigned as the β anomer (400 MHz, D_2O). The $^{3}J_{H\text{-}F}$ value in the ^{1}H (400 MHz, D_2O) and ^{19}F NMR (282 MHz, D_2O) for the α anomer did not match very well one with another, although the values were close to the value stated in the literature for the $^{3}J_{H\text{-}F}$ of the α anomer of 2-deoxy-2,2-difluorocarbohydrates.[41c]. A $^{3}J_{H\text{-}F}$ = 15.3 Hz was found for the β anomer, which is in agreement with the literature data.[41c]

4.4. Summary

- 2,3-Dideoxy-2,2,3,3-tetrafluoro-glucose was successfully synthesized from diol *ent*-**1.4**;

- Four methods were investigated for the inversion at C5 (sugar numbering): Mitsunobu inversion, inversion via the isourea, via the mesylate intermediate and via the cyclic sulfate. Only the cyclic sulfate led to the successful reaction.

However, the obtained formate appeared to be unstable towards the subsequent hydrolysis step, leading to the synthesis of *anti*-1,2-diol **1.5**.

- The proposed synthesis of 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose was adjusted and *anti*-diol **1.5** was considered the precursor of **1.2**;

- The cyclic sulfate **4.2** was synthesized in 59% from *ent*-**1.4**;

- *Anti*-diol **1.5** was synthesized in 68% yield from the cyclic sulfate **4.2**;

- The benzyl monoprotected diol **4.8** was synthesized in 58% yield from diol **1.5**;

- Formic ester **4.1** was synthesized in 86% yield from **4.8**;

- 4,6-dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-glucose **1.2** was synthesized in 83% yield from **4.1**;

- 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose **4.13** was synthesized in 86% yield from **1.2**;

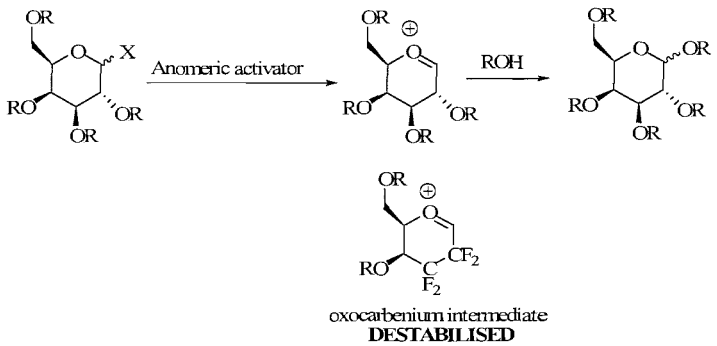
- 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose **4.13** was synthesized in 14.3 % overall yield from diol *ent*-**1.4** and in 12% overall yield from allyl benzyl ether **2.1**.

Chapter 5. Anomeric Alkylation

5.1. Conventional Glycosylation for 2-Deoxy-2,2-Difluoro-Carbohydrates?

Glycosylation of biological active compounds has a remarkable influence on the biological activity, for example for modulating pharmacological and pharmacokinetic properties, and governing the specificity at the tissue, cellular and/or molecular level.[93] Hence, incorporation of polyfluorianted sugars into biologically active compounds is a main future goal.

To our knowledge, the glycosylation of 2-deoxy-2,2-difluoro-carbohydrates and of 2,3-dideoxy-2,2,3,3-tetrafluoro-carbohydrates is not well developed to date. It is expected that glycosylation of 2-deoxy-2,2-difluoro-carbohydrates by the conventional glycosylation reactions (which typically have S_N1 character) would be impeded by the destabilizing effect of the fluorine atoms on the adjacent oxocarbonium ion intermediate (Scheme 5.1).

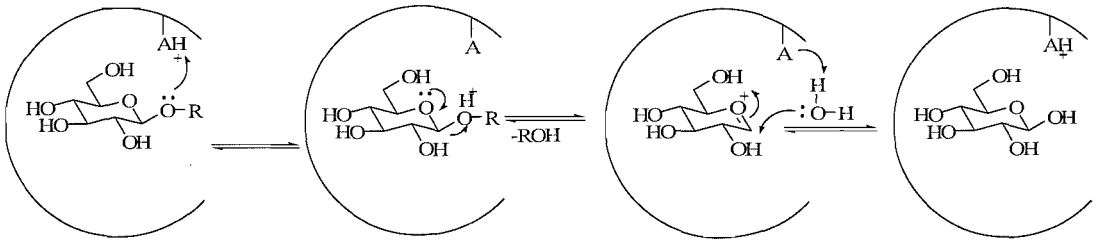


Scheme 5.1

Tidwell *et al.* have shown that solvolysis reactions of 2-(trifluoromethyl)-2-propyl triflate occur at much lower rates than the solvolysis of isopropyl triflate and that the cationic transition state is destabilized by the electron withdrawing effect of the $-CF_3$ group.[94] Olah *et.al* have shown that 1,1,1-trifluoropropanol does not ionize, even in the superacid conditions (FSO_3H-SbF_5-SO_2); instead, the alcohol is quantitatively protonated.[95] These

examples prove the inability of a full cationic charge to form at a carbon adjacent to perfluoroalkyl groups.

It has been demonstrated that the enzymatic hydrolysis by glucosidazes proceeds through the formation of an oxocarbenium ion transition state (Scheme 5.2).[96]



Scheme 5.2

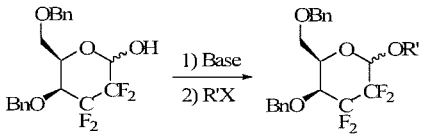
Consequently, the substitution of the C-2 hydroxyl with a fluorine atom should destabilize the transition state and decrease the rate of hydrolysis.[97] On these grounds, 2-deoxy-2-fluoro carbohydrates and 2-deoxy-2,2-difluoro-carbohydrates are used as glucosidase inhibitors.

Withers and co-workers have demonstrated that 2,4-dinitrophenyl-2-deoxy-2-fluoro-glucopyranoside[96] and 2',4',6'-trinitrophenyl 2-deoxy-2,2-difluoro-hexopyranoside[97] inhibit the hydrolytic activity of galactosidases. Withers *et al.* have studied the role of sugar substituents in glycoside hydrolysis.[23] The rate of the hydrolysis for the deoxyfluoro-carbohydrates decreases as follows: parent > 6-deoxyfluoro > 3-deoxyfluoro > 4-deoxyfluoro > 2-deoxyfluoro.[23] The low rate of the hydrolysis of 2-deoxyfluoro carbohydrates is a strong evidence of the destabilizing effect of the fluorine atom on the adjacent oxocarbonium ion intermediate.

These considerations together with the consideration that the fluorine effect is cumulative (*i.e.* perfluoroalkyl groups are more electron-withdrawing than trifluoromethyl groups), dictate that a good leaving group and/or strong ionizing conditions are necessary for the effective substitution at the anomeric position of polyfluorinatred carbohydrate analogues.[15a]

In Section 5.2.2.2 are presented a number of literature precedents relevant for the description of the up to date progress in the glycosylation of 2-deoxy-2,2-difluoro carbohydrates and polyfluorinated carbohydrates. However, to our knowledge, a methodology for the glycosylation of 2-deoxy-2,2-difluoro carbohydrates and polyfluorinated carbohydrates has not been developed thus far.

The proposed alternative for the glycosylation of 2-deoxy-2,2-difluoro carbohydrates and heavily fluorinated carbohydrates is anomeric alkylation. The anomeric alkylation of 4,6-dibenzyl-2, 3-dideoxy-2,2,3,3-tetrafluoro-galactose **1.1** was envisaged (Scheme 5.3).



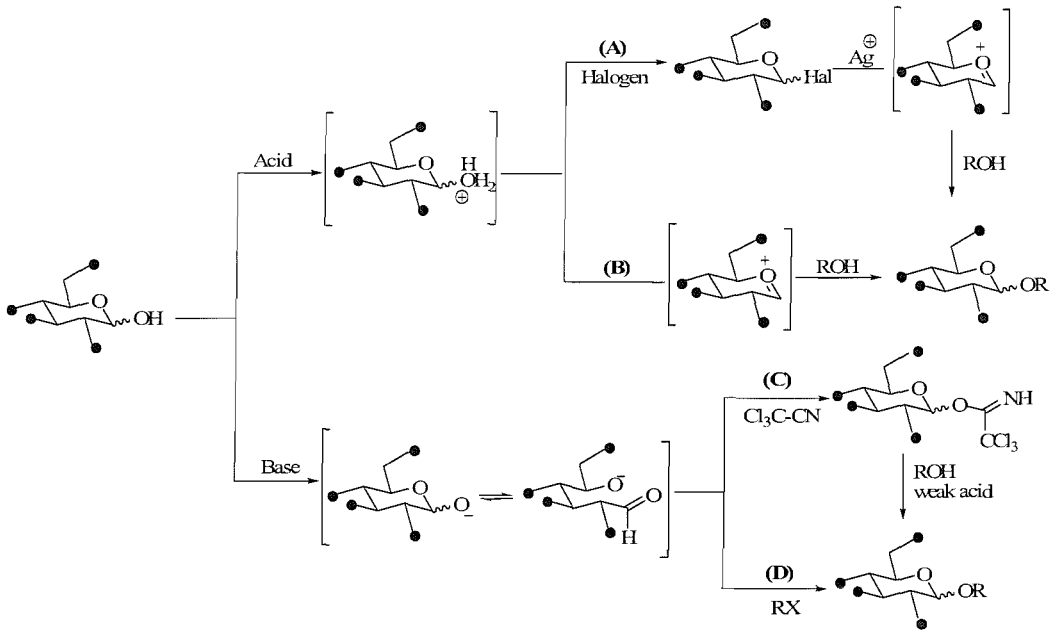
1.1 **5.1**, R'= Me
5.4, R'= $C_{18}H_{37}$

Scheme 5.3

5.2. Introduction

5.2.1. General Glycosylation Methods

The most known methods for the glycosylation of carbohydrates are depicted in Scheme 5.4.[36, 38]



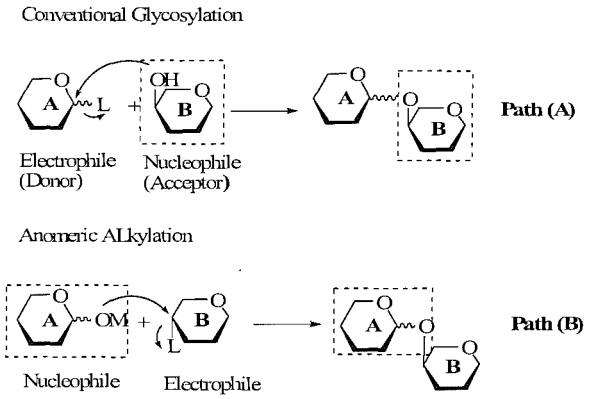
[A]: Koenigs-Knorr method; [B]: Fischer –Helferich method;
[C]: Trichloroacetimidate method; [D] Anomeric Alkylation.

Scheme 5.4[36]

The Koenigs-Knorr method uses glycosyl bromides and chlorides as donors in the glycosylation reaction and Ag- or Hg-salts to promote the reaction (Scheme 5.1, path A).[36] Both the Koenigs-Knorr and the Fischer –Helferich method (Scheme 5.1, path B) involve the formation of an oxocarbenium ion intermediate, which is subsequently attacked by the nucleophile.[36] The anomeric alkylation method (Scheme 5.1, path C) involves deprotonation of the anomeric hydroxyl and the generated anomeric oxide is then alkylated, leading directly and irreversibly to a glycoside. In the trichloroacetimidate method the anomeric hydroxyl is activated by the reaction with trichloroacetonitrile. The formed tricholoroacetimidate reacts further with the nucleophile under acid catalysis, leading to the glycosylation product. The trichloroacetimidate method also involves the oxocarbenium-ion type intermediate.[36]

In the conventional glycosylation methods the glycosidic bond is formed by the nucleophilic attack of the aglyconic oxygen (Scheme 5.5, path A).[38] In contrast, in the anomeric alkylation and the trichloroacetimidate formation the glycosydic bond is formed by nucleophilic attack of the anomeric oxygen (Scheme 5.5, path B).[38] In the anomeric

alkylation the anomeric oxygen is retained in the glycosidic bond and there is inversion of configuration at the carbon containing the leaving group (in the electrophile).



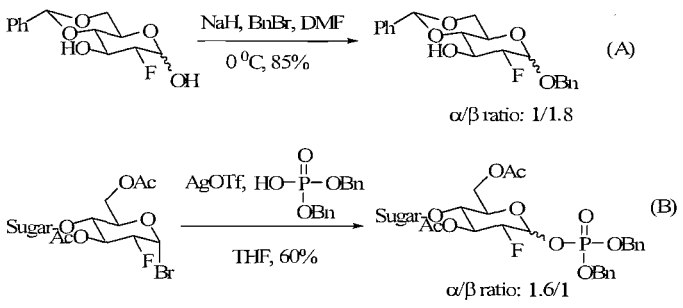
Scheme 5.5

5.2.2. Glycosylation of C-2 Fluorinated Carbohydrates

5.2.2.1. Glycosylation of 2-Deoxy-2-Fluoro-Carbohydrates

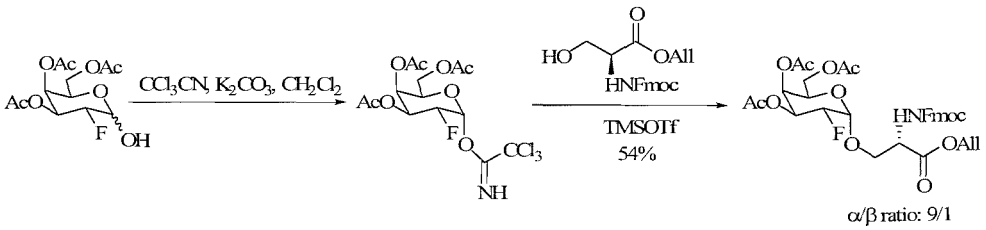
Both acidic (involving an oxocarbenium ion intermediate) and basic mediated glycosylation methods proved to be fruitful in the case of 2-deoxy-2-fluorocarbohydrates.

Imperiali *et al.* have demonstrated that the anomeric alkylation and Koenigs-Knorr type glycosylation are successful for 2-deoxy-2-fluoro-glucose derivatives (Scheme 5.6).[99]



Scheme 5.6

Dax *et al.* reported that the glycosylation of tri-O-acetyl-2-deoxy-2-fluoro-D-galactopyranose by Koenigs-Knorr method gave an unalluring mixture of anomers, while the trichloroacetimidate method led to the formation of an α/β mixture in a 9/1 ratio (Scheme 5.7).[100]

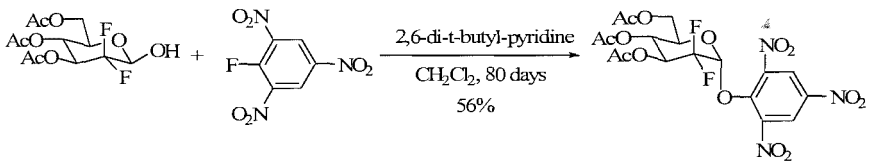


Scheme 5.7

5.2.2.2. Glycosylation of 2-Deoxy-2,2-Difluoro-Carbohydrates

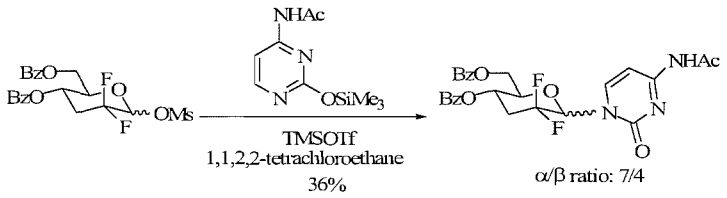
Our literature research on the glycosylation reactions of 2-deoxy-2,2-difluoro-carbohydrates did not furnish examples of glycosylation by the conventional glycosylation methods. However, examples of glycosylation achieved by the alternative methods (S_NAr reactions or reactions with a S_N1 character (excluding the typical glycosylation reactions)) could be found.

Whithers *et al.* published the S_NAr of picryl fluoride with tri-O-acetyl-2-deoxy-2,2-difluoro-D-galactopyranose (Scheme 5.8).[97] In the conventional glycosylation methods, the carbohydrate is the electrophile; in this example the authors used the carbohydrate as the nucleophile in a S_NAr reaction.



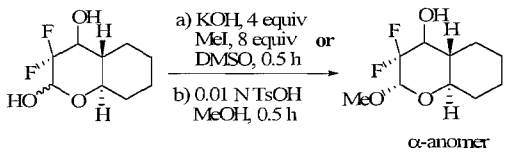
Scheme 5.8

Castillon *et al.* have shown a nucleophilic displacement reaction (S_N1) at the anomeric mesylate of a 2-deoxy-2,2-difluorocarbohydrate mimic (Scheme 5.9).[101]



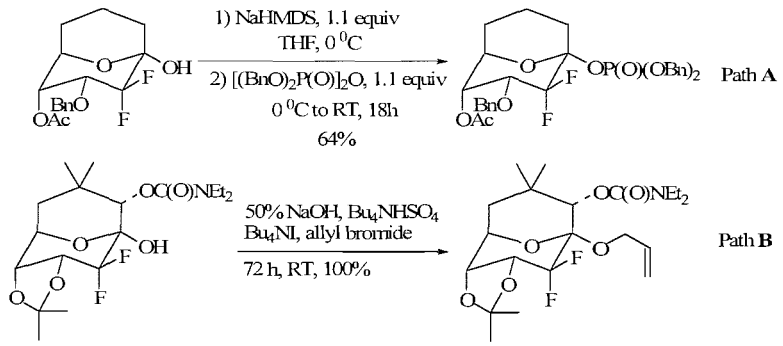
Scheme 5.9

Fried *et al.* have described the anomeric alkylation and the methanolysis of difluorinated cyclic hemiacetals (Scheme 5.10).[102] To our knowledge, this is the first example of anomeric alkylation of C-2 difluorinated carbohydrate mimics. The embryonic character of the research on this field could explain the utilization of a large excess of base and alkylating agent. Unfortunately, the reaction yield was not stated and thus a conclusion regarding the efficiency of the reaction using these conditions could not be obtained.



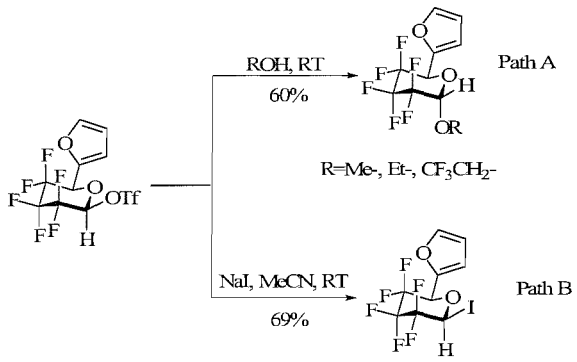
Scheme 5.10

In 2007 Percy *et al.* reported an example of anomeric alkylation of a 2-deoxy-2,2-difluorocarbohydrate analogue with tetrabenzyl pyrophosphate (Scheme 5.11, path A).[103a] A high yield of the product was obtained after the reaction with 1.1 equivalents of base and 1.1 equivalents of tetrabenzyl pyrophosphate, after 18 h. The quantitative allylation of a 2-deoxy-2,2-difluoro-carbohydrate mimic with aqueous NaOH and allyl bromide was also shown by Percy *et al.* (Scheme 5.11, path B).[103b]



Scheme 5.11

DiMagno *et al.* reported pioneering results on derivatization of a hexafluorinated hexose. It was shown that 1-tosyl, bromo and iodo derivatives are inert to anomeric activation. Only the anomeric triflate of DiMagno's hexafluorinated hexose could be displaced by a variety of nucleophiles. The authors have demonstrated the solvolysis of the triflate of the hexafluorinated hexose (Scheme 5.12, path A) as well as the nucleophilic substitution with a number of nucleophiles (Scheme 5.12, path B).[15a]



Scheme 5.12

It can be considered that the glycosylation of 2-deoxy-2, 2-difluoro carbohydrates by alternative methods illustrate the difficulty of the conventional glycosylation of these substrates.

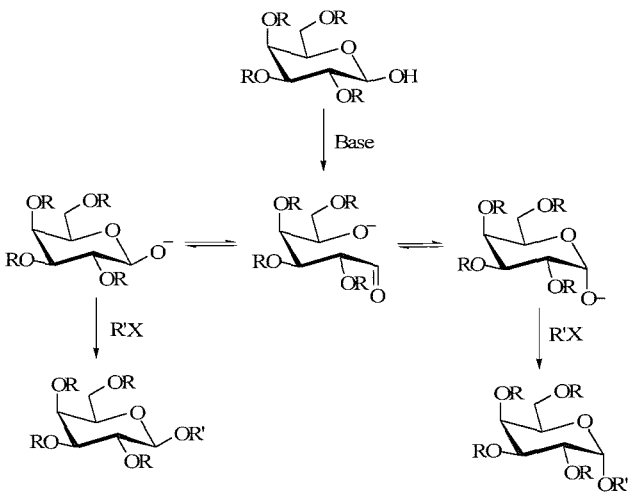
5.2.3. Anomeric Alkylation

Although the direct 1-*O*-alkylation of furanoses and pyranoses with simple alkylating agents (*i.e.* methyl iodide or dimethyl sulfate) has long been known, Schmidt and co-workers developed the anomeric alkylation reaction.[36]

The yield and stereoselectivity of the anomeric alkylation is controlled by the following factors: the dynamics of the alkoxide, the anomeric kinetic effect and the reaction conditions. Schmidt stated that for the furanoses the stereocontrol results mainly from steric and chelate effects, while for pyranoses, the rate of anomerization and the different reactivities of the α- and β-anomers are the most important factors.[36b]

A) The Dynamics of the Alkoxide

It is expected that the ring-chain tautomerization between the two anomeric forms and the open-chain form of the anomeric alkoxides (when the remaining ring-hydroxyl groups are protected) would give already three possible sites of attack of the alkylating agent (Scheme 5.13).[36b] Therefore, the ring-chain tautomerism could have an important role in determining the anomeric ratio of the product and in the alkylation of the acyclic form.

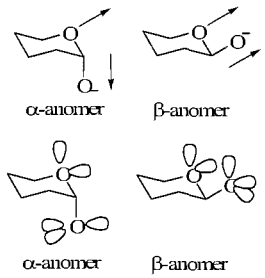


Scheme 5.13

B) The Anomeric Kinetic Effect

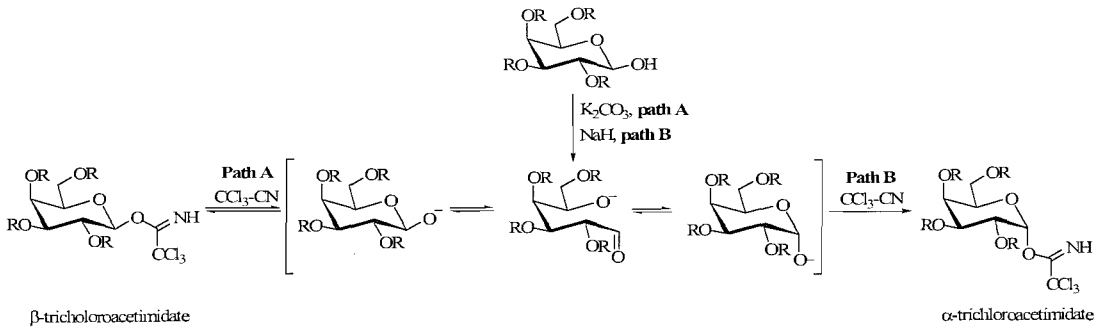
The higher nucleophilicty of the pyranosyl-β-oxides is defined as the anomeric kinetic effect.[36b, 104]

The anomeric kinetic effect leads to the formation of the thermodynamically less stable anomer, the β anomer.[36b] The kinetic anomeric effect is a result of the unfavourable dipole-dipole interactions and free orbital repulsion in the β-anomer (Scheme 5.14).[104] Hence, the accessibility of the free electrons to electrophiles is increased for the β-anomer and this leads to an enhanced reactivity.



Scheme 5.14

An excellent example of the anomeric kinetic effect is the formation of trichloroacetimidates. A detailed study has shown that β-trichloroacetimidates are formed preferentially or even exclusively under kinetic reaction conditions (Scheme 5.15, path A).[36b] However, the β-trichloroacetimidate formation is reversible and the back-reaction can be followed by anomerization and then the anomeric alkoxide reacts once more with the trichloroacetonitrile to lead to the thermodynamically more stable α-trichloroacetimidate (Scheme 5.15, path B).[36b,104] The higher reactivity of the equatorial anomeric oxide was demonstrated by the use of weak bases such as K_2CO_3, which do not catalyse the retroreaction. Thus, for instance, with K_2CO_3 [36b,105] the β-anomer is formed, while the utilization of NaH leads to the preferential formation of the α-anomer.[36b,104]



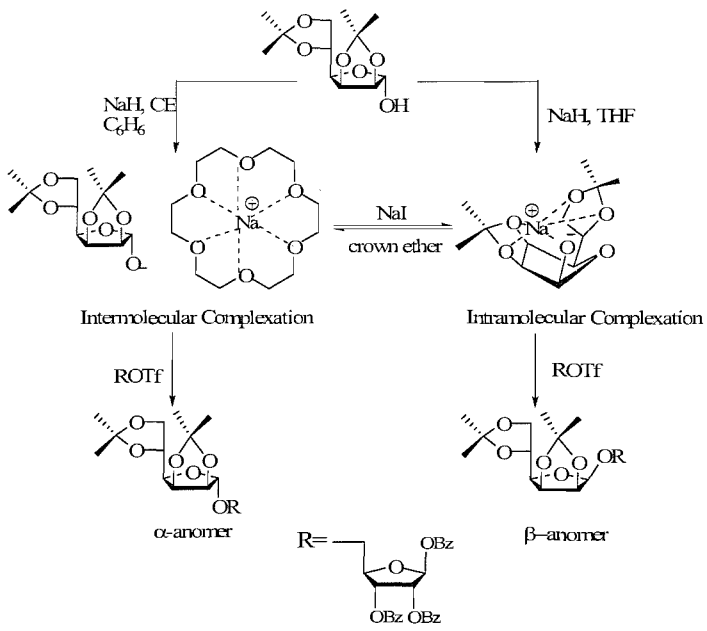
Scheme 5.15

C) Reaction Conditions

It has been shown that the *temperature* and *solvent* could play an important role in determining the stereochemistry of the anomeric alkylation product. Reactions of primary alkyl triflates with various pyranoses have shown that the equatorial product is formed in nonpolar solvents at RT and that the axial product is formed in polar solvents at temperatures below 0 °C.[36a,105]

Steric factors also play an important role in the stereochemistry of the anomeric alkylation product. Schmidt *et al.* indicated that the formation of the α-anomer is favoured by the presence of bulky protecting groups at *O*-6.[106]

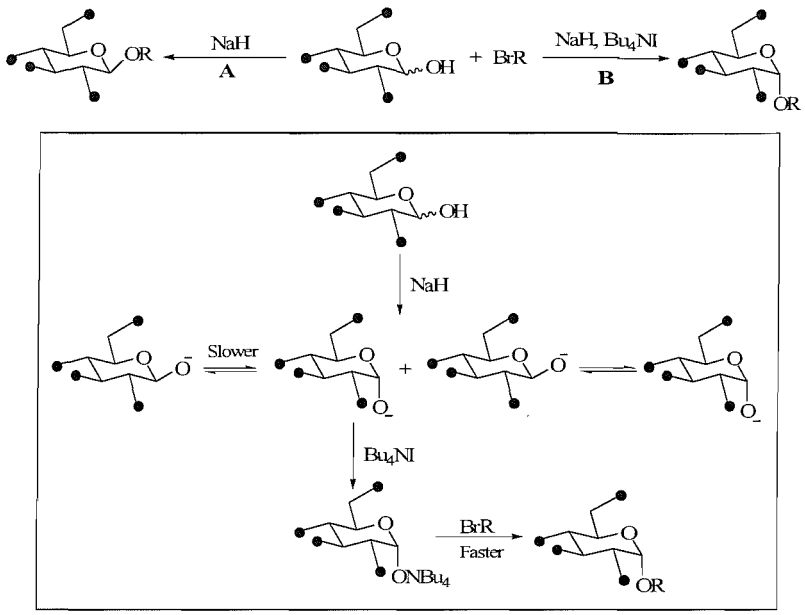
Schmidt *et al.* have shown that the control of *intra- or intermolecular complexation* of the metal ion (the counterion of the alkoxide) could lead to the preferential formation of the β- or α-anomer, respectively.[107]



Scheme 5.16

Whilst the intramolecular complexation is responsible for the high β-selectivity, the addition of an equimolar amount of the crown ether which complexes in an intermolecular fashion with Na^+ leads to high α-stereoslectivity. Addition of NaI leads to competition of the sodium ions for the crown ether and the α-alkoxide could equilibrate partly to the β-alkoxide.[107]

Lubineau *et al.* have demonstrated that the *reactivity of the alkoxide and the rate of the anomerization* could be controlled.[108] The authors have shown that the presence of tetrabutylammonium salts could influence the stereoselectivity of *O*-anomeric alkylation and increase the α-selectivity (Scheme 5.17).[108] This phenomenon was explained by the formation of tetrabutylammonium alkoxides which are more reactive than their sodium analogues. It is thought that the alkylation reaction become faster than the alkoxide anomerization.[108]



Scheme 5.17

It can be concluded that although the ring-chain equilibration in the anomeric alkoxides could permit the formation of many products, the regiocontrol of the glycoside bond formation is generally high. *O*-alkylation reactions at C-5 are generally not observed.[109]

5.3. Results and Discussion

2,3-Dibenzyl-2,3-didexoy-2,2,3,3-tetrafluoro-galactose **1.1** was used as a model for the anomeric alkylation experiments. This work is preliminary and the alkylation experiments were carried out with only two alkylating agents.

5.3.1. Anomeric Alkylation with MeI

Fried's[102] example of anomeric alkylation furnished a set of conditions for our initial experiments of anomeric alkylation reaction. The results of anomeric alkylation of **1.1** with KOH, MeI are presented in Table 5.1.

1.1 5.1

Scheme 5.18

Entry	MeI (equiv)	KOH (equiv)	Time (h)	Yield 5.1 (anomeric mixture) (%)	α / β ratio
1	8	4	1	70	1/1.5[a]
2	8	4	20	94	1/1.5[a]
3	**1.5**	**1.3**	**24**	**86[c]**	**1.1/1[b]**

[a] α / β ratio established by the ratio of the isolated yields of the α- and β-anomers;
[b] α/β ratio established by crude ^{19}F NMR;
[c] Calculated from the ratio of the integrals of the α- and β-anomers and of the starting material in ^{19}F NMR.

Table 5.1

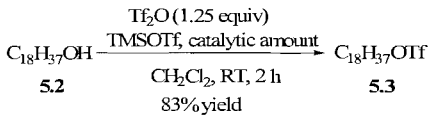
The utilization of a large excess of KOH (4 equiv) and MeI (8 equiv) in DMSO at RT, as in Fried's example of anomeric alkylation, led to 70% yield of **5.1** after 1 h. The anomeric ratio of α/β: 1/1.5 is in line with both the kinetic anomeric effect and the influence of temperature on the stereoselectivity of the reaction (entry 1). The yield increased to 94% after 20 h (entry 2). The first quest for the optimization of the conditions of anomeric alkylation was the reduction of the excess of KOH and MeI. Upon utilization of 1.3 equiv KOH and 1.5 equiv MeI, a high yield (86%) was obtained after 24 h (entry 3). The yield of the reaction obtained upon the utilization of a small excess of base is very similar to the yield obtained with a large excess of base (entry 2 *vs.* entry 3). The anomeric mixture contained traces of the starting material, even after column chromatography. The yield of the anomeric mixture (86%) could be calculated from the ratio of the integrals of the fluorine atoms of the α- and β-anomer and of the starting material in ^{19}F NMR. Under the conditions depicted in Table 5.1, the reaction is not highly stereoselective, *i.e.* the anomeric ratio is either α/β: 1/1.5 (entries 1 and 2) or α/β: 1.1/1 (entry 3). However, the stereoselectivity changes from the β-stereoselectivity to the α-stereoselectivity upon the

utilization of a smaller number of equivalents of the base. This is accounted for in the fact that with KOH, the deprotonation reaction is reversible. Hence, more kinetic product is formed with an excess of KOH. However, the selectivity is very poor and the reason could be the equilibration of the α- and β-alkoxide, allowed by the fact that the deprotonation of **1.1** with KOH is reversible.

5.3.2. Anomeric Alkylation with $C_{18}H_{37}OTf$

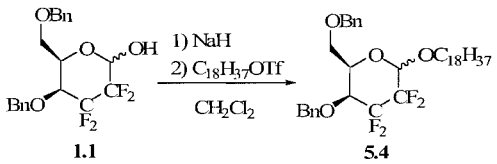
It has been proven that direct anomeric *O*-alkylation of carbohydrates with primary triflates is an efficient method of glycosylation.[36b] The glycosylation of sphingosines and ceramides has been well studied.[36b, 110,111] The glycosylation of **1.1** with **5.3** could be a model system for the glycosylation of 2-deoxy-2,2-difluoro-carbohydrates with sphingosines or ceramides.

Following a literature procedure, octadecyl triflate **5.3** was synthesized from octadecyl alcohol **5.2** and Tf_2O in 83% yield (Scheme 5.19).[112]



Scheme 5.19

The anomeric alkylation of **1.1** with **5.3** is presented in Table 5.2.



Scheme 5.20

Entry	Base (equiv)	5.3 (equiv)	Temp (°C)	Time (h)	α/β ratio	Yield 5.4 (anomeric mixture) (%)
1	NaH (2.075)	1.5	-10	24	9/91[a]	72
2	NaH (2.075)	1.5	RT	21.5	6/94[b] and 9/91[c]	79
3	**NaH (1.3)**	**1.3**	**RT**	**21**	**7/93[b,c]**	**78**

[a] α/β ratio established by the ratio of the isolated yields of the α- and β-anomers;
[b] α/β ratio established by crude ^{19}F NMR;
[c] α/β ratio established by ^{19}F NMR of the anomeric mixture.

Table 5.2

Following a literature precedent for the anomeric alkylation of carbohydrates with primary triflates, [113] **1.1** was treated with NaH and **5.3** in CH_2Cl_2.

The utilization of 2.075 equiv NaH and 1.5 equiv **5.3** at -10°C gave 72% yield after 24 h and an anomeric ratio α/β: 9/91. The increase of the temperature from -10°C to RT increased the yield slightly and did not modify the stereoselectivity (α/β: 9/91) (entry 1 *vs.* entry 2). The utilization of a smaller excess of NaH (1.3 equiv) and **5.3** (1.3 equiv) led to a similar yield to the yield obtained with a larger excess of NaH (2.075 equiv) and **5.3** (1.5 equiv). Since the deprotonation of **1.1** with NaH is not reversible, the stereoslectivity of the reaction did not change upon the utilization of a smaller excess of NaH. A higher stereoselectivity of the anomeric alkylation was obtained upon the utilization of NaH than upon the utilization and KOH. This could be accounted for the fact that with KOH the reaction is reversible and hence the equilibration between the anomers occurs at a higher extent than in the case of the utilization of NaH.

5.3.3. Determination of the Anomeric Ratio

The R_f values of α- and β-anomers for both methyl- and octadecylgalactosides were similar and consequently the separation of the anomers by the column chromatography was

tedious. The anomeric ratio was determined by ^{19}F NMR of the crude reaction or by ^{19}F NMR of the anomeric mixture (after column chromatography) or by the isolated yields of the α- and β-galactosides.

In Figure 5.1 is represented the ^{19}F NMR of the anomeric mixture of **5.4** with the anomeric ratio α/β: 7/93.

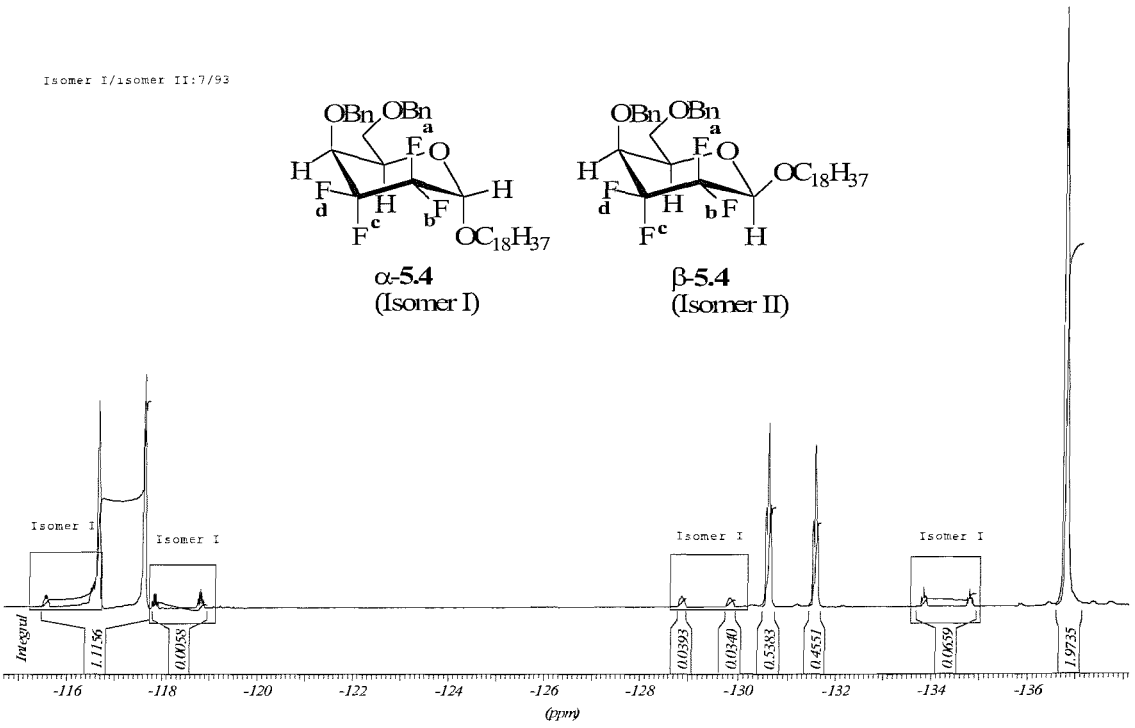


Figure 5.1

The fluorine atoms of the α- and β-anomers are clearly distinct, with the exception of the fluorine $F_{a/b}$ at δ -116.03 (α-anomer), which overlaps with the fluorine $Fa_{/b}$ at δ -116.96 (β-anomer). In Figure 5.2 are presented the fluorine at δ -129.31 ($F_{c/d}$, α-anomer) and the fluorine at δ -130.92 ($F_{a/b}$, β-anomer). The integrals are 0.0733 for the fluorine at δ -129.31 ($F_{c/d}$, α-anomer) and 0.9934 for the fluorine at δ -130.92 ($F_{a/b}$, β-anomer), establishing an anomeric ratio of α/β: 7/93.

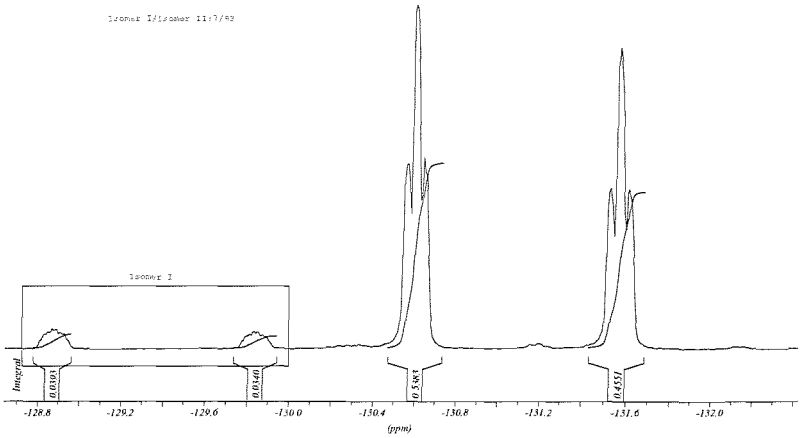


Figure 5.2

The assignment of α- and β-anomers of both **5.1** and **5.4** was done on the basis of the ^{1}H NMR proton shifts values and the coupling constant value ($^{3}J_{H\text{-}F}$) between the anomeric protons and the fluorine atoms at C2.

5.4 Summary

The anomeric alkylation of 4,6-dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-galactose **1.1** was successful, leading to high yields of galactosides **5.1** and **5.4**. The reduction of the excess of the base and alkylating agent did not affect the yield of the alkylation reaction. The anomeric alkylation of **1.1** with MeI was not highly stereoselective, while the alkylation of **1.1** with $C_{18}H_{37}OTf$ led to high stereoselectivity. The results presented are preliminary and further development of the anomeric alkylation will be carried out in our group.

Chapter 6. Project Summary

- 2,3-dideoxy-2,2,3,3-tetrafluoro-galactose **1.1** was synthesised in 50% overall yield on a large scale (30% yield on a small scale) after 7 steps, starting from allyl benzyl ether;

- 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose **1.2** was synthesised in 12% overall yield after 9 steps, starting from allyl benzyl ether;

- The alkene **1.6**, the α-diol *ent*-**1.4** and the β-diol **1.4** were synthesised with high selectivities (*i.e.* the alkene with an *E*/*Z* ratio of 98/2 and the α- and the β-diols with *ee* values of 83% and 90%, respectively);

- It was found that 1,2-vicinal diols flanked by the perfluorolakyl groups could encounter racemization during the benzylation reaction, even upon the utilization of only 1 equivalent of base for deprotonation;

- The inversion at C5 (glucose numbering) with formic acid/formates was difficult to achieve (the Mitsunobu reaction, the isourea mediated inversion and the mesylate inversion failed). The inversion was accomplished with the cyclic sulphate, but the formate functionality hydrolysed during the subsequent hydrolysis step;

- Conditions were found for the successful synthesis of the *anti* 1,2-diol **1.5** from the cyclic sulphate **4.2** (68%, one step). Consequently, **1.5** was used as the precursor in the synthesis of **1.2** and the synthesis of the necessary formate was achieved in an additional step.

- The anionic cylcization was successful for both carbohydrates, with the side-products being synthesised in a total of <5% yield;

- Preliminary results for the anomeric alkylation of **1.1** have shown that 2-deoxy-2,2-difluoro-galactosides could be synthesised in high yields by this method. However,

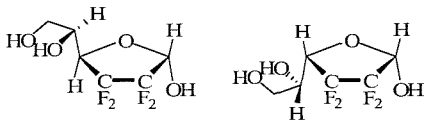
the stereoselectivitities obtained after the anomeric alkylation experiments were not high.

Chapter 7. Future Work

- Biological tests for the investigation of the capability of **3.14** and **4.13** to bind to proteins;

- Fuller investigation of the racemization of 1,2-diols flanked by the perfluoroalkyl groups during the benzylation reaction;

- The synthesis of the furanosic forms of 2,3-dideoxy-2,2,3,3-tetrafluoro-galactose and 2,3-dideoxy-2,2,3,3-tetrafluoro-glucose;



glucose galactose

- The further development of the anomeric alkylation of 2-deoxy-2,2-difluoro-carbohydrates and polyfluorinated carbohydrates, for example the anomeric alkylation with a wide range of alkylating agents and the development of the conditions for the achievement of the α- and the β-anomers in a stereoselective manner.

Chapter 8. Experimental

General Methods

All melting points were uncorrected and were recorded on a Gallekamp electrothermal melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on Bruker AC300, Bruker AV300 spectrometer and Bruker DPX 400 spectrometers. Chemical shifts are quoted in ppm relative to residual solvent peaks as appropriate. ^{19}F spectra were recorded on a Bruker AC300 spectrometer and externally referenced to $CFCl_3$. Low resolution ES and EI/CI mass spectra were recorded on Waters ZMD and Thermoquest TraceMS spectrometers respectively. High resolution mass spectra were recorded on the Bruker Apex III FT-ICR-MS. IR spectra were recorded as neat films on a Thermo Nicolet 380 spectrometer. Optical rotations were recorded on an Optical Activity Polaar 2001 polarimeter.

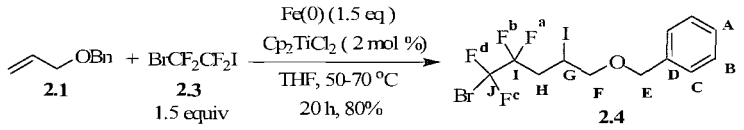
Column chromatography was performed on Fisher's Davisil grade silica gel (60 Å, 35-70 μm). Preparative HPLC was carried out using Biorad Bio-Sil D 90-10 columns (250 x 22 mm at 20 mL min^{-1} and 250 x 10 mm at 5 mL min^{-1}). Chiral analytical HPLC was performed on either a HP 1050 or a HP 1090 Series II LC system using a normal phase Chiralcel OD-H and Chiralcel OJ column with 254 nm detection, eluted with IPA/hexane mixtures. TLC analyses were performed on Merk silica gel 60 F_{254} aluminium plates and were developed with $KMnO_4$ or with anisaldehyde dye.

Anhydrous solvents were distilled immediately prior to use, with the exception of anhydrous DMF which was purchased in sealed containers containing molecular sieves from commercial sources. Pyridine was distilled from CaH_2 and stored in a Schlenk flask. Triethylamine was distilled from CaH_2 immediately prior to use. NaH was 60 % in mineral oil and $Pd(OH)_2$ was 20% on C. All other reagents were purchased from commercial sources and used without further purification, unless specifically stated.

All reactions were carried out under N_2 atmosphere.

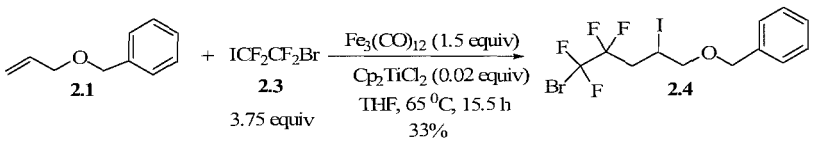
1-(5-bromo-4,4,5,5-tetrafluoro-2-iodopentyloxy)methyl)benzene (2.4)

Perfluroalkyl radical addition initiated by $Fe(0)/Cp_2TiCl_2$



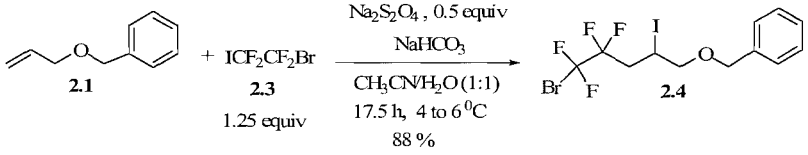
A suspension consisting of Fe(0) powder (82.5 mg, 1.5 mmol, 1.5 equiv), Cp_2TiCl_2 (5 mg, 0.02 mmol, 2 mol %), **2.1** (0.15 mL, 1 mmol, 1 equiv), **2.3** (0.48 mL, 3.75 mmol, 3.75 equiv) was stirred in THF (2.5 mL) at 50-70 °C for 20 h. The mixture was poured into water (2.5 mL) and filtered and the residue was washed with Et_2O. After the separation of phases, the aqueous phase was extracted with Et_2O (3 x 3 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a dark brown liquid. Column chromatography (Petroleum ether/ EtOAc: 98.5/1.5) gave the product **2.4** as a colorless liquid (363.0 mg, 0.8 mmol, 80% yield).

Perfluoroalkyl radical addition initiated by soluble $Fe(0)/Cp_2TiCl_2$



A mixture of $Fe_3(CO)_{12}$ (3.40 g, 6.75 mmol, 1.5 equiv), Cp_2TiCl_2 (0.0225g, 0.09 mmol, 0.02 equiv), **2.1** (0.7 mL, 4.5 mmol, 1 equiv), **2.3** (2.14 mL, 16.87 mmol, 3.75 equiv) in THF (11.25 mL) was stirred at 65^0C for 15.5 h. The mixture was poured into water (10 mL) and filtered through a plug of silica gel. The residue was washed with Et_2O (10 mL), extracted with Et_2O (2 x 10 mL), washed with brine (2 x 10 mL) and the combined organic phaes was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a brown liquid. Column chromatography (Petroleum ether/Et_2O: 98/2) gave the product **2.4** as a colorless liquid (0.69 g, 1.51 mmol, 33% yield).

Perfluoroalkyl radical addition initiated by $Na_2S_2O_4$/$NaHCO_3$



To a stirring solution of CH_3CN/H_2O (5 mL, 1:1 ratio), at 0 ^{0}C, were added **2.1** (0.62 mL, 4 mmol, 1 equiv) and **2.3** (0.63 mL, 5 mmol, 1.25 equiv), immediately followed by $NaHCO_3$ (0.168 g, 2 mmol, 0.5 equiv) and $Na_2S_2O_4$ (0.348g, 2 mmol, 0.5 equiv). The most of inorganic salts dissolved at the beginning of reaction. The reaction was stirred vigorously at 4 to 6 ^{0}C for 17.5 h. H_2O (3 mL) was added to the reaction and the aqueous layer was extracted with Et_2O (3 x 5 mL) and washed with brine (2 x 10 mL).The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a transparent liquid. Column chromatography (Petroleum ether/Et_2O: 98/2) gave the product **2.4** as a colorless liquid (1.61 g, 3.54 mmol, 88% yield).

MW 455.03

R_f 0.37 (Petroleum ether /Et_2O:98/2)

IR (neat): 2927 (w), 2855 (w), 1517 (w), 1454 (m), 1143 (s), 1071 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.40 (5H, m, H_{Ar}), 4.61 (2H, s, $H_E + H_{E'}$), 4.334-4.61 (1H, m, H_G), 3.76 (1H, dd, J=10.6, 5.2 Hz, H_F), 3.69 (1H, dd, J=10.6, 6.4 Hz, $H_{F'}$), 3.00-3.19 (1H, m, H_H), 2.62-2.82 (1H, m, $H_{H'}$).

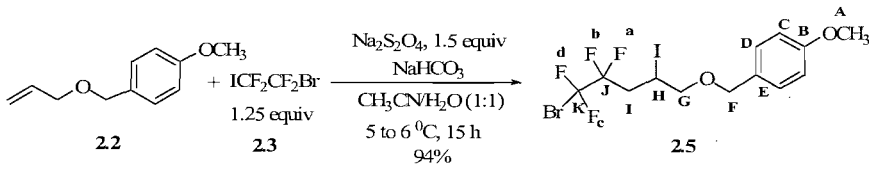
^{13}C NMR (75 MHz, $CDCl_3$) and **DEPT135**: δ 137.58 (C_{Ar}), 128.66(2 x C, CH_{Ar}), 128.12(CH_{Ar}), 127.91(2 x C, CH_{Ar}), 74.95 (C_E), 73.20 (C_F), 37.48 (t, J=21.4 Hz, C_H), 15.42 (C_G), C_I and C_J not clearly observed.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -111.46 to -111.24 (2F, m, $F_a + F_b$), -66.38 (2F, s, $F_c + F_d$).

LR MS (EI) *m/z* (%): 454 and 456 (M^+, 1:1 ratio, 25), 91(100).

HR MS (EI) for $C_{12}H_{12}O_1{}^{79}Br_1F_4I_1$ $(M)^+$ calcd 453.90524, found 453.90545.

1-(5-Bromo-4,4,5,5-tetrafluoro-2-iodo-pentyloxymethyl)-4-methoxy-benzene (2.5)



To a stirring solution of **2.2** (1.78g, 10 mmol, 1 equiv) in a mixture of CH_3CN/H_2O (18.5 mL, 1:1 ratio) at 0 °C was added **2.3** (1.56 mL, 12.5 mmol, 1.25 equiv), followed by a mixture of $Na_2S_2O_4$ (2.685 g, 15 mmol, 1.5 equiv) and $NaHCO_3$ (1.26 g, 15 mmol, 1.5 equiv). The heterogeneous solution was stirred at 5-6 °C for 15 h. To the white suspension was added H_2O (30 mL) and the aqueous phase was extracted with Et_2O (4 x 50 mL). The combined organic phase was washed with brine (1 x 150 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo* to give the crude product. Column chromatography (Petroleum ether/ Et_2O: 95/5) gave **2.5** as a pale yellow liquid (4.57g, 9.42 mmol, 94% yield). The presence of traces of an unknown impurity was observed by ^1H NMR, ^{19}F NMR and ^{13}C NMR.

MW 485.05

R_f 0.35 (Petroleum ether/ Et_2O: 94/6)

IR (neat): 2857 (w), 1610 (m), 1511 (s), 1244 (s), 1142 (s), 1069 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.25-7.29 (2H, m, H_{Ar}), 6.88-6.93 (2H, m, H_{Ar}), 4.54 (2H, s, $H_F + H_{F'}$), 4.32-4.54 (1H, m, H_H), 3.83 (3H, s, H_A), 3.73 (1H, dd, J=10.6; 5.2 Hz, H_G), 3.65 (1H, dd, J=10.6; 6.6 Hz, $H_{G'}$), 2.98-3.17 (1H, m, H_I), 2.60-2.80 (1H, m, $H_{I'}$).

^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 159.57 (C_{Ar}), 129.60 (C_{Ar}), 129.52 (2 x C, CH_{Ar}), 119.28 (dt, J=309.0, 38.8 Hz, C_K), 118.40 (dt, J=255.5, 31.3 Hz, C_J), 114.03(2 x C, CH_{Ar}), 74.63 (C_F), 72.79 (C_G), 55.37 (C_A), 37.40 (t, J=21.2 Hz, C_I), 15.52 (C_H).

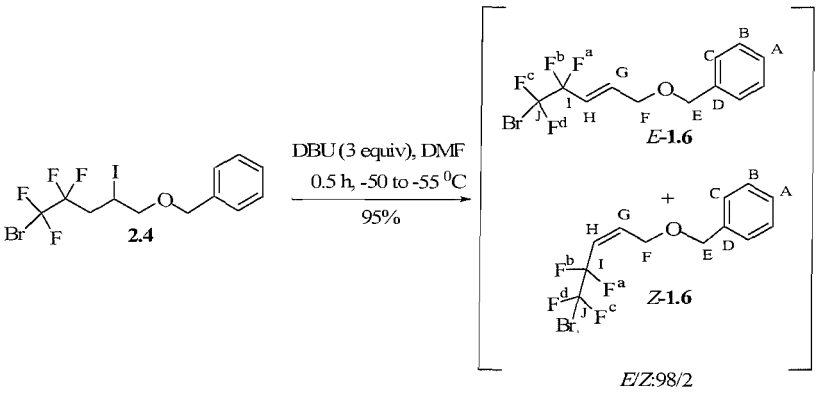
^{19}F NMR ($CDCl_3$, 282 MHz): δ – 111.37 to -111.53 (2F, m, $F_c + F_d$), -66.49 (2F, s, $F_a + F_b$).

LR MS (EI) *m/z* (%): 484 and 486 (M^+, 1:1 ratio 26); 121 (100).

HR MS (EI) for $C_{13}H_{14}{}^{79}Br_1F_4I_1O_2$ $(M)^+$ calcd 483.91581, found 483.91510.

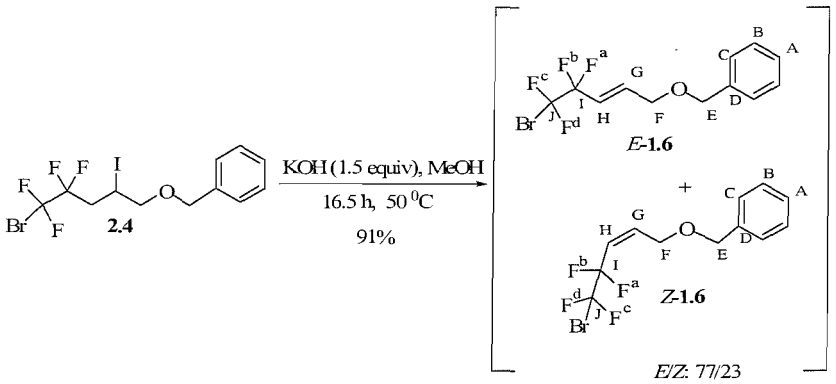
(E)- 5-bromo-4,4,5,5- tetrafluoropent-2-enyloxy)methyl)benzene (1.6)

Elimination reaction promoted by DBU



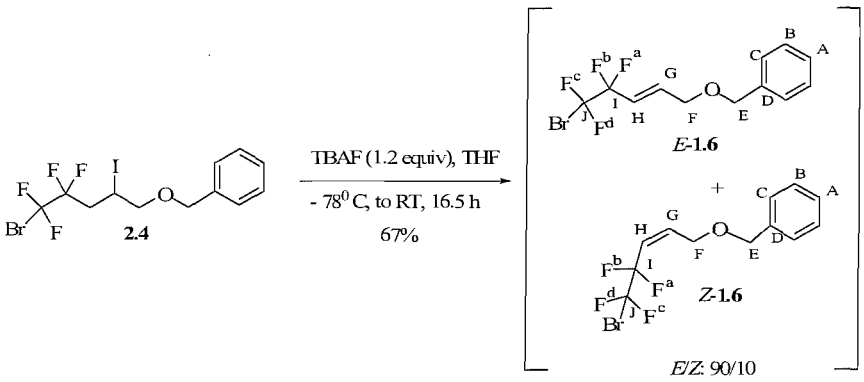
To a stirring solution of **2.7** (4.098 g, 9 mmol, 1 equiv) in DMF (15 mL) at -50°C, DBU (4.04 mL, 27 mmol, 3 equiv) was added dropwise The reaction was allowed to stir at -50 to - 55°C for 0.5 h. To the organic layer was added 1N aqueous HCl (30 mL) and the aqueous phase was extracted with Et_2O (4 x 40 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product as a yellow liquid. Column chromatography (Petroleum ether/ Et_2O: 96/4) gave the product **1.6** as a colorless liquid (2.785 g, 8.5 mmol, 95% yield).

Elimination reaction promoted by KOH



To a stirred solution of **2.4** (0.91 g, 2 mmol, 1 equiv) in MeOH (2.5 mL) at RT was added KOH (0.168 g, 3 mmol, 1.5 equiv). The mixture was warmed at 50 ^{0}C and stirred for 16.5 h. After the removal of MeOH *in vacuo*, the residue was dissolved in H_2O (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **1.6** as a colorless liquid (0.60 g, 1.83 mmol, 91% yield).

Elimination reaction promoted by TBAF



A solution of **2.4** (0.455 g,1 mmol, 1 equiv) in THF (2 mL) was treated with 1M solution of TBAF in THF (1.2 mL, 1.2 mmol, 1.2 equiv) and stirred at -78^{0}C for 1 h. The reaction was stirred at -78^{0}C to RT for 15.5 h. The mixture was quenched with H_2O (10 mL), extracted with Et_2O (3 x 10 mL) and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a colorless liquid. Column chromatography (Petroleum ether/Et_2O: 96/4) gave the product **1.6** as a colorless liquid (0.217g, 0.663 mmol, 66% yield).

Cis-trans isomerisation using I_2

To a solution of alkene **1.6** (*E/Z*: 93/7) (0.045 g, 0.138 mmol, 1 equiv) in Et_2O (2 mL) was added I_2 (0.035 g, 0.138 mmol, 1 equiv). The resulting solution was stirred at RT for 38 h, while illuminated with a desk lamp at 32 cm. The reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$ (3mL), stirred for 0.5 h at RT and then washed with $Na_2S_2O_3$ (2 x 3mL), washed with brine (2 x 3mL) and dried over $CaCl_2$. The organic layer was

filtered and concentrated *in vacuo*. The ^{1}H NMR of the crude has proven that the *E*/*Z* ratio of the crude is similar to the *E*/*Z* ratio of the strating material.

E-**1.6**

MW 327.11

R$_f$ 0.33 (Petroleum ether/Et_2O: 96/4)

IR (neat): 2922 (w), 2850 (w), 1679 (m), 1232 (m), 1145 (s), 1079 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.43 (5H, m, H_{Ar}), 6.51 (1H, dtt, *J*=15.7, 4.2, 2.2 Hz, H_G), 5.96-6.10 (1H, m, H_H), 4.61 (2H, s, H_E +$H_{E'}$), 4.16- 4.20 (2H, m, H_F + $H_{F'}$).

^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 139.07 (t, *J*=8.2 Hz, C_G), 137.68 (C_{Ar}), 128.67 (2 x C, CH_{Ar}), 128.08 (CH_{Ar}), 127.85 (2 x C, CH_{Ar}), 117.45 (tt, *J*=310.0, 41.5 Hz, C_J), 117.35 (t, *J*=24.2 Hz, C_H), 114.13 (tt, *J*=250.0, 32.0 Hz, C_I), 73.04 (C_E), 68.32 (C_F).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -109. 70 (2F, app d, J=3.3 Hz, F_a + F_b), - 66.02 (2F, app t, *J*= 5.4 Hz, F_c + F_d).

LR MS (CI) *m/z* (%): 344 and 346 ($(M + NH_4)^+$, 1:1 ratio, 60), 327 and 329 ($(M + H)^+$, 1:1 ratio, 32), 91(100).

HR MS (EI) for $C_{12}H_{11}O_1{}^{79}Br_1F_4$ $(M)^+$: calcd 325.99294, found 325.99244.

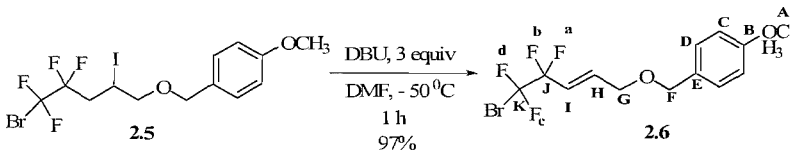
Z-**1.6**

δ values for ^{19}F NMR and ^{1}H NMR are quoted from the spectra recorded on a mixture *E*/*Z*: 77/23.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29-7.42 (5H, m, H_{Ar}), 6.34 (1H, dm, *J*=12.5 Hz, H_G), 5.57-5.63 (1H, m, H_H), 4.54 (2H, s, H_E + $H_{E'}$), 4.33- 4.38 (2H, m, H_F + $H_{F'}$).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -105.89 to -105.95 (2F, m, F_a + F_b), - 66.77 (1F, d, *J*= 6.4 Hz, F_c or F_d, overlaps with F_d or F_c), -66.79 (1F, d, *J*= 6.4 Hz, F_d or F_c, overlaps with F_c or F_d).

1-(5-Bromo-4,4,5,5-tetrafluoro-pent-2-enyloxymethyl)-4-methoxy-benzene (2.6)



To a stirring solution of **2.5** (0.6245g, 1.28 mmol, 1 equiv) in DMF (2.1 mL) at – 50 °C DBU (0.58 mL, 3.84 mmol, 3 equiv) was added dropwise and the reaction was stirred at – 50 °C for 1 h. To the reaction mixture was added HCl (1N aqueous solution, 10 mL) and then the aqueous solution was extracted with Et_2O (4 x 10 mL). The combined organic phase was washed with H_2O (4 x 40 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product **2.6** as a yellow liquid (0.4411 g, 12.39 mmol, 97% yield). The presence of some traces of an unknown impurity was observed by ^1H NMR, ^{19}F NMR and ^{13}C NMR.

MW 357.14

R_f 0.24 (Petroleum ether/Et_2O: 96/4)

IR (neat): 2937 (w), 2904 (w), 2839 (w), 1611 (m), 1511 (s), 1243 (s), 1078 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.26-7.30 (2H, m, H_{Ar}), 6.89-6.94 (2H, m, H_{Ar}), 6.49 (1H, dtt, J=15.8; 4.1; 2.1 Hz, H_H), 5.99 (1H, m, H_I), 4.52 (2H, s, $H_F + H_{F'}$), 4.11-4.16 (2H, m, $H_G + H_{G'}$), 3.83 (3H, s, H_A).

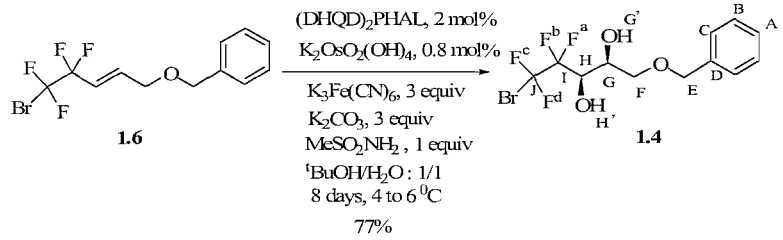
^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 159.59 (C_{Ar}), 139.23 (C_H), 129.70 (C_{Ar}), 129.50 (2 x C, CH_{Ar}), 121.56 (t, J= 41.8 Hz, C_K), 117.14 (t, J = 23.9 Hz, C_I), 114.03 (2 x C, CH_{Ar}), 110.79 (t, J=31.3 Hz, C_J), 72.66 (C_F), 67.97 (C_G), 55.31(C_A).

^{19}F NMR ($CDCl_3$, 282 MHz): δ –109.71 (2F, s, $F_a + F_b$), -66.03 (2F, s, $F_c + F_d$).

LR MS (CI) *m/z* (%): 357 and 359 ($(M + H)^+$, 1:1 ratio, 1), 356 and 358 (M^+, 1:1 ratio, 1), 121 (100%).

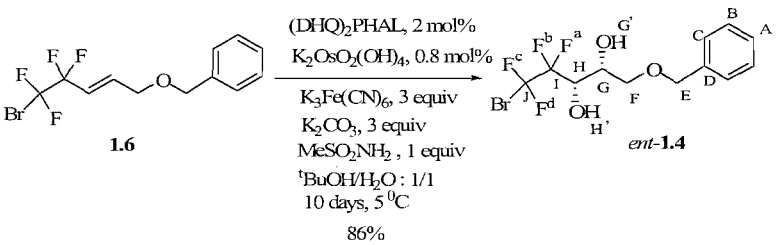
HR MS (EI) for $C_{13}H_{13}{}^{79}Br_1F_4O_2$ $(M)^+$ calcd 356.00350, found 356.00189.

(2S, 3S) -1-Benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentane-2,3-diol (1.4)



To a stirred mixture of $^{t}BuOH/H_2O$ (14.8 mL, 1:1 ratio) at RT, were added $(DHQD)_2PHAL$ (0.0229g, 0.03 mmol, 2 mol%), $K_3Fe(CN)_6$ (1.4520 g, 4.41 mmol, 3 equiv), K_2CO_3 (0.6095 g, 4.41 mmol, 3 equiv), $K_2OsO_2(OH)_4$ (0.0044g, 0.01176 mmol, 0.8 mol%). After the solids were dissolved, $MeSO_2NH_2$ (0.1398 g, 1.47 mmol, 1 equiv) was added. Then the mixture was cooled to 0^0C, whereupon the inorganic salts partially precipitate and the olefin **1.6** (0.4824 g, 1.47 mmol, 1 equiv) was added at once. The heterogeneous slurry was stirred vigorously at 4 to 6^0C for 8 days. The yellow colored mixture was quenched with Na_2SO_3 at RT and stirred for 2 h and then extracted with EtOAc (4 x 15mL). The combined organic layer was washed with 2N aqueous KOH (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a pale yellow solid. Column chromatography (Petroleum ether/ EtOAc: 70/30) gave the product **1.4** as a white solid (0.408 g, 1.27 mmol, 77 % yield).

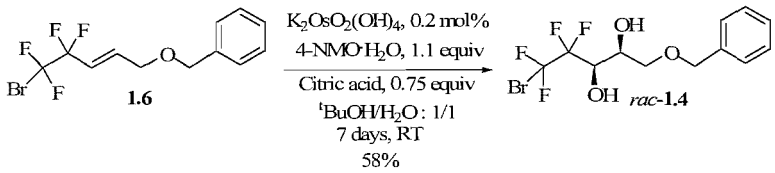
(2R, 3R) -1-Benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentane-2,3-diol (ent-1.4)



To a stirred mixture of $^{t}BuOH/H_2O$ (15.2 mL, 1:1 ratio) at RT, were added $(DHQ)_2PHAL$ (0.0239 g, 0.03 mmol, 2 mol%), $K_3Fe(CN)_6$ (1.51 g, 4.587 mmol, 3 equiv), K_2CO_3 (0.634 g, 4.587 mmol, 3 equiv), $K_2OsO_2(OH)_4$ (0.00451 g, 0.0123 mmol, 0.8 mol%). After the

solids were dissolved, $MeSO_2NH_2$ (0.1455 g, 1.529 mmol, 1 equiv) was added. Then the mixture was cooled to 0^0C, whereupon the inorganic salts partially precipitate and the olefin **1.6** (0.5 g, 1.529 mmol, 1 equiv) was added at once. The heterogeneous slurry was stirred vigorously at 5 ^{0}C for 10 days. The yellow colored mixture was quenched with Na_2SO_3 at RT and stirred for 2 h and then extracted with EtOAc (4 x 15mL). The combined organic layer was washed with 2N aqueous KOH (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a pale yellow solid. Column chromatography (Petroleum ether/ EtOAc: 70/30) gave the product *ent*-**1.4** as a white solid (0.47 g, 1.30 mmol, 86% yield).

1-Benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentane-2,3-diol (rac-1.4)



The olefin **1.6** (0.4576g, 1.4 mmol, 1 equiv) and citric acid (0.2 g, 1.05 mmol, 0.75 equiv) were dissolved in a mixture of ^{t}BuOH /H_2O (3 mL, 1:1 ratio). The addition of $K_2OsO_2(OH)_4$ (0.001 g, 0.0028 mmol, 0.2 mol%) was followed by the addition of a solution of 4-NMO·H_2O (0.2 g, 1.54 mmol, 1.1 equiv) in H_2O (0.35 mL). The reaction turned bright green. The reaction was stirred at RT for 7 days. ^{t}BuOH was removed *in vacuo* and then the aqueous residue was acidified with HCl 1N (3.5 mL) and extracted with EtOAc (2 x 10 mL).The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a white solid. Column chromatography (Petroleum ether/ EtOAc: 70/30) gave the product *rac*-**1.4** as a white solid (0.295 g, 0.82 mmol, 58%).

MW 361.13

R_f 0.30 (Petroleum ether/EtOAc: 70/30).

Mp 89°C (chiral diol), 94°C (racemic diol)

$[\alpha]_D$ -1.62 (*c* 1.05, $CHCl_3$, 24°C)

IR (neat): 3312 (w), 3217 (m), 2956 (w), 2935 (w), 1452 (w), 1205 (m), 1123 (s), 1069(s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.41 (5H, m, H_{Ar}), 4.60 (2H, s, H_E +$H_{E'}$), 4.29 (1H, m, H_G), 4.16 (1H, app dddt, *J*= 21.5, 8.7, 4.1, 1.1 Hz, H_H), 3.62 (2H, d, *J*= 6.0 Hz, H_F + $H_{F'}$); 3.20 (1H, d, *J*=8.7 Hz, $H_{H'}$, *-OH,* disappears after D_2O shake), 2.58 (1H, d, *J*= 4.5 Hz, $H_{G'}$, *-OH*, disappears after D_2O shake).

^{13}C NMR (75 MHz, $CDCl_3$) and **DEPT135**: δ 137.31 (C_{Ar}), 128.76 (2 x C, CH_{Ar}), 128.29 (CH_{Ar}), 128.02 (2 x C, CH_{Ar}), 71.17 (C_E), 68.85 (C_F), 68.50 (dd, *J*=29.4; 21.7 Hz, C_H), 66.78 (d, *J*=2.7 Hz, C_G), C_I and C_J not seen.

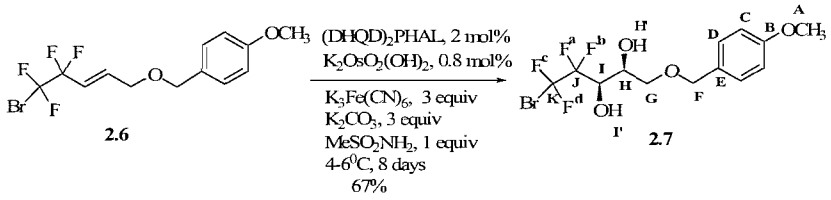
^{19}F NMR (282 MHz, $CDCl_3$): δ -125.49 (1F, ddd, *J*=270, 21.5, 8.6 Hz, F_a or F_b), -113.86 (1F, d, *J*=270 Hz, F_a or F_b), -63.86 (1F, dd, *J*=179.0, 8.6 Hz, Fc or Fd), -62.70 (1F, dd, *J*=179.0, 8.6 Hz, Fc or Fd).

LR MS (ES^+) *m/z* (%): 383 and 385 ($(M + Na)^+$, 1:1 ratio, 45), 242 (100%).

HR MS (ES^+) for $C_{12}H_{13}{}^{79}Br_1F_4O_3Na_1$ $(M + Na)^+$ calcd 382.9876, found 382.9874.

Microanalysis for $C_{12}H_{13}Br_1F_4O_3$: calcd C, 39.91, H, 3.63; found: C, 39.86, H, 3.63.

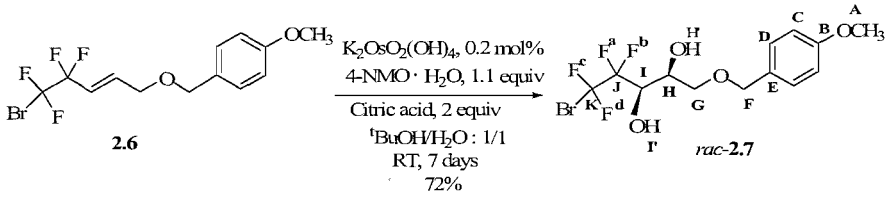
***(2S, 3S)* -5-Bromo-4,4,5,5-tetrafluoro-1-(4-methoxy-benzyloxy)-pentane-2,3-diol (2.7)**



To a stirred mixture of ^{t}BuOH /H_2O (16.8 mL, 1:1 ratio) at RT, were added $(DHQD)_2PHAL$ (0.0262g, 0.0336 mmol, 2 mol%), $K_3Fe(CN)_6$ (1.66 g, 5.04 mmol, 3 equiv), K_2CO_3 (0.6970 g, 5.04 mmol, 3 equiv), $K_2OsO_2(OH)_4$ (0.005g, 0.0135 mmol, 0.8 mol%). After the solids were dissolved, $MeSO_2NH_2$ (0.1598 g, 1.68 mmol, 1 equiv) was added. The mixture was cooled at 0^0C, whereupon the inorganic salts partially precipitate and the olefin **2.6** (0.60 g, 1.68 mmol, 1 equiv) was added at once. The heterogeneous slurry was stirred vigorously at 4 to 6^0C for 8 days. The yellow colored mixture was quenched with Na_2SO_3 (2.12 g) at RT and then stirred for 2 h. To the solution was added H_2O (20 mL) and then the aqueous phase was extracted with EtOAc (4 x 40mL). The

combined organic layer was washed with 2N aqueous KOH (3 x 100 mL), brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a pale yellow solid. Column chromatography (CH_2Cl_2/ MeOH: 97/3 containing small amount of NEt_3) gave the product **2.10** as a white solid (0.44 g, 1.12 mmol, 67% yield).

(2S,3S)-5-Bromo-4,4,5,5-tetrafluoro-1-(4-methoxy-benzyloxy)-pentane-2,3-diol *(rac-2.7)*



To a solution of citric acid (0.645 g, 1.05 mmol, 2 equiv) in a mixture of $^tBuOH/H_2O$ (1.7 mL, 1:1 ratio) were added the olefin **2.6** (0.60 g, 1.68 mmol, 1 equiv), $K_2OsO_2(OH)_4$ (0.0013 g, 0.00336 mmol, 0.2 mol%) and 4-NMO·H_2O (0.25 g, 1.85 mmol, 1.1 equiv). The color of the solution turned bright green. The reaction was stirred at RT for 7 days. ^tBuOH was removed *in vacuo* and then the aqueous residue was acidified with 1N aqueous HCl (2.5 mL) and extracted with EtOAc (4 x 2.5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a pale yellow solid. Column chromatography (CH_2Cl_2/ MeOH: 97/3 conatining a small amount of NEt_3) gave the product *rac*-**2.7** as a pale yellow solid (0.470 g, 1.2 mmol, 72% yield).

MW 391.15

R_f 0.30 (CH_2Cl_2/MeOH: 97/3)

Mp 68°C (chiral diol), 76°C (racemic diol)

$[\alpha]_D$ -1.12 (*c* 1.075, $CHCl_3$, 28°C)

IR (neat): 3211 (w), 2933 (w), 2908 (w), 2860 (w), 2836 (w), 1610 (m), 1510 (s), 1455 (m), 1249 (s), 1066 (s) cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.26-7.30 (2H, m, H_{Ar}), 6.91-6.96 (2H, m, H_{Ar}), 4.54 (2H, s, $H_F + H_{F'}$), 4.27 (1H, app t, *J*= 5.8 Hz, H_H), 4.11 (1H, app d, *J*= 16.5 Hz, H_I), 3.85 (3H, s, H_A), 3.60 (2H, d, *J*=5.8 Hz, H_G), 3.40 (1H, br s, $H_{I'}$), 2.85 (1H, br s, $H_{H'}$).

^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 159.71 (C_{Ar}), 129.69 (2 x C, CH_{Ar}), 129.39 (CH_{Ar}), 114.15 (2 x C, CH_{Ar}), 73.45 (C_F), 70.88 (C_G), 68.54 (dd, J=29.0, 22.0 Hz, C_I), 66.75 (d, J=2.8 Hz, C_H), 55.43 (C_A), C_K and C_J not seen.

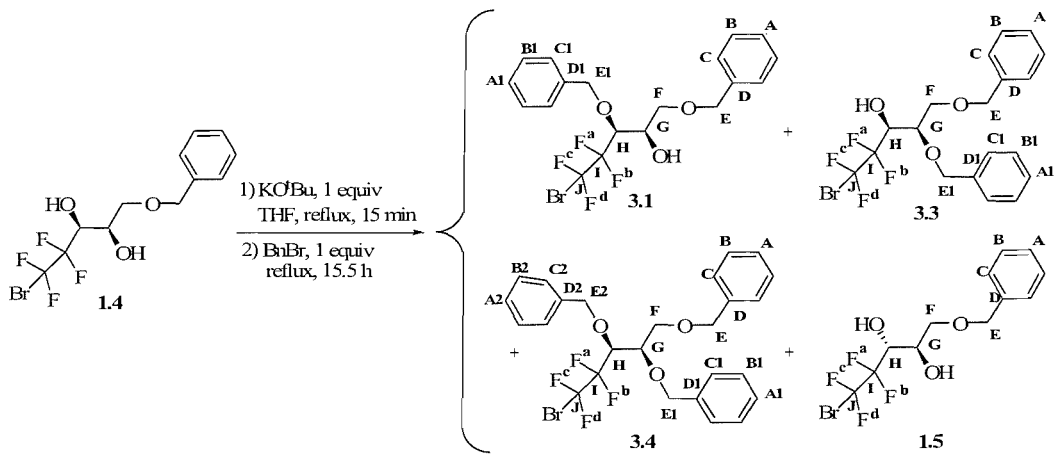
^{19}F NMR ($CDCl_3$, 282 MHz): δ – 125.49 (1F, ddd, J=270.6 Hz, 22.0, 8.6, F_a or F_b), -113.84 (1F, d, J=270.6 Hz, F_a or F_b), -63.85 (1F, dd, J=178.1, 4.3 Hz, F_c or F_d), -62.67 (1F, dd, J=178.1, 8.6 Hz, F_c or F_d).

LR MS (ES$^+$) *m/z* (%): 413 and 415 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES$^+$) for $C_{13}H_{15}O_4F_4{}^{79}Br_1Na_1$ $(M + Na)^+$ calcd 412.99820, found 412.99789.

Microanalysis for $C_{13}H_{15}Br_1F_4O_4$ calcd: C, 39.92, H, 3.87; found: C, 39.89, H, 3.87.

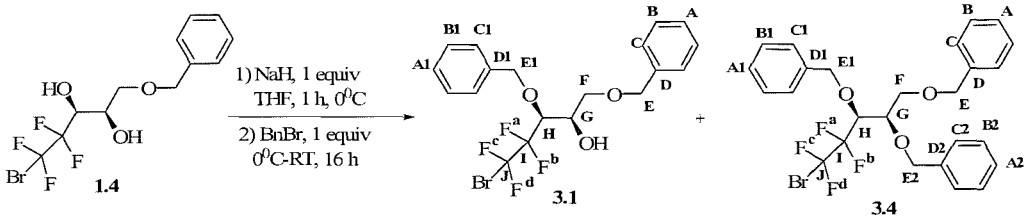
The benzyl monoprotection of diol (1.4) in the presence of ^{t}BuOK



To a stirring solution of diol **1.4** (1.090 g, 3.02 mmol, 1 equiv) in THF (14.4 mL) was added KO^{t}Bu (0.3388 g, 3.02 mmol, 1 equiv) and the mixture was heated at reflux for 15 minutes, followed by the addition of BnBr (0.36 mL, 3.02 mmol, 1 equiv). The mixture was refluxed for 15.5 h and the yellow coloured suspension was diluted was diluted with 1N aqueous HCl (15 mL), extracted with EtOAc (3 x 30 mL) and the combined organic phase was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtrated, concentrated *in vacuo* to give the crude as a yellow liquid. Repeated column chromatography (Petroleum Ether/EtOAC: 70/30) gave **3.1** as a transparent liquid (1.019 g, 2.26 mmol, 75% yield). Repeated HPLC (Hexane/Acetone: 85/15) gave **3.3** as a brown gel (0.0169 g, 0.0375 mmol, 1.24% yield). Repeated HPLC (Hexane/Acetone: 95/05) gave **3.4** as transparent liquid

(0.0455 g, 0.084 mmol, 2.8% yield). Repeated HPLC (Hexane/Acetone: 75/25) gave **1.5** as a cream coloured solid, which contained traces of an unknown impurity (0.0242 g, 0.067 mmol, 2.22% yield).

The benzyl monoprotection of diol 1.4 in the presence of NaH



To a stirring solution of diol **1.4** (0.212 g, 0.587 mmol, 1 equiv) in THF (3.8 mL), at 0°C was added NaH (0.0235 g, 0.587 mmol, 1 equiv) and stirred for 1 h. BnBr (0.07 mL, 0.587 mmol, 1 equiv) was added and the mixture was stirred for 16 h at 0°C to RT. To the reaction was added saturated aqueous NH_4Cl (5 mL) and stirred for 0.5 h at RT. The aqueous phase was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a yellow liquid. Column chromatography (Petroleum Ether/EtOAc: 70/30) gave **3.1** as a transparent liquid (0.1868g, 0.4142 mmol, 71% yield) and **3.4** as a transparent liquid (0.0145 g, 0.0268 mmol, 4.5% yield).

(2S,3S)-1,3-Bis-benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentan-2-ol (3.1)

MW 451.25

R_f 0.28 (Petroleum ether/ EtOAc: 90/10)

$[\alpha]_D$ -31.77 (*c* 1.185, $CHCl_3$, 28°C)

IR (neat): 3545 (w), 3460 (w), 3030 (w), 2918 (w), 2864 (w), 1453 (m), 1211 (m), 1087 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25-7.41 (10H, m, H_{Ar}), 4.83 (1H, d, *J*=10.6 Hz, C<u>H</u>HC$_6$H$_5$), 4.55 (1H, d, *J*= 10.6 Hz, CH<u>H</u>C$_6$H$_5$, overlaps with the H at δ 4.54 and with the H at δ 4.48), 4.54 (1H, d, *J*= 12.0 Hz, C<u>H</u>HC$_6$H$_5$), 4.48 (1H, d, *J*=12.0 Hz, CH<u>H</u>C$_6$H$_5$),

4.28 (1H, app ddd, J=15.8, 8.5, 2.1 Hz, H_H), 4.17 (1H, app quartet, J= 6.4 Hz, H_G), 3.54 (1H, dd, J=9.5, 5.1 Hz, H_F), 3.44 (1H, dd, J= 9.5, 5.1 Hz, $H_{F'}$), 2.42 (1H, d, J=8.6 Hz, *-OH*, $H_{G'}$).

^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 137.69 (C_{Ar}), 136.56 (C_{Ar}), 128.69 (2 x C, CH_{Ar}), 128.67 (2 x C, CH_{Ar}), 128.55 (CH_{Ar}), 128.48 (CH_{Ar}), 128.13 (2 x C, CH_{Ar}), 128.09 (2 x C, CH_{Ar}), 75.98 ($\underline{C}H_2C_6H_5$), 75.05 (app dd, J=27.5, 20.9 Hz, C_H), 73.58($\underline{C}H_2C_6H_5$), 70.27 (C_F), 67.92 (C_G), C_I and C_J not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ – 118.04 (1F, ddm, J=274.4, 15.8 Hz, F_a or F_b), -115.81 (1F, ddm, J= 274. 7, 8.5 Hz, F_a or F_b), -63.10 (2F, br s, F_c + F_d).

LR MS (ES$^+$) *m/z* (%): 473 and 475 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES$^+$) for $C_{12}H_{19}{}^{79}Br_1F_4O_3Na_1$ $(M + Na)^+$ calcd. 473.0346, found 473.0349.

***(2S,3S)* -1,2- Bis-benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentan-3-ol (3.3)**

MW 451.25

R_f 0.44 (Petroleum Ether/ EtOAc: 80/20).

$[\alpha]_D$ -1.17 (*c* 0.17, $CHCl_3$, 29°C).

IR (neat): 3524 (w), 3065 (w), 3032(w), 2928(w), 2868(w), 2361(w), 1497(w), 1454(w), 1209 (m), 1150 (s), 1126 (s), 1083 (s) cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.38 (10 H, m, H_{Ar}), 4.69 (1H, d, J=11.4 Hz, $C\underline{H}HC_6H_5$, overlaps with $CH\underline{H}C_6H_5$), 4.62 (1H, d, J=11.4 Hz, $C\underline{H}HC_6H_5$), 4.57 (1H, d, J=12.0 Hz, $CH\underline{H}C_6H_5$, overlaps with $C\underline{H}HC_6H_5$), 4.53 (1H, d, J=12.0 Hz, $C\underline{H}HC_6H_5$, overlaps with $CH\underline{H}C_6H_5$), 4.30 (1H, app dd, J=21.4, 7.2 Hz, H_H), 4.05 (1H, app t, J=6.3 Hz, H_G), 3.61 (2H, d, J=6.3 Hz, $H_F + H_{F'}$), 3.07 (1H, d, J=10.6 Hz, *-OH*, $H_{H'}$).

^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 137.75 (C_{Ar}), 137.27 (C_{Ar}), 128.66 (4C, CH_{Ar}), 128.35 (3C, CH_{Ar}), 128.04 (CH_{Ar}), 127.80 (2 x C, CH_{Ar}), 73.94 (d, J=2.8 Hz, C_G), 73.69 (2C, $\underline{C}H_2C_6H_5$), 68.87 (C_F), 67.97 (dd, J=29.1, 21.4 Hz, C_H), C_I and C_J not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -125. 98 (1F, ddd, J=268.2, 21.4, 8.6 Hz, F_a or F_b), -113.38 (1F, d, J=268.2 Hz, F_a or F_b), -63.74 (1F, dd, J=178.7, 5.4 Hz, F_c or F_d), -62.60 (1F, dd, J=178.7, 8.6 Hz, F_c or F_d).

LR MS (ES$^+$) *m/z* (%): 473 and 475 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES$^+$) for $C_{19}H_{19}{}^{79}Br_1F_4O_3Na_1$ $(M + Na)^+$ calcd 473.0346, found 473.0356.

(2S,3S) - **2,3-Dibenzyl-1-benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentane-2,3-diol (3.4)**

MW 541.37

R_f 0.28 (Hexane/Acetone: 95/05)

$[\alpha]_D$ -4.49 (*c* 1.08, $CHCl_3$, 29°C)

IR (neat): 3089 (w), 3064 (w), 3031 (w), 2916 (w), 2869, 1497 (w), 1454 (w), 1360 (w), 1210 (m), 1094 (s), 1027(s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.34 (15H, m, H_{Ar}), 4.71 (1H, d, *J*=10.9 Hz, $CHHC_6H_5$), 4.67 (1H, d, *J*=11.5 Hz, $CHHC_6H_5$), 4.65 (1H, d, *J*=10.9 Hz, $CHHC_6H_5$), 4.59 (1H, d, *J*=11.5 Hz, $CHHC_6H_5$), 4.46 (1H, d, *J*=13 Hz, $CHHC_6H_5$), 4.43 (1H, d, *J*=13.0 Hz, $CHHC_6H_5$), 4.30 (1H, app dt, *J*=18.8, 5.1 Hz, H_H), 3.97 (1H, m, H_G), 3.63 (1H, dd, *J*=9.9, 5.6 Hz, H_F), 3.53 (1H, dd, *J*=9.9, 5.4 Hz, $H_{F'}$).

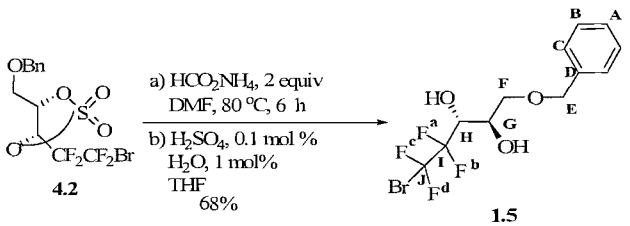
^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 138.03 (C_{Ar}), 137.91 (C_{Ar}), 136.96 (C_{Ar}), 128.53 (2 x C, CH_{Ar}), 128.45 (2 x C, CH_{Ar}), 28.42 (2 x C, CH_{Ar}), 128.37 (2 x C, CH_{Ar}), 128.15 (3 x C, CH_{Ar}), 127.88 (CH_{Ar}), 127.85 (CH_{Ar}), 127.82 (2 x C, CH_{Ar}), 118.01 (tt, *J*=312.0, 39.6 Hz, C_J), 115. 10 (ddt, *J*=263.7, 257.0, 30.4 Hz, C_I), 76.48 (C_G), 75.57 ($CH_2C_6H_5$), 75.14 (dd, *J*=27.1, 20.3 Hz, C_H), 73.64 ($CH_2C_6H_5$), 73.48 ($CH_2C_6H_5$), 68.96 (C_F).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -119.38 (1F, ddd, *J*=273.0, 18.8, 6.4 Hz, F_a or F_b), -110.82 (1F, d, *J*=273.0 Hz, F_a or F_b), -62.57 to -62.54 (2F, m, $F_c + F_d$).

LR MS (ES$^+$) *m/z* (%): 563.1 and 565.1 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES$^+$) for $C_{26}H_{25}{}^{79}Br_1F_4O_3Na_1$ ($M + Na^+$) calcd 563.0815, found 563.0815.

(2S, 3R) **-1-Benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentane-2,3-diol (1.5)**



A solution of **4.2** (0.1513 g, 0.3576 mmol, 1 equiv) and HCO_2NH_4 (0.0677 g, 1.073 mmol, 3 equiv) in DMF (3 mL) was stirred at 80°C for 6 h. The reaction was concentrated *in vacuo* and to the residue, a light brown suspension, was added THF (2.5 mL), H_2O (66.3 μL, 1 mol %) and H_2SO_4 (18.5 μL, 0.1 mol %). The reaction was stirred at RT for 0.5 h. After the addition of $NaHCO_3$ (0.07g), the reaction was stirred at RT for 20 minutes. The reaction was filtered, concentrated *in vacuo*, to give the crude product as light brown gel. Column chromatography (Petroleum ether/EtOAc: 70/30) gave **1.5** as a transparent gel which solidifies after a long period of time in the freezer (0.0874g, 0.242 mmol, 68% yield).

MW 361.13

R_f 0.31 (Hexane/Acetone: 75/25)

Mp 40 °C

$[\alpha]_D$ + 18.2 (*c* 1.0, $CHCl_3$, 30°C)

IR (neat): 3398 (m), 3067 (w), 3030 (w), 2918 (w), 2872 (w), 1495 (w), 1454 (m), 1392 (m), 1335 (w), 1266 (w), 1207 (m), 1143 (s), 1130 (s), 1987 (s), 1059 (s), 1038 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.41 (5H, m, H_{Ar}), 4.59 (1H, d, *J*=12.0 Hz, H_E, overlaps with $H_{E'}$), 4.56 (1H, d, *J*=12.0 Hz, $H_{E'}$, overlaps with H_E), 4.43 (1H, app ddt, *J*=17.8, 8.4, 4.2 Hz, H_H), 4.06 (1H, m, H_G), 3.90 (1H, dd, *J*=10.0, 4.2 Hz, H_F), 3.81 (1H, dd, *J*=10.0, 2.6 Hz, $H_{F'}$, overlaps with $H_{H'}$), 3.77 (1H, d, *J*=8.4 Hz, *-OH*, $H_{H'}$, overlaps with $H_{F'}$), 3.09 (1H, d, *J*=7.3 Hz, *-OH*, $H_{G'}$).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 136.86 (C_{Ar}), 128.81 (2 x C, CH_{Ar}), 128.44 (CH_{Ar}), 128.13 (2 x C, CH_{Ar}), 117.90 (ddt, *J*=312.3, 306.7, 39.6, C_J), 115.23 (m, C_I), 74.28 (C_E), 72.00 (C_F, overlaps with C_H), 71.76 (dd, *J*=28.0, 21.1 Hz, C_H, overlaps with C_F), 67.91 (C_G).

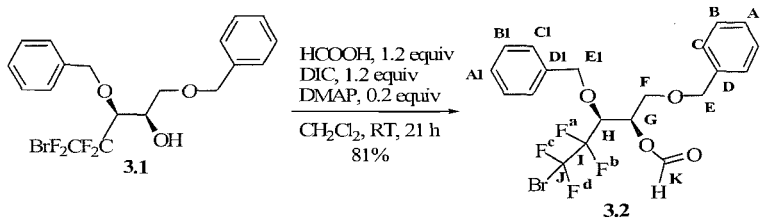
^{19}F NMR ($CDCl_3$, 282 MHz): δ –124.46 (1F, ddd, *J*=270.4, 21.1, 6.5 Hz, F_a or F_b), -115.98 (1F, d, *J*=270.4 Hz, F_a or F_b), -64.03 (1F, dd, *J*=178.1, 4.3 Hz, F_c or F_d), -63.16 (1F, dd, *J*=178.1, 6.5 Hz, F_c or F_d).

LR MS (ES^+) *m/z* (%): 383 and 385 $((M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+) for $C_{12}H_{13}{}^{79}Br_1F_4O_3Na_1$ $(M + Na)^+$calcd.382.9876, found 382.9874.

Microanalysis for $C_{12}H_{13}Br_1F_4O_3$: calcd. C, 39.91, H, 3.63; found: C, 39.84, H, 3.56.

***(2S, 3S)* -Formic acid 2-benzyloxy-1-benzyloxymethyl-4-bromo-3,3,4,4-tetrafluoro-butyl ester (3.2)**



To a stirred solution of **3.1** (0.1868 g, 0.414 mmol, 1 equiv) and DIC (0.077 mL, 0.497 mmol, 1.2 equiv) in CH_2Cl_2 (1.7 mL) was added DMAP (0.010 g, 0.083 mmol, 0.2 equiv). The mixture was stirred until complete dissolution and formic acid (0.019 mL, 0.497 mmol, 1.2 equiv) was added. The reaction was stirred at RT for 21 h followed by filtration to remove the white precipitate (DIC urea), and the residue washed with hexane (3 x 10 mL). The combined filtrate was concentrated *in vacuo* to give a yellow suspension. Column chromatography (Petroleum ether/ EtOAC: 70/30) gave the product **3.2** as a transparent liquid (0.16 g, 0.34 mmol, 81%).

MW 479.26

R_f 0.78 (Petroleum ether/EtOAc: 70/30)

$[\alpha]_D$ -8.14 (*c* 1.8, $CHCl_3$, 30°C)

IR (Neat): 3087 (w), 3030 (w), 2932 (w), 2872 (w), 1729 (s), 1454 (m), 1152 (s), 1082 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (1H, s, H_K), 7.28-7.41 (10H, m, H_{Ar}), 5.55 (1H, td, *J*= 6.2, 5.6 Hz, H_G), 4.82 (1H, d, *J*= 10.8 Hz, C<u>H</u>HC$_6$H$_5$), 4.63 (1H, d, *J*= 10.8 Hz, CH<u>H</u>C$_6$H$_5$), 4.54 (1H, d, *J*= 11. 7 Hz, C<u>H</u>HC$_6$H$_5$), 4.48 (1H, d, *J*= 11.7 Hz, C<u>H</u>HC$_6$H$_5$, overlaps with H_H), 4.45 (1H, m, H_H), 3.59-3.69 (2H, m, H_F + $H_{F'}$).

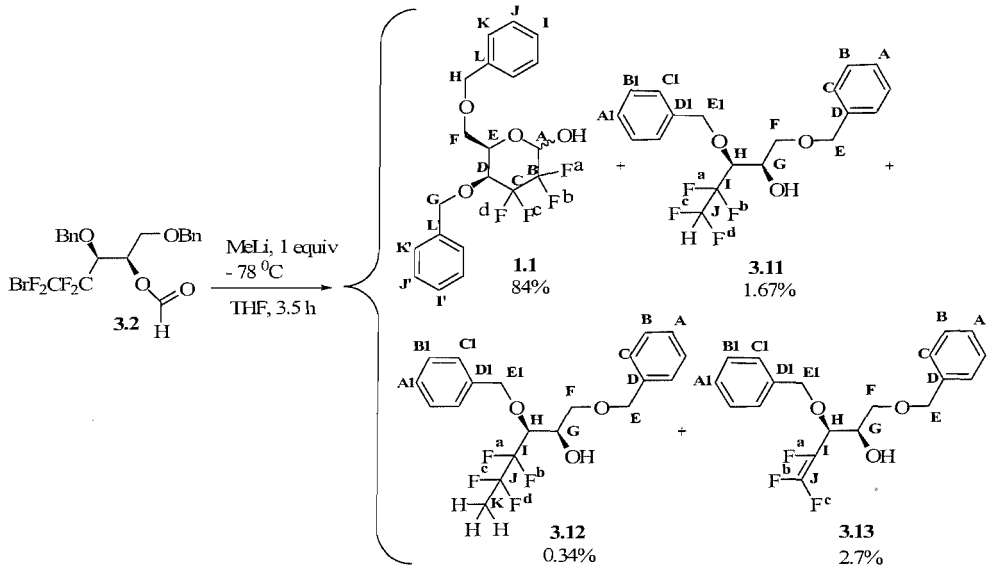
^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 159.80 (C_K), 137.34 (C_{Ar}), 136.41 (C_{Ar}), 128.67 (4 x C, CHAr), 128.50 (CH_{Ar}), 128.41 (2 x C, CH_{Ar}), 128.21 (CH_{Ar}), 128.00 (2 x C, CH_{Ar}), 76.03 (<u>C</u>H$_2$C$_6$H$_5$), 73.93 (dd, *J*=26.4, 22.0 Hz, C_H), 73.60 (<u>C</u>H$_2$C$_6$H$_5$), 69.04 (C_G), 66.69 (C_F), C_I and C_J not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -118.44 (1F, app dd, J=273.0, 16.0 Hz, F_a or F_b), -112.13 (1F, d, J=273.0 Hz, F_a or F_b), -63.46 (2F, s, F_c + F_d).

LR MS (ES^+): m/z (%): 501 and 503 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+) for $C_{20}H_{19}{}^{79}Br_1F_4O_4Na_1$ $(M + Na)^+$calcd. 501.0295, found 501.0298.

The anionic cyclization reaction



A stirred solution of **3.2** (4.6 g, 9.536 mmol, 1 equiv) in THF (95 mL) was cooled to – 78 °C and MeLi (5.96 mL, 9.536 mmol, 1 equiv) was added dropwise. The reaction was stirred at – 78 °C for 3.5 h. To the reaction was added saturated aqueous NH_4Cl (95 mL) and stirred at RT for 10 minutes. The aqueous solution was extracted with EtOAc (3 x 200 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a yellow liquid. Column chromatography (Petroleum Ether/Acetone: 75/25) gave **1.1** as a white crystalline solid (3.22 g, 8.043 mmol, 84% yield). Column chromatography (neat CH_2Cl_2), followed by HPLC (Hexane/EtOAc: 80/20) gave **3.11** as a pale yellow liquid (0.0598 g, 0.16 mmol, 1.67% yield). Column chromatography (neat CH_2Cl_2), followed by HPLC (neat CH_2Cl_2) gave **3.12** as a pale yellow gel (0.0125 g, 0.0324 mmol, 0.34% yield). Column chromatography (neat CH_2Cl_2), followed by HPLC (neat CH_2Cl_2) gave **3.13** as a transparent gel (0.0903 g, 0.257 mmol, 2.7% yield).

4,6-Dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-galactose (1.1)

(Mixture of α and β anomers)

MW 400.36

R_f 0.33 (Petroleum ether/Acetone: 75/25)

Mp 97°C (chiral)

$[\alpha]_D$ +0.58 (*c* 1.03, $CHCl_3$, 30°C)

IR (Neat): 3312(w), 3064(w), 3033(w), 2885(w), 1454(w), 1211(m), 1163(m), 1146(s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400MHz): δ 7.21-7.33 (16 H, m, H_{Ar}), 5.18 (1H, dd, *J*=8.6, 5.9 Hz, $H_{A\alpha}$), 4.86 (1H, d, *J*=4.0 Hz, $C\underline{H}HC_6H_5$), 4.82 (1H, d, *J*=4.0 Hz, $CH\underline{H}C_6H_5$), 4.78 (1H, dd, *J*=14.1, 3.8 Hz, $H_{A\beta}$), 4.35-4.51 (7H, m, $C\underline{H}_2C_6H_5$(6H) +$H_{E\alpha}$(1H)), 3.85-3.89 (2H, m, $H_{E\beta}$ +$H_{D\beta}$), 3.78 (1H, m, $H_{D\alpha}$), 3.56-3.62 (2H, m, $H_{F\alpha}$+ $H_{F'\alpha}$), 3.50 (1H, dd, *J*=9.7, 6.8 Hz, $H_{F\beta}$), 3.30 (1H, dd, *J*=9.7, 5.0 Hz, $H_{F'\beta}$).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 137.13 (C_{Ar}), 136.77 (C_{Ar}), 136.49 (2 x C, C_{Ar}), 128.63 (3 x C, CH_{Ar}), 128.56 (5 x C, CH_{Ar}), 128.44 (2 x C, CH_{Ar}), 128.35 (4 x C, CH_{Ar}), 128.22 (2 x C, CH_{Ar}), 128.13 (2 x C, CH_{Ar}), 128.08 (2 x C, CH_{Ar}), 107.3-117.2 (4 x C, m, $\underline{C}F_2$), 91.42-92.24 (2 x C, $C_{A\alpha}$+ $C_{A\beta}$), 75.20-75.50 (2 x C, $C_{D\alpha}$+ $C_{D\beta}$), 74.74-75.03 (2 x C, m, $C_{G\alpha}$+ $C_{G\beta}$), 73.64 (2 x C, $C_{H\alpha}$+$C_{H\beta}$), 72.71 (d, *J*=9.0 Hz, $C_{E\beta}$), 68.26 ($C_{F\alpha}$), 67.90(d, *J*=5.8 Hz, $C_{E\alpha}$), 67.38 ($C_{F\beta}$).

^{19}F NMR ($CDCl_3$, 282 MHz): **α-anomer**: δ -134.21 (1F, d, *J*=270.4 Hz, F_c or F_d), -129.23 (1F, dt, *J*=274.7, 5.9 Hz, F_a or F_b), -119.54 (1F, app dtd, *J*=270.4, 17.2, 8.6 Hz, F_a or F_b), -115.49 (1F, d, *J*=274.7 Hz, F_c or F_d). **β-anomer**: δ -138.53 (1F, app dd, *J*=259.7, 6.4 Hz, F_a or F_b), -136.38 (1F, app d, *J*=259.7 Hz, F_c or F_d), 130.81 (1F, dt, *J*=273.7, 11.8 Hz, F_c or F_d), -117.07 (1F, d, *J*=273.7 Hz, F_a or F_b).

LR MS (ES^+) *m/z* (%): 423.3 ($(M + Na)^+$, 100).

HR MS (ES^+) for $C_{20}H_{20}F_4O_4Na_1$ $(M + Na)^+$calcd. 423.1190, found 423.1189.

Microanalysis for $C_{20}H_{20}F_4O_4$ calcd: C, 60.00, H, 5.03, found C, 59.80, H, 5.10.

***(2S, 3S)*-1,3-Bis-benzyloxy-4,4,5,5-tetrafluoro-pentan-2-ol (3.11)**

MW 372.35

R_f 0.3 (Petroleum ether/EtOAc: 80/20)

$[\alpha]_D$ -31.64 (*c* 0.70, $CHCl_3$, 29°C)

IR (neat): 3438 (w), 3066 (w), 3032 (w), 2869 (w), 1497 (w), 1455 (m), 1400 (w), 1361 (w), 1092(s), 1028 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.39 (10H, m, H_{Ar}), 6.01 (1H, tdd, *J*=53.0, 8.9, 3.0 Hz, H_J), 4.79 (1H, d, *J*=10.8 Hz, $C\underline{H}HC_6H_5$), 4.61(1H, d, *J*=10.8 Hz, $CH\underline{H}C_6H_5$), 4.53 (1H, d, *J*=11.8 Hz, $C\underline{H}HC_6H_5$), 4.47 (1H, d, *J*= 11.8 Hz, $C\underline{H}HC_6H_5$), 4.09 (1H, app d, *J*=5.7 Hz, H_G), 4.02 (1H, app t, *J*= 10.6 Hz, H_H), 3.53 (1H, dd, *J*=9.4, 5.7 Hz, H_F), 3.46 (1H, dd, *J*=9.4, 6.7 Hz, $H_{F'}$), 2.49 (1H, d, *J*=7.8 Hz, *-OH*, $H_{G'}$).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 137.66 (C_{Ar}), 136.72 (C_{Ar}), 128.71 (2 x C, CH_{Ar}), 128.66 (2 x C, CH_{Ar}), 128.57 (2 x C, CH_{Ar}), 128.54 (2 x C, CH_{Ar}), 128.13 (CH_{Ar}), 128.08 (3 x C, CH_{Ar}), 116.43 (app tt, *J*=255.0, 26.0 Hz, C_J), 109.52 (tdd, *J*=249.1, 35.1, 28.9 Hz, C_I), 76.45 (t, *J*=25.1 Hz, C_H), 75.67 ($\underline{C}H_2C_6H_5$), 73.59 ($\underline{C}H_2C_6H_5$), 70.31 (C_F), 68.09 (t, *J*=2.9 Hz, C_G).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -139.78 (1F, ddt, *J*=300.4, 53.0, 8.6 Hz, F_c or F_d), -136.51 (1F, ddd, *J*=300.4, 53.0, 9.6 Hz, F_c or F_d), -124.87 (1F, dtt, *J*=278.0, 17.2, 8.6 Hz, F_a or F_b), -123.37 (1F, dt, *J*=278.0, 9.6 Hz, F_a or F_b).

LR MS (ES^+) *m/z* (%): 395.2 ($(M + Na)^+$, 100).

HR MS (ES^+) for $C_{19}H_{20}F_4O_3Na_1$ $(M + Na)^+$ calcd. 395.1241, found 395.1255.

***(2S,3S)*-1,3-Bis-benzyloxy-4,4,5,5-tetrafluoro-hexan-2-ol (3.12)**

MW 386.38

R_f 0.46 (Petroleum ether/Acetone: 75/25)

$[\alpha]_D$ -23.34 (*c* 0.135, $CHCl_3$, 29°C)

IR (neat): 3561 (w), 3461 (w), 3065 (w), 3032 (w), 2925 (w), 2867 (w), 1454 (m), 1212 (w), 1167 (m), 1095 (s), 1028 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.39 (10H, m, H_{Ar}), 4.84 (1H, d, *J*=9.3 Hz, CHHC6H5), 4.57 (1H, d, *J*=9.3 Hz, CHHC6H5), 4.54 (1H, d, *J*=10.6 Hz, CHHC6H5), 4.48

(1H, d, *J*=10.6 Hz, CHHC6H5), 4.14-4.20 (2H, m, H_H+H_G), 3.53 (1H, dd, *J*=9.6, 5.0 Hz, H_F), 3.46 (1H, dd, *J*=9.6, 7.0 Hz, $H_{F'}$), 2.44 (1H, br s, -*OH*, $H_{G'}$), 1.80 (3H, tt, *J*=19.3, 2.0 Hz, H_K).

^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135** : δ 137.87 (C_{Ar}), 137.04 (C_{Ar}), 128.63 (2 x C, CH_{Ar}), 128.62 (2 x C, CH_{Ar}), 128.48 (CH_{Ar}), 128.38 (CH_{Ar}), 128.06 (2 x C, CH_{Ar}), 128.02 (2 x C, CH_{Ar}), 75.87 ($\underline{C}H_2C_6H_5$), 75.21 (dd, *J*=25.5, 22.3 Hz, C_H), 73.51 ($\underline{C}H_2C_6H_5$), 70.62 (C_F), 67.93 (m, C_G), 18.47 (t, *J*=24.7 Hz, C_K), C_I and C_J not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -121.26 (1F, dt, *J*=280.0, 12.9 Hz, F_a or F_b), -118.42 (1F, dt, *J*=280.0, 10.7 Hz, F_a or F_b), -106.73 (1F, dqd, *J*=263.0, 19.3, 10.7 Hz, F_c or F_d), -105.06 (1F, dqd, *J*=263.0, 19.3, 10.7 Hz, F_c or F_d).

LR MS (ES$^+$) *m/z* (%): 409.2 ($(M + Na)^+$, 100).

HR MS (ES$^+$) for $C_{20}H_{22}F_4O_3Na_1$ $(M + Na)^+$ calcd. 409.1397, found 409.1395.

(*2S,3S*)-1,3-Bis-benzyloxy-4,4,5-trifluoro-pent-4-en-2-ol (3.13)

MW 352.35

R_f 0.44 (Petroleum ether/Acetone: 75/25)

$[\alpha]_D$ -1.27 (*c* 0.75, $CHCl_3$, 29°C)

IR (neat): 3448 (w), 3065 (w), 3032 (w), 2869 (w), 1256 (m), 1207 (w), 1177 (w), 1092 (s), 1050 (s) cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.37 (10H, m, H_{Ar}), 4.67 (1H, d, *J*=11.5 Hz, $C\underline{H}HC_6H_5$), 4.56 (1H, d, *J*=11.9 Hz, $C\underline{H}HC_6H_5$), 4.48 (1H, d, *J*=11.9, $CH\underline{H}C_6H_5$), 4.44 (1H, d, *J*=11.5 Hz, $CH\underline{H}C_6H_5$), 4.27 (1H, dddd, *J*= 27.6, 7.3, 3.5, 2.0 Hz, H_H), 4.08 (1H, dt, *J*=7.3, 4.0 Hz, H_G), 3.62 (1H, dd, *J*=10.3, 4.0 Hz, H_F), 3.49 (1H, dd, *J*=10.3, 4.0 Hz, $H_{F'}$), 2.63 (1H, br s, -*OH*, $H_{G'}$).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 154.70 (ddd, *J*=291.5, 277.5, 43.5 Hz, C_J), 137.78 (C_{Ar}), 136.93 (C_{Ar}), 128.69 (2 x C, CH_{Ar}), 128.53 (2 x C, CH_{Ar}), 128.33 (CH_{Ar}), 128.19 (CH_{Ar}), 127.91 (4 x C, CH_{Ar}), 124.92 (ddd, *J*=240.5, 49.3, 13.5 Hz, C_I), 73.75 ($\underline{C}H_2C_6H_5$), 73.45 (d, *J*=20.3 Hz, H_H), 71.42 ($\underline{C}H_2C_6H_5$), 70.47 (C_G), 70.00 (C_F).

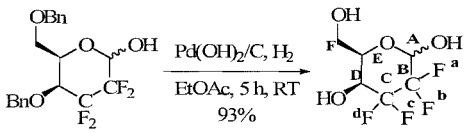
^{19}F NMR ($CDCl_3$, 282 MHz): δ -186.78 (1F, ddd, *J*=114.3, 32.2, 27.6 Hz, F_a), -118.62 (1F, dd, *J*=114.3, 73.5 Hz, F_c), -99.83 (1F, dd, *J*=73.5, 32.2 Hz, F_b).

LR MS (ES$^+$) *m/z* (%): 375.1 ($(M + Na)^+$, 100).

HR MS (ES$^+$) for $C_{19}H_{19}F_3O_3Na_1$ $(M + Na)^+$ calcd. 375.1178, found 375.1180.

2,3-dideoxy-2,2,3,3-tetrafluoro-galactose (3.14)

To a stirred solution of **1.1** (0.4 g, 1 mmol, 1 equiv) in EtOAc (8 mL) was added $Pd(OH)_2$ /C (0.32 g, 0.6 mmol, 0.6 equiv) . The flask was evacuated and purged twice with H_2. The reaction was stirred for 5 h at RT and then diluted with EtOAc (20 mL). The organic phase was filtered and the filtrate was concentrated *in vacuo* to give the crude as a transparent gel. Column chromatography (neat EtOAc) gave the product **3.14** as a transparent, dense gel (0.2034 g, 0.925 mmol, 93% yield).



(Mixture of α and β anomers)

MW 220.12

Rf 0.25 (Petroleum ether/Acetone: 50/50)

$[\alpha]_D$ +31.22 (*c* 1.06, MeOH, 29.5°C)

IR (Neat): 3354 (w), 2946 (w), 1378 (m), 1189 (m), 1042 (s) cm^{-1}.

^{1}H NMR (D_2O, 400 MHz): δ 5.52 (1H, dd, *J*=9.3, 6.3 Hz, $H_{A\alpha}$), 5.21 (1H, dt, *J*=13.3, 3.3 Hz, $H_{A\beta}$), 4.50 (1H, m, $H_{E\alpha}$), 4.33-4.36 (2H, m, $H_{D\alpha}$+$H_{D\beta}$), 4.06 (1H, m, $H_{E\beta}$), 3.87-3.90 (4H, m, $H_{F\alpha}$+ $H_{F'\alpha}$ + $H_{F\beta}$+ $H_{F'\beta}$).

^{13}C NMR (D_2O, 100 MHz) and **DEPT135**: δ 109.26-114.67 (4**C**, m, $C_{B\alpha}$+$C_{B\beta}$+ $C_{C\alpha}$+$C_{C\beta}$), 89.43-90.20 (2C, m, $C_{A\alpha}$+ $C_{A\beta}$), 72.93 (d, *J*=5.8 Hz, $C_{E\beta}$), 68.03 (d, *J*= 4.8 Hz, $C_{E\alpha}$), 66.78-67.40 (2C, m, $C_{D\alpha}$+$C_{D\beta}$), 58.60 (d, *J*=2.9 Hz, $C_{F\alpha}$), 58.45 (d, *J*=2.9 Hz, $C_{F\beta}$).[1]

^{19}F NMR (D_2O, 282 MHz): δ **α anomer**: -134.11 (1F, dddd, *J*=270.4, 15.7, 10.7, 6.3 Hz, F_a or F_b), -130.36 (1F, dddt, *J*=269.1, 17.2, 10.7, 6.3 Hz, F_a or F_b), -119.71 (1F, ddt, *J*=216.8, 17.2, 8.6 Hz, F_c or F_d), -118.75 (1F, ddt, *J*=216.8, 19.3, 8.6 Hz, F_c or F_d). **β**

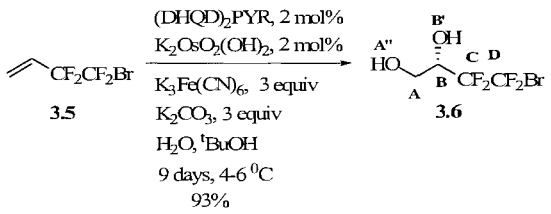
[1] The ^{13}C NMR of **3.14** has shown that the sample contained traces of solvent, even after repeated attempts of drying the compound *in vacuo*.

anomer: -137.76 (1F, dt, *J*=261.0, 15.0 Hz, F_a or F_b), - 136.66 (1F, dm, *J*=261.0 Hz, F_a or F_b), -132.62 (1F, dtd, *J*=270.4, 14.0, 4.3 Hz, F_c or F_d), -120.94 (1F, dm, *J*=270.4 Hz, F_c or F_d).

LR MS (ES^-) *m/z* (%): 219.2 ($(M - H)^+$, 100).

HR MS (ES^-) for $C_6H_8F_4O_4$ (M - H_2O) calcd 202.02531, found 202.02561.

(*2R*)-4-Bromo-3,3,4,4-tetarfluro-butane-1,2-diol (3.6)



A single necked 1L RB flask was charged with $K_3Fe(CN)_6$ (52.68 g, 0.16 mmol, 3 equiv), K_2CO_3 (22.11 g, 0.16 mmol, 3 equiv), $K_2OsO_4.2H_2O$ (0.40 g, 1.08 mmol, 2 mol %), and $(DHQ)_2PYR$ (0.95 g, 1.08 mmol, 2mol%). H_2O (270 mL) and ^tBuOH (270 mL) were added, and the reaction stirred until complete dissolution occurred. The reaction was cooled at 0°C whilst stirring and **3.5** (11.8 g, 54 mmol, 1 equiv) was added via a syringe and the reaction stirred at 4-6°C for 9 days. Solid Na_2SO_3 (81.0g) was added and the reaction allowed to warm at RT with vigorous stirring over 2h. The reaction was diluted with H_2O (50 mL) and Et_2O (200 mL), the layers were separated and the aqueous phase extracted with Et_2O (2 x 200 mL). The combined organic phase
was washed with HCl (2M, aq, 2 x 50 mL) and brine (50 mL) then dried over MgSO4, filtered and concentrated i*n vacuo* to give a colorless oil. The oil was purified by column chromatography (Petroleum ether/EtOAc: 70/30) to give a colorless oil which crystallized on standing to give the product **3.6** as a white deliquescent solid (12.05 g, 50.00 mmol, 93% yield). The acidic extracts were netralised with NaOH (2M, aq) and then extracted with EtOAc (2 x 100 mL). The EtOAc extracts were dried over MgSO4, filtered then concentrated *in vacuo* to give a white solid, $(DHQ)_2PYR$.

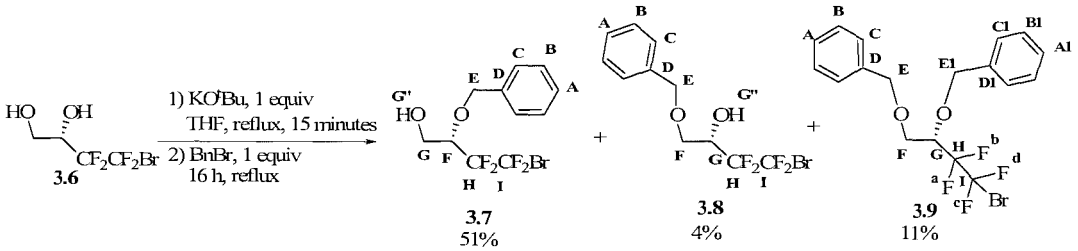
δ_H (CD_3CN, 400MHz) and δ_C ($CDCl_3$, 75 MHz) corresponded to the literature data.[73]

$[\alpha]_D$ -7.31 (*c* 1.17, $CHCl_3$, 28°C)

^{1}H NMR (CD_3CN, 400 MHz): δ 4.00 (1H, dm, *J*= 18.6 Hz, H_B), 3.79 (1H, d, *J*=6.0 Hz, $H_{B'}$), 3.59 (1H, m, H_A), 3.47 (1H, m, $H_{A'}$), 2.87 (1H, m, $H_{A''}$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ: 117.05 (tt, *J*=312.5, 39.5 Hz, C_D), 114.38 (ddt, *J*=262.0, 257.8, 31.0 Hz, C_C), 69.73 (dd, *J*=27.5, 22.0 Hz, C_B), 60.65 (tt, *J*=3.3, 1.7 Hz, C_A).

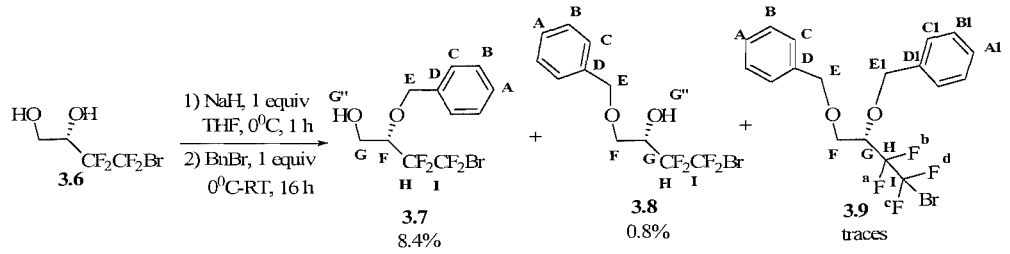
The monobenzylation reaction in the presence of KO^{t}Bu



To a stirring solution of **3.6** (0.2 g, 0.83 mmol, 1 equiv) in THF (4 mL), KO^{t}Bu (0.0932 g, 0.83 mmol, 1 equiv) was added and the mixture was heated at reflux for 15 minutes. Then BnBr (0.1 mL, 0.83 mmol, 1 equiv) was added and the reaction was refluxed for 16 h. The yellow colored suspension was diluted with 1N aqueous HCl (5 mL) and the aqueous phase was extracted with EtOAc (4 x 5mL). The combined organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* to give the crude as a yellow gel. Column

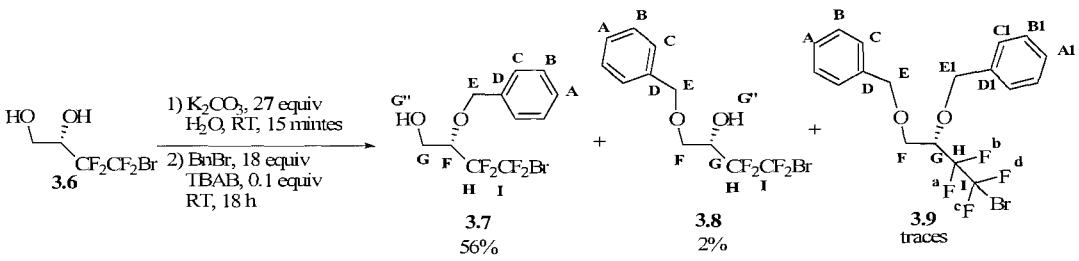
chromatography (Petroleum ether/EtOAc: 70/30) gave **3.7** as a transparent gel (0.1394 g, 0.42 mmol, 51% yield), **3.9** as a transparent gel (0.0376 g, 0.089 mmol, 11% yield), **3.8** as a transparent gel (0.011 g, 0.033 mmol, 4% yield) and unreacted **3.6** as a transparent gel (0.03 g, 0.125 mmol, 15%).

The monobenzylation reaction in the presence of NaH



To a stirring solution of diol **3.6** (1.00g, 4.1497 mmol, 1 equiv) in THF (26.9 mL) at 0°C was added NaH (0.166 g, 4.1497 mmol, 1 equiv) and the mixture was stirred for 1 h. Then BnBr (0.49 mL, 4.1497 mmol, 1 equiv) was added and the reaction was stirred at 0°C-RT for 16 h. To the reaction was added saturated aqueous NH_4Cl (27 mL) and stirred for 0.5 h at RT. The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a yellow liquid. Column chromatography (Petroleum Ether/EtOAc: 70/30) gave **3.7** as a transparent gel (0.09 g, 0.272 mmol, 6.6% yield) and **3.8** as a transparent gel (0.0104 g, 0.0314, 0.8% yield), traces of **3.9** as a transparent gel and recovered **3.6** as a transparent gel (0.8376g, 3.476 mmol, 84%).

The monobenzylation reaction in the presence of Na_2CO_3



The diol **3.6** (0.3 g, 1.25 mmol, 1 equiv) was added to a 1.9 M aqueous solution (17.8 mL) of Na_2CO_3 (3.56 g, 33.61 mmol, 27 equiv) and was stirred at RT for 15 minutes. Then BnBr (2.7 mL, 22.41 mmol, 18 equiv) and TBAB (0.041 g, 0.125 mmol, and 0.1 equiv) were added and the reaction was stirred at RT for 18 h. To the aqueous phase was added CH_2Cl_2 (10 mL), the phases were separated and the aqueous phase was extracted with

CH_2Cl_2 (2 x 10 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude reaction. Column chromatography (Petroleum ether/EtOAc: 70/30) gave product **3.7** as transparent gel (0.2304 g, 0.70 mmol, 56% yield), **3.8** as a transparent gel (0.0083 g, 0.025 mmol, 2% yield) and **3.9** as a transparent gel (traces).

(*2R*)-2-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro-butan-1-ol (3.7)

δ_H ($CDCl_3$, 400MHz) and δ_C ($CDCl_3$, 100 MHz) corresponded to the literature data.[73]

^{1}H NMR ($CDCl_3$, 400 MHz): δ: 7.22-7.30 (5H, m, H_{Ar}), 4.75 (1H, d, *J*= 11.0 Hz, H_E), 4.57 (1H, d, *J*=11.0 Hz, $H_{E'}$), 4.01 (1H, m, H_F), 3.76 (1H, apparent d, *J*=11.0 Hz, H_G), 3.70 (1H, dd, *J*=11.8, 7.3 Hz, $H_{G'}$), 2.25 (1H, s, $H_{G''}$, *-OH*).
^{13}C NMR ($CDCl_3$, 100 MHz): δ: 136.73 (C_{Ar}), 128.77 (2 x C, CH_{Ar}), 128.60 (CH_{Ar}), 128.30 (2 x C, CH_{Ar}), 117.47 (tt, *J*=310.6, 39.1 Hz, C_I), 114.78 (ddt, *J*=260.8, 257.0, 31.9 Hz, C_H), 77.80 (dd, *J*=25.1, 22.2 Hz, C_F), 75.17 ($\underline{C}H_2C_6H_5$), 60.33 (C_G).

(*2R*)-1-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro-butan-2-ol (3.8)

δ_H ($CDCl_3$, 300MHz) and δ_C ($CDCl_3$, 75 MHz) corresponded to the literature data.[73]

^{1}H NMR ($CDCl_3$, 300 MHz): δ (7.23-7.40 5H, m, H_{Ar}), 4.61 (2H, s, $H_E + H_{E'}$), 4.36 (1H, dm, *J*= 18.4 Hz, H_G), 3.72-3.82 (2H, m, $H_F + H_{F'}$), $H_{G'}$ (*-OH*) not seen.
^{13}C NMR ($CDCl_3$, 100 MHz): δ: 130.84(C_{Ar}), 128.76 (2 x C, CH_{Ar}), 128.31 (CH_{Ar}), 127.96 (2 x C, CH_{Ar}), 73.97 ($\underline{C}H_2C_6H_5$), 68.59 (C_G), 67.64 (C_F), C_I and C_H not seen. [2]

(*2R*)-1,2-bisbenzyl -4-bromo-3,3,4,4-tetrafluoro-butane-1,2-diol (3.9)

MW 421.22
Rf 0.68 (Petroleum ether/EtOAc: 70/30)
$[\alpha]_D$ -8.00 (*c* 0.25, $CHCl_3$, 30°)

[2] ^{13}C NMR of **3.8** has shown that the sample contains traces of an unknown impurity.

IR (Neat): 3090 (w), 3065 (w), 3032 (w), 2922 (w), 2873 (w), 1497 (w), 1454 (m), 1367 (w), 1210 (w), 1127 (s), 1097 (s), 1027 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.39 (10 H, m,H_{Ar}), 4.82 (1H, d, *J*=11.0 Hz, C$\underline{H}$HC$_6$H$_5$), 4.77 (1H, d, *J*=11.0 Hz, CH$\underline{H}$C$_6$H$_5$), 4.58 (2H, s, C$\underline{H}$HC$_6$H$_5$ + CH$\underline{H}$C$_6$H$_5$), 4.27 (1H, dtd, *J*=15.8, 7.3, 2.8 Hz, H_G), 3.89 (1H, app d, *J*=10.6 Hz, H_F), 3.79 (1H, dd, *J*=10.6, 7.4 Hz, $H_{F'}$).

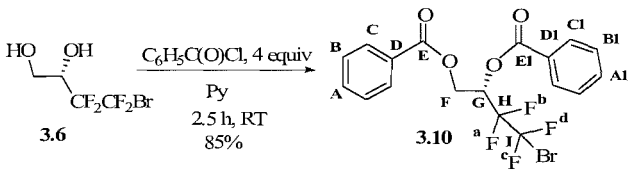
^{13}C NMR and DEPT 135 (Acetone, 100 MHz): δ 139.38 (C_{Ar}), 138.69 (C_{Ar}), 129.36 (2 x C, CH_{Ar}), 129.29 (2 x C, CH_{Ar}),129.07 (2 x C, CH_{Ar}), 128.89 (CH_{Ar}), 128.68 (2 x C, CH_{Ar}), 128.65 (CH_{Ar}), 121.44 (s, C_I, expected m), 118.29 (s, C_H, expected m), 76.77 (dd, *J*=27.5, 22.5 Hz, C_G), 75.2 1(C$\underline{H}_2$C$_6$H$_5$), 74.18 (C$\underline{H}_2$C$_6$H$_5$), 69.46 (C_F).

^{19}F NMR ($CDCl_3$): δ -120.43 (1F, ddd, *J*=273.1, 16.1, 6.4 Hz, F_a or F_b), -112.42 (1F, d, *J*=273.1 Hz, F_a or F_b), -63.15 (1F, dd, *J*=178.1, 4.3 Hz, F_c or F_d), -62.43 (1F, dd, *J*=178.1, 6.5 Hz, F_c or F_d).

LR MS (ES^+) *m/z* (%): 443 and 445 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+) for $C_{18}H_{17}{}^{79}Br_1F_4O_2Na_1$ $(M + Na)^+$ calcd 443.0240, found 443.0238.

(*2R*)-1,2-Bisbenzoate-4-bromo-3,3,4,4-tetrafluoro-butane-1,2-diol (3.10)



To a solution of **3.6** (0.30 g, 1.25 mmol, 1 equiv) in pyridine (3.00 mL), BzCl (0.58 mL, 4.98 mmol, 4 equiv) was added. The reaction was stirred at RT for 2.5 h. To the reaction was added water (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), 1N aqueous HCl (2 x 10 mL), brine (2 x 10 mL) and dried over MgSO4, filtered, concentrated *in vacuo* to give the crude as a transparent gel. Column chromatography (Petroleum ether/EtOAc: 90/10) gave the product **3.10** as a transparent gel (0.4772 g, 1.06 mmol, 85% yield).

MW 449.191

R_f 0.36 (Petroleum ether/ EtOAc: 90/10)

$[\alpha]_D$ -21.18 (*c* 1.31, $CHCl_3$, 30°C)

IR (Neat): 3065 (w), 2971 (w), 1728 (s), 1452 (m), 1274 (m), 1244 (s), 1144 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (10H, m, H_{Ar}), 6.21 (1H, dtd, *J*=16.3, 6.8, 3.5 Hz, H_G), 4.91 (1H, ddd, *J*=12.2, 3.4, 1.5 Hz, H_F), 4.69 (1H, dd, *J*=12.3, 7.0 Hz, $H_{F'}$).

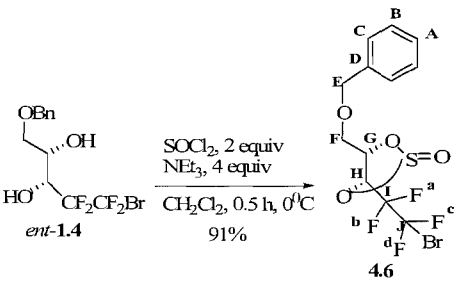
^{13}C NMR and DEPT135 ($CDCl_3$, 100 MHz): δ 165.91 (C(O)), 164.50 (C(O)), 134.09(C_{Ar}), 133.53 (C_{Ar}) 130.24 (2 x C, CH_{Ar}), 129.91 (2 x C, CH_{Ar}), 129.25 (CH_{Ar}), 128.76 (2 x C, CH_{Ar}), 128.60 (2 x C, CH_{Ar}), 128.39(CH_{Ar}), 116.69 (tt, *J*=310.6, 38.6 Hz, C_H), 113.63 (ddt, *J*=262.7, 255.0, 31.9Hz, C_I), 67.43 (dd, *J*=30.5, 22.7 Hz, C_G), 60.94 (C_F).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -119.64 (1F, app dd, *J*=174.7, 16.0 Hz, F_a or F_b), -113.47 (1F, d, *J*=174.7 Hz, F_a or F_b), -64.29 (2F, s, F_c + F_d).

LR MS (ES^+) m/*z* (%): 471 and 473 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+): for $C_{18}H_{13}{}^{79}Br_1F_4O_4Na_1$ $(M + Na)^+$: calcd: 470.9826, found 470.9824.

(*2R, 3R*)-4-Benzyloxymethyl-5(2-bromo-1,1,2,2-tetrafluoroethyl)-[1,3,2]dioxathiolane-2-oxide (4.6)



To a solution of *ent*-**1.4** (0.1 g, 0.277 mmol, 1 equiv) and NEt_3 (0.155 mL, 1.108 mmol, 4 equiv) in CH_2Cl_2 (1.3 mL) at 0°C, thionyl chloride (0.04 mL, 0.554 mmol, 2 equiv) was added dropwise, over a period of 5 minutes. The reaction was stirred at 0°C for 25 minutes and was diluted with cold Et_2O (2 mL). To the organic phase was added H_2O (4 mL). The aqueous phase was extracted with Et_2O (4 x 4mL) and the combined organic phase was washed with brine (4 x 4 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude as a brown gel. Column chromatography (Petroleum ether/EtOAc: 70/30)

gave the product **4.6** as a mixture of two stereoisomers as a light brown gel (0.1028 g, 0.253 mmol, 91% yield). Pure samples of isomer I (transparent gel) and isomer II (transparent gel) could be obtained by HPLC (Hexane/EtOAc: 95/5).

Isomer I

MW 407.18

R_f 0.36 (Hexane/EtOAc: 95/5)

IR (Neat): 3090 (w), 3033 (w), 2870 (w), 1455 (w), 1224 (s), 1140 (s), 1077 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.43 (5H, m, H_{Ar}), 5.41 (1H, dt, J=18.6, 4.0 Hz, H_H), 5.13 (1H, dd, J=10.6, 5.5 Hz, H_G), 4.69 (1H, d, J=12.0 Hz, C_E, overlaps with $C_{E'}$), 4.65 (1H, d, J=12.0 Hz, $C_{E'}$), 3.92 (1H, dd, J=10.5, 5.5 Hz, H_F, overlap with $H_{F'}$), 3.89 (1H, dd, J=10.5, 5.5 Hz, $H_{F'}$, overlap with H_F).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 137.11 (C_{Ar}), 128.69 (2 x C, CH_{Ar}), 128.20 (C_{Ar}), 127.82 (2 x C, CH_{Ar}), 116.05 (tt, J=310.6, 38.7 Hz, C_J, overlap with C_I), 112.54 (ddt, J=263.7, 254.0, 30.9 Hz, C_I, overlap with C_J), 82.01 (C_G), 77.74 (dd, J=33.8, 23.2 Hz, C_H), 73.78 (C_E), 69.48 (C_F).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -125.56 (1F, ddd, J=272.4, 19.3, 6.4 Hz, F_a or F_b), -115.97 (1F, d, J=272.4 Hz, F_a or F_b), -64.61 (1F, d, J=186.7 Hz, F_c or F_d), -63.91 (1F, d, J=186.7 Hz, F_c or F_d).

LRMS (EI) *m/z* (%): 406 and 408 ($(M)^+$, 1:1 ratio, 9), 342 and 344 ($(M - 64)^+$, 1:1 ratio, 4.5), 91 (100).

HRMS (EI) for $C_{12}H_{11}{}^{79}Br_1F_4O_4S_1$ $(M)^+$ calcd. 405.94975, found 405.95024.

Isomer II

MW 407.18

R_f 0.21 (Hexane/EtOAc: 95/5)

IR (Neat): 3066 (w), 3033 (w), 2870 (w), 1455 (w), 1277 (s), 1128 (s), 1086 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.43 (5H, m, H_{Ar}), 5.37 (1H, dt, J=6.9, 2.8 Hz, H_G), 5.06 (1H, ddd, J=19.5, 6.9, 3.8 Hz, H_H), 4.68 (1H, d, J=12.0 Hz, C_E), 4.61 (1H, d, J=12.0 Hz, $C_{E'}$), 3.93 (1H, dd, J=11.7, 2.8 Hz, H_F), 3.74 (1H, dd, J=11.7, 2.8 Hz, $H_{F'}$).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 136.92 (C_{Ar}), 128.73 (2 x C, CH_{Ar}), 128.33 (CH_{Ar}), 127.85 (2 x C, CH_{Ar}), 116.20 (ddt, *J*=311.6, 309.6, 38.6 Hz, C_J, overlap with C_I), 112.44 (ddt, *J*=266.1, 252.6, 31.9 Hz, C_I, overlap with C_J), 80.45 (C_G), 76.37 (dd, *J*=34.8, 23.2 Hz, C_H), 73.87 (C_E), 67.20 (C_F).

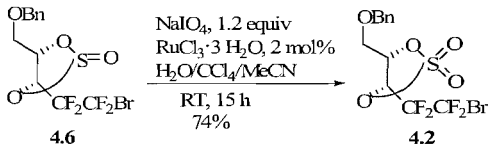
^{19}F NMR ($CDCl_3$, 282 MHz): δ -121.80 (1F, ddd, *J*=272.6, 19.5, 8.6 Hz, F_a or F_b), -115.93 (1F, d, *J*=272.6 Hz, F_a or F_b), -64.74 (1F, dd, *J*=182.4, 4.3 Hz, F_c or F_d), -63.87 (1F, dd, *J*=182.4, 6.4 Hz, F_c or F_d).

LRMS (EI) *m/z* (%): 406 and 408 ($(M)^+$, 1:1 ratio, 10), 342 and 344 ($(M - 64)^+$, 1:1 ratio, 12), 91 (100).

HRMS (EI) for $C_{12}H_{11}{}^{79}Br_1F_4O_4S_1$ $(M)^+$ calcd. 405.94975, found 405.94837.

(*2R, 3R*)-4-Benzyloxymethyl-5(2-bromo-1,1,2,2-tetrafluoro-ethyl)-[1,3,2]dioxathiolane-2,2-dioxide (4.2)

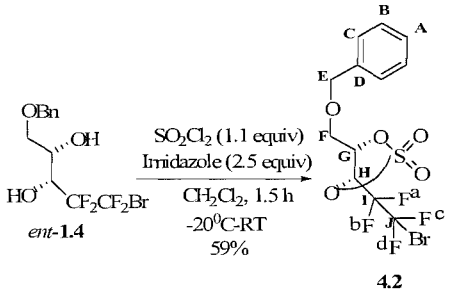
*Oxidation of cyclic sulfite **4.6** to cyclic sulphate **4.2***



4.6 **4.2**

To a mixture of cyclic sulfite **4.6** (0.1 g, 0.2456 mmol, 1 equiv), H_2O (0.59 mL), MeCN (0.39 mL) and CCl_4 (0.39 mL) were added $NaIO_4$ (0.063 g, 0.295 mmol, 1.2 equiv) and $RuCl_3 \cdot 3\ H_2O$ (0.0013 g, 0.0049 mmol, 2 mol %). The reaction was stirred vigorously at RT for 15 h and diluted with EtOAc (1 mL). The black coloured organic layer was filtered through a pad of celite. The filtrate was washed with H_2O (1.5 mL), saturated aqueous $NaHCO_3$ (1.5 mL), brine (1.5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product as a brown coloured gel. Column chromatography (Petroleum ether/ EtOAc: 90/10) gave the product **4.2** as a transparent gel (0.0771 g, 0.1823 mmol, 74% yield).

*Reaction of diol ent-**1.4** with sulfuryl chloride*



To solution of diol *ent*-**1.4** (0.5 g, 1.385 mmol, 1 equiv) and imidazole (0.236 g, 3.463 mmol, 2.5 equiv) in CH_2Cl_2 (2.3 mL) at -20°C, sulfuryl chloride (0.12 mL, 1.524 mmol, 1.1 equiv) was added dropwise. The reaction was stopped after 1.5 h and diluted with CH_2Cl_2 (2.3 mL). To the organic phase was added 5% aqueous H_2SO_4 (0.4 mL) and the organic layer was separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as transparent gel. Column chromatography (Petroleum ether/EtOAc: 90/10) gave the product **4.2** as a transparent gel (0.3472 g, 0.82 mmol, 59% yield).

MW 423.18

R_f 0.24 (Petroleum ether/ EtOAc: 90/10)

$[\alpha]_D$ -23.57 (*c* 0.575, $CHCl_3$, 29°C)

IR (Neat): 3033 (w), 2873 (w), 1455 (w), 1404 (s), 1365 (w), 1216 (s), 1145 (s), 1091 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32-7.43 (5H, m, H_{Ar}), 5.37 (1H, ddd, *J*=18.1, 6.4, 2.8 Hz, H_H), 5.18 (1H, dt, *J*=6.4, 3.4 Hz, H_G), 4.71 (1H, d, *J*=12.0 Hz, H_E), 4.62 (1H, d, *J*=12.0 Hz, $H_{E'}$), 3.95 (1H, ddd, *J*=12.0, 3.4, 1.1 Hz, H_F), 3.80 (1H, ddd, *J*=12.0, 3.8,1.1 Hz, $H_{F'}$).

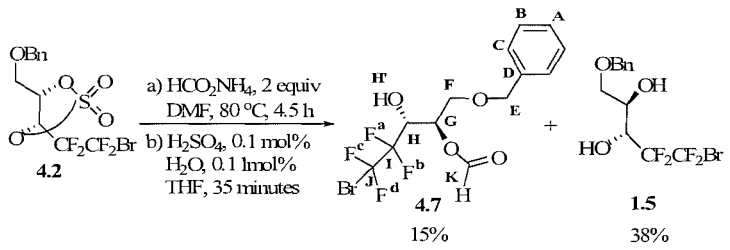
^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 136.45 (C_{Ar}), 128.86 (2 x C, CH_{Ar}), 128.56 (CH_{Ar}), 128.02 (2 x C, CH_{Ar}), 115.38 (tt, *J*=311.0, 37.7 Hz, C_J), 111.91 (ddt, *J*=267.6, 253.1, 32.8 Hz, C_I), 79.10 (C_G), 74.53 (dd, *J*=37.7, 23.2 Hz, C_H), 74.13 (C_E), 66.57 (C_F).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -123.69 (1F, app dd, *J*=276.8, 19.3 Hz, F_a or F_b), -118.07 (1F, app d, *J*=276.8 Hz, F_a or F_b), -65.11 (2F, s, $F_c + F_d$).

LR MS (EI) *m/z* (%): 421 and 423 ($(M)^+$, 1:1 ratio, 4), 91 (52), 44 (100).

HR MS (EI) for $C_{12}H_{11}O_5{}^{79}Br_1F_4S_1$ $(M)^+$ calcd 421.94467, found 421.94511.

(*2S, 3R*)-Formic acid of 1-benzyloxymethyl-4-bromo-3,3,4,4-tetrafluoro-2-hydroxy-butyl ester (4.7)



A solution of **4.2** (0.1232 g, 0.2911 mmol, 1 equiv) and HCO_2NH_4 (0.0364 g, 0.5822 mmol, 2 equiv) in DMF (2.4 mL) was stirred at 80°C for 4.5 h. The reaction becomes yellow and a white precipitate is formed during reaction. The reaction was concentrated *in vacuo* and to the residue, a light brown suspension, was added THF (2 mL), H_2O (5.4 μL, 0.1 mol %) and H_2SO_4 (15μL, 0.1 mol %). The reaction was stirred at RT for 0.5 h. After the addition of $NaHCO_3$ (0.0587g), the reaction was stirred at RT for 20 minutes. The reaction was filtered, concentrated *in vacuo* to give the crude product as light brown gel. Column chromatography (Petroleum ether/ EtOAc: 90/10) gave **4.7** as a transparent gel (0.0172 g, 0.0442 mmol, 15% yield), which was further purified by HPLC (Hexane/Acetone: 75/25). Elution with MeOH of the column gave **1.5** as a transparent gel (0.0402g, 0.111 mmol, 38% yield), which was further purified by HPLC (Hexane/ EtOAc: 65/35).

MW 389.14

R_f 0.40 (Petroleum ether/ EtOAc: 70/30).

$[\alpha]_D$ +2.34 (*c* 0.3, $CHCl_3$, 29.5°C)

IR (Neat): 3434 (w), 3087 (w), 3033 (w), 2933 (w), 2874 (w), 1726 (s), 1455 (m), 1150 (s), 1183 (s), 1079 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (1H, s, C_K), 7.32-7.42 (5H, m, H_{Ar}), 5.37 (1H, dm, *J*=1.7 Hz, H_G), 4.52-4.65 (3H, m, H_H +H_E + $H_{E'}$), 4.11 (1H, d, *J*=8.5 Hz, *-OH*, $H_{H'}$), 4.02 (1H, dd, *J*=11.3,3.0 Hz, H_F), 3.85 (1H, dd, *J*=11.3, 2.6 Hz, $H_{F'}$).

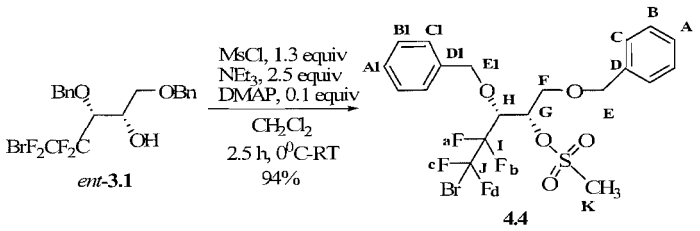
^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.85 (C_K), 136.54 (C_{Ar}), 128.82 (2 x C, CH_{Ar}), 128.51 (CH_{Ar}), 128.11 (2 x C, CH_{Ar}), 74.30 (C_E), 70.15 (dd, J=26.9, 22.0 Hz, C_H, overlaps with C_G), 69.96 (C_G, overlaps with C_H), 68.88 (C_F), C_I and C_J not seen.

^{19}F NMR (Acetone d6, 282 MHz): δ -123.58 (1F, app ddd, J=268.3, 20.4, 9.6 Hz, F_a or F_b), -111.67 (1F, d, J=268.3 Hz, F_a or F_b), -63.78 (1F, dm, J=180.3 Hz, F_c or F_d), –62.39 (1F, dd, J=180.3, 9.6 Hz, F_c or F_d).

LR MS (ES^+) *m/z* (%): 411 and 413 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+) for $C_{13}H_{13}{}^{79}Br_1F_4O_4Na_1$ $(M + Na)^+$: calcd 410.9826, found 410.9822.

(*2R, 3R*)-Trifluoro-methanesulfonic acid 2-benzyoxy-1-benzyloxymethyl-4-bromo-3,3,4,4-tetrafluorobutyl ester (4.4)



To a stirred solution of *ent*-**3.1** (0.3717 g, 0.8237 mmol, 1 equiv) in CH_2Cl_2 (4.1 mL) were added NEt_3 (0.29 mL, 2.06 mmol, 2.5 equiv) and DMAP (0.01 g, 0.08237 mmol, 0.1 equiv). MsCl (0.083 mL, 1.071 mmol, 1.3 equiv) was added dropwise at 0°C. The reaction was stirred at 0°C to RT for 2.5 h and then filtered. The filtrate was washed with H_2O (4 mL) and brine (2 x 4 mL) and the organic phase was dried over Na_2SO_4. Column chromatography of the crude reaction (Petroleum ether/EtOAc: 70/30) gave the product **4.4** as transparent gel (0.409 g, 0.773 mmol, 94% yield).

MW 529.34

R_f 0.38 (Petroleum ether/EtOAc: 80/20)

$[\alpha]_D$ +8.18 (*c* 0.55, $CHCl_3$, 29.5°C)

IR (Neat): 2878 (w), 1455 (m), 1359 (s), 1175 (s), 1079 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.42 (10 H, m, H_{Ar}), 5.10 (1H, m, H_G), 4.80 (1H, d, J=10.8 Hz, C<u>H</u>HC_6H_5), 4.71 (1H,d, J=10.8 Hz, CH<u>H</u>C_6H_5), 4.59 (1H, d, J=11.8 Hz,

C<u>H</u>HC$_6$H$_5$), 4.56 (1H, d, *J*=11.8 Hz, CH<u>H</u>C$_6$H$_5$, overlaps with H$_H$), 4.52 (1H, dt, *J*=18.6, 4.4 Hz, H$_H$), 3.88 (1H, dd, *J*=10.8, 5.6 Hz, H$_F$, overlapS with H$_{F'}$), 3.84 (1H, dd, *J*=10.8, 6.6 Hz, H$_{F'}$), 3.00 (3H, s, H$_K$).

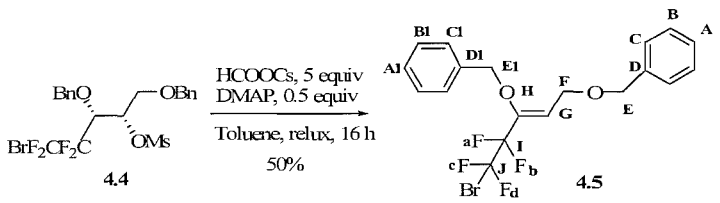
^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.14 (C$_{Ar}$),136.07 (C$_{Ar}$), 128.67 (2 x C, CH$_{Ar}$), 128.64 (2 x C, CH$_{Ar}$), 128.55 (CH$_{Ar}$), 128.40 (2 x C, CH$_{Ar}$), 128.22 (C$_{Ar}$), 128.01 (2 x C, CH$_{Ar}$), 111.43-120.81 (2C, m, C$_I$ and C$_J$), 77.20(C$_G$), 75.70 (<u>C</u>H$_2$C$_6$H$_5$), 74.11 (dd, *J*=28.5, 20.8, C$_H$), 73.69 (<u>C</u>H$_2$C$_6$H$_5$), 67.85 (C$_F$), 38.59 (C$_K$).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -120.03 (1F, dd, *J*=272.6, 17.2 Hz, F$_a$ or F$_b$), -63.23 (2F, s, F$_c$ + F$_d$), -111.18 (1F, d, *J*=272.6 Hz, F$_a$ or F$_b$).

LR MS (ES$^+$) *m/z* (%): 551 and 553 ((M + Na)$^+$, 1:1 ratio, 25), 546 and 548 ((M + NH$_4$)$^+$, 1:1 ratio, 100).

HR MS (ES$^+$) for $C_{20}H_{21}{}^{79}Br_1F_4O_5S_1Na_1$ (M + Na)$^+$ calcd 551.0121, found 551.0130.

1-((5-(Benzyloxy)-1-bromo-1,1,2,2-tetrafluoro-pent-3-en-3-yloxy)methyl)benzene (4.5)



To a solution of **4.4** (0.05 g, 0.09446 mmol, 1 equiv) in toluene (0.3 mL) were added HCOOCs (0.084 g, 0.4723 mmol, 5 equiv) and DMAP (0.0058 g, 0.04723 mmol, 0.5 equiv). After the reaction was heated at reflux for 16 h, EtOAc (1 mL) was added. The organic phase washed with brine (2 x 1 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (Petroleum ether /EtOAc: 90/10) of the crude reaction gave **4.5** as a transparent liquid. (0.0204 g, 0.0471 mmol, 50% yield).

MW 433.23

R$_f$ 0.57 (Petroleum ether/EtOAc: 90/10)

IR (Neat): 3033 (w), 2860 (w), 1673 (w), 1455 (m), 1233 (m), 1147 (s), 1082 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.37 (10H, m, H_{Ar}), 6.00 (1H, t, J=6.5 Hz, H_G), 4.88 (2H, s, $C\underline{H}HC_6H_5$ + $CH\underline{H}C_6H_5$), 4.47 (2H, s, $C\underline{H}HC_6H_5$ + $CH\underline{H}C_6H_5$), 4.11 (2H, app dt, J=6.5, 2.3 Hz, H_F + $H_{F'}$).

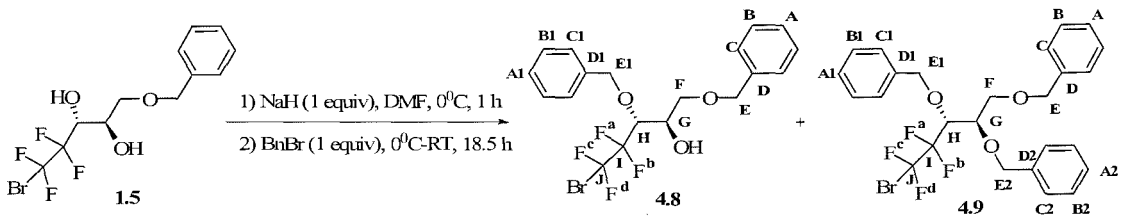
^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 137.73 (C_{Ar}), 136.07 (C_{Ar}), 128.71 (2 x C, CH_{Ar}), 128.64 (3 x C, CH_{Ar}), 128.33 (CH_{Ar}), 128.11 (2 x C, CH_{Ar}), 128.05 (2 x C, CH_{Ar}), 121.42 (app t, J=4.4 Hz, C_G), 77.36 (C_H), 76.84 ($\underline{C}H_2C_6H_5$), 72.82 ($\underline{C}H_2C_6H_5$), 63.57 (C_F), C_I and C_J not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -110.79 (2F, s, F_a +F_b), -64.03 (1F, d, J=6.4 Hz, F_c or F_d, overlap with F_d or F_c), -64.01 (1F, d, J=6.4 Hz, F_c or F_d, overlaps with F_d or F_c).

LR MS (ES^+) *m/z* (%): 450.2 and 452.2 ($(M + NH_4)^+$, 1:1 ratio, 100)

HR MS (ES^+) for $C_{19}H_{17}{}^{79}Br_1F_4O_2Na_1$ $(M + Na)^+$: calcd 455.0240, found 455.0232.

The benzyl monoprotection reaction of 1.5



To a solution of **1.5** (1.9015 g, 5.2673 mmol, 1 equiv) in DMF (36 mL) at 0°C was added NaH (0.211 g, 5.2673 mmol, 1 equiv) and the mixture was stirred for 1 h. Then BnBr (0.63 mL, 5.2673 mmol, 1 equiv) was added and the reaction was stirred at 0°C-RT for 18.5 h. To the reaction was added saturated aqueous NH_4Cl (36 mL) and stirred for 0.5 h at RT. The aqueous phase was extracted with EtOAc (3 x 50 mL) and the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a yellow liquid. Column chromatography (Petroleum ether/EtOAc: 70/30) gave **4.8** as a transparent gel (1.3841 g, 3.07 mmol, 58 % yield), **4.9** as transparent gel (0.6586 g, 1.22 mmol, 23% yield) and the recovered starting material **1.5** (0.314 g, 0.87 mmol, 16.5 %). Products **4.8** and **4.9** were purified by HPLC (Hexane/EtOAc: 85/15 and Hexane/EtOAc: 97/3, respectively).

(*2S, 3R*)-1,3-Bis-benzyloxy-5-bromo-4,4,5,5-tetrafluoro-pentan-2-ol (4.8)

MW 451.25

R_f 0.56 (Petroleum ether/EtOAc: 70/30)

$[\alpha]_D$ +13.63 (*c* 1.09, $CHCl_3$, 30°C)

IR (Neat): 3064 (w), 3032 (w), 2924 (w), 2871 (w), 1497 (w), 1455 (m), 1212 (w), 1131 (s), 1093 (s), 1028 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.41 (5H, m, H_{Ar}), 4.78 (1H, d, *J*=10.8 Hz, $C\underline{H}HC_6H_5$), 4.75 (1H, d, *J*=10.8 Hz, $CH\underline{H}C_6H_5$), 4.61 (1H, d, *J*=11.7 Hz, $C\underline{H}HC_6H_5$), 4.56 (1H, d, *J*=11.7 Hz, $CH\underline{H}C_6H_5$), 4.32 (1H, app dd, *J*= 11.3, 4.5 Hz, H_G), 4.26 (1H, m, H_H), 3.72-3.79 (2H, m, $H_F + H_{F'}$), 2.73 (1H, d, *J*=4.8 Hz, *-OH*, $H_{G'}$).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 137.66 (C_{Ar}), 136.89 (C_{Ar}), 128.72 (2 x C, CH_{Ar}), 128.59 (2 x C, CH_{Ar}), 128.30 (CH_{Ar}), 128.26 (CH_{Ar}), 128.17 (2 x C, CH_{Ar}), 128.09 (2 x C, CH_{Ar}), 117.72 (tt, *J*=312.0, 39.6 Hz, C_J, overlaps with C_I), 114.60 (m, C_I, overlaps with C_J), 77.73 (dd, *J*=26.1, 21.3 Hz, C_H), 75.87 ($\underline{C}H_2C_6H_5$), 73.73 ($\underline{C}H_2C_6H_5$), 70.07 (m, C_F), 69.73 (C_G).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -119.32 (1F, ddd, *J*=273.7, 19.3, 6.5 Hz, F_a or F_b), -110.67 (1F, d, *J*=273.7 Hz, F_a or F_b), -63.09 (1F, app d, *J*=176.0 Hz, F_c or F_d), -62.35 (1F, dd, *J*=176.0, 6.5 Hz, F_c or F_d).

LR MS (ES^+) *m/z* (%): 468 and 470 ($(M + NH_4)^+$, 1:1 ratio, 16), 473 and 475 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+) for $C_{19}H_{19}{}^{79}Br_1F_4O_3Na_1$ $(M + Na)^+$ calcd 473.0346, found 473.0344.

(*2S, 3R*)-1-Benzyloxy-5-bromo-2,3-dibenzyl-4,4,5,5-tetrafluoro-pentane-2,3-diol (4.9)

MW 541.37

R_f 0.77 (Petroleum ether/EtOAc: 70/30)

$[\alpha]_D$ +7.23 (*c* 0.9, $CHCl_3$, 30°C)

IR (Neat): 3089 (w), 3064 (w), 3031 (w), 2915 (w), 2870 (w), 1497 (w), 1454 (m), 1364 (w), 1209 (w), 1096 (s), 1071 (s), 1027 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.40 (15 H,m, H_{Ar}), 4.81 (1H,d, *J*= 10.9 Hz, $C\underline{H}HC_6H_5$), 4.79 (1H, d, *J*=11.8 Hz, $C\underline{H}HC_6H_5$), 4.714 (1H, d, *J*=10.9 Hz, $CH\underline{H}C_6H_5$), 4.69

(1H, d, J=11.8 Hz, CH$\underline{H}$C$_6$H$_5$),4.61 (1H, d, J=11.9 Hz, C$\underline{H}$HC$_6$H$_5$), 4.58 (1H, d, J=11.9 Hz, H$\underline{H}$C$_6$H$_5$), 4.37 (1H, ddd, J=18.9, 6.2, 3.5 Hz, H_H), 4.10 (1H, m, H_G), 3.88 (1H, dd, J=10.8, 2.6 Hz, H_F), 3.83 (1H, dd, J=10.8, 6.0 Hz, $H_{F'}$).

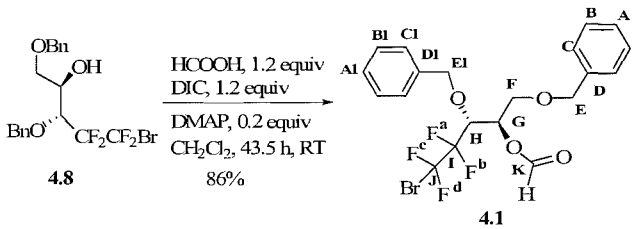
^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT135**: δ 137.93 (C_{Ar}), 137.76 (C_{Ar}), 136.52 (C_{Ar}), 128.20 (6 x C, CH_{Ar}), 128.02 (CH_{Ar}), 127.91 (CH_{Ar}), 127.69 (2 x C, CH_{Ar}), 127.58 (CH_{Ar}), 127.47 (4 x C, CH_{Ar}), 118.14 (tt, J=312.0, 39.6 Hz, C_J), 115.67 (m, C_I), 77.64 (C_G), 76.76 (dd, J=27.1, 21.3, C_H), 74.99 ($\underline{C}H_2C_6H_5$), 73.30 ($\underline{C}H_2C_6H_5$), 72.77 ($\underline{C}H_2C_6H_5$), 69.60 (C_F).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -120.59 (1F, ddd, J=272.6, 18.5, 7.5 Hz, F_a or F_b), -110.61 (1F, d, J=272.6 Hz, F_a or F_b), -63.06 (1F, dd, J=177.0, 4.3 Hz, F_c or F_d), -62.20 (1F, dd, J=177.0, 6.2 Hz, F_c or F_d).

LR MS (ES^+) m/z (%): 558 and 560 $((M + NH_4)^+$, 1:1 ratio, 72), 563 and 565 $((M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+): for $C_{26}H_{25}{}^{79}Br_1F_4O_3Na_1$ $(M + Na)^+$ calcd 563.0815, found 563.0804.

(*2S, 3R*)-Formic acid of 2-benzyloxy-1-benzyloxymethyl-4-bromo-3,3,4,4-tetrafluoro-butyl ester (4.1)



To a stirred solution of **4.8** (1.3208 g, 2.93 mmol, 1 equiv) in CH_2Cl_2 (14.6 mL) were added DIC (0.55 mL, 3.51 mmol, 1.2 equiv) and DMAP (0.072 g, 0.59 mmol, 0.2 equiv). The mixture was stirred until complete dissolution and formic acid (0.14 mL, 3.51 mmol, 1.2 equiv) was added. The reaction was stirred at RT for 43.5 h followed by filtration to remove the white precipitate formed during reaction (DIC urea), and the residue washed with hexane (3 x 20 mL). The filtrate was concentrated *in vacuo* to give a yellow suspension. Column chromatography (Petroleum ether/EtOAc: 90/10) followed by HPLC (Hexane/EtOAc: 90/10) gave the product **4.1** as a transparent liquid (1.20 g, 2.51 mmol, 86% yield).

MW 479.26

R_f 0.61 (Petroleum ether/EtOAc: 70/30)

$[\alpha]_D$ +12.77 (*c* 0.325, $CHCl_3$, 29.5°C)

IR (Neat): 3087 (w), 3066 (w), 3033 (w), 2934 (w), 2874 (w), 1728 (s), 1455 (m), 1365 (w), 1147 (s), 1077 (s) cm^{-1}.

^{1}H NMR (Acetone d6, 400 MHz) and **DEPT135**: δ 8.25 (1H, s, H_K), 7.28-7.30 (10H, m, H_{Ar}), 5.61 (1H, app dt, *J*=6.5, 3.8 Hz, H_G), 4.87 (1H, d, *J*=10.8 Hz, $C\underline{H}HC_6H_5$), 4.78 (1H, d, *J*=10.8 Hz, $CH\underline{H}C_6H_5$, overlaps with H_H), 4.62 (1H, m, H_H), 4.61 (1H, d, *J*=11.8 Hz, $C\underline{H}HC_6H_5$), 4.56 (1H,d, *J*=11.8 Hz, $CH\underline{H}C_6H_5$), 3.89 (1H, dd, *J*=11.0, 6.5 Hz, H_F), 3.84 (1H,dd, *J*=11.0, 2.9 Hz, $H_{F'}$).

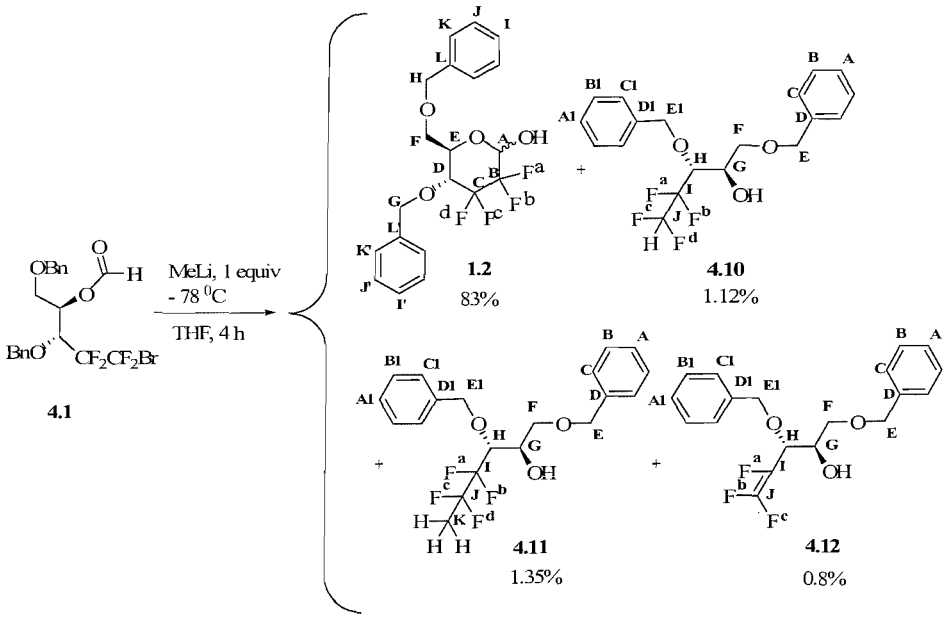
^{13}C NMR (Acetone d6, 100 MHz): δ 161.14 (C_K), 139.00 (C_{Ar}), 137.65 (C_{Ar}), 129.23 (2 x C, CH_{Ar}), 129.17 (2 x C, CH_{Ar}), 129.10 (2 x C, CH_{Ar}), 129.0 (CH_{Ar}), 128.51 (2 x C, CH_{Ar}), 128.47 (CH_{Ar}), 118.78 (tt, *J*=310.0, 110.3 Hz, C_J), 115.81 (m, C_I), 76.59 (dd, *J*=27.1, 21.3 Hz, C_H), 75.94 ($\underline{C}H_2C_6H_5$), 73.71 ($\underline{C}H_2C_6H_5$), 70.83 (C_G), 68.76 (C_F).

^{19}F NMR (Acetone d6, 282 MHz): δ -110.15 (1F, d, *J*=272.6 Hz, F_a or F_b), -119.91 (1F, ddd, *J*=272.6, 19.3, 6.4 Hz, F_a or F_b), -63.61 (1F, d, *J*=181.3 Hz, F_c or F_d), -62.90 (1F, dd, *J*=181.3, 6.4 Hz, F_c or F_d).

LR MS (ES^+) *m/z* (%): 501 and 503 ($(M + Na)^+$, 1:1 ratio, 100).

HR MS (ES^+) for $C_{20}H_{19}{}^{79}Br_1F_4O_4Na_1$ $(M + Na)^+$ calcd 501.0295, found 501.0289.

Anionic Cyclization



To a stirred solution of **4.1** (1.082 g, 2.27 mmol, 1 equiv) in THF (23 mL) at -78°C, MeLi (1.41 mL, 2.27 mL, 1 equiv) was added dropwise and the reaction was stirred at -78°C for 4 h. To the reaction was added saturated aqueous NH_4Cl (23 mL) and stirred at RT for 10 minutes. The aqueous solution was extracted with EtOAc (3 x 50 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude as a yellow liquid. Column chromatography (Petroleum Ether/EtOAc: 70/30) followed by HPLC (Hexane/EtOAc: 80/20) gave **1.2** as a transparent gel (0.75 g, 1.88 mmol, 83 % yiled). Column chromatography (Petroleum Ether/EtOAc: 70/30) followed by HPLC (neat CH_2Cl_2) gave **4.10** as a transparent gel (0.0094 g, 0.025 mmol, 1.12 % yield). Column chromatography (Petroleum Ether/EtOAc: 70/30) followed by HPLC (neat CH_2Cl_2) gave **4.11** as a transparent gel (0.0118 g, 0.03 mmol, 1.35 % yield). %). Column chromatography (Petroleum Ether/EtOAc: 70/30) followed by HPLC (neat CH_2Cl_2) gave **4.12** as a transparent gel (0.0064 g, 0.018 mmol, 0.8 % yield).

4,6-Dibenzyl-2,3-dideoxy-2,2,3,3-tetrafluoro-glucose (1.2)

(Mixture of α- and β-anomers)

MW 400.36

R_f 0.31 (Neat CH_2Cl_2)

$[\alpha]_D$ +68.05 (*c* 0.925, $CHCl_3$, 31.5°C)

IR (Neat): 3395 (w), 3065 (w), 3032 (w), 2936 (w), 2874 (w), 1455 (m), 1208 (m), 1145 (s), 1108 (s), 1064 (s), 1026 (s) cm^{-1}.

^{1}H NMR (Acetone, 400 MHz): δ 7.29-7.39 (17H, m, H_{Ar}), 6.92 (1H, br s, $-OH_\alpha$), 5.40 (1H, dd, *J*=8.1, 5.7 Hz, $H_{A\alpha}$), 5.08 (1H, dd, *J*= 15.3, 2.5 Hz, $H_{A\beta}$), 4.87 (1H, d, *J*= 11.2 Hz, $C\underline{H}HC_6H_5\alpha$), 4.86 (1H, d, *J*=11.0 Hz, $C\underline{H}HC_6H_5\beta$), 4.74 (1H, d, *J*=11.2 Hz, $CH\underline{H}C_6H_5\alpha$), 4.73 (1H, d, *J*= 11.0 Hz, $CH\underline{H}C_6H_5\beta$), 4.62 (1H, d, *J*=12.0 Hz, $C\underline{H}HC_6H_{5\beta}$), 4.61 (1H, d, *J*=12.0 Hz, $C\underline{H}HC_6H_5\alpha$), 4.55 (2H, d, *J*=12.0 Hz, $CH\underline{H}C_6H_5\alpha + CH\underline{H}C_6H_5\beta$), 4.32 (1H, app d, *J*= 10.0, 2.5 Hz, $H_{E\alpha}$), 4.06-4.18 (2H, m, $H_{D\alpha} + H_{D\beta}$), 3.85 (1H, dd, *J*=11.2, 3.8 Hz, $H_{F\alpha}$), 3.80-3.82 (3H, m, $H_{F\alpha} + H_{F'\alpha} + H_{E\beta}$), 3.74 (1H, dt, *J*=11.2, 1.8 Hz, $H_{F\alpha}$), 3.34 (1H, br s, $-OH_\beta$).

^{13}C NMR (Acetone, 100 MHz) and **DEPT135**: δ 139.12 (C_{Ar}), 139.04 (C_{Ar}), 138.27 (C_{Ar}), 138.14 (C_{Ar}), 129.12 and 129.09 (8 x C, CH_{Ar}), 128.87 (CH_{Ar}), 128.81 (2 x C, CH_{Ar}), 128.74 (CH_{Ar}), 128.58 (CH_{Ar}), 128.5 (CH_{Ar}), 128.38 (CH_{Ar}), 128.35 (CH_{Ar}), 109.86-119.61 (4 x C, m, CF_2), 92.37(ddm, *J*= 26.1, 19.3 Hz, $C_{A\beta}$), 92.03 (dd, *J*=35.7, 25.1 Hz, $C_{A\alpha}$), 75.83 (2 x C, $\underline{C}H_2C_6H_5$), 74.82 (dd, *J*=18.4, 7.7 Hz, $C_{D\alpha}$), 74.63 (dd, *J*=17.9, 8.2 Hz, $C_{D\beta}$), 73.86 (app d, *J*=3.9 Hz, $C_{G\alpha}$), 73.73 (app dm, *J*=5.8 Hz, $C_{G\beta}$), 69.60 ($C_{E\alpha}$ or $C_{E\beta}$), 69.53 ($C_{E\alpha}$ or $C_{E\beta}$), 68.86 ($C_{F\alpha}$), 68.75 ($C_{F\beta}$).

^{19}F NMR ($CDCl_3$, 282 MHz): δ: **α isomer** -134.47 (1F, ddd, *J*=268.8, 15.0, 8.6 Hz, F_c or F_d), -128.14 (1F, dtd, *J*=257.5, 17.5, 6.4 Hz, F_a or F_b), -126.44 (1F, dd, *J*=257.5, 6.4 Hz, F_a or F_b),

-120.29 (1F, app dd, *J*=268.8, 7.5 Hz, F_c or F_d). **β isomer** -140.12 (1F, dt, *J*=259.7, 12.9 Hz, F_c or F_d), -136.93 (1F, dt, *J*=259.7, 14.0 Hz, F_c or F_d), -130.79 (1F, dt, *J*=259.7, 15.3 Hz, F_a or F_b), -129.67 (1F, ddd, *J*=259.7, 19.3, 9.7 Hz, F_a or F_b).

LR MS (ES^+) *m/z* (%): 423 ($(M + Na)^+$, 100).

HR MS (ES^+) for $C_{20}H_{20}F_4O_4Na_1$ $(M + Na)^+$ calcd 423.1190, found 423.1182.

(*2S, 3R*)-1,3-bis-benzyloxy-4,4,5,5-tetrafluoro-pentan-2-ol (4.10)

MW 372.35

R_f 0.42 (Neat CH_2Cl_2)

$[\alpha]_D$ +28.12 (*c* 0.265, $CHCl_3$, 31.5°C)

IR (Neat): 3090 (w), 3065 (w), 3033 (w), 2871 (w), 1455 (w), 1395 (w), 1360 (w), 1092 (s), 1028 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25-7.41 (10H, m, H_{Ar}), 6.14 (1H, tdd, *J*=53.5, 6.8, 5.2 Hz, H_J), 4.78 (1H, d, *J*=10.7 Hz, $C\underline{H}HC_6H_5$), 4.61 (1H, d, *J*=10.7 Hz, $CH\underline{H}C_6H_5$), 4.57 (1H, d, *J*=11.5 Hz, $C\underline{H}HC_6H_5$), 4.50 (1H, d, *J*=11.5 Hz, $CH\underline{H}C_6H_5$), 3.91-4.01 (2H, m, H_G+H_H), 3.67 (2H, d, *J*=3.9 Hz, $H_F + H_{F'}$), 2.63 (1H, d, *J*=4.9 Hz, *-OH*, $H_{G'}$).

^{13}C NMR ($CDCl_3$, 75MHz) and **DEPT135**: δ 137.50 (C_{Ar}), 136.95 (C_{Ar}), 128.74 (2 x C, CH_{Ar}), 128.68 (2 x C, CH_{Ar}), 128.41(3 x C, CH_{Ar}), 128.26 (CH_{Ar}), 128.15 (2 x C, CH_{Ar}), 77.04 (m, C_H), 75.86 ($\underline{C}H_2C_6H_5$), 73.67 ($\underline{C}H_2C_6H_5$), 69.84 (C_F), 68.87 (C_G), C_I and C_J not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -139.53 (1F, ddt, *J*=300.5, 53.5, 6.4 Hz, F_c or F_d), -138.28 (1F, ddm, *J*=300.5, 53.5 Hz, F_c or F_d), -129.13 (1F, dm, *J*=274.7 Hz, F_a or F_b), -127.99 (1F, dm, *J*=274.7 Hz, F_a or F_b).

LR MS (ES^+) *m/z* (%): 395 ($(M + Na)^+$, 100).

HR MS (ES^+) for $C_{19}H_{20}F_4O_3Na_1$ $(M + Na)^+$ calcd 395.1241, found 395.1235.

(*2S, 3R*)-1,3-Bis-benzyloxy-4,4,5,5-tetrafluoro-hexan-2-ol (4.11)

MW 386.38

R_f 0.33 (Neat CH_2Cl_2)

$[\alpha]_D$ +13.88 (*c* 0.335, $CHCl_3$, 31.5 °C)

IR (Neat): 3460 (w), 3065 (w), 3032 (w), 2926 (w), 2872 (w), 1454 (m), 1390 (m), 1213 (m), 1166 (s), 1101 (s), 1028 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.39 (10H, m, H_{Ar}), 4.76 (2H, s, $C\underline{H}HC_6H_5$ + $CH\underline{H}C_6H_5$), 4.60 (1H, d, *J*=11.8 Hz, $C\underline{H}HC_6H_5$), 4.55 (1H, d, *J*=11.8 Hz, $CH\underline{H}C_6H_5$), 4.27 (1H, m, H_G), 4.20 (1H, app ddd, *J*= 17.3, 8.5, 4.1 Hz, H_H), 3.76 (2H, d, *J*=5.3 Hz, H_F + $H_{F'}$), 2.65 (1H, d, *J*=4.0, *-OH*, $H_{G'}$), 1.76 (3H, tt, *J*=19.3, 2.0 Hz, H_K).

^{13}C NMR ($CDCl_3$, 75 MHz) and **DEPT135**: δ 137.86 (C_{Ar}), 137.36 (C_{Ar}), 128.65 (2 x C, CH_{Ar}), 128.55 (2 x C, CH_{Ar}), 128.21 (2 x C, CH_{Ar}), 128.14 (CH_{Ar}), 128.02 (3 x C, CH_{Ar}), 77.98 (dd, *J*=25.8, 21.6 Hz, C_H), 75.86 ($\underline{C}H_2C_6H_5$), 73.63 ($\underline{C}H_2C_6H_5$), 70.31 (C_F), 69.79 (C_G), 18.67 (t, *J*=24.5 Hz, C_K), C_I and C_J not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -121.82 (1F, ddd, *J*=279.0, 17.3, 6.4 Hz, F_a or F_b), -117.74 (1F, dm, *J*=279.0 Hz, F_a or F_b), -106.58 (1F, dqd, *J*=262.9, 19.3, 7.5 Hz, F_c or F_d), -105.24 (1F, dqd, *J*=262.9, 19.3, 7.5 Hz, F_c or Fd).

LR MS (ES^+) *m/z* (%): 409 ($(M + Na)^+$, 100).

HR MS (ES^+) for $C_{20}H_{22}F_4O_3Na_1$ $(M + Na)^+$ calcd 409.1379, found 409.1400.

(*2S, 3R*)-1,3-Bisbenzyloxy-4,4,5,5-trifluoro-pent-4-en-2-ol (4.12)

MW 352.35

R_f 0.23 (Neat CH_2Cl_2)

IR (Neat): 3448 (w), 3065 (w), 3032 (w), 2867 (w), 1454 (m), 1304 (m), 1257 (s), 1207 (w), 1086 (s), 1071 (s), 1028 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.39 (10H, m, H_{Ar}), 4.64 (1H, d, *J*=15.4 Hz, $CHHC_6H_5$), 4.56 (1H, d, *J*=15.6 Hz, $CHHC_6H_5$), 4.49 (1H, d, *J*=15.6 Hz, $CHHC_6H_5$), 4.36 (1H, d, *J*=15.4 Hz, $CHHC_6H_5$), 4.16 (1H, app dddd, *J*=27.8, 8.6, 3.5, 2.3 Hz, H_H); 4.02 (1H, apparent tt, *J*=7.7, 3.9 Hz, H_G), 3.72 (1H, dd, *J*=9.8, 3.5 Hz, H_F), 3.68 (1H, dd, *J*=9.8, 4.3 Hz, $H_{F'}$), 2.43 (1H, d, *J*=9.2 Hz, *-OH*, $H_{G'}$).

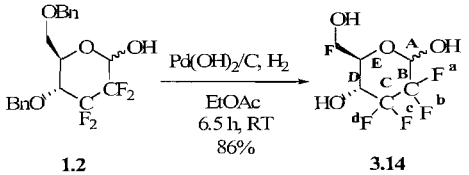
^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.77 (C_{Ar}), 137.04 (C_{Ar}), 128.64 (4 x C, CH_{Ar}), 128.25 (CH_{Ar}), 128.21 (2 x C, CH_{Ar}), 128.08 (CH_{Ar}), 127.99 (2 x C, CH_{Ar}), 77.36 (C_H), 73.62 ($CH_2C_6H_5$), 71.07 ($CH_2C_6H_5$), 70.11 (C_F), 68.71 (C_G).

^{19}F NMR ($CDCl_3$, 282 MHz): δ -188.90 (1F, ddd, *J*=115.4, 32.2, 27.8 Hz, F_a), -120.34 (1F, dd, *J*=115.4, 77.3 Hz, F_b or F_c), -98.87 (1F, dd, *J*=77.3, 32.2 Hz, F_b or F_c).

LR MS (ES^+) *m/z* (%): 375 ($(M + Na)^+$, 100).

HR MS (ES^+) for $C_{19}H_{19}F_4O_3Na_1$ ($(M + Na)^+$ calcd 375.1179, found 375.1172.

2,3-dideoxy-2,2,3,3-tetrafluoro-glucose (4.13)



1.2 3.14

To a stirred solution of **1.2** (0.25 g, 0.624 mmol, 1 equiv) in EtOAc (5 mL) was added $Pd(OH)_2$ /C (0.2 g, 0.375 mmol, 0.6 equiv). The flask was evacuated and purged twice with H_2. The reaction was stirred for 6.5 h at RT and then diluted with EtOAc (10 mL). The organic phase was filtered and the filtrate was concentrated *in vacuo* to give the crude as a transparent gel. Column chromatography (neat EtOAc) followed by HPLC (Hexane/Acetone: 47/53) gave the product as a transparent gel (0.1175 g, 0.534 mmol, 86% yield).

(Mixture of α and β anomers)

MW 220.12

R_f 0.40 (neat EtOAc)

$[\alpha]_D$ +30.32 (*c* 0.94, MeOH, 23°C)

IR (Neat): 3280 (w), 2944 (w), 1379 (w), 1207 (m), 1150 (s), 1097 (s), 1074 (s), 1039 (s), 1011 (s) cm^{-1}.

^{1}H NMR (D_2O, 400 MHz): δ 5.48 (1H, app dt, *J*=5.5, 2.5 Hz, $H_{A\alpha}$), 5.20 (1H, app d, *J*=15.3 Hz, $H_{A\beta}$), 4.07-4.16 (3H, m), 3.89-3.99 (3H, m), 3.86 (1H, m), 3.83 (1H, br s, *-OH*), 3.81 (1H, br s, *-OH*), 3.77 (1H, ddd, *J*=10.0, 4.8, 1.6 Hz).[3]

^{13}C NMR (D_2O, 100 MHz) and **DEPT135**: δ 109.42-115.25 (4 x C, CF_2), 91.27 (dd, *J*=25.5, 11.1 Hz, $C_{A\alpha}$), 90.98 (dd, *J*=26.6, 5.3 Hz, $C_{A\beta}$), 74.24 (m, $C_{E\alpha/\beta}$), 70.17 (m, $C_{E\alpha/\beta}$), 66.65 (d, *J*=19.3, $C_{D\alpha/\beta}$), 66.45 (d, *J*=19.8 Hz, $C_{D\alpha/\beta}$), 60.17 ($C_{F\alpha/\beta}$), 59.98 ($C_{F\alpha/\beta}$).

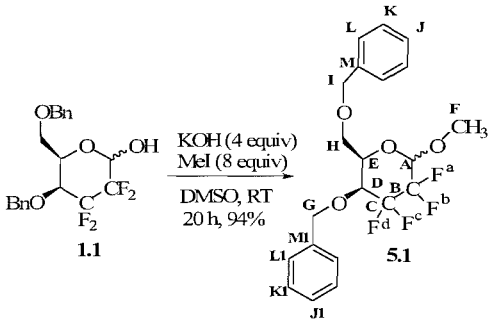
^{19}F NMR (D_2O, 282 MHz): δ **α-anomer** -132.53 (2F, app t, *J*=12.9 Hz, $F_a + F_b$), -130.01 (2F, app t, *J*=11.8 Hz, $F_c + F_d$). **β-anomer**: -139.93 (1F, app dd, *J*=257.6, 15.3 Hz, F_a or F_b), -136.91(1F, app dt, *J*=257.6, 12.9 Hz, F_a or F_b), -134.55 (1F, dt, *J*=268.3, 12.9 Hz, F_c or F_d), -121.31 (1F, dm, *J*=268.3 Hz, F_c or F_d).

LR MS (ES^-) *m/z* (%): 219.1 ($(M - H)^+$, 100).

HR MS : Unable to acquire.

[3] Apart from the anomeric protons, the protons of **3.14** (anomeric mixture) could not be assigned.

4,6-Dibenzyl-1-methyl-2,3-dideoxy-2,2,3,3-tetrafluorogalactoside (5.1)



To a stirred solution of **1.1** (0.5 g, 1.25 mmol, 1 equiv) in DMSO (5 mL) was added KOH (0.281g, 5.0 mmol, 4 equiv) and the reaction stirred at RT for 20 minutes. The solution became yellow and MeI (0.63 mL, 10 mmol, 8 equiv) was added dropwise. The reaction was stirred at RT for 20 h. To the organic phase was added 1N aqueous HCl (15 mL) and the aqueous phase was extracted with EtOAc (4 x 20 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product as a brown gel. Column chromatography (Petroleum ether/Acetone: 85/15) followed by HPLC (Hexane/Acetone: 85/15) gave the α-anomer **5.1** as a transparent gel (0.2 g, 0.483 mmol, 38% yield). Column chromatography (Petroleum ether/Acetone: 85/15) followed by HPLC (Hexane/Acetone: 80/20) gave the β-anomer **5.1** as a transparent gel (0.292 g, 0.705 mmol, 56.3%). The total yield for the reaction was 94% and the α/β ratio: 1/1.5.

α-5.1

MW 414.39

R_f 0.20 (Hexane/Acetone: 85/15)

$[\alpha]_D$ +37.96 (*c* 0.735, $CHCl_3$, 27.5°C)

IR (Neat): 3065 (w), 3032 (w), 2936 (w), 2914 (w), 2872 (w), 1454 (m), 1184 (m), 1152 (s), 1115 (s), 1060 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.37 (10 H, m, H_{Ar}), 4.90 (1H, d, *J*= 11.4 Hz, C$\underline{H}$HC$_6$H$_5$), 4.86 (1H, dd, *J*=9.0, 6.0 Hz, H_A, overlaps with CH$\underline{H}$C$_6$H$_5$), 4.54 (1H, d, *J*=11.4 Hz, CH$\underline{H}$C$_6$H$_5$), 4.50 (1H,d, *J*=12.0 Hz, C$\underline{H}$HC$_6$H$_5$), 4.44 (1H,d, *J*=12.0Hz, CH$\underline{H}$C$_6$H$_5$),

4.30 (1H, m, H_E), 3.93 (1H, m, H_D), 3.56-3.65 (2H, app pentet m, J=9.5 Hz, $H_H + H_{H'}$), 3.46 (3H, s, H_F).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT $_{135}$:** δ 137.75 (C_{Ar}), 136.89 (C_{Ar}), 128.57 (4 x C, CH_{Ar}), 128.52 (2 x C, CH_{Ar}), 128.30 (CH_{Ar}), 127.98 (CH_{Ar}), 127.81 (2 x C, CH_{Ar}), 113.24 (dddd, J=269.3, 250.7, 27.3, 21.3 Hz, C_B), 109.90 (dddd, J=268.9, 247.4, 29.4, 21.7 Hz, C_C), 98.33 (apparent dd, J=37.7, 25.1 Hz, C_A), 75.46 (dd, J=30.0, 17.4 Hz, C_D, overlaps with C_G), 75.15 (d, J=3.9 Hz, C_G), 73.67 (C_I), 68.14 (d, J=5.8 Hz, C_E), 67.73 (C_H), 56.14 (C_F).

^{19}F NMR ($CDCl_3$, 376.5 MHz): - 134.52 (1F, app dtt, J=203.9, 7.7, 4.6 Hz, F_a or F_b), -129.24 (1F, app tt, J=203.9, 7.7, 4.6 Hz, F_a or F_b), -118.05 (1F, ddt, J=272.1, 18.6, 8.3 Hz, F_c or F_d), -116.01 (1F, dtt, J=272.1, 15.5, 7.2 Hz, F_c or F_d).[4]

LRMS (ES^+) *m/z* (%): 437.3 ($(M + Na)^+$, 100).

HRMS (ES^+) for $C_{21}H_{22}F_4O_4Na_1$ $(M + Na)^+$ calcd 437.1346, found 437.1340.

β-5.1

MW 414.39

R_f 0.145 (Hexane/Acetone: 85/15)

$[\alpha]_D$ -43.94 (*c* 1.015, $CHCl_3$, 27.5°C)

IR (Neat): 3065 (w), 3032 (w), 2936 (w), 2914 (w), 2872 (w), 1454 (m), 1184 (m), 1115 (s), 1060 (s) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.39 (10H, m, H_{Ar}), 4.92 (1H,d, J=11.4 Hz, $CH\underline{H}C_6H_5$), 4.61 (1H, m, H_A), 4.58 (1H, d, J=11.4 Hz, $CH\underline{H}C_6H_5$), 4.50 (1H,d, J=11.9 Hz, $CH\underline{H}C_6H_5$), 4.46 (1H,d, J=11.9 Hz, $CH\underline{H}C_6H_5$), 3.91-3.99 (2H, m, H_D+H_E), 3.66-3.72 (2H, m, H_H), 3.63 (3H, s, H_F).

^{13}C NMR ($CDCl_3$, 100 MHz) and **DEPT 135**: δ 137.65 (C_{Ar}), 136.82 (C_{Ar}), 128.55 (2 x C, CH_{Ar}), 128.47 (2 x C, CH_{Ar}), 128.35 (CH_{Ar}), 128.18 (CH_{Ar}), 127.99 (2 x C, CH_{Ar}), 127.85 (2 x C, CH_{Ar}), 114.50 (ddt, J=271.0, 246.8, 23.2 Hz, C_B), 110.62 (tdd, J=261.8, 28.5, 21.7 Hz, C_C), 98.53 (td, J=23.2, 3.9 Hz, C_A), 75.10 (dd, J=29.0, 18.4 Hz, C_D), 75.00 (d, J=3.9 Hz, C_G), 73.66 (C_I), 72.82 (d, J=6.8 Hz, C_E), 67.35 (d, J=1.9 Hz, C_H), 57.88 (C_F).

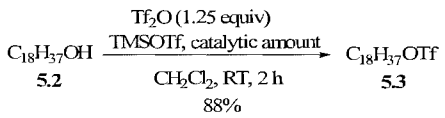
[4] ^{19}F NMR shows that the sample contains traces of an impurity.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -136.67 to -136.59 (2F, s, F_a + F_b), -131.14 (1F, J=272.5, 10.7 Hz, F_c or F_d), -117.17 (1F, J=272.5 Hz, F_c or F_d).

LR MS (ES^+) *m/z* (%): 437.3 $((M + Na)^+$, 100).

HR MS (ES^+)for $C_{21}H_{22}F_4O_4Na_1$ $(M + Na)^+$ calcd. 437.1346, found 437.1336.

1-Octadecyl trifluoromethanesulfonate (5.3)



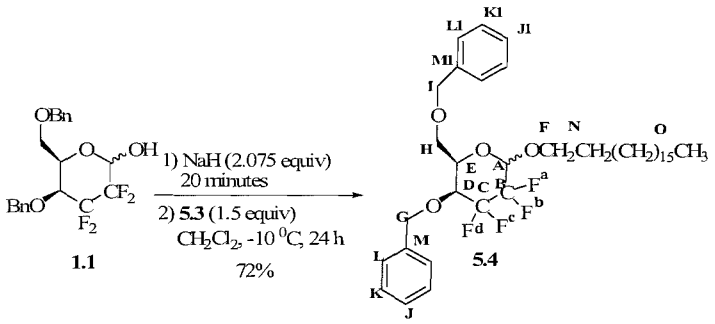
A suspension of **5.2** (1.2853 g, 4.75 mmol, 1 equiv) in CH_2Cl_2 (15mL) at RT was treated with Tf_2O (1.1 mL, 5.94 mmol, 1.4 equiv) and TMSOTf (2 μL, $2.5 \cdot 10^{-4}$ mmol, $5.26 \cdot 10^{-24}$ equiv). The reaction was stirred at RT for 2 h and then quenched with saturated aqueous $NaHCO_3$ (10mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 x 20mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the **5.3** as a white crystalline solid (1.69 g, 4.20 mmol, 83% yield).

δ ^{1}H NMR and δ ^{13}C NMR corresponded to the literature data.[112]

^{1}H NMR (CDCl3, 300 MHz): δ 4.54 (2H, t, J=6.6 MHz, C$\underline{H}_2$OTf), 1.79-1.88 (2H, m, C$\underline{H}_2$CH_2OTf), 1.27 (30H, br s, CH_2), 0.89 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$).

^{13}C NMR (CDCl3, 75 MHz): δ 119.27 (m, $OSO_2\underline{C}F_3$), 77.86 ($\underline{C}H_2$OTf), 32.09 ($\underline{C}H_2$), 29.86 (4 x C, $\underline{C}H_2$), 29.83 (2 x C, $\underline{C}H_2$), 29.79 ($\underline{C}H_2$), 29.74 ($\underline{C}H_2$), 29.62 ($\underline{C}H_2$), 29.53 ($\underline{C}H_2$), 29.48 ($\underline{C}H_2$), 29.40 ($\underline{C}H_2$), 29.02 ($\underline{C}H_2$), 25.21 ($\underline{C}H_2$), 22.85 ($\underline{C}H_2$), 14.25 ($\underline{C}H_3$).

4,6-dibenzyl-1-octadecyl-2,3-dideoxy-2,2,3,3-tetrafluorogalactoside (5.4)



To a stirred solution of **1.1** (0.2478g, 0.619 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at -10 °C, NaH (0.0514g, 1.285 mmol, 2.075 equiv) was added. After stirring at -10 °C for 20 minutes, a solution of **5.3** (0.3718 g, 0.929 mmol, 1.5 equiv) in CH_2Cl_2 (3.7 mL) was added dropwise. The reaction was stirred at -10 °C for 24 h. The crude was filtered over celite, and the filtrate was concentrated *in vacuo* to give the crude as a white solid. Repeated column chromatography (3 x, Petroleum Ether/EtOAc: 90/10) and HPLC (Hexane/EtOAc: 94/6) gave the ***α*-5.4** as transparent gel (0.0261 g, 0.404 mmol, 6.5% yield) and ***β*-5.4** as transparent gel (0.02636g, 4.04 mmol, 65.2% yield). The total yield for reaction was 72% and the *α*/*β* ratio: 91/9.

***α*-5.4**

MW 652.84

Rf 0.33 (Petroleum ether/EtOAc: 94/6)

$[\alpha]_D$ +21.23 (*c* 0.65, $CHCl_3$, 27.5°C)

IR (Neat): 3065 (w), 3032 (w), 2922 (m), 2852 (m), 1455 (m), 1217 (m), 1128 (s), 1059 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.37 (10H, m, H_{Ar}), 4.95 (1H, dd, *J*=9.4, 6.3 Hz, H_A, overlaps with C<u>H</u>HC$_6$H$_5$), 4.92 (1H, d, *J*=11.3 Hz, C<u>H</u>HC$_6$H$_5$), 4.56 (1H, d, *J*=11.3 Hz, CH<u>H</u>C$_6$H$_5$), 4.51 (1H, d, *J*=11.8 Hz, C<u>H</u>HC$_6$H$_5$), 4.44 (1H, d, *J*=11.8 Hz, CH<u>H</u>C$_6$H$_5$), 4.34 (1H, m, H_E), 3.93 (1H, m, H_D), 3.74 (1H, dt, *J*=9.4, 6.8 Hz, H_F), 3.57-3.53 (2H, m, H_H), 3.53 (1H, dt, *J*=9.4, 6.8 Hz, $H_{F'}$), 1.60-1.65 (2H, m, H_N), 1.27 (30 H, br s, C<u>H</u>$_2$ alifatic), 0.90 (3H, t, *J*=6.7 Hz, H_O).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.83 (C_{Ar}), 136.98 (C_{Ar}), 128.59 (4 x C, CH_{Ar}), 128.31 (2 x C, CH_{Ar}), 127.98 (2 x C, CH_{Ar}), 127.79 (2 x C, CH_{Ar}), 97.38 (ddm, *J*=34.8, 24.2 Hz, C_A), 75.57 (m, C_D), 75.18 (d, *J*=3.9 Hz, C_G), 73.68 (C_I), 69.50 (C_H), 68.16 (d, *J*=5.8 Hz, C_E), 67.80 (C_F), 32.08 (C_N), 29.86 and 29.82 (8C, $\underline{C}H_2$ aliphatic), 29.74 ($\underline{C}H_2$ aliphatic), 29.68 ($\underline{C}H_2$ aliphatic), 29.51($\underline{C}H_2$ aliphatic), 29.43 ($\underline{C}H_2$ aliphatic), 29.28 ($\underline{C}H_2$ aliphatic), 26.04 ($\underline{C}H_2$ aliphatic), 22.84 ($\underline{C}H_2$ aliphatic), 14.26 (C_O), C_B and C_C not seen.

^{19}F NMR ($CDCl_3$, 282 MHz): δ -134.54 (1F, dm, *J*=272.6 Hz, F_c or F_d), -129.31 (1F, dm, *J*=272.6 Hz, F_c or F_d), -118.07 (1F, ddt, *J*=272.6, 17.2, 8.6 Hz, F_a or F_b), -116.03 (1F, ddt, *J*=272.6, 15.0, 6.3 Hz, F_a or F_b).

LRMS (ES$^+$) *m/z* (%): 675.4 ($(M + Na)^+$, 18), 670.5 ($(M + NH_4)^+$, 38), 145.1(100).

HRMS (ES$^+$) for $C_{38}H_{56}F_4O_4\ NH_4^+$ $(M + NH_4)^+$ calcd. 670.4453, found 670.4440.

β- 5.4

MW 652.84

R_f 0.28 (Petroleum ether/EtOAc: 94/6)

$[\alpha]_D$ -28.12 (*c* 0.98, $CHCl_3$, 27.5°C)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.32 (10H, m, HAr), 4.86 (1H, d, *J*=11.5 Hz, $C\underline{H}HC_6H_5$), 4.61 (1H, m, H_A), 4.52 (1H, d, *J*=11.5 Hz, $CH\underline{H}C_6H_5$), 4.44 (1H, d, *J*=11.8 Hz, $C\underline{H}HC_6H_5$), 4.40 (1H, d, *J*=11.8 Hz, $CH\underline{H}C_6H_5$), 3.85-3.92 (3H, m, $H_D + H_H$), 3.53-3.66 (3H, m, $H_E + H_F + H_{F'}$),1.55-1.65 (2H, m, H_N), 1.24-1.29 (30 H, m, $C\underline{H}_2$ aliphatic), 0.8 7 (3H, t, *J*=6.8 Hz, H_O).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.73 (C_{Ar}), 136.89 (C_{Ar}), 128.57 (2 x C, CH_{Ar}), 128.49 (2 x C, CH_{Ar}), 128.4 (2 x C, CH_{Ar}),128.21 (CH_{Ar}), 128.01 (CH_{Ar}), 127.86 (2 x C, CH_{Ar}), 114.63 (apparent tt, *J*=259.4, 24.1 Hz, C_B), 110.71(tdd, *J*=261.80, 28.01, 21.3 Hz, C_C), 97.75 (td, *J*=23.2, 3.9 Hz, C_A), 75.14 (dd, *J*=30.0, 18.4 Hz, C_D), 75.00 (d, *J*=2.9 Hz, C_G), 73.71 (C_I), 72.84 (d, *J*=6.8 Hz, C_E), 71.38 (C_H), 67.49 (C_F), 32.06 (C_N), 29.83 (9C, $\underline{C}H_2$ aliphatic), 29.71 ($\underline{C}H_2$ aliphatic), 29.64 ($\underline{C}H_2$ aliphatic), 29.47 ($\underline{C}H_2$ aliphatic), 29.45 ($\underline{C}H_2$ aliphatic), 25.83 ($\underline{C}H_2$ aliphatic), 22.81($\underline{C}H_2$ aliphatic), 14.22 (C_O).

^{19}F NMR (CDCl3, 282 MHz): δ -136.656 to -136.63 (2F, m, F_c or F_d), -130.92 (1F, dt, *J*=271.5, 12.9 Hz, F_a or F_b), -116.96 (1F, d, *J*=271.5 Hz, F_a or F_b).

LRMS (ES$^+$) *m/z* (%): 675.41($(M + Na)^+$, 15), 670.6 ($(M + NH_4)^+$, 100).

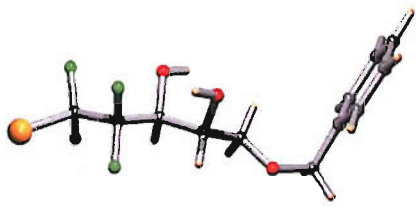
HRMS (ES^+) for $C_{38}H_{56}F_4O_4\ NH_4^+$ $(M + NH_4)^+$ calcd. 670.4453, found 670.4435.

Appendix

X-ray Analysis Data

Crystallographic Data for Compound 1.4

Table 1. Crystal data and structure refinement details.



Identification code	**2006sot0216 (RST/4390/51)**
Empirical formula	$C_{12}H_{13}BrF_4O_3$
Formula weight	361.13
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 4.8135(6)$ Å
	$b = 9.7967(10)$ Å
	$c = 28.665(3)$ Å
Volume	1351.8(3) Å^3
Z	4
Density (calculated)	1.775 Mg / m^3
Absorption coefficient	3.092 mm^{-1}
F(000)	720
Crystal	Plate; Colourless
Crystal size	0.2 × 0.11 × 0.02 mm^3
θ range for data collection	2.98 – 27.48°
Index ranges	$-6 \le h \le 6$, $-12 \le k \le 12$, $-37 \le l \le 36$
Reflections collected	10841
Independent reflections	3052 [$R_{int} = 0.0933$]
Completeness to $\theta = 27.48°$	99.4 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9407 and 0.5667
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3052 / 0 / 182
Goodness-of-fit on F^2	1.045
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0599$, $wR2 = 0.1189$
R indices (all data)	$R1 = 0.1027$, $wR2 = 0.1328$
Absolute structure parameter	0.088(19)
Extinction coefficient	0.0109(16)
Largest diff. peak and hole	0.499 and –0.420 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G.

M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	4876(13)	5496(6)	8565(2)	30(1)	1
C2	3934(11)	4602(7)	8148(2)	27(1)	1
C3	3268(11)	5405(6)	7710(2)	23(1)	1
C4	2029(12)	4511(6)	7316(2)	23(1)	1
C5	846(11)	5392(6)	6927(2)	27(1)	1
C6	−1992(12)	5178(6)	6248(2)	29(1)	1
C7	220(13)	5043(6)	5881(2)	27(1)	1
C8	1205(13)	6179(8)	5659(2)	39(2)	1
C9	3291(14)	6019(8)	5300(2)	40(2)	1
C10	4200(13)	4763(7)	5175(2)	36(2)	1
C11	3108(14)	3599(8)	5393(2)	38(2)	1
C12	1116(14)	3747(7)	5746(2)	38(2)	1
O1	5703(8)	6035(4)	7546(1)	28(1)	1
O2	4079(8)	3602(4)	7134(1)	26(1)	1
O3	−1149(8)	4569(4)	6687(1)	28(1)	1
F1	3149(7)	6579(4)	8607(1)	35(1)	1
F2	7412(7)	5979(4)	8493(1)	36(1)	1
F3	1599(7)	3916(3)	8289(1)	33(1)	1
F4	5954(7)	3648(3)	8083(1)	31(1)	1
Br1	4854(2)	4521(1)	9152(1)	49(1)	1

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

C1–F2	1.326(7)
C1–F1	1.353(7)
C1–C2	1.551(8)
C1–Br1	1.934(5)
C2–F4	1.361(6)
C2–F3	1.371(7)
C2–C3	1.514(8)
C3–O1	1.406(6)
C3–C4	1.548(8)
C4–O2	1.428(7)
C4–C5	1.521(8)

C5–O3	1.430(7)
C6–O3	1.452(6)
C6–C7	1.502(8)
C7–C8	1.366(9)
C7–C12	1.396(9)
C8–C9	1.447(9)
C9–C10	1.354(9)
C10–C11	1.403(9)
C11–C12	1.401(9)
F2–C1–F1	107.4(5)
F2–C1–C2	110.5(5)
F1–C1–C2	109.4(5)
F2–C1–Br1	108.5(4)
F1–C1–Br1	107.9(4)
C2–C1–Br1	113.0(4)
F4–C2–F3	106.8(5)
F4–C2–C3	113.3(4)
F3–C2–C3	109.0(4)
F4–C2–C1	106.5(5)
F3–C2–C1	106.8(4)
C3–C2–C1	114.0(5)
O1–C3–C2	109.2(4)
O1–C3–C4	109.0(4)
C2–C3–C4	113.0(5)
O2–C4–C5	110.1(4)
O2–C4–C3	110.7(4)
C5–C4–C3	111.0(5)
O3–C5–C4	106.5(5)
O3–C6–C7	111.9(5)
C8–C7–C12	120.3(6)
C8–C7–C6	120.0(5)
C12–C7–C6	119.5(5)
C7–C8–C9	119.0(7)
C10–C9–C8	120.7(6)
C9–C10–C11	119.9(6)
C12–C11–C10	119.7(7)
C7–C12–C11	120.4(6)
C5–O3–C6	112.0(5)

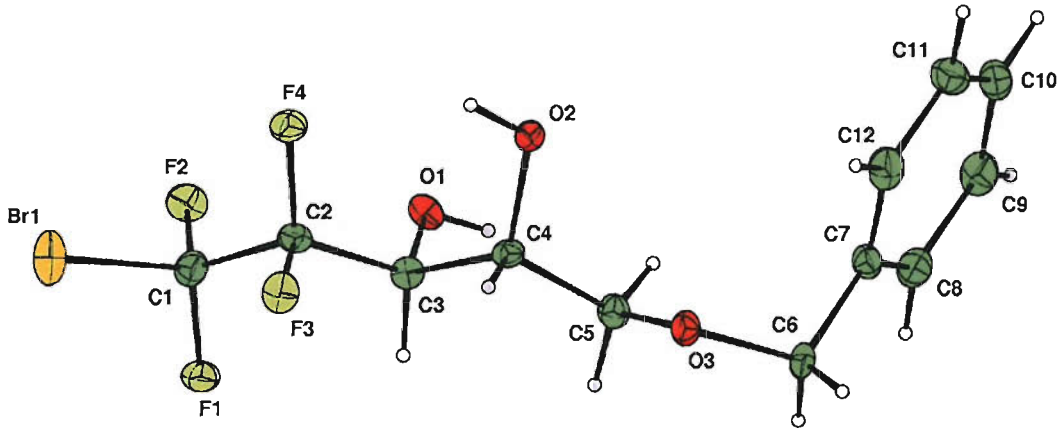
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}\,]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	26(3)	37(3)	27(3)	6(3)	−1(3)	−1(4)

C2	23(3)	30(3)	28(3)	0(3)	4(2)	3(3)
C3	25(3)	15(3)	28(3)	2(3)	1(2)	−4(3)
C4	24(3)	19(3)	26(3)	3(3)	2(2)	3(3)
C5	28(3)	27(3)	24(3)	2(3)	1(2)	−1(3)
C6	30(3)	39(4)	17(3)	5(3)	−4(2)	4(3)
C7	24(3)	37(3)	20(2)	0(2)	1(3)	−2(3)
C8	32(4)	53(4)	32(3)	7(3)	−1(3)	3(3)
C9	34(4)	48(4)	36(4)	15(3)	5(3)	−8(3)
C10	34(4)	48(4)	27(3)	−1(3)	0(3)	−2(3)
C11	31(4)	47(4)	37(4)	−8(3)	3(3)	1(3)
C12	36(4)	45(4)	32(4)	4(3)	−2(3)	−7(3)
O1	30(3)	25(2)	28(2)	−1(2)	8(2)	−7(2)
O2	31(2)	25(2)	22(2)	1(2)	−1(2)	7(2)
O3	27(2)	33(2)	22(2)	−2(2)	−3(2)	−2(2)
F1	32(2)	36(2)	37(2)	−9(2)	−1(2)	9(2)
F2	28(2)	38(2)	42(2)	−6(2)	0(2)	−7(2)
F3	29(2)	36(2)	34(2)	6(2)	0(2)	−11(2)
F4	35(2)	24(2)	35(2)	−4(2)	−3(2)	7(2)
Br1	65(1)	55(1)	29(1)	6(1)	−9(1)	−11(1)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3	1892	6132	7791	27	1
H4	484	3953	7451	28	1
H5A	−53	6217	7058	32	1
H5B	2340	5682	6712	32	1
H6A	−2408	6157	6297	35	1
H6B	−3712	4729	6137	35	1
H8	530	7059	5739	47	1
H9	4031	6803	5150	47	1
H10	5576	4670	4939	44	1
H11	3717	2716	5303	46	1
H12	370	2961	5894	45	1
H1	5342	6482	7304	41	1
H2	4719	3119	7351	39	1



Thermal ellipsoids drawn at the 35% probability level.

Crystallographic Data for Compound 1.5

Table 1. Crystal data and structure refinement details.

Identification code	**2006sot0237 (RST/4390/35)**
Empirical formula	$C_{12}H_{13}BrF_4O_3$
Formula weight	361.13
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 16.2088(9) Å
	b = 4.9409(2) Å β = 111.500(2)°
	c = 18.1121(11) Å
Volume	1349.60(12) Å^3
Z	4
Density (calculated)	1.777 Mg / m^3
Absorption coefficient	3.097 mm^{-1}
$F(000)$	720
Crystal	Lath; Colourless
Crystal size	0.2 × 0.04 × 0.02 mm^3
θ range for data collection	3.37 – 26.37°
Index ranges	$-20 \le h \le 20, -6 \le k \le 6, -22 \le l \le 22$
Reflections collected	17459
Independent reflections	2753 [R_{int} = 0.0997]
Completeness to θ = 26.37°	99.8 %
Absorption correction	Semi–empirical from equivalents

Max. and min. transmission	0.9406 and 0.5663
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2753 / 0 / 189
Goodness-of-fit on F^2	1.036
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0444, $wR2$ = 0.0743
R indices (all data)	$R1$ = 0.0824, $wR2$ = 0.0841
Largest diff. peak and hole	0.401 and −0.520 e Å^{-3}

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

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except those of the 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.*
C1	860(2)	1551(7)	8056(2)	23(1)	1
C2	553(2)	2336(6)	7175(2)	19(1)	1
C3	1273(2)	2485(6)	6823(2)	19(1)	1
C4	896(2)	3409(6)	5950(2)	19(1)	1
C5	1608(2)	3294(7)	5592(2)	25(1)	1
C6	1839(2)	5191(7)	4456(2)	26(1)	1
C7	2338(2)	3028(7)	4210(2)	21(1)	1
C8	1974(2)	1872(7)	3456(2)	24(1)	1
C9	2418(3)	−140(7)	3225(2)	30(1)	1
C10	3234(3)	−1025(7)	3735(2)	32(1)	1
C11	3607(3)	97(8)	4481(2)	34(1)	1
C12	3158(2)	2086(7)	4721(2)	29(1)	1
O1	1704(2)	−44(5)	6912(2)	24(1)	1
O2	606(2)	6166(5)	5897(1)	22(1)	1
O3	1216(2)	4112(5)	4781(1)	25(1)	1
F1	1542(1)	3136(4)	8482(1)	28(1)	1
F2	1151(1)	−1015(4)	8172(1)	33(1)	1
F3	−83(1)	540(4)	6763(1)	24(1)	1
F4	141(1)	4781(4)	7119(1)	26(1)	1
Br1	−78(1)	1932(1)	8470(1)	36(1)	1

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

C1–F1	1.343(4)
C1–C2	1.536(5)
C1–Br1	1.936(3)
C2–F3	1.358(4)
C2–F4	1.366(4)
C2–C3	1.522(5)
C3–O1	1.412(4)
C3–C4	1.542(5)
C4–O2	1.432(4)
C4–C5	1.519(5)
C5–O3	1.428(4)
C6–O3	1.445(4)
C6–C7	1.504(5)
C7–C12	1.391(5)
C7–C8	1.396(5)
C8–C9	1.379(5)
C9–C10	1.378(5)
C10–C11	1.379(5)
C11–C12	1.383(5)
F2–C1–F1	107.0(3)
F2–C1–C2	111.3(3)
F1–C1–C2	109.6(3)
F2–C1–Br1	108.1(2)
F1–C1–Br1	108.6(2)
C2–C1–Br1	112.1(2)
F3–C2–F4	106.6(3)
F3–C2–C3	110.2(3)
F4–C2–C3	110.8(3)
F3–C2–C1	107.4(3)
F4–C2–C1	105.4(3)
C3–C2–C1	116.1(3)
O1–C3–C2	109.5(3)
O1–C3–C4	111.9(3)
C2–C3–C4	111.6(3)
O2–C4–C5	106.8(3)
O2–C4–C3	110.3(3)
C5–C4–C3	110.4(3)
O3–C5–C4	107.8(3)
O3–C6–C7	113.0(3)
C12–C7–C8	118.2(3)
C12–C7–C6	121.8(3)
C8–C7–C6	120.0(3)

C9–C8–C7	120.7(3)
C10–C9–C8	120.3(4)
C9–C10–C11	119.8(4)
C10–C11–C12	120.1(4)
C11–C12–C7	120.9(3)
C5–O3–C6	114.1(3)

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	20(2)	25(2)	24(2)	2(2)	6(2)	0(2)
C2	20(2)	19(2)	18(2)	1(2)	6(2)	2(2)
C3	16(2)	17(2)	24(2)	−1(2)	7(2)	−2(1)
C4	21(2)	16(2)	22(2)	2(2)	8(2)	1(2)
C5	23(2)	34(2)	20(2)	2(2)	10(2)	3(2)
C6	30(2)	26(2)	27(2)	−1(2)	15(2)	−4(2)
C7	21(2)	22(2)	21(2)	3(2)	10(2)	−2(2)
C8	19(2)	31(2)	22(2)	6(2)	8(2)	−1(2)
C9	37(3)	28(2)	28(2)	1(2)	18(2)	−1(2)
C10	37(2)	28(2)	44(3)	8(2)	28(2)	8(2)
C11	24(2)	45(3)	35(2)	11(2)	13(2)	9(2)
C12	26(2)	39(2)	21(2)	4(2)	10(2)	−2(2)
O1	23(2)	20(2)	30(2)	−2(1)	9(1)	2(1)
O2	17(2)	21(2)	27(2)	1(1)	8(1)	3(1)
O3	22(1)	34(1)	21(1)	4(1)	11(1)	1(1)
F1	24(1)	35(1)	20(1)	−2(1)	2(1)	−4(1)
F2	39(1)	28(1)	28(1)	7(1)	9(1)	5(1)
F3	20(1)	27(1)	24(1)	−3(1)	7(1)	−4(1)
F4	27(1)	23(1)	28(1)	1(1)	12(1)	7(1)
Br1	30(1)	57(1)	25(1)	0(1)	14(1)	−4(1)

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

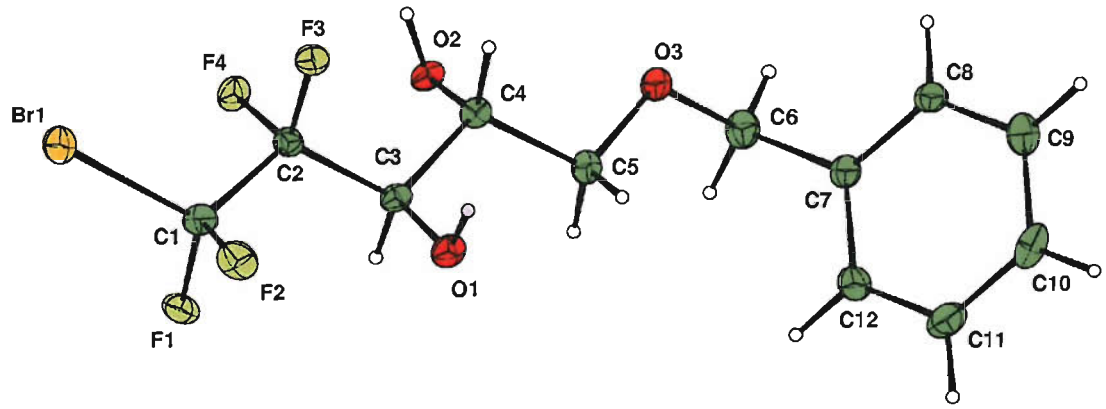
Atom	x	y	z	U_{eq}	*S.o.f.*
H3	1720	3854	7133	23	1
H4	387	2222	5639	23	1
H5A	2104	4521	5884	30	1
H5B	1844	1431	5627	30	1
H6A	2269	6366	4858	32	1
H6B	1515	6328	3990	32	1
H8	1414	2478	3098	29	1

H9	2159	−920	2712	36	1
H10	3539	−2404	3572	39	1
H11	4172	−496	4831	41	1
H12	3413	2818	5240	34	1
H92	80(30)	6060(70)	5730(20)	23(11)	1
H91	1410(20)	−1100(70)	6680(20)	20(13)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O2–H92···O3^{i}	0.80(4)	1.96(4)	2.755(4)	174(4)
O1–H91···O2^{ii}	0.73(3)	2.04(4)	2.767(4)	173(4)

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



Thermal ellipsoids drawn at the 35% probability level

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