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„Expanding the principle of metabolic trapping to the ketoses of the pentose phosphate pathway“

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Abbreviations

1,3-BPG	1,3-bisphosphoglycerate
1DFRu	1-deoxy-1-fluoro-D-ribulose
2-PG	2-phosphoglycerate
2,2-DMP	2,2-dimethoxypropane
3DFRu	3-deoxy-3-fluoro-D-ribulose
3-PG	3-phosphoglycerate
4DFS	4-deoxy-4-fluoro-D-sedoheptulose
6PG	6-phosphogluconate
6PGD	6-phosphogluconate dehydrogenase
6PGL	6-phosphoglucono-δ-lactone
Ac	acetyl
ACO	aconitase
ADMET	absorption, distribution, metabolism, excretion, toxicology
ADP	adenosine diphosphate
ALDO	aldolase
ATP	adenosine triphosphate
Bn	benzyl
Bz	benzoyl
CARLK	carbohydrate kinase-like protein
ClAc	chloroacetyl
CoA	coenzyme A
CS	citrate synthase
CT	computed tomography
***m*-CPBA**	*meta*-chloroperbenzoic acid
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DHAP	dihydroxyacetone phosphate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutlyaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMEM	Dulbecco's modified Eagle's medium
DMF	dimethylformamide
DME	1,2-dimethoxyethane
DMP	Dess-Martin-periodinane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
E4P	erythrose-4-phosphate
EA	ethyl acetate
ENO	enolase
ESI	electrospray ionization
F1,6BP	fructose-1,6-bisphosphate
F6P	fructose-6-phosphate
FAD^+	flavin adenine dinucleotide ox. form
$FADH_2$	flavin adenine dinucleotide red. form
FBP	fructose-1,6-phosphatase
FBS	fetal bovine serum
FDA	United States food and drug administration
FDG	2-deoxy-2-fluoro-D-glucose
FH	fumarate hydratase
FMISO	fluoromisonidazole
G3P	gylceraldehyde-3-phosphate
G6P	glucose-6-phosphate
G6Pase	glucose-6-phosphatase
G6PDH	glucose-6-phosphate dehydrogenase
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GDP	guanosine diphosphate
GlcNAc	2-acetylamino-2-deoxy-D-glucose
GLUT	glucose transporter
GTP	guanosine triphosphate
HDTC	hydrazine dithiocarbonate
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HILIC	hydrophilic interaction liquid chromatography
HPAEC	high performance anion exchange chromatography
HRMS	high resolution mass spectrometry
IDH	isocitrate dehydrogenase
LDA	lithium diisopropylamide
LDH	lactate dehydrogenase
LG	leaving group
MeCN	acetonitrile
MDH	malate dehydrogenase
MPLC	medium performance liquid chromatography
$NAD(P)^+$	nicotinamide adenine dinucleotide (phosphate) ox. form
NAD(P)H	nicotinamide adenine dinucleotide (phosphate) red. form
NFSI	*N*-fluorobenzenesulfonimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ns	4-nitrobenzensulfonyl
OGDC	α-oxoglutarate decarboxylase
PAD	pulsed amperometric detection

PC	pyruvate carboxylase
PDB	protein data bank
PDC	pyruvate decarboxylase
PEP	phosphoenolpyruvate
PEPCK	phosphoenolpyruvate carboxykinase
PET	positron emission tomography
PFA	perfluoroalkoxy
PFK	phosphofructokinase
PG	protecting group
PGI	phosphoglucose isomerase
PGK	phosphoglycerate kinase
PGLS	6-phosphogluconolactonase
PGM	phosphoglycerate mutase
Ph	phenyl
P_i	phosphate
PK	pyruvate kinase
PPP	pentose phosphate pathway
py	pyridine
R5P	ribose-5-phosphate
RNA	ribonucleic acid
ROS	reactive oxygen species
RPE	ribulose-5-phosphate epimerase
RPI	ribose-5-phosphate isomerase
Ru5P	ribulose-5-phosphate
S7P	sedoheptulose-7-phosphate
SCS	succinyl CoA synthetase
SDH	succinate dehydrogenase
SGLT	sodium-dependent D-glucose cotransporters
SHPK	sedoheptulose kinase
TALDO1	transaldolase
TBA	tetrabutylammonium
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TCA	tricarboxylic acid cycle
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
ThDP	thiamine diphosphate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TKT	transketolase
TLC	thin layer chromatography
tol	toluene
TPAP	tetrapropylammonium perruthenate
TPI	triosephosphate isomerase
***p*-Ts**	*para*-toluenesulfonyl
Xu5P	xylulose-5-phosphate

Abstract

One of the most important applications of fluorinated carbohydrates lies in the field of molecular imaging: Fluorinating selected positions within the sugar scaffold can lead to enhanced metabolic stability after phosphorylation and subsequent accumulation in cells. This is also the underlying principle of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), the most frequently applied positron emission tomography (PET) tracer for imaging alterations in glucose demand in patients. This work tries to expand this principle to two rare sugars involved in the pentose phosphate pathway (PPP): D-sedoheptulose and D-ribulose. Thus, syntheses for 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**), 1-deoxy-1-fluoro-D-ribulose (**1DFRu**) and 3-deoxy-3-fluoro-D-ribulose (**3DFRu**) were developed. Cellular uptake assays showed that **4DFS** is readily taken up by human fibroblasts. Furthermore, *in vitro* assays revealed that **4DFS** is phosphorylated by sedoheptulose kinase (SHPK) and that fluorination in position 4 of D-sedoheptulose halts the enzymatic degradation of the sugar phosphate by transaldolase (TALDO1) and transketolase (TKT). This makes **4DFS** a promising new PPP imaging probe. Therefore, potential radiolabeling precursors for **4DFS** were also synthesized to allow the late-stage introduction of fluorine-18. Furthermore, syntheses for potential radiolabeling precursors of **1DFRu** and **3DFRu** were developed.

Zusammenfassung

Eines der wichtigsten Anwendungsgebiete von fluorierten Kohlenhydraten liegt in der molekularen Bildgebung: Die Fluorierung bestimmter Positionen im Zuckerskelett kann zu einer verbesserten metabolischen Stabilität der Zucker und infolgedessen zur Anreicherung in Zellen führen. Das ist auch das zugrundeliegende Prinzip von 2-Desoxy-2-[^{18}F]Fluor-D-Glukose ([^{18}F]FDG), dem am meisten verwendeten Positronenemissionstomographie (PET) Tracer um Veränderungen des Glukosebedarfs in Patienten zu visualisieren. Diese Arbeit versucht dieses Prinzip auf zwei seltene Zucker mit einer wichtigen Funktion im Pentosephosphatweg (PPP) auszudehnen: D-Sedoheptulose und D-Ribulose. Dafür wurden Synthesen für 4-Desoxy-4-Fluor-D-Sedoheptulose (**4DFS**), 1-Desoxy-1-Fluor-D-Ribulose (**1DFRu**) and 3-Desoxy-3-Fluor-D-Ribulose (**3DFRu**) entwickelt. Zellbasierte Assays konnten zeigen, dass **4DFS** von menschlichen Fibroblasten aufgenommen wird. Außerdem konnte mit *in vitro* Experimenten gezeigt werden, dass **4DFS** von Sedoheptulosekinase (SHPK) phosphoryliert wird und dass die Fluorierung von D-Sedoheptulose in Position 4 den enzymatischen Abbau des entstehenden Zuckerphosphats durch die Enzyme Transaldolase (TALDO1) und Transketolase (TKT) verhindert. Diese Ergebnisse machen **4DFS** zu einer vielversprechenden Verbindung für die Entwicklung von bildgebenden Verfahren zur Erforschung des PPP auf molekularer Ebene. Daher wurde des Weiteren eine Syntheseroute für Vorstufen entwickelt, die eine Radiomarkierung von **4DFS** mit Fluor-18 ermöglichen sollen. Außerdem wurden auch Synthesen entwickelt, die eine Radiofluorierung von **1DFRu** und **3DFRu** ermöglichen sollen.

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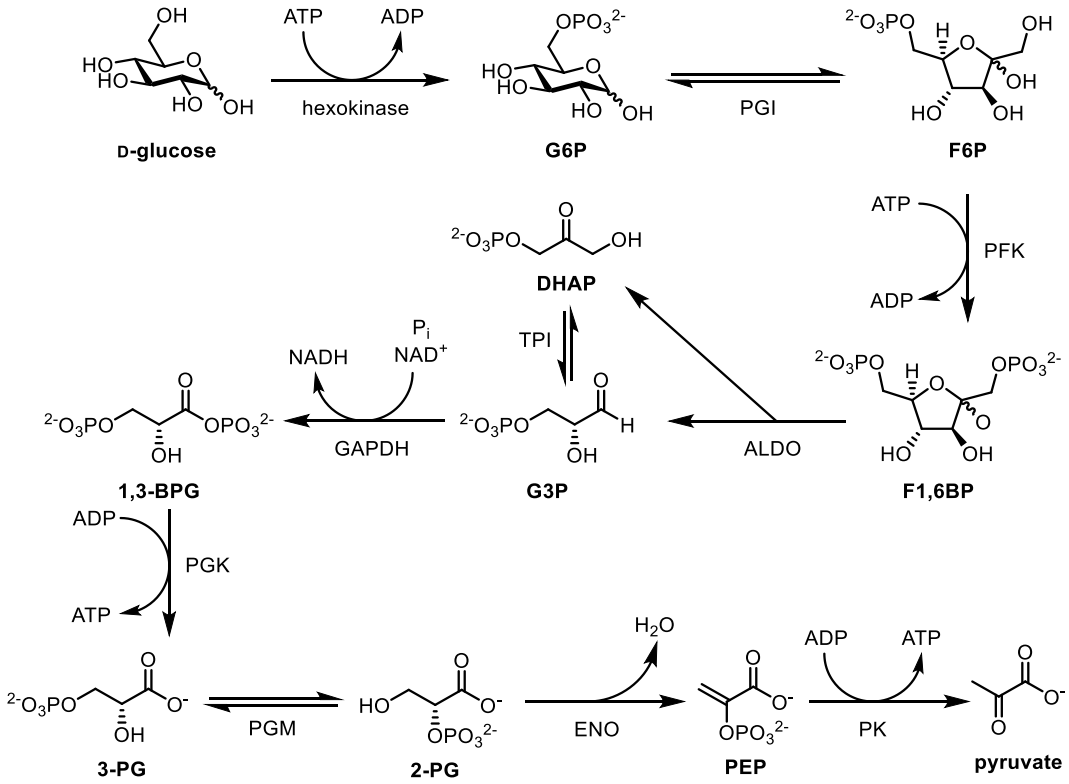
1 Introduction

1.1 Carbohydrates

Carbohydrates are the most abundant group of biomolecules on earth and account for more than 50% of the dry biomass on the planet. Plants build up carbohydrates through photosynthesis by fixating CO_2 from the atmosphere and producing mono-, di-, oligo- and polysaccharides and O_2.[1–3] The plant-derived saccharides range from structural (e.g.: cellulose) to storage poly- or disaccharides (e.g.: starch, sucrose) and are composed of simpler monosaccharides linked together through glycosidic bonds. These plant-derived sugars form the basis for energy consumption for a wide range of animals and for humans alike. After food intake, the glycosidic bonds are split by glycosidases to make the polysaccharide available for other metabolic processes. This process first yields smaller fragments of the polymers and finally gives D-glucose and other monosaccharides which are then absorbed by the intestine and reach the blood stream.[1]

1.1.1 Catabolism

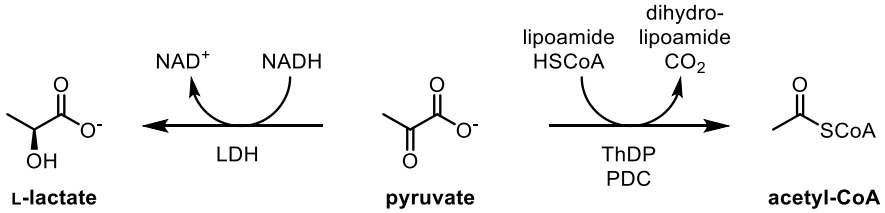
Glycolysis is the most important catabolic pathway for carbohydrates, especially for covering immediate energy demands (Scheme 1). After D-glucose is taken up by cells



Scheme 1: Enzymatic reactions of glycolysis.

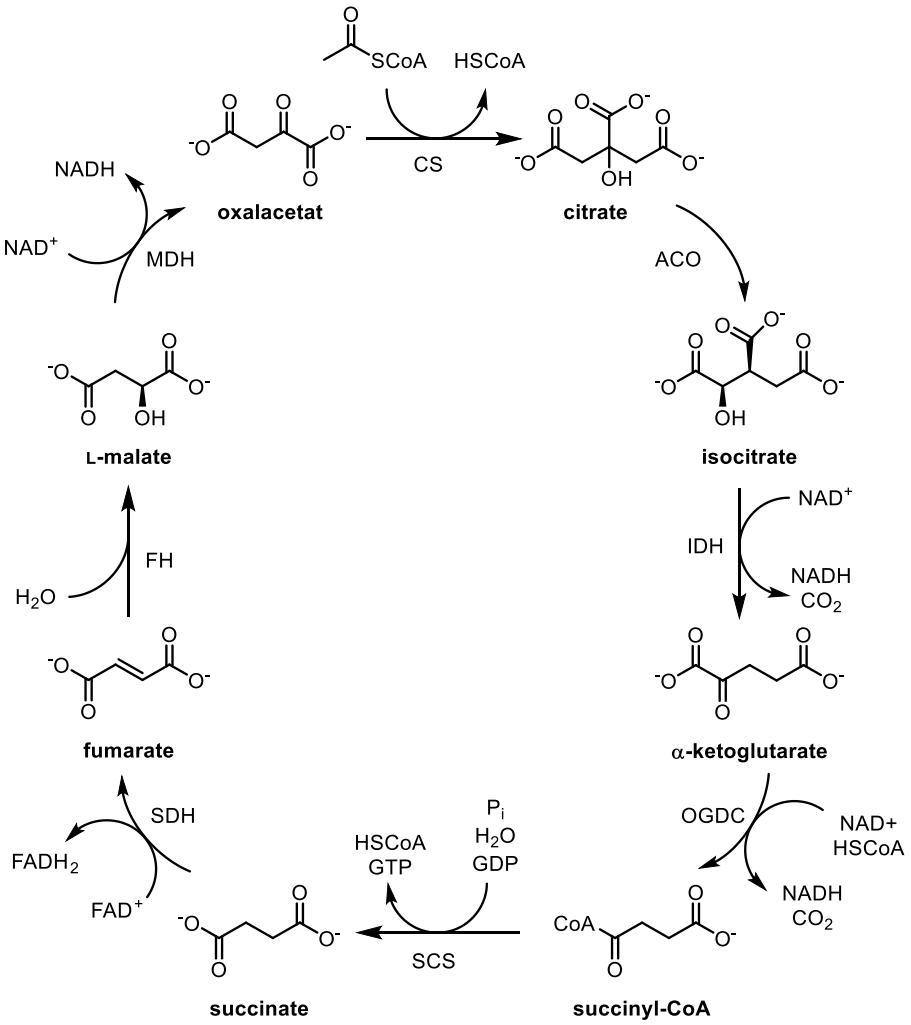
via glucose transporters (GLUTs) the first step of glycolysis is the phosphorylation of D-glucose at position 6 by hexokinase to from glucose-6-phosphate (**G6P**).[1] In the next steps, **G6P** is isomerized to fructose-6-phosphate (**F6P**) by phosphoglucose isomerase (PGI) followed by phosphorylation by phosphofructose kinase (PFK) at position 1 to give fructose-1,6-bisphophate (**F1,6BP**). Then, **F1,6BP** is split into two C_3-fragments by fructose-bisphosphate aldolase (ALDO) to form one molecule of glyceraldehyde-3-phosphate (**G3P**) and one molecule of dihydroxyacetone phosphate (**DHAP**). **DHAP** can then be converted to **G3P** by triosephosphate isomerase (TPI). Subsequently, **G3P** undergoes oxidation and phosphorylation by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) to yield NADH and 1,3-bisphophoglycerate (**1,3-BPG**) which is then dephosphorylated at position 1 by phospoglycerate kinase to generate 3-phosphoglycerate (**3-PG**) and adenosine triphosphate (ATP). Phosphoglycerate mutase (PGM) converts **3-PG** into 2-phosphoglycerate (**2-PG**) which then serves as a precursor for phosphoenolpyruvate (**PEP**). In the last step of glycolysis, pyruvate kinase (PK) dephosphorylates **PEP** to give pyruvate and ATP. Therefore, the net reaction of glycolysis gives two molecules each of pyruvate, NADH, ATP and water from one molecule D-glucose.

In animal cells, pyruvate is then either reduced to L-lactate, especially under anaerobic conditions, or undergoes oxidative decarboxylation catalyzed by pyruvate decarboxylase under regular aerobic conditions to give acetyl-CoA (Scheme 2).



Scheme 2: Conversion of pyruvate to L-lactate or acetyl-CoA.

Acetyl-CoA is a key metabolic intermediate stemming not only from glycolysis but also from fatty acid- and to some extent amino acid catabolism and it is the starting point for the Krebs cycle, *aka* tricarboxylic acid cycle (TCA cycle, Scheme 3). The first step in the TCA cycle is an aldol-type reaction of acetyl-CoA with oxaloacetate to release citrate and coenzyme A. Then, citrate undergoes an isomerization to give isocitrate which is then oxidatively decarboxylated to form NADH, CO_2 and α-ketoglutarate. A second oxidative decarboxylation then produces another equivalent of NADH and CO_2

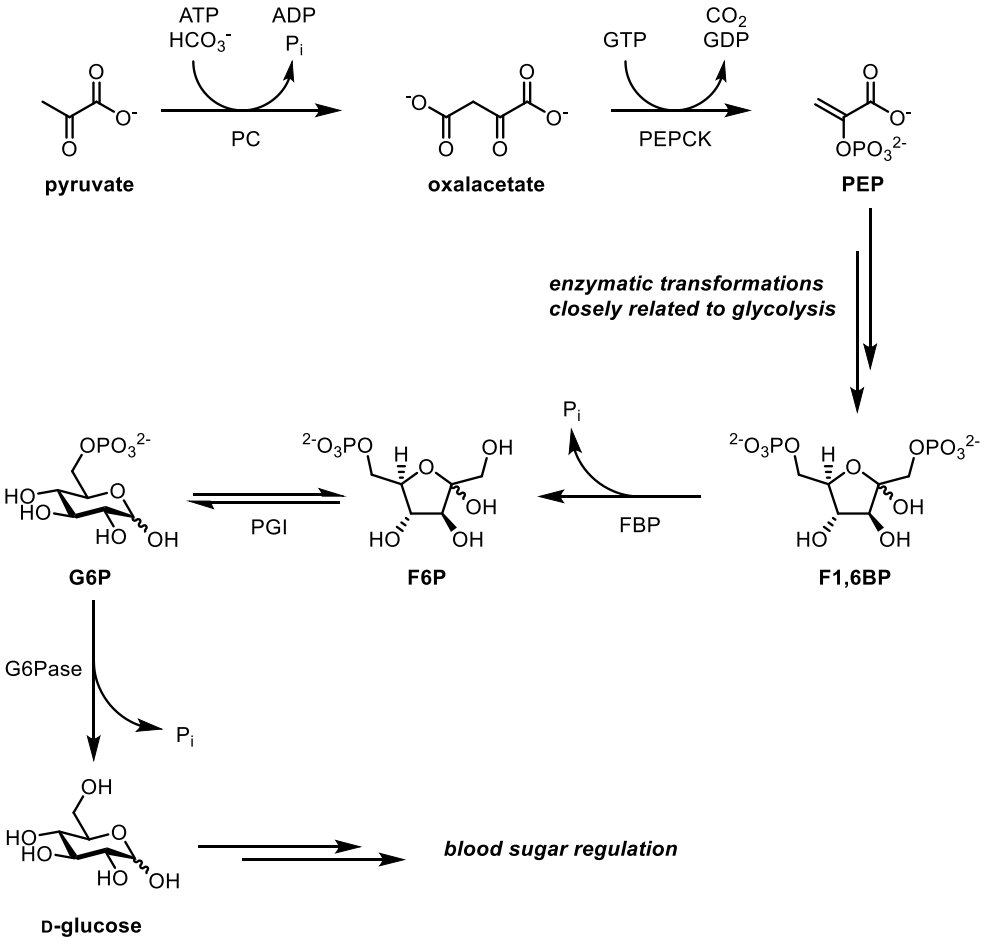


Scheme 3: Reactions of the tricarboxylic acid cycle (TCA cycle).

as well as succinyl-CoA. In the next step, coenzyme A is again released by an enzymatic reaction coupled to a phosphorylation / dephosphorylation sequence of succinate to yield CoA, GTP and succinate. Subsequent oxidation of succinate gives fumarate and $FADH_2$. The last two steps of the TCA cycle involve the addition of a water molecule to fumarate giving L-malate and the consecutive oxidation to form NADH and α-ketoglutarate. Taking the total cycle into consideration, the TCA cycle produces six equivalents of NADH and two equivalents of each $FADH_2$ and GTP per molecule D-glucose.

1.1.2 Anabolism

Gluconeogenesis is the anabolic pathway for D-glucose formation.[1] It builds up D-glucose from L-lactate, pyruvate or oxalacetate (stemming from glucogenic amino acid catabolism) or from glycerol (stemming from triglyceride degradation). Gluconeogenesis provides key metabolic intermediates from scratch or helps to regulate blood sugar levels and to avoid hypoglycemia by synthesizing D-glucose. The biosynthetic pathway is similar but not identical to opposite direction of glycolysis: First, pyruvate is carboxylated at the β-position under consumption of ATP and HCO_3^- to give oxalacetate (Scheme 4). Then, phosphorylation and a following decarboxylation yield **PEP**. A conjugate addition of water to the double bond of **PEP** results in **2-PG** formation. Subsequent isomerization to **3-PG** and phosphorylation of position 1 gives **1,3-BPG** which is reduced to **G3P** in the presence of NADH in the next step. Then, **G3P** can isomerize again to **DHAP** to form the reaction partner for the subsequent aldol reaction giving **F1,6BP**. Fructose-1,6-bisphophate is then dephosphorylated by the corresponding phosphatase to yield **F6P** which isomerizes again to **G6P**. The last



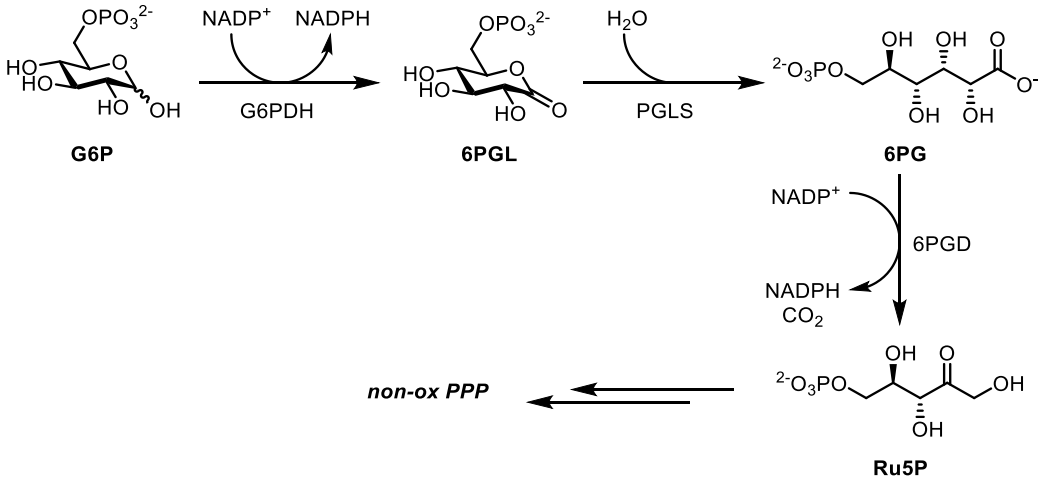
Scheme 4: Enzymatic steps of gluconeogenesis.

step of gluconeogenesis is the glucose-6-phosphatase (G6Pase) mediated dephosphorylation of **G6P** to give D-glucose.

1.1.3 Pentose Phosphate Pathway

Another important carbohydrate metabolic pathway is the pentose phosphate pathway (PPP) which cannot be categorized as entirely catabolic or anabolic. 5-30% of D-glucose are metabolized via the PPP depending on the metabolic state of the cell. It can be divided into two branches: an oxidative (ox-PPP) and a non-oxidative branch (non-ox-PPP).[1,4] While the oxidative branch can be clearly termed catabolic for D-glucose, the non-oxidative branch consists of a complex network of reversible enzymatic reactions involving seven C_3-, C_4-, C_5-, C_6- and C_7-sugar phosphates which fulfill both catabolic and anabolic purposes.

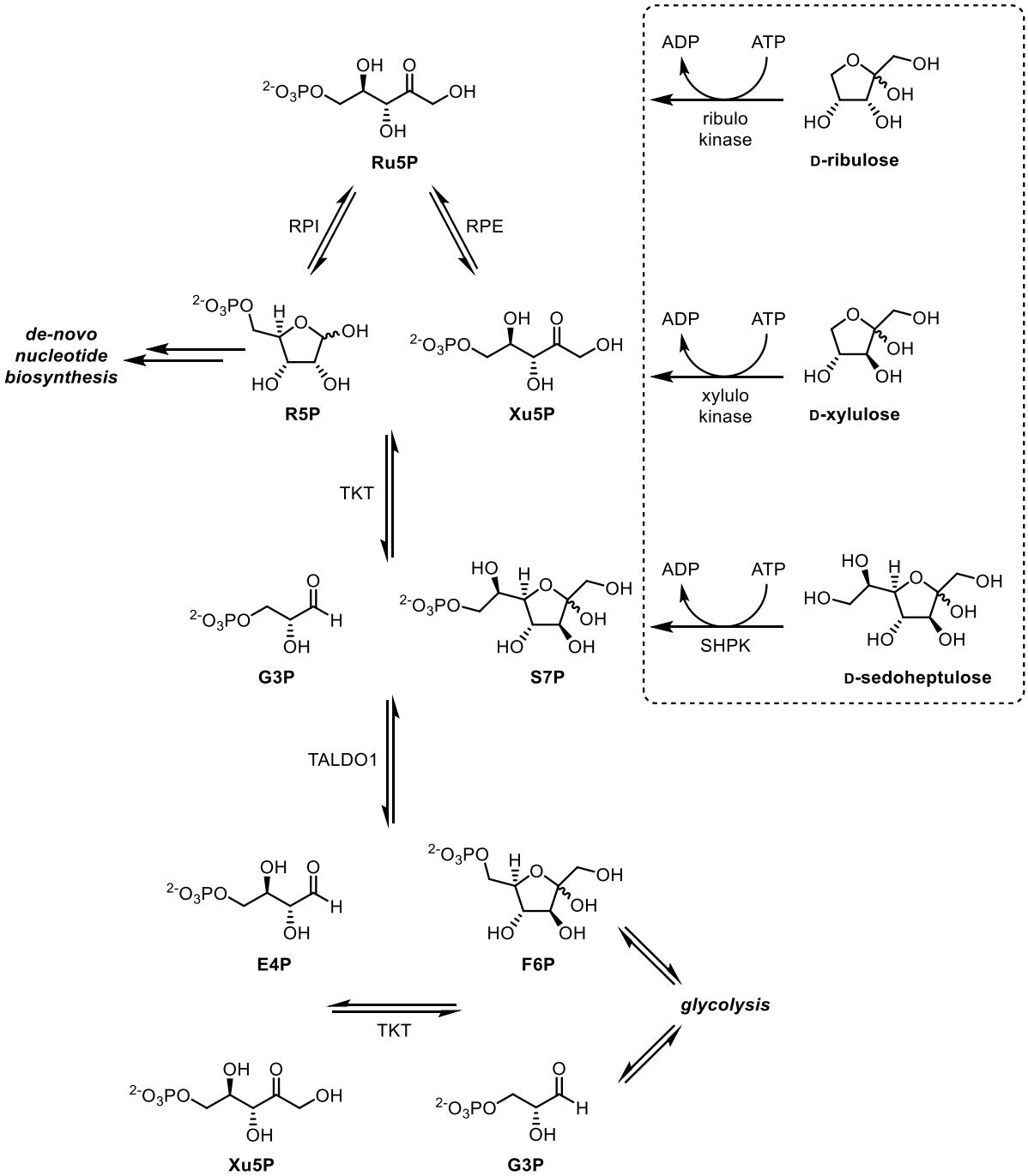
The ox-PPP splits from glycolysis after the first step: **G6P** is the substrate for the first oxidative transformation of the PPP catalyzed by G6PDH to give the corresponding 6-phospho-δ-*glucono*-lactone (**6PGL**) and NADPH (Scheme 5). This reaction is also the rate-determining step of the ox-PPP.[5]



Scheme 5: Oxidative branch of the pentose phosphate pathway.

This lactone is then hydrolyzed with the help of 6-phosphogluconolactonase (PGLS) to yield 6-phosphogluconate (**6PG**) in an open-chain conformation.[1] Subsequently, **6PG** is oxidatively decarboxylated by 6-phosphogluconate dehydrogenase (6PGD) to form ribulose-5-phosphate (**Ru5P**), CO_2 and another equivalent of NADPH. Therefore, the ox-PPP can generate two equivalents of NADPH and one equivalent each of **Ru5P** and CO_2 per molecule **G6P**.

The formation of **Ru5P** marks the end of the irreversible, oxidative branch of the PPP and the starting point of the reversible, non-oxidative branch (Scheme 6). The pentulose **Ru5P** is the substrate for two enzymes of the non-oxPPP: ribose-5-phosphate isomerase (RPI) and ribulose-5-phosphate epimerase (RPE). The former catalyzes the reaction of **Ru5P** to ribose-5-phosphate (**R5P**) while the latter epimerizes the stereocenter at position 3 in **Ru5P** to give xylulose-5-phosphate (**Xu5P**). These two



Scheme 6: Non-oxidative branch of the pentose phosphate pathway. Recently discovered kinase reactions which can directly phosphorylate D-ribulose, D-xylulose and D-sedoheptulose are shown in a dashed box.

C_5-sugar phosphates can now engage in a C_2-body transfer: A C_2-unit can be split off the ketose donor **Xu5P** and is transferred to the aldose acceptor **R5P** to give **G3P** and sedoheptulose-7-phosphate (**S7P**). This reaction is catalyzed by the enzyme transketolase (TKT) and needs thiamine diphosphate (ThDP) as cofactor. Alternatively, TKT can convert **Xu5P** and **E4P** to **F6P** and **G3P** which both are part of glycolysis. In another reversible equilibrium, a C_3-unit is transferred from **S7P** to **G3P** by transaldolase (TALDO1) to furnish **E4P** and **F6P**.

As a cytosolic metabolic pathway, the PPP fulfills multiple important intracellular tasks. The ox-PPP provides cells with the reducing agent NADPH needed for detoxifying reactive oxygen species (ROS), for fatty acid biosynthesis and for keeping redox homeostasis. The PPP is also the sole source of ribose-5-phosphate (**R5P**) for *de-novo* RNA and DNA biosynthesis and is therefore crucial for cell proliferation and DNA repair.[5,6]

The reversibility of the non-ox PPP gives cells a high flexibility to react to different metabolic demands. In case cells are in need of high levels of NADPH to deal with oxidative stress but do not need excessive amounts of RNA or new DNA building blocks, it can metabolize **G6P** via the ox-PPP to generate enough NADPH and funnel the newly formed **Ru5P** from the non-ox PPP to glycolysis via **F6P** and **G3P** as intermediates. Gluconeogenesis then in turn replenishes the ox-PPP. Similarly, should the demand for **R5P** be high but newly formed NADPH would disturb the redox balance, the cell can shift the necessary equilibria again and funnel the glycolytic intermediates **F6P** and **G3P** into the non-ox PPP to generate sufficient nucleotide building block precursors.[5]

Unsurprisingly, due the significance of the PPP for carbohydrate metabolism, the enzymes of the PPP are also linked to several pathological conditions. G6PDH deficiency leads to hemolytic anemia and is one of the most common inherited genetic diseases. In red blood cells, the ox-PPP is the sole source of NADPH and decreased levels of intact G6PDH result in reduced amounts of NADPH which in turn leads to oxidative stress and break down of red blood cells.[6] Cancer cells typically show reduced mitochondrial oxidative phosphorylation for ATP generation and rely on elevated rates of glycolysis to ensure energy supply.[7,8] Increased flux rates through the PPP for nucleotide and fatty acid biosynthesis are also observed to allow higher

proliferation rates compared to normal cells.[9] G6PDH overexpression has been observed in prostate carcinoma[10] and lung cancer cells.[11] Shorter overall survival has been associated with overexpression of PGLS in bone metastases bearing breast cancer patients[12] and increased levels of 6PGD have been found in several types of leukemia, as well as in cervical, non-small cell pulmonary, ovarian, thyroid, breast and hepatic carcinoma.[13] The enzymes of the non-oxPPP have also been associated with multiple pathologies. The oncogenic $KRAS^{G12D}$ mutation induces elevated expression of RPI and RPE.[14] RPI and TALDO1 are also overexpressed in hepatocellular carcinoma cells[15–17] while TKT levels are increased in multiple cancer types.[18–20]

The connection of the involved reaction equilibria makes the regulation of the PPP extremely complex. Some enzymatic transformations rely on the same substrates or share them with other metabolic pathways (e.g. glycolysis). While numerous different proteins play key roles in the modulation of the PPP,[5,13] the substrates/products of the metabolic reactions also regulate their enzymes allosterically.[21] Another level of complexity in the modulation of the PPP is added by the recent discovery of specific kinases for D-ribulose,[22] D-xylulose[23] and D-sedoheptulose (dashed box in Scheme 6).[24] It was long believed that the corresponding sugar phosphates only exist as metabolic intermediates, however, the existence of kinases for the parent sugars suggests yet another regulatory control mechanism to fine tune carbohydrate metabolism in the PPP and raises question on the extent to which cells rely on these sugars and the respective kinases in healthy or pathological states.

Novel tools and imaging probes are therefore needed to the study the (de)regulation of the PPP. Sedoheptulose kinase (SHPK), formerly known as CARKL (carbohydrate kinase-like protein), phosphorylates the rare natural heptulose D-sedoheptulose, at position 7 to give **S7P** allowing it to directly enter primary carbohydrate metabolism.[24] In a similar manner, ribulo- and xylulokinase phosphorylate D-ribulose and D-xylulose, respectively. All these carbohydrate kinases might play an active role in the modulation of carbon flux between the non-oxPPP and glycolysis by influencing the above-mentioned reaction equilibria.

1.2 Positron Emission Tomography

Positron emission tomography (PET) is one of the most sensitive non-invasive imaging technique to visualize metabolic alterations on a molecular level in patients.[25] PET takes advantage of highly selective tracer molecules that are linked to short-lived radioisotopes such as carbon-11, fluorine-18, gallium-68 etc. (Table 1) to detect specific biomarkers. These radionuclides decay by positron emission (β^+-decay), the antiparticles of electrons, and are produced via nuclear reactions in particle accelerators (^{11}C, ^{13}N, ^{18}F and ^{64}Cu)[25] or in generators (^{68}Ga and ^{82}Rb).[26] Some of them are used as simple ionic salts ([^{18}F]NaF for bone metastases imaging[27] or ^{82}RbCl = Cardiogen-82® for myocardial perfusion imaging)[28] but most of them are covalently incorporated into organic compounds[29] or are linked to peptide tracers via a chelating moiety (^{64}Cu or ^{68}Ga).[30]

Table 1: Half-life and generation method of radionuclides in FDA-approved PET radiopharmaceuticals.[25,31] p = proton. α = ^{4}He, n = neutron, ε = electron capture, $t_{1/2}$ = half-life.

radionuclide	$t_{1/2}$	nuclear reaction	production mode
^{11}C	20 min	^{14}N(p,α)^{11}C	cyclotron
^{13}N	10 min	^{16}O(p,α)^{13}N	cyclotron
^{18}F	110 min	^{18}O(p,n)^{18}F	cyclotron
^{64}Cu	12.7 h	^{64}Ni(p,n)^{64}Cu	cyclotron
^{68}Ga	68 min	^{68}Ge(ε)^{68}Ga	generator
^{82}Rb	1 min	^{82}Sr(ε)^{82}Rb	generator

Due to the short half-life of the used radioisotopes, PET tracers must be synthesized directly before their administration to patients. Their syntheses must be highly optimized regarding time, yield and purity and are typically carried out in automated

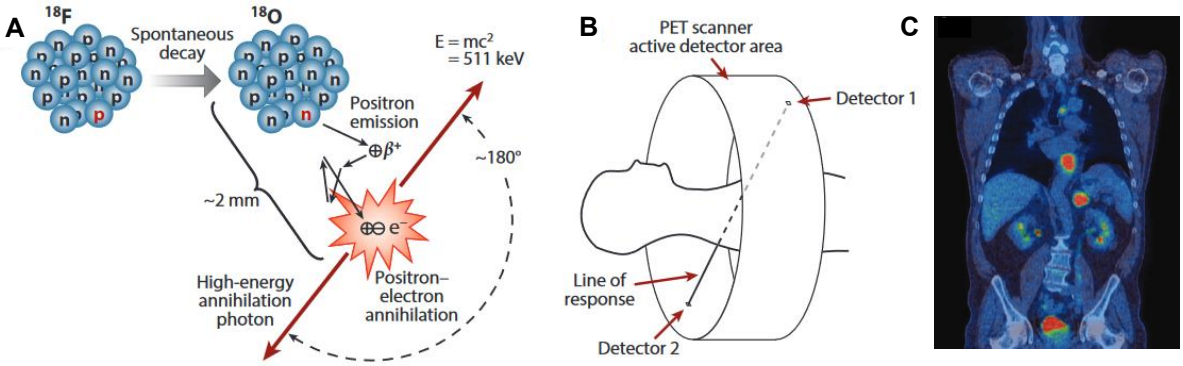
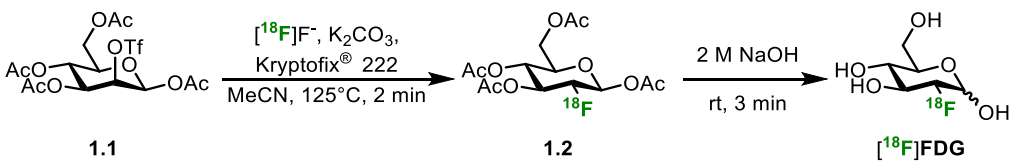


Figure 1: A: Visualization of the β^+-decay of fluorine-18. **B:** Schematic representation of a patient in a PET scanner.[32] **C:** Representative [^{18}F]**FDG** PET/CT image of a patient with esophageal cancer showing adrenal and lymph node metastases.[33]

synthesis modules.[29] After formulation and quality control, the tracers are applied intravenously and to enter the patient's systemic distribution immediately. Subsequently, the tracer gets distributed within the body and binds to its (protein) target or accumulates in the target tissue. Throughout this process, the applied radioisotopes are constantly decaying by emitting positrons (β^+-particles, Figure 1A).[32] After emission from the nucleus, a positron can cover a distance of a few millimeters until an annihilation event with an electron occurs. This event sends off two gamma rays in opposite directions that can be detected outside the body by scintillation crystals in typical circular PET scanners (Figure 1B). Thereby, the exact localization of the annihilation event in the body can be determined and the biodistribution of the applied PET tracer can be assessed and quantified in a time- and space-resolved way. This allows to visualize receptor overexpression or metabolic aberrations in order to diagnose diseases or to monitor disease progression or therapy (Figure 1C).[33] Additionally, the extreme sensitivity of the method allows for the use of minute amounts, typically picomolar quantities of the tracer, without triggering pharmacological effects.[34,35] This micro-dosing principle can also be used in the pharmaceutical industry to determine pharmacokinetic properties with minute amounts of "regular" drug candidates labeled with PET radionuclides.

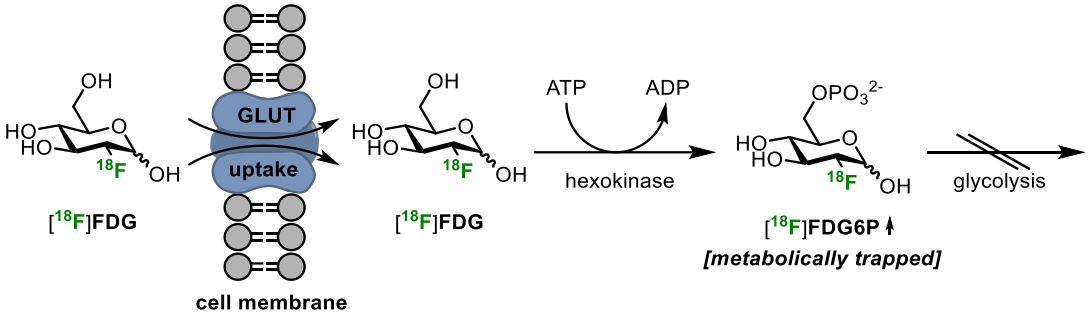
1.2.1 Metabolic Trapping

Gallagher *et al.* introduced the principle of metabolic trapping as a key feature of PET radiopharmaceutical design in the late 1970s.[36] It is described as the property of radiotracers to be taken up by cells, enzymatically converted to a metabolite that cannot be further processed and therefore accumulates in key tissue. The prime example for this principle is 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]**FDG**), the most frequently applied PET tracer in clinics. It is synthesized via a nucleophilic fluorination of 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannose (**1.1**) with potassium fluoride in the presence of potassium carbonate and Kryptofix® 222 in acetonitrile at 125°C for two minutes (Scheme 7). Subsequent deacetylation under



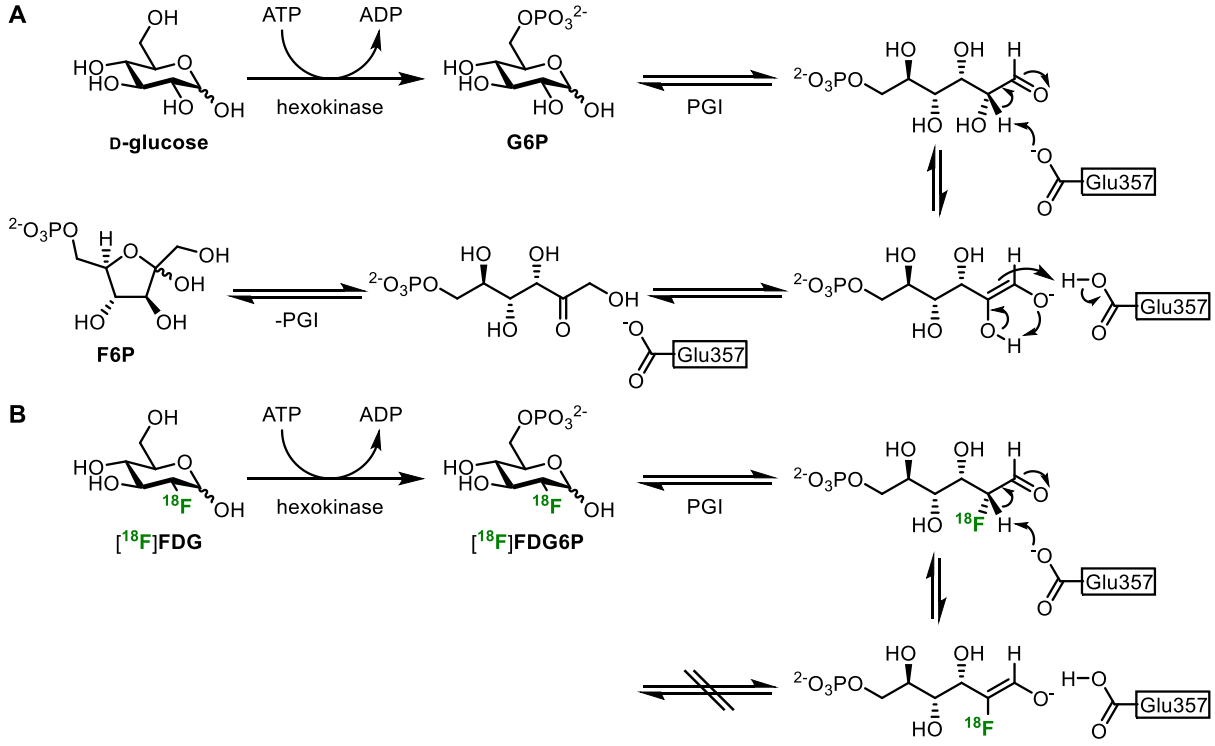
Scheme 7: Radiosynthesis of [^{18}F]**FDG** from mannose **1.1**.

basic conditions gives [^{18}F]**FDG**.[37] Although [^{18}F]**FDG** was first introduced in the 1970s, it still is the working horse of PET imaging today and is clinically used for applications in neurology, cardiology and especially in oncology.[38] As mentioned above, its mode of action relies on the principle of metabolic trapping: [^{18}F]**FDG** is taken up by cells via GLUTs and phosphorylated by hexokinase during the first step of glycolysis to give the corresponding sugar phosphate [^{18}F]**FDG6P** (Scheme 8). [^{18}F]**FDG6P**, however, cannot be further processed by glycolytic metabolism.[39–41] Therefore, [^{18}F]**FDG6P** accumulates in cells and can be used to visualize tissue with altered or pathologic D-glucose demand and high proliferation rates (e.g. tumor tissue).



Scheme 8: Schematic representation of the metabolic trapping of [^{18}F]**FDG**.

A closer look at the enzymatic mechanism of the second step of glycolysis helps to understand why [^{18}F]**FDG6P** cannot be further metabolized by PGI (Scheme 9A). The

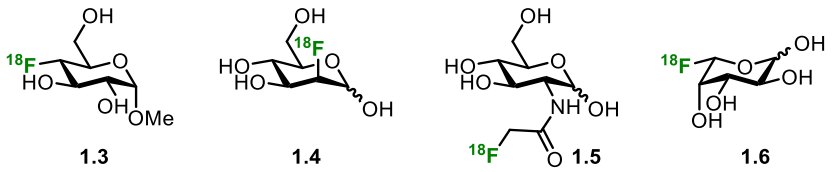


Scheme 9: A: Phosphorylation of D-glucose and enzymatic mechanism of PGI with **G6P** to give **F6P**. **B:** Phosphorylation of [^{18}F]**FDG** and blocked enzymatic transformation catalyzed by PGI due to the fluorine atom at position 2.

open-chain conformation of **G6P** can be deprotonated at position 2 by glutamate-357 of PGI to give an enediolate ion.[1] Then, the oxygen atom at position 1 deprotonates the hydroxyl group at position 2 leading to subsequent oxidation of C-2. Protonation of C-1 by glutamatic acid-357 furnishes **F6P**. In case of [^{18}F]**FDG6P**, the enolate formation might still occur but the fluorine atom simply prevents oxidation of C-2 leading to metabolic trapping and accumulation of the radiotracer (Scheme 9B).

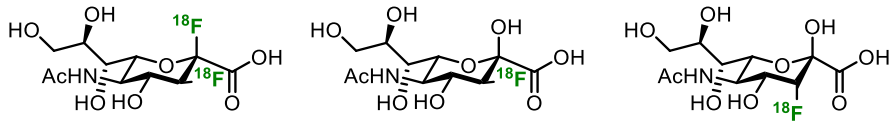
1.2.2 ^{18}F-Fluorinated Carbohydrate-based PET Tracers

Apart from [^{18}F]**FDG**, a plethora of other carbohydrate-based PET tracers was developed over the last 40 years and other fields of application for fluorinated derivatives of D-glucose were examined: Compound **1.3** (Scheme 10) was developed to image GLUT independent glucose uptake via sodium-dependent D-glucose cotransporters (SGLTs) and has been successfully used as an imaging probe in a study with patients with high-grade astrocytoma.[42] Fluorinated mannose **1.4** was investigated as alternative to [^{18}F]**FDG** in tumor uptake studies in rats[43] and for the id-



Scheme 10: Chemical structures of investigational carbohydrate-based PET tracers.

entification of inflammatory plaques in rabbits.[44] The GlcNAc analog *N*-fluoroacetyl glucosamine **1.5** was investigated as a PET tracer to image bacterial infections since GlcNAc is highly abundant in bacterial cell walls. While [^{18}F]**FDG** showed both bacterial infection and non-related inflammations, compound **1.5** was able to selectively image bacterial infection.[45] L-Fucose is found in glycolipids of the cell membrane, hence, the potential to monitor deregulated glycoconjugate synthesis in tumors of fluorinated fucose derivative **1.6** was explored. Unfortunately, tumor uptake in mice and rats was poor compared to [^{18}F]**FDG**.[46]

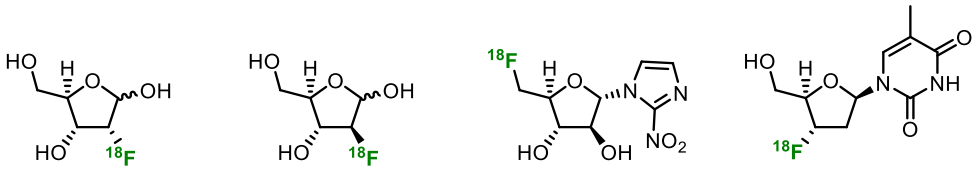


1.9 **1.10** **1.11**

Scheme 11: Chemical structures of sialic acid-based PET tracers.

Sialic acid-based tracers (Scheme 11) were also investigated for PET imaging purposes since sialic acids decorate the ends of many oligosaccharides in glycoproteins on the cell surface. The application of compounds **1.9**, **1.10** and **1.11**, however, was severely hampered by the poor cellular uptake, uptake selectivity and fast clearance.[47]

Pentose family members 2-deoxy-2-[^{18}F]fluoro-D-ribose (**1.12**)[48] and -arabinose (**1.13**)[49] were evaluated as liver imaging agents and ribose salvage probes, respectively (Scheme 12).



1.12 **1.13** **1.14** **1.15**

Scheme 12: Chemical structures of pentose-based PET tracers.

A long-standing goal in PET is related to the imaging of the hypoxic microenvironment of tumor tissue. In this regard, a FMISO derived pentose tracer (**1.14**) showed promising results in glioblastoma patients[50] as well as in mice with colon carcinoma.[51]

Thymidine-based radiotracer **1.15** is phosphorylated after uptake to give the corresponding triphosphate, however, the fluorine substitution in position 3 prevents DNA incorporation and leads to metabolic trapping in proliferating cells.[52]

Although some of the above-mentioned carbohydrate-based PET tracers showed promising results in clinical trials, none of them has been approved by the FDA for clinical use.[31]

1.3 Chemistry

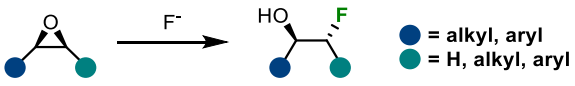
1.3.1 Fluorination Reactions

Introduction of fluorine into an organic compound can have severe impact on the lipophilicity, steric conformation, pK_a and metabolic stability of a substance compared to the non-fluorinated counterpart.[53] This is particularly exploited in the pharmaceutical industry when potential drugs candidates are optimized regarding their potency and ADMET properties, which is exemplified by the steady rise of fluorinated marketed drugs over the last decades.[54] Hence, chemical reactions to fluorinate small molecules are of high scientific and pharmaceutical interest.

Fluorination reactions can be divided into nucleophilic and electrophilic fluorinations. Classical nucleophilic approaches to introduce a fluorine atom at aliphatic positions involve the use of alkali fluorides such as potassium fluoride or cesium fluoride[55] and good leaving groups (Scheme 13). Typically, these reactions proceed via inversion of configuration at the carbon atom and are typically carried out in polar, aprotic solvents at elevated temperatures to improve the solubility and reactivity of the alkali fluorides. The use of cryptands (e.g. Kryptofix® 222) together with potassium fluoride defined a hallmark in the history of nucleophilic fluorinations, and especially in nuclear medicine.[56] This method is still used today to synthesize [^{18}F]**FDG**.[37] It significantly increases the nucleophilicity of the used fluoride ion by coordinating its counterion. Tetrabutylammonium fluoride (TBAF), tris(dimethylamino)sulfonium difluoro-trimethylsilicate (TASF)[57] or tetrabutylammonium difluorotriphenylsilicate (TBAT)[58] are better soluble nucleophilic fluoride sources which can be used alternatively.

Scheme 13: S_N2-type nucleophilic fluorination.

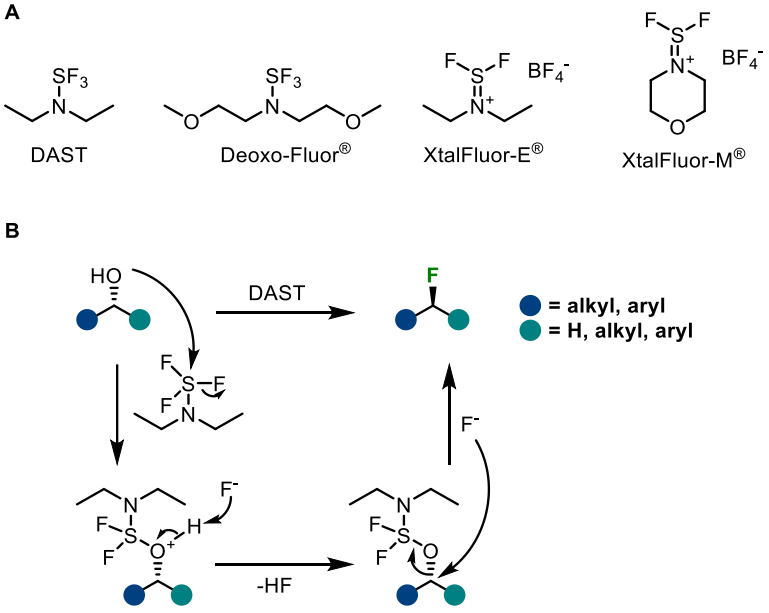
Another method to generate aliphatic fluorides is via ring-opening of epoxides to yield α-fluorinated alcohols (Scheme 14). Percy *et al.* discovered a particularly useful reagent combination for this purpose: potassium bifluoride and TBAF trihydrate.[59] This reagent combination can effect regioselective fluorinations on carbohydrate scaffolds



Scheme 14: Fluoride-mediated epoxide opening to give α-fluorinated alcohols.

as a molten salt mixture under neat conditions.[60,61] Other reported methods for epoxide opening-based fluorination approaches include the use of hydrogen fluoride amine complexes such as pyridine hydrogen fluoride (Olah's reagent)[62] or triethylamine trihydrogenfluoride.[63]

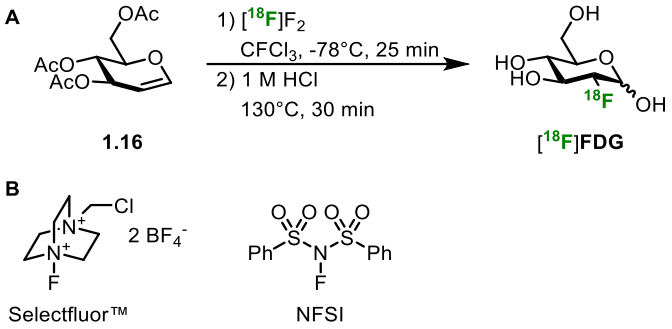
Sulfur (IV) fluorides were already applied in direct deoxyfluorinations of alcohols. Although synthetically useful, the routine use of SF_4 gas is hampered by its toxicity and corrosiveness. Aminosulfurane fluorides are viable alternatives to gaseous SF_4. The most prominent examples of these commercially available reagents are diethylaminosulfur trifluoride (DAST),[64] Deoxo-Fluor®,[65] XtalFluor-E® and XtalFluor-M® (Scheme 15A).[66,67] Mechanistically, these reactions proceeds via a nucleophilic attack of the alcohol at the sulfur atom leading to the loss of hydrogen fluoride (Scheme 15B). A subsequent nucleophilic attack of a fluoride ion at the former alcohol carbon atom gives the deoxyfluorinated product.



Scheme 15: A: Chemical structures of the deoxyfluorinating reagents DAST, Deoxo-Fluor®, XtalFluor-E® and XtalFluor-M®. **B:** Deoxyfluorination mechanism of DAST.

Next to nucleophilic fluorinations, electrophilic methods also found broad applicability in organic synthesis. Initially, [^{18}F]**FDG** was synthesized via an electrophilic fluorination of 3,4,6-tri-*O*-acetyl-D-glucal (**1.16**) with [^{18}F]F_2 gas and subsequent deprotection (Scheme 16A).[68–70] However, solid reagents that are safer and easier to handle than corrosive fluorine gas are preferentially used today. Examples of such compounds include the electrophilic N-F reagents Selectfluor™ and *N*-fluorobenzensulfonimide

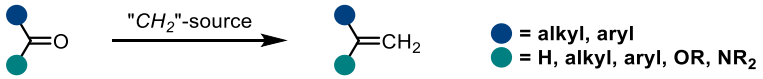
(NFSI, Scheme 16B).[71,72] Both react with a broad range of carbon nucleophiles such as enolates or electron rich double bonds.[73,74]



Scheme 16: A: Electrophilic fluorination of glucal **1.16** and subsequent deprotection to yield [^{18}F]**FDG**. Formation of *manno*-configured byproduct not shown. **B:** Chemical structures of Selectfluor™ and NFSI.

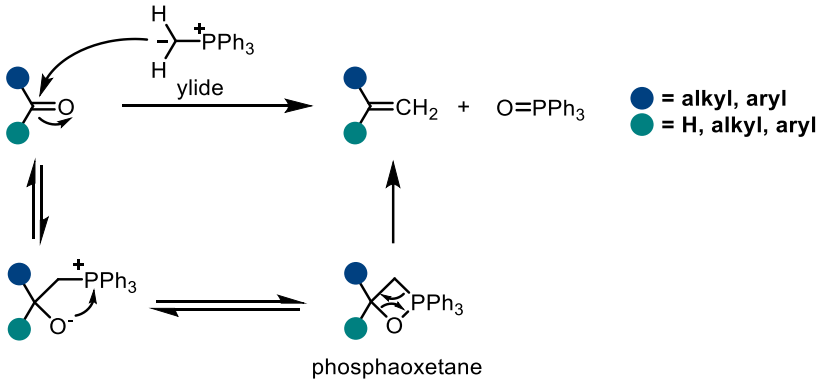
1.3.2 Methylenation Reactions

As the name suggests, methylenation reactions add methylene (CH_2 groups) to various carbonyl compounds (aldehydes, ketones, esters or amides) to give alkenes (Scheme 17). This method can be used to either simply perform an elongation by one carbon atom or to subject the newly formed olefin to additional functional group interconversions.



Scheme 17: General concept of methylenation reactions.

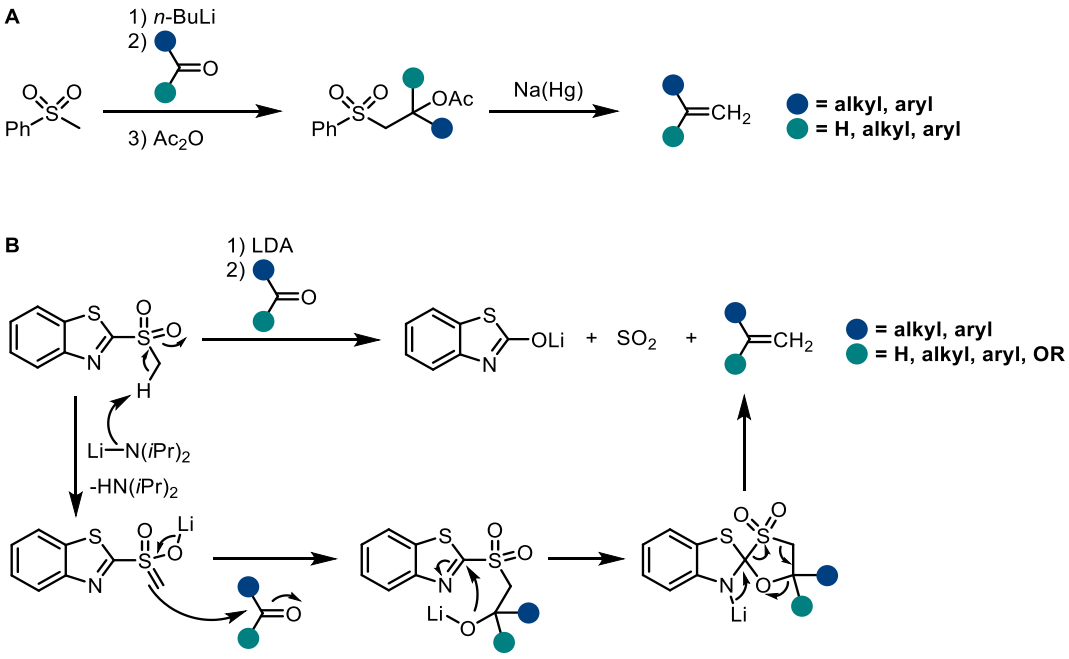
One of the most prominent methylenation reactions is the Wittig reaction with methylene triphenylphosphorane (Scheme 18).[75,76] Mechanistically, the reaction proceeds via a nucleophilic attack of a phosphorus ylide, which is typically generated *in-situ*[77] from methyl phosphonium bromide (or iodide) with strong bases (*n*-BuLi,



Scheme 18: Mechanism of the Wittig olefination of aldehydes or ketones with methylene triphenylphosphorane.

t-BuOK etc.), at a carbonyl C. This leads to the formation of a phosphaoxetane intermediate which subsequently collapses to yields the methylenated product and triphenylphosphine oxide.

Another methylenation reaction was developed by the French chemist Marc Julia. The original version of the Julia olefination[78] was a multistep process that used phenyl sulfones in the presence of *n*-BuLi, an aldehyde or a ketone to give the corresponding alkoxides which were trapped *in-situ* with acetic anhydride to yield β-acetoxy sulfones (Scheme 19A). In a second step, these β-acetoxy sulfones were then reduced with sodium amalgam to the respective olefin. The modified Julia olefination avoids the isolation of the β-acetoxy sulfones and proceeds as a one-pot reaction (Scheme 19B).[79] For this purpose, benzothiazole sulfones are deprotonated in α-position to the sulfur, followed by the nucleophilic addition of the metalated sulfone to a carbonyl. Subsequent attack of the resulting alkoxide at position 2 of the benzothiazole ring leads to the formation and immediately following collapse of a 5-membered ring via extrusion of sulfur dioxide to finally give the desired alkene. The modified Julia olefination approach can also be used for the formation of lactones to give exocyclic enol ethers.

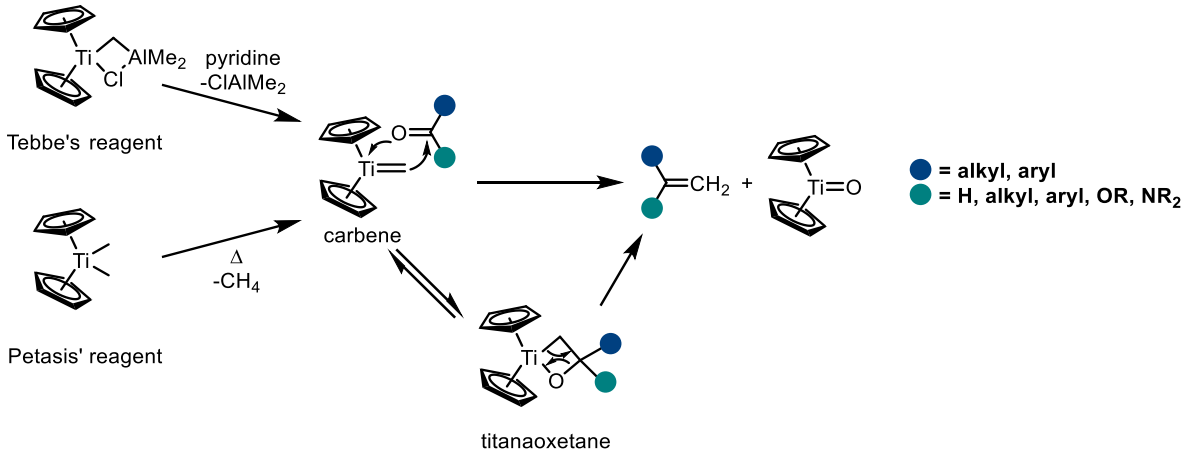


Scheme 19: A: Classical Julia olefination protocol. **B:** Mechanism of the modified Julia olefination.

The Takai-Lombardo methylenation is yet another alternative methylenation strategy which takes advantage of a structurally undefined reagent prepared from Zn dust, CH_2Br_2 and $TiCl_4$ (Lombardo's reagent) which is added to ketones or aldehydes to give

the corresponding olefins.[80,81] The procedure is mild and does not lead to racemization of stereocenters in α-position to the carbonyl.

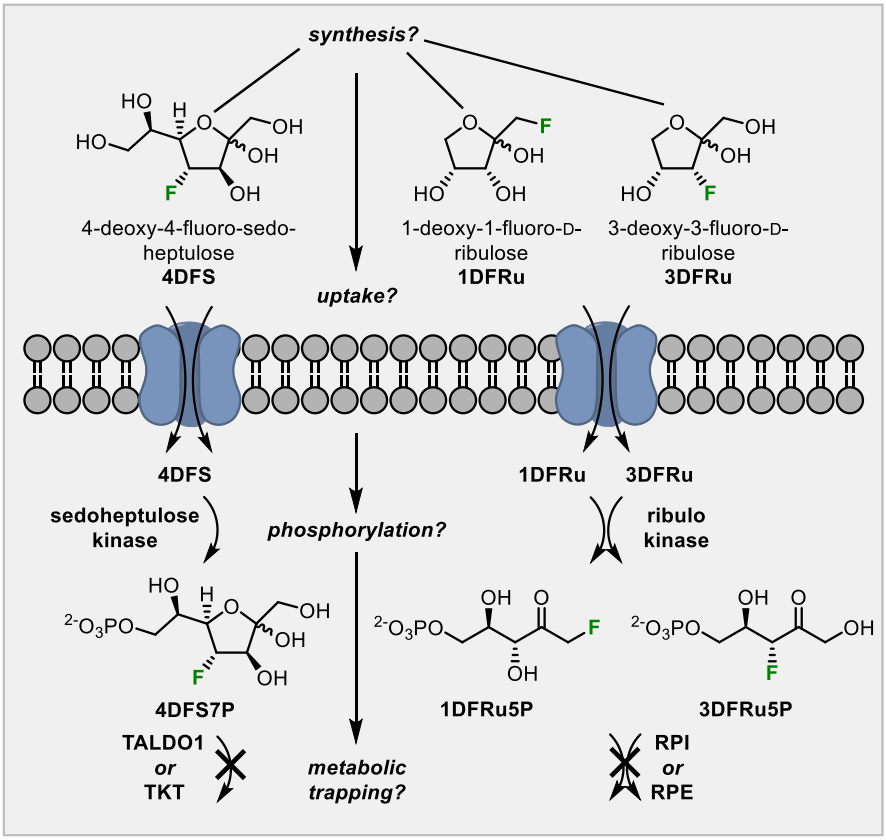
Two other titanium-based reagents are used for methylenations today. They are known as Tebbe's reagent[82] and Petasis' reagent (Scheme 20).[83] Although they both form the same carbene intermediate during their reaction with carbonyls, their mode of activation is slightly different: While Tebbe's reagent must be activated by Lewis' bases such as pyridine to form the active carbene species, Petasis' reagent only requires heat to lose one equivalent of methane and form the active species. Then, the metal carbene and the carbonyl group form a titanaoxetane which collapses to give the methylenated product and bis(cyclopentadienyl)titanium oxide. Both reagents can be used to methylenate aldehydes, ketones, esters, lactones and even amides.[84]



Scheme 20: Activation and reaction mechanism of Tebbe's and Petasis' reagent with carbonyl compounds.

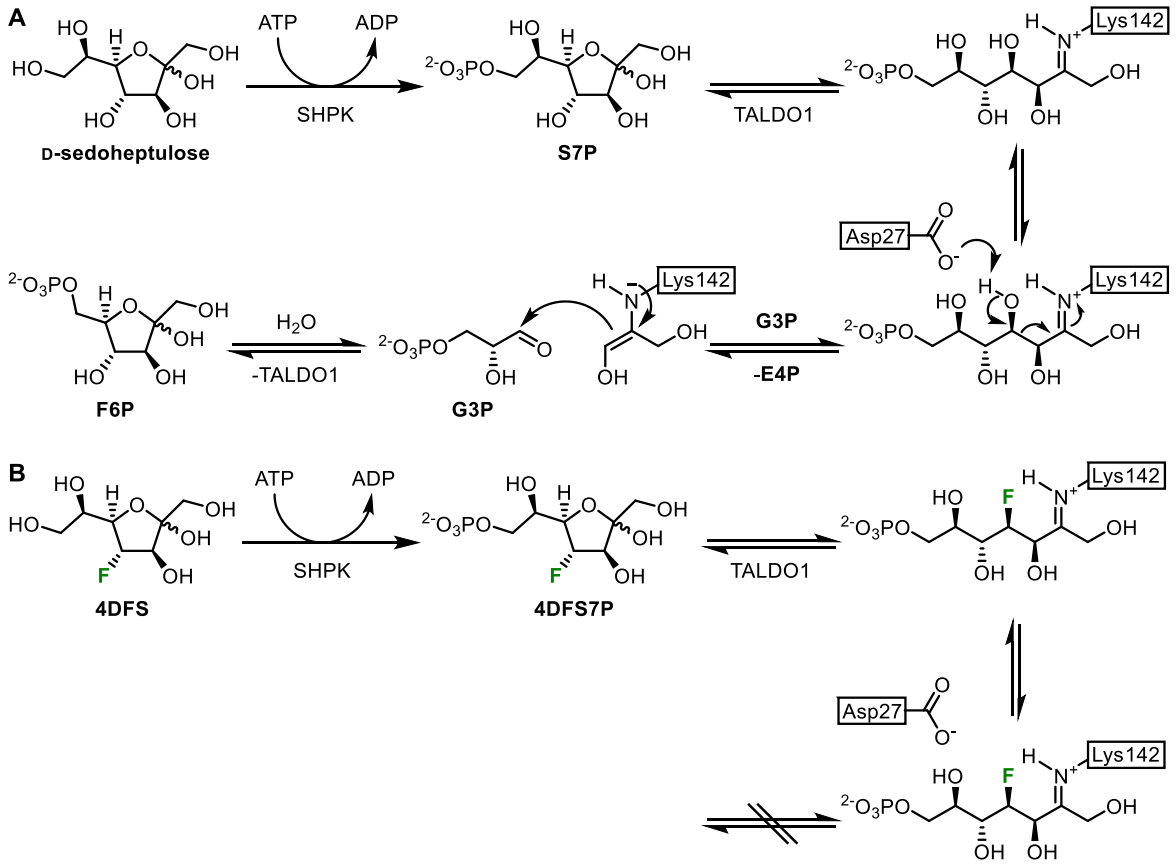
2 Aim of the Thesis

The overall aim of this thesis is to expand the principle of metabolic trapping to two rare sugars involved in the non-oxidative pentose-phosphate-pathway: D-sedoheptulose and D-ribulose. The recent discovery of specific kinases[22,24,85] for these sugars suggests that they can be directly shuffled into primary carbohydrate metabolism and enter the PPP. This opens up the possibility to design fluorinated derivatives of these sugars that will, after uptake into cells and phosphorylation by the respective kinase, be metabolically trapped. The fluorine atom mechanistically blocks further enzymatic degradation by enzymes of the PPP. The general idea is depicted in Scheme 21: the aims are to (i) develop synthetic routes to access 4-deoxy-4-fluoro-D-sedoheptulose, 1-deoxy-1-fluoro-D-ribulose and 3-deoxy-3-fluoro-D-ribulose; (ii) study the cellular uptake of these novel fluorinated sugars , (iii) check whether they are accepted by their respective kinases and (iv) see whether fluorination halts their enzymatic degradation in the PPP. In case all aims can be accomplished, this could pave the way for the development of new heptulose- and pentulose-based PET tracers.



Scheme 21: General overview of the thesis' aims.

In case of D-sedoheptulose, the reasoning to fluorinate position 4 can be seen in Scheme 22A: After phosphorylation by sedoheptulose kinase (SHPK), sedoheptulose-7-phosphate forms an iminium with lysine-142 of transaldolase (TALDO1).[1] In the next step, aspartate-27 can deprotonate the hydroxyl group at position 4 which in turn leads to oxidation of this position and C-C bond cleavage between carbon 3 and 4.



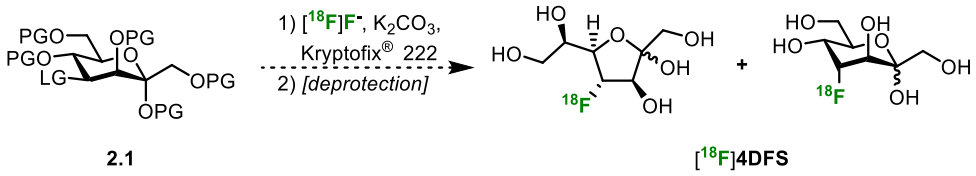
Scheme 22: Comparison of the enzymatic mechanism of TALDO1 with its natural substrates, **S7P** and **G3P** (**A**), and **4DFS7P** (**B**).

This releases **E4P** and an enamine that further reacts with **G3P** to give **F6P** after the final hydrolysis of the iminium.

Substituting the hydroxyl group at position 4 with fluorine might also allow iminium formation after phosphorylation (Scheme 22B). However, the subsequent deprotonation and C-C bond cleavage cannot take place because the fluorine in position 4 prevents this transformation. Thus, **4DFS7P** should be metabolically trapped inside cells and might be used to identify body areas, cells or organs with deregulations of the non-oxPPP or deregulated SHPK expression. There is already evidence that supports this hypothesis: Evdokimov *et al.* showed that 2-deoxy-2-[^{18}F]fluoro-D-ribose-

5-phosphate is converted to **4DFS7P** by transketolase (TKT) and that the latter is no substrate for transaldolase and thereby metabolically trapped *in vivo*.[48]

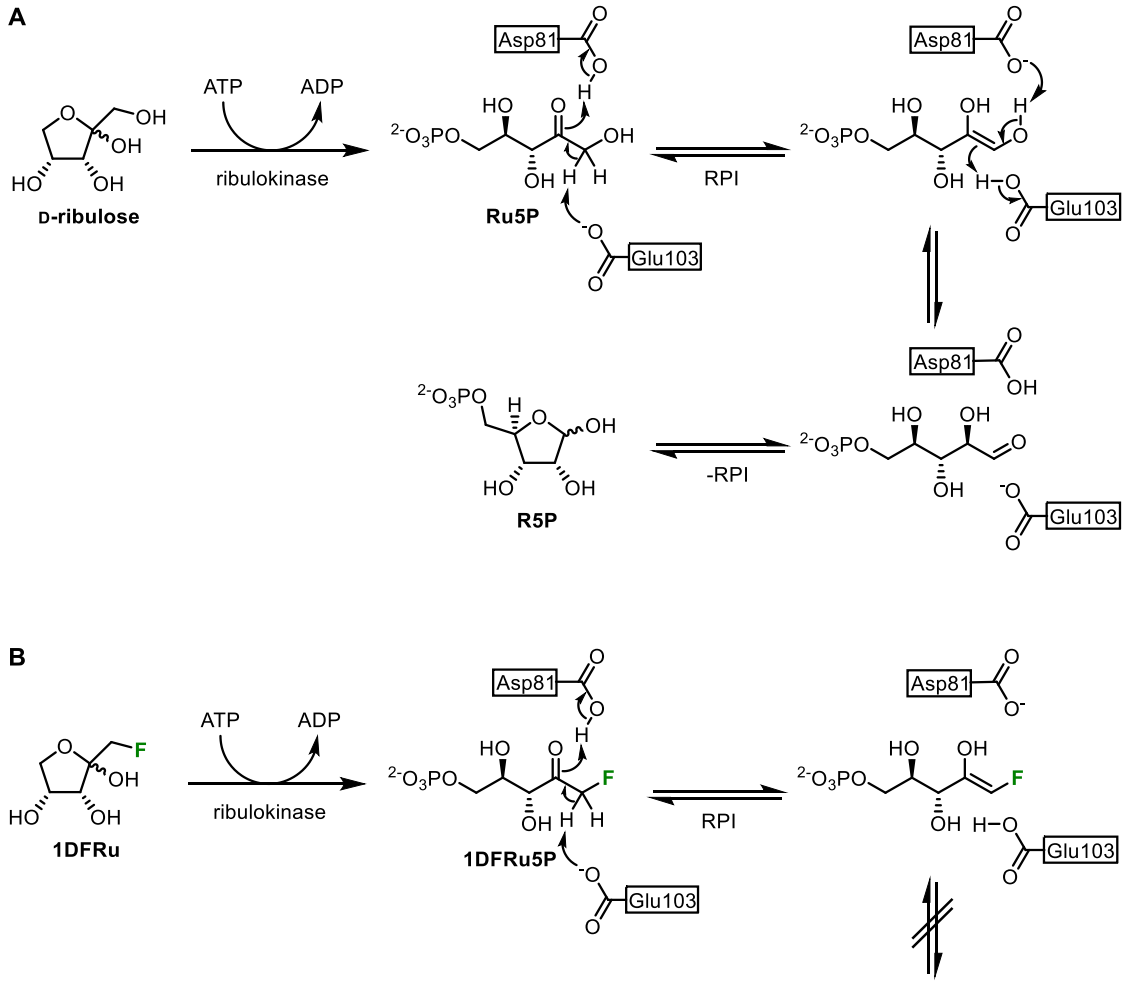
The anticipated metabolic trapping of **4DFS** is planned to be verified by cellular uptake-, kinase- and stability assays (with TALDO1 and TKT). An additional aim was the development of a synthetic route for a potential radiolabeling precursor for [^{18}F]**4DFS**. This precursor should allow the late-stage introduction of fluorine-18, ideally as the last or penultimate synthetic step, and have the general structure of compound **2.1** (Scheme 23). Since the radiolabeling process itself must be as fast as possible, good leaving groups such as triflates or nosylates are required. The same time constraints apply to the subsequent global deprotection, therefore acyl protecting groups (acetates or benzoates) are desired protecting groups.



2.1 [^{18}F]**4DFS**

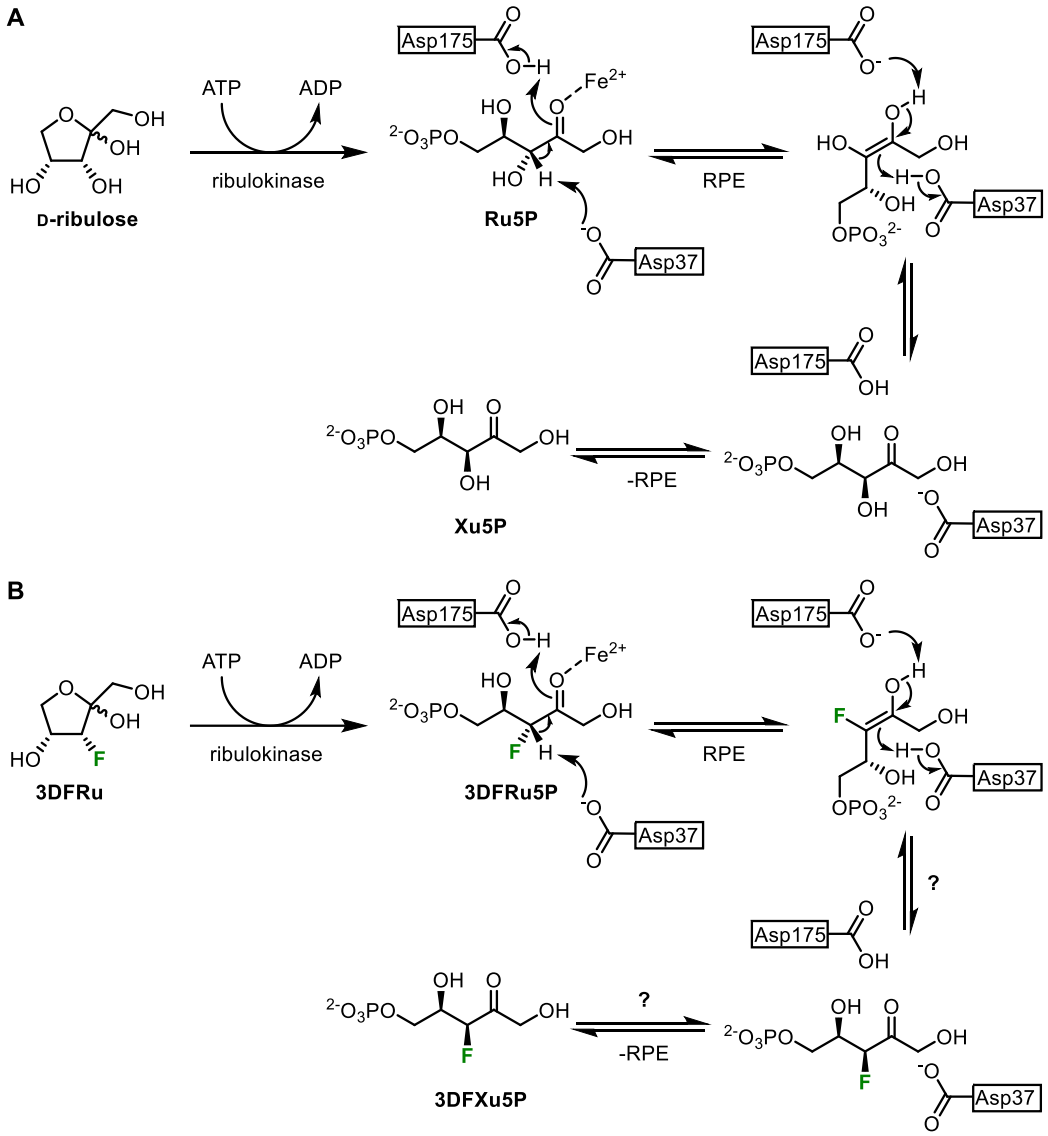
Scheme 23: General chemical structure of potential radiolabeling precursors for [^{18}F]**4DFS**. PG = protecting group, LG = leaving group.

The same principle should be applied for imaging of D-ribulose metabolism by the PPP. Ribulose-5-phosphate is a substrate for two enzymes in the PPP: ribose-5-phosphate isomerase (RPI) and ribulose-5-phosphate epimerase (RPE). RPI catalyzes the isomerization of **Ru5P** into **R5P** via an enediol mechanism with two carboxylate residues (Scheme 24A).[1] 1-Deoxy-1-fluoro-D-ribulose-5-phosphate (**1DFRu5P**, Scheme 24B) should not undergo this transformation since oxidation of position 1 is blocked. Therefore, **1DFRu** might serve as a metabolic trapping probe after phosphorylation by ribulokinase.



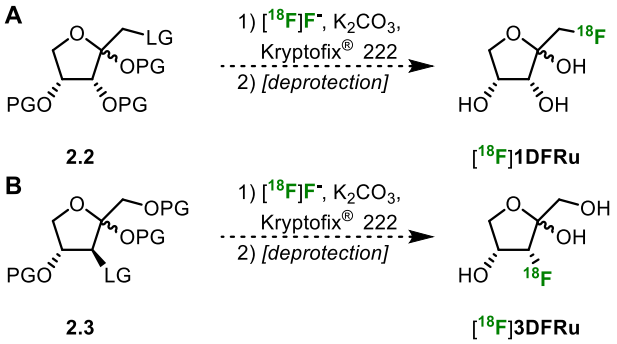
Scheme 24: Comparison of the enzymatic mechanism of RPI with its natural substrate, **Ru5P** (**A**), and **1DFRu5P** (**B**).

RPE on the other hand, catalyzes the epimerization of **Ru5P** to **Xu5P** again via an enediol intermediate (Scheme 25).[1] Here, it is unclear if fluorination at position 3, as in **3DFRu**, would perturb or prevent the enzymatic reaction as the hydroxyl group at position 3 is not directly involved in the mechanism, however, it might be crucial for the formation and stabilization of the substrate-enzyme complex.



Scheme 25: Comparison of the enzymatic mechanism of RPE with its natural substrate, **Ru5P** (**A**), and **3DFRu5P** (**B**).

Additionally, syntheses for potential radiolabeling precursors for [^{18}F]**1DFRu** and [^{18}F]**3DFRu** should be developed. The synthetic routes should give compounds with the general structures **2.2** for [^{18}F]**1DFRu** and **2.3** for [^{18}F]**3DFRu** (Scheme 26A & B).



Scheme 26: (**A**) General chemical structures and envisaged radiolabeling strategy for [^{18}F]**1DFRu** and (**B**) for [^{18}F]**3DFRu**; PG = protecting group, LG = leaving group.

3 Results & Discussion

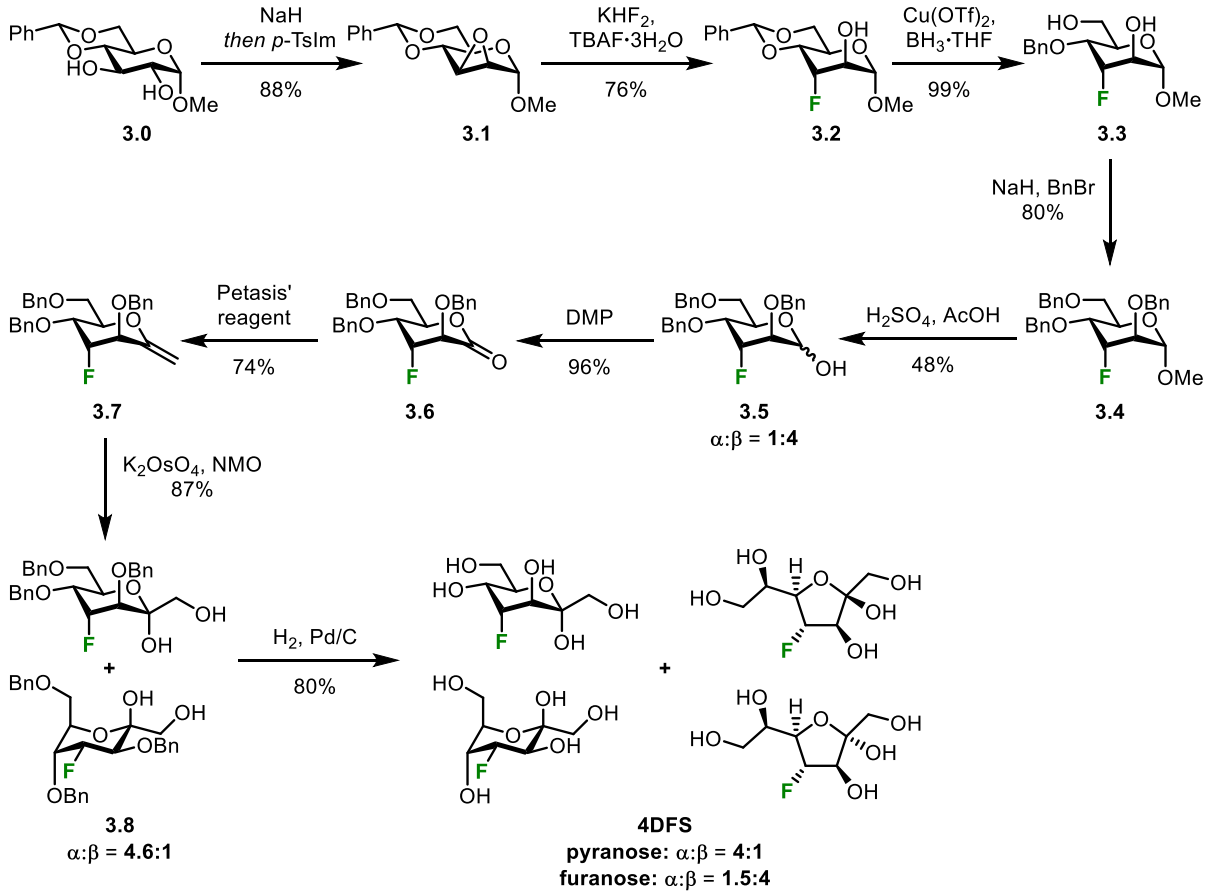
Two manuscripts have been published based on the results of this thesis:

- Lukas Scheibelberger, Toda Stankovic, Marlene Pühringer, Hanspeter Kählig, Theresa Balber, Eva-Maria Patronas, Evelyn Rampler, Markus Mitterhauser, Arvand Haschemi and Katharina Pallitsch, Synthesis of 4-Deoxy-4-fluoro-D-sedoheptulose: A Promising New Fluorinated Sugar to Apply the Principle of Metabolic Trapping, *Chem. Eur. J.* **2023**, e202302277.[86]
- Lukas Scheibelberger, Toda Stankovic, Kaja Liepert, Andreas Kienzle, Eva-Maria Patronas, Theresa Balber, Markus Mitterhauser, Arvand Haschemi and Katharina Pallitsch, Fluorinated Analogues to the Pentuloses of the Pentose-Phosphate-Pathway, *Eur. J. Org. Chem.* **2023**, e202300339.[87]

3.1 4-Deoxy-4-fluoro-D-sedoheptulose

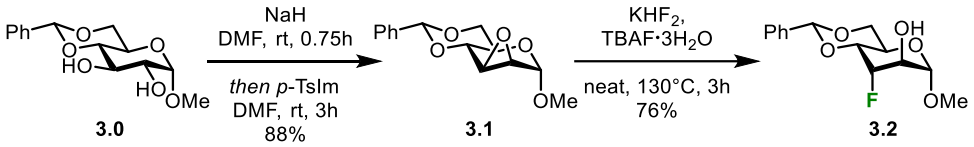
3.1.1 Synthesis of 4-Deoxy-4-fluoro-D-sedoheptulose

The final synthesis of 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**) is summarized in Scheme 27 and will be discussed in detail in the following chapter.



Scheme 27: Synthesis of **4DFS** from methyl 4,6-*O*-benzylidene-α-D-*gluco*-pyranoside (**3.0**).

The first two reactions in the synthesis of **4DFS** were literature-known: First, methyl 4,6-*O*-benzylidene-α-D-*gluco*-pyranoside (**3.0**) was treated with sodium hydride in DMF to generate the corresponsing dialkoxide followed by the addition of a solution of 1-(*para*-toluenesulfonyl)imidazole (*p*-TsIm) in DMF to form the *manno*-configured epoxide **3.1** (Scheme 28).[88] Special attention was paid to the addition speed of the *p*-TsIm solution: Best results were obtained by adding *p*-TsIm over 2 h with a syringe pump whereby the formation of the undesired ditosylate (methyl 4,6-*O*-benzylidene-2,3-di-*O*-*para*-toluenesulfonyl-α-D-*gluco*-pyranoside) could be avoided.



Scheme 28: Synthesis of fluorinated altrose **3.2** from methyl 4,6-*O*-benzylidene-α-D-*gluco*-pyranoside (**3.0**).

Thereby, epoxide **3.1** could be obtained on a multigram scale in 88% yield which was then used to follow the protocol published by Yan *et al*.[60] In their work, potassium bifluoride and tetrabutylammonium fluoride trihydrate were used to obtain various fluorinated carbohydrates from sugar epoxides. The only adaption to the published procedure was the doubling of equivalents of the respective reagents. 4 Equivalents of KHF_2 and 8 equivalents of $TBAF{\cdot}3H_2O$ were necessary to complete the reaction. The correct stereochemistry of **3.2** was confirmed by ^{1}H and ^{19}F NMR spectroscopy: The ^{19}F signal of the product was observed to be a ddd at -205.71 ppm ($^{2}J_{F,3}$ = 49.8 Hz, $^{3}J_{F,4}$ = 30.2 Hz, $^{3}J_{F,2}$ = 6.2 Hz, Figure 2) with a large vicinal coupling constant between the fluorine atom and the proton at position 4 which is consistent with a $^{3}J_{F\text{-}H}$-coupling in an ~180° angle.[89]

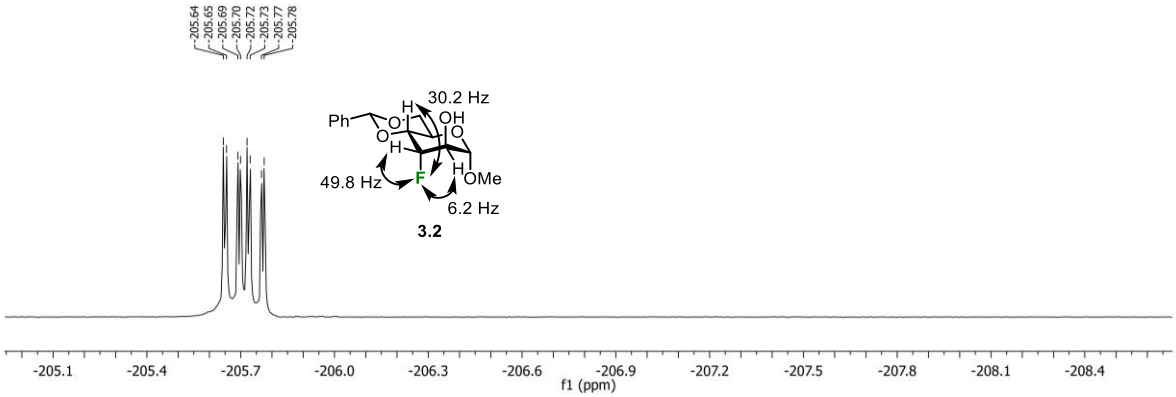
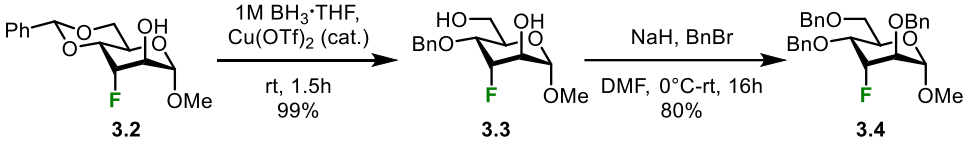


Figure 2: ^{19}F NMR spectrum of altroside **3.2** ($CDCl_3$, 659 MHz) showing a ddd at -205.71 ppm ($^{2}J_{F,3}$ = 49.8 Hz, $^{3}J_{F,4}$ = 30.2 Hz, $^{3}J_{F,2}$ = 6.2 Hz). Fluorine-proton couplings are given in Hertz and are indicated by black arrows.

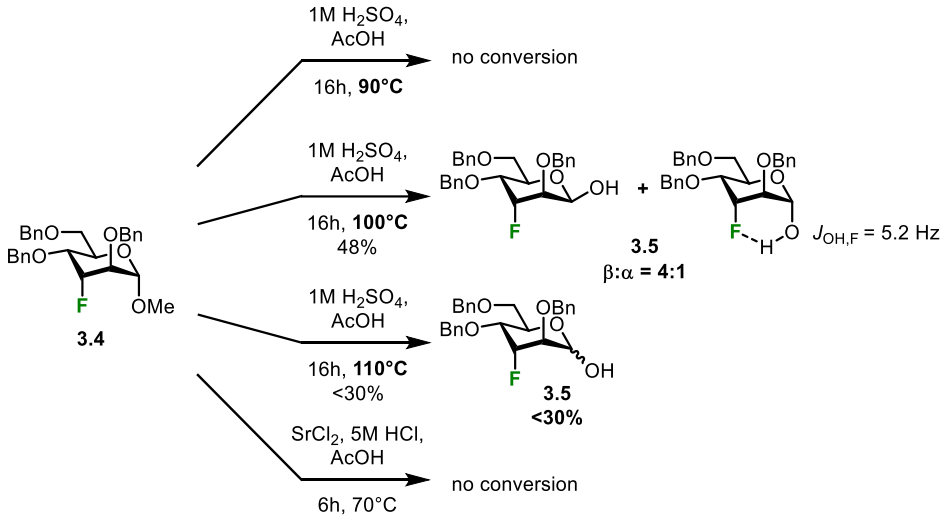
Fluorinated altroside **3.2** then underwent several protecting group manipulations (Scheme 29). First, the 4,6-*O*-benzylidene acetal was opened reductively at position 6 using the conditions reported by Shie *et al*.[90] Then, borane THF complex in the presence of catalytic amounts of copper(II) triflate led to selective deprotection at position 6 to give diol **3.3** in quantitative yield.



Scheme 29: Protecting group manipulations to yield fully protected altroside **3.4**.

Compound **3.3** was then dibenzylated using standard conditions (sodium hydride and benzyl bromide in dimethylformamide) to give fully protected altroside **3.4** in 80% yield.

Acidic hydrolysis of the methyl glycoside in the next step proved to be troublesome. The reaction was only successful in a mixture of aqueous 1 M sulfuric acid and glacial acetic acid[91] and was found to be very temperature sensitive (Scheme 30). Alternative approaches for glycoside hydrolysis using Lewis acids (e.g. $SrCl_2$)[92] did not yield the desired product.

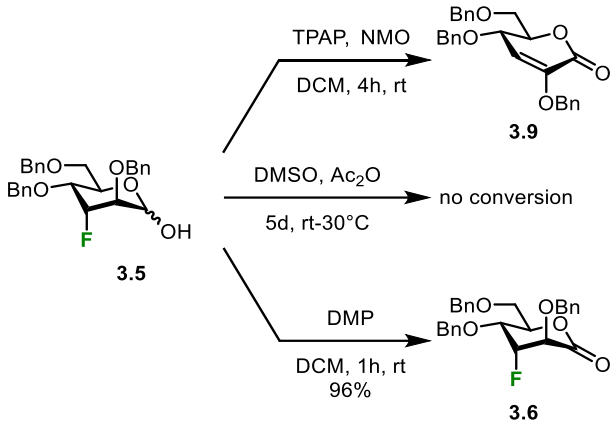


Scheme 30: Tested conditions for the hydrolysis of methyl glycoside **3.4**.

While stirring overnight at 90°C did not lead to conversion of the starting material, applying temperatures above 100°C led to partial decomposition and diminished yields (<30%). The best results were obtained by stirring the reaction mixture at exactly 100°C for 16 h. This gave lactol **3.5** in a moderate yield of 48%. The anomeric ratio was 4:1 (β:α). Interestingly, hydrogen bonding between the anomeric OH-group and

the axial fluorine atom could be observed in the α-anomer by ^{1}H NMR spectroscopy as indicated by the dd at 3.27 ppm: $^{3}J_{OH,1}$ = 7.9 Hz, $J_{OH,F}$ = 5.2 Hz.

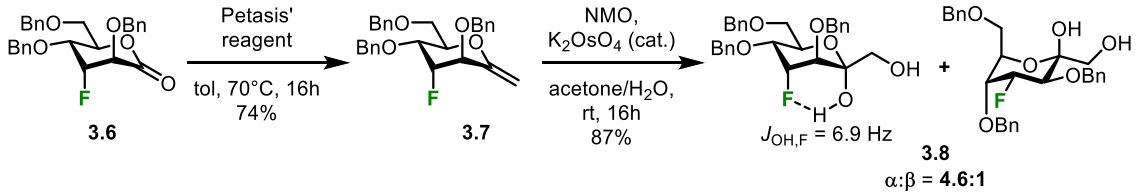
Subsequent oxidation attempts with the Ley-Griffith reagent (TPAP)[93] and NMO as co-oxidant to form lactone **3.6** led to elimination of HF and formation of the α,β-unsaturated lactone **3.9** instead (Scheme 31). The formation of **3.9** was confirmed by ^{1}H NMR spectroscopy, mass spectrometry (*m/z* calc. for $C_{27}H_{26}O_5Na^+$: 453.1672, found: 453.1669) and by the absence of any signals in the ^{19}F NMR spectrum.



Scheme 31: Synthetic attempts to oxidize lactol **3.5** to lactone **3.6**.

An Albright-Goldman oxidation (acetic anhydride in dimethyl sulfoxide) did not lead to any conversion.[94] Oxidation with DMP, however, gave the desired lactone **3.6** in an excellent yield of 96%.[95]

C_1-Elongation of the *altrono*-lactone giving exocyclic enol ether **3.7** was achieved with Petasis' reagent (bis(cyclopentadienyl)dimethyltitanium) in toluene at 70°C overnight and under the exclusion of light in 74% yield (Scheme 32).[74,83,96] The double bond of compound **3.7** could then be dihydroxylated with catalytic amounts of potassium osmate dihydrate in the presence of NMO[97] to yield heptulose **3.8** as a 4.6:1 mixture of its α- and β-anomers with the β-anomer adopting a $^{2}C_5$-conformation.



Scheme 32: Synthesis of heptulose **3.8** from 2,4,6-tri-*O*-benzyl-3-deoxy-3-fluoro-D-*altrono*-1,5-lactone (**3.6**).

Again, a hydrogen bond between the anomeric OH-group of the α-anomer and the fluorine atom was detected as can be seen by the additional coupling in the ^{19}F NMR spectrum ($J_{F,OH}$ = 6.9 Hz, Figure 3A) which disappeared in *d*$_4$-MeOH (Figure 3B).

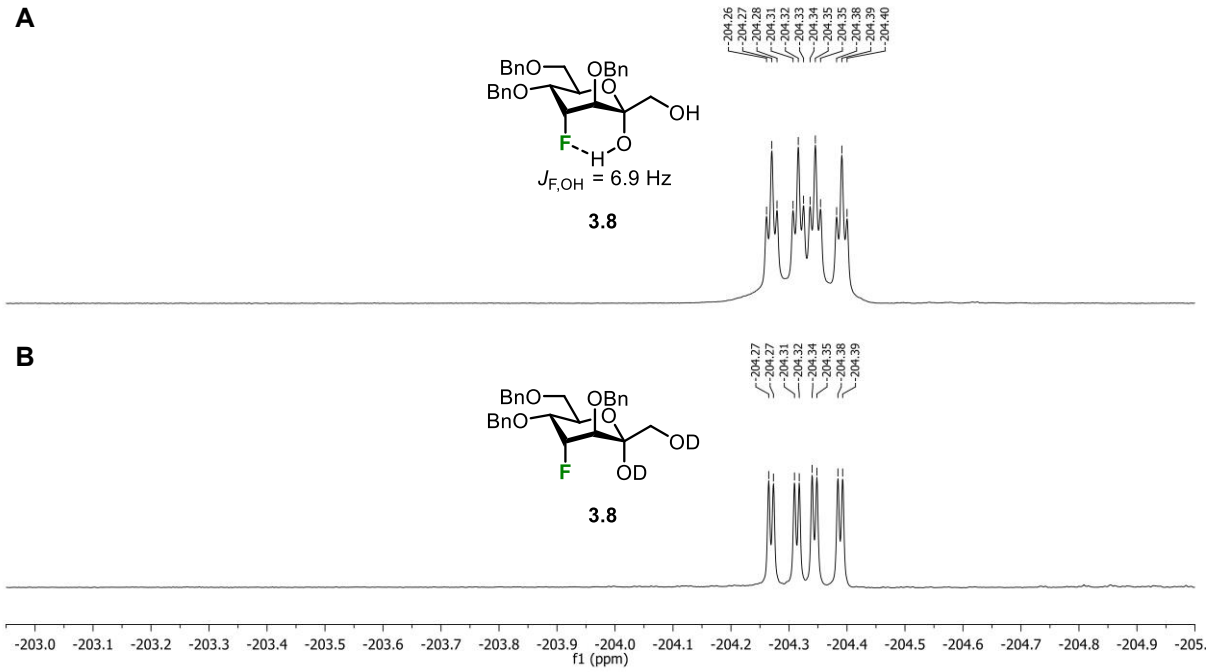
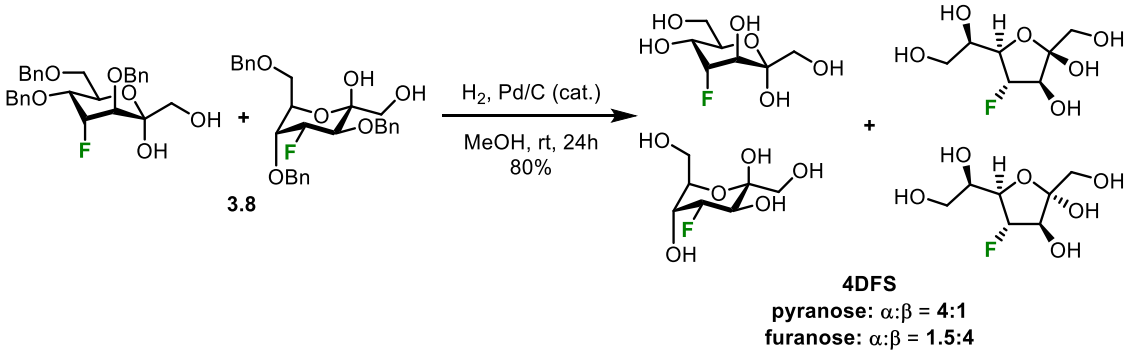


Figure 3: A: ^{19}F NMR spectrum (659 MHz, $CDCl_3$) of heptulose **3.8** showing a ddt at -204.33 ppm ($^2J_{F,4}$ = 49.5 Hz, $^3J_{F,5}$ = 30.1 Hz, $^3J_{F,3}$ = $J_{F,OH}$ = 6.9 Hz). **B:** ^{19}F NMR spectrum (659 MHz, *d*$_4$-MeOH) of heptulose **3.8** showing a ddd at -204.33 ppm ($^2J_{F,4}$ = 49.3 Hz, $^3J_{F,5}$ = 29.3 Hz, $^3J_{F,3}$ = 5.4 Hz).

Global deprotection with hydrogen gas (1 atm) and palladium on charcoal[74] gave 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**, Scheme 33) as a colorless oil and as a mixture of its α- and β-furanose and its α- and β-pyranose in a 1.3:4:4:1 ratio. The overall yield of **4DFS** over 9-steps was 13%.



Scheme 33: Final global deprotection during the synthesis of 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**).

3.1.2 First Biochemical Evaluations

4DFS was then subjected to first biochemical assays in order to see whether the novel fluorinated sugar is taken up by cells, phosphorylated by sedoheptulose kinase (SHPK) and if fluorination at position 4 really halts the enzymatic degradation of the corresponding sugar phosphate.

The first goal was to set up a qualitative cellular uptake assay. First attempts to use HPAEC-PAD as a separation and detection method were not successful. Figure 4 shows the chromatograms of **4DFS** standards of different concentrations in a stacked diagram. This clearly shows decomposition of the sugar under the tested conditions (see chapter 5.2.1 for chromatographic details).

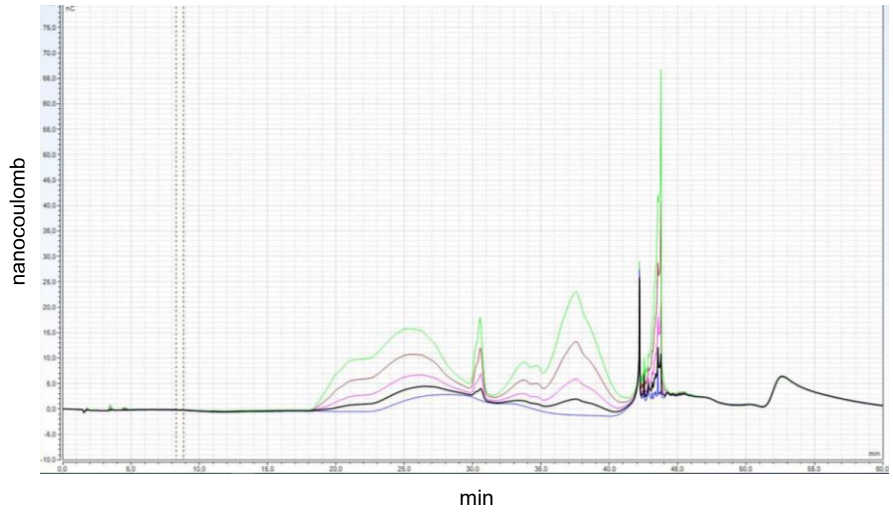


Figure 4: HPAEC-PAD chromatograms of **4DFS** standards: green = 400 µg/ml, dark red = 200 µg/ml, pink = 100 µg/ml, black = 50 µg/ml, blue = blank.

The basic pH of the eluent (0.1 M - 0.2 M aq. NaOH) was suspected to be the cause of the observed decompostion and indeed subsequent NMR measurements confirmed the lability of **4DFS** under basic conditions. The ^{19}F NMR spectrum of **4DFS** in 0.1 M NaOD in D_2O showed only one peak at -122.31 ppm (Figure 5B), characteristic for an aqueous fluoride ion (Figure 5C).

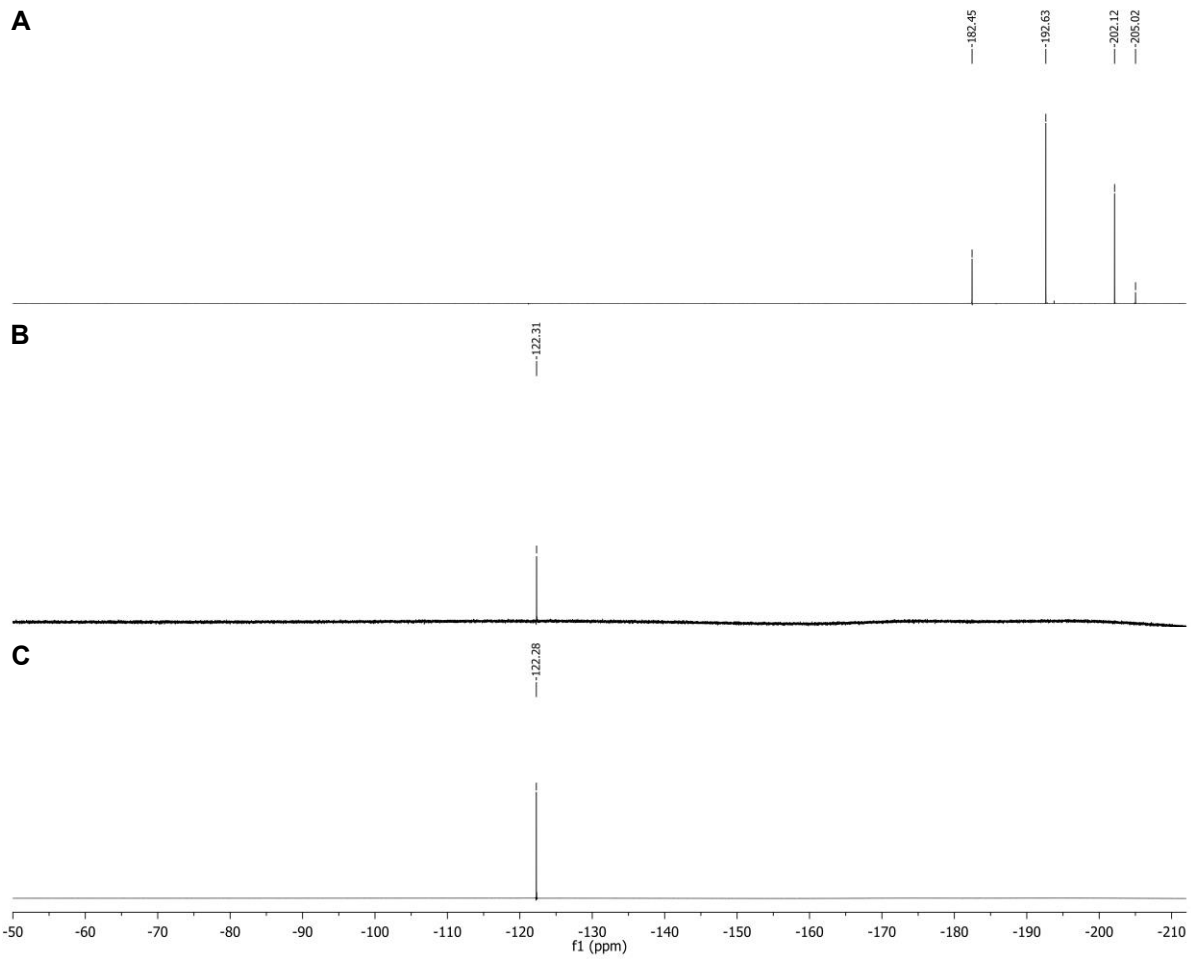


Figure 5: A: $^{19}F\{^{1}H\}$ NMR spectrum of **4DFS** in D_2O (659 MHz). **B**: ^{19}F NMR spectrum of **4DFS** in 0.1 M NaOD in D_2O (377 MHz). **C**: ^{19}F NMR spectrum of KF in 0.1 M NaOD in D_2O (377 MHz).

Due to the observed elimination reaction, a milder chromatographic method was needed, a criterium which HILIC-MS-based identification of compounds could fulfill (see chapter 5.2.2 for experimental details).[98]

With a suitable separation and detection method in hand, the growth medium of human fibroblasts was supplemented with an aqueous solution of **4DFS**. The cells were then incubated for 10 min and washed thoroughly thereafter with water. Lysis of the cells with methanol and water, subsequent centrifugation of the lysate to remove precipitates and evaporation of the supernatant gave the small molecule-containing fraction of cellular compounds which was dissolved in acetonitrile and water (1:1, v/v) for HILIC-MS analysis.

Figure 6 shows the extracted-ion chromatograms of the cellular uptake assay: **4DFS** (*m/z* = 211.0623, $[M\text{-}H]^-$, Figure 6B) could be detected in the sample with a retention time of 4.74 min which is in good agreement with the **4DFS** standard (R_T = 4.66 min,

Figure 6A). Additionally, the mass of the respective phosphate of **4DFS** (*m/z* = 291.0286, R_T = 9.73 min, Figure 6C) was also present in the same sample, hinting at first signs of metabolism and at acceptance of **4DFS** as a substrate by SHPK. Both peaks were absent in the control sample (Figure 10, chapter 6.1.1).

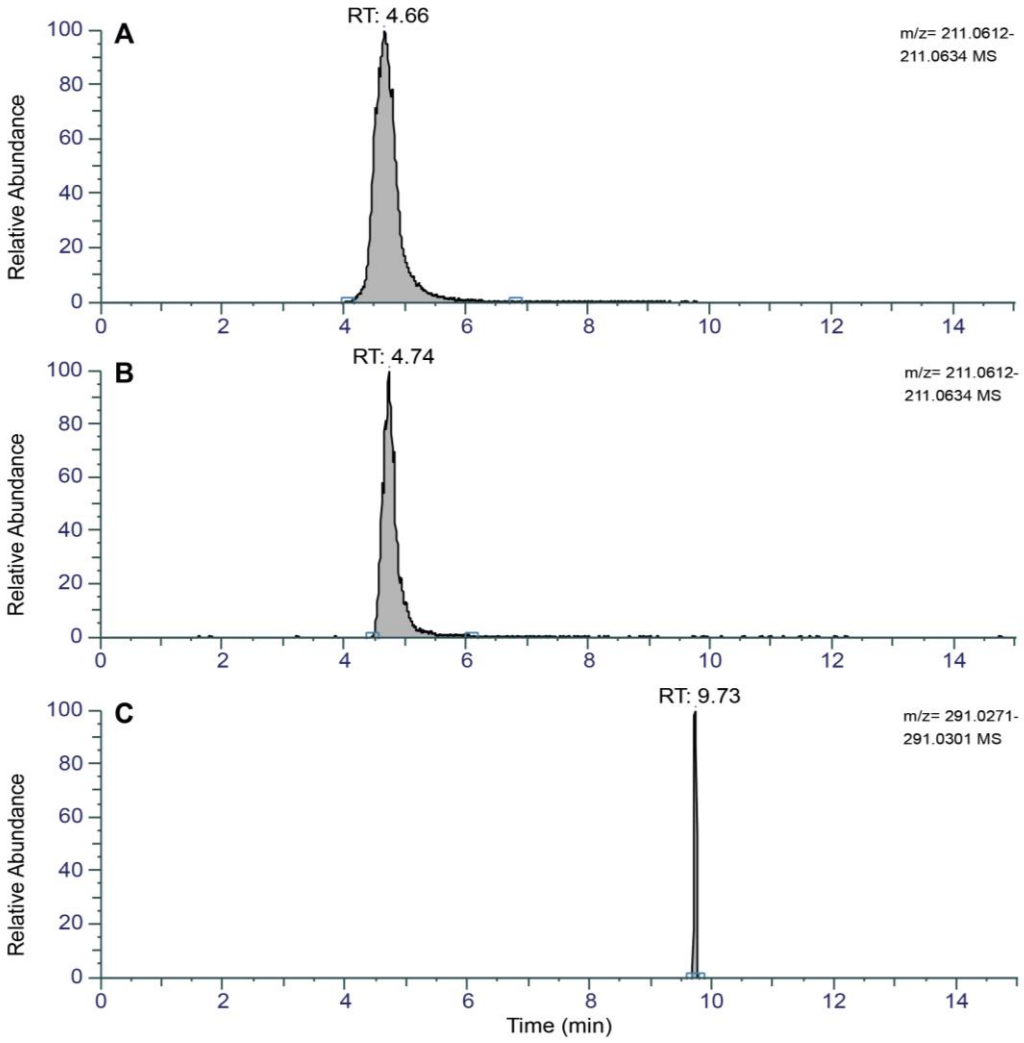


Figure 6: A: Extracted-ion chromatogram (*m/z* 211.0623, mass tolerance = 5 ppm) of **4DFS** standard (10 µM in MeCN/H_2O). **B:** Extracted-ion chromatogram (*m/z* 211.0623, mass tolerance = 5 ppm) of **4DFS** uptake assays with human fibroblasts. **C:** Extracted-ion chromatogram (*m/z* 291.0286, mass tolerance = 5 ppm) for corresponding sugar phosphate **4DFS7P** in the same uptake assay sample. HILIC-MS analysis was done with cell lysates, see chapter 5.2.3 for experimental details. RT = retention time.

An *in vitro* fluorescence-based ADP-accumulation assay was then used to verify the phosphorylation of **4DFS** by SHPK.[24] The results (Figure 7) clearly show that **4DFS** is indeed phosphorylated by SHPK with no significant difference to its native substrate, D-sedoheptulose. The observed fluorescence signal in the absence of substrate presumably stems from endogenously bound substrate (D-sedoheptulose) since non-dialyzed samples of SHPK were used.

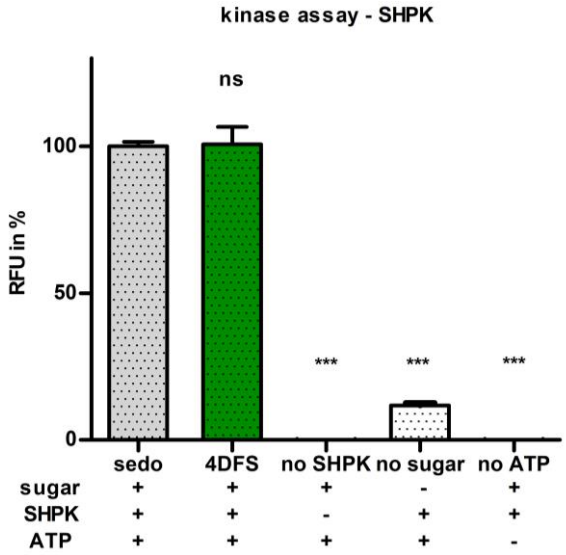


Figure 7: Fluorescence-based ADP-accumulation assay with sedoheptulose kinase (SHPK). Data is presented as the mean + standard error of mean (SEM) and was analyzed with an unpaired two-samples t-test in comparison to positive control (**sedo**): *** $P < 0.001$, ns = not significant. RFU = relative fluorescence units, **sedo** = D-sedoheptulose, **4DFS** = 4-deoxy-4-fluoro-D-sedoheptulose.

Having proof that **4DFS** is converted into the corresponding sugar phosphate, the next step in the process was to have a look at the enzymatic stability of the resulting sugar phosphate. For this purpose, an assay developed by Clark *et al.* was used.[49] The only major adaption was the use of HILIC-MS instead of ion-pair chromatography followed by MS detection. The basic principle relies on two subsequent enzymatic reactions in one pot: First, the sugar was phosphorylated by SHPK to form the corresponding sugar phosphate which was then enzymatically degraded by TALDO1 or TKT. Initial experiments for the negative control samples contained 10 mM sedoheptulose, 1.5 µg SHPK, 10 mM ATP, 10 mM G3P, 20 mM KCl, 10 mM $MgCl_2$ and 10 mM HEPES (pH 7.6) in a final volume of 25 µL water. Unfortunately, the mass of **S7P** (*m/z* = 289.0330) could not be detected. Optimizations led to more dilute reaction conditions: Negative controls contained 1 mM sugar (**sedo** or **4DFS**), 0.045 µg SHPK, 1 mM ATP, 1 mM G3P, 20 mM KCl, 10 mM $MgCl_2$, 10 mM HEPES (pH 7.6) (and 0.5 mM ThDP in the case of TKT reactions) in a final volume of 25 µL water. Actual reactions contained all the above-mentioned ingredients and either 1 µg TALDO1 ***or*** TKT.

After HILIC-MS analysis, the peak area of the respective heptulose phosphate (**S7P** or **4DFS**-phosphate) was used for relative quantification in all experiments. As mentioned above, TALDO1 and TKT were omitted in the negative control samples which were normalized to 100%.

The results of the enzymatic stability assays are summarized in Figure 8. The two graphs show that **4DFS**-phosphate is neither a substrate for transaldolase nor, surprisingly, for transketolase.

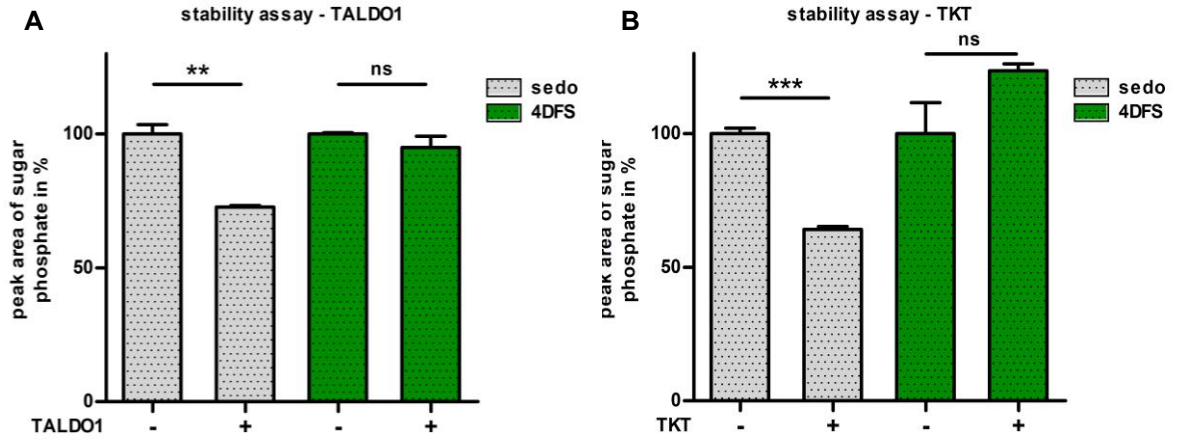
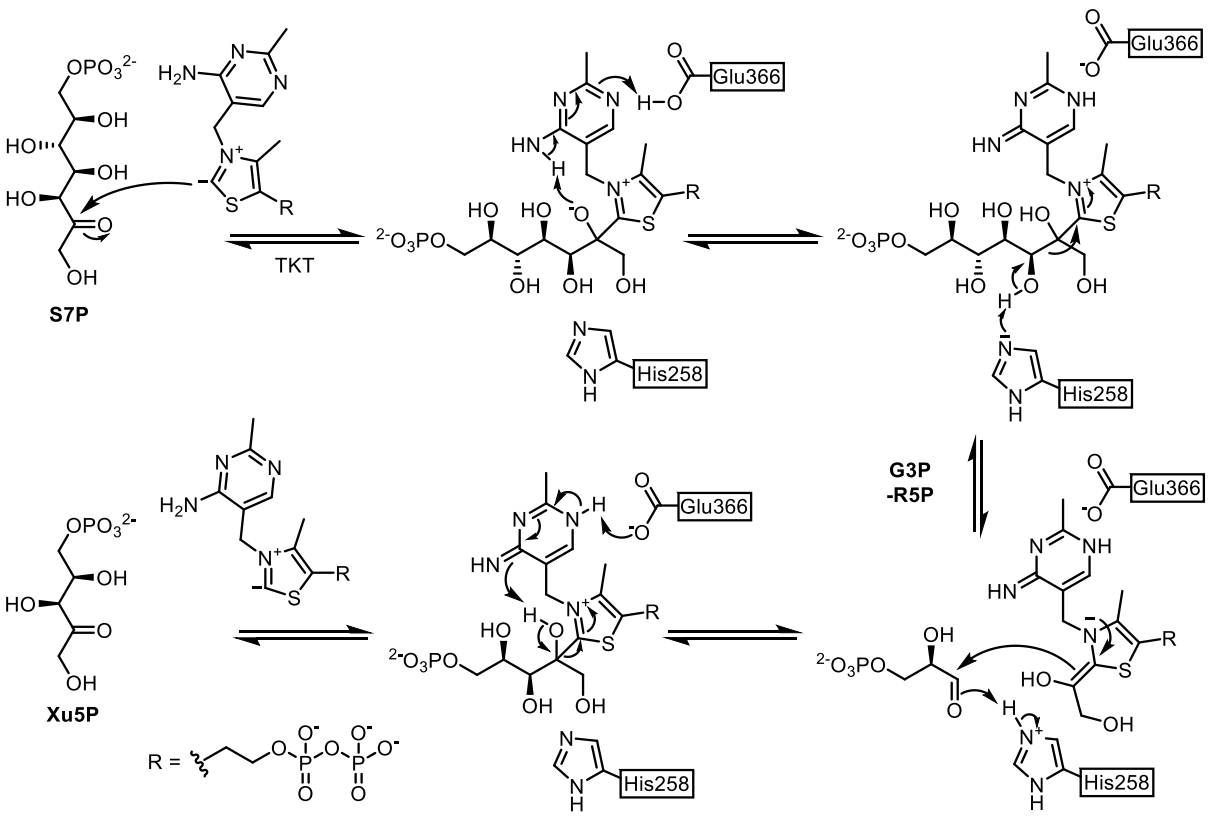


Figure 8: A & **B**: Enzymatic stability assays of **4DFS** in the presence of SHPK and either transaldolase (TALDO1) or transketolase (TKT). Data is presented as the mean + standard error of mean (SEM) and was analyzed with an unpaired two-samples t-test in comparison to negative control: *** $P < 0.001$, ** $P < 0.01$, ns = not significant. **sedo** = D-sedoheptulose, **4DFS** = 4-deoxy-4-fluoro-D-sedoheptulose.

While the results with TALDO1 can be explained mechanistically (Scheme 22), the results with TKT are more puzzling and cannot be rationalized with the reaction mechanism alone (Scheme 34)[1,99–101] since the hydroxyl group at position 4 is not di-



Scheme 34: Enzymatic mechanism of TKT with activated ThDP,[102] **S7P** and **G3P**.

rectly involved in any step. The crystal structure of TKT and **S7P** covalently bound to cofactor ThDP in the active site (Figure 9) however indicates that the hydroxyl groups in position 3 and 4 in **S7P** are involved in a hydrogen bond network with histidine-37, histidine-258, glutamine-189 and aspartate-424 of human TKT.[101] These H-bonds might contribute to the initial substrate-enzyme recognition and are both crucial for formation and stabilization of the complex. The absence of one of these interactions may suffice for not accepting **4DFS7P** as a substrate.

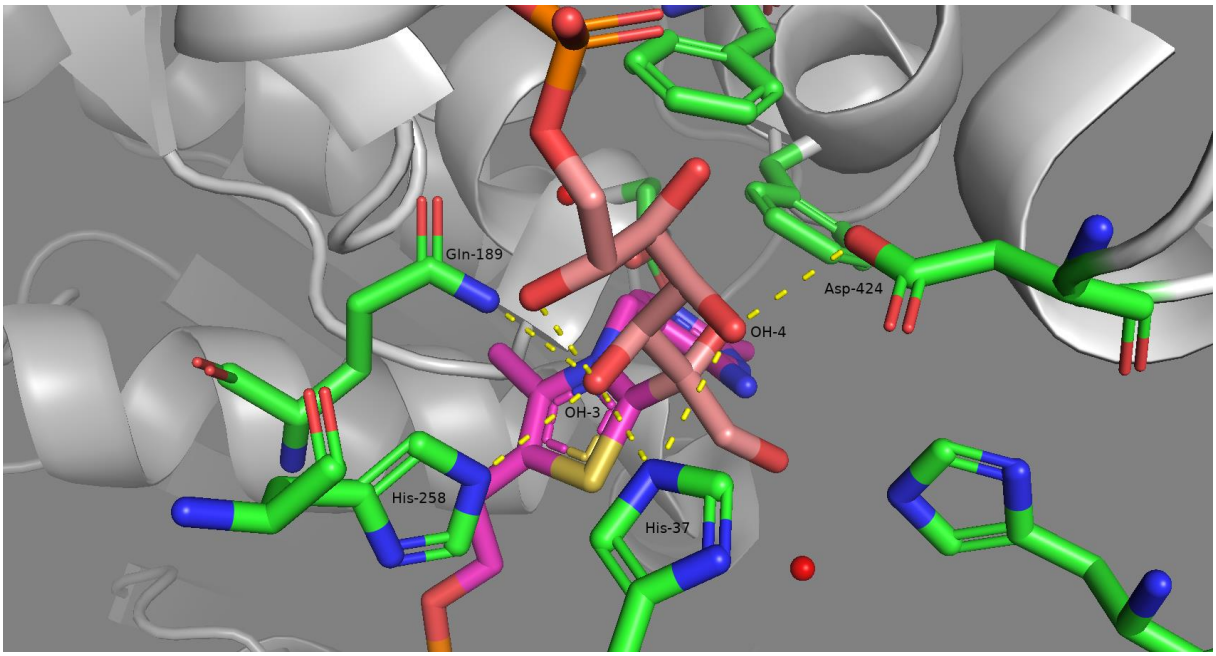
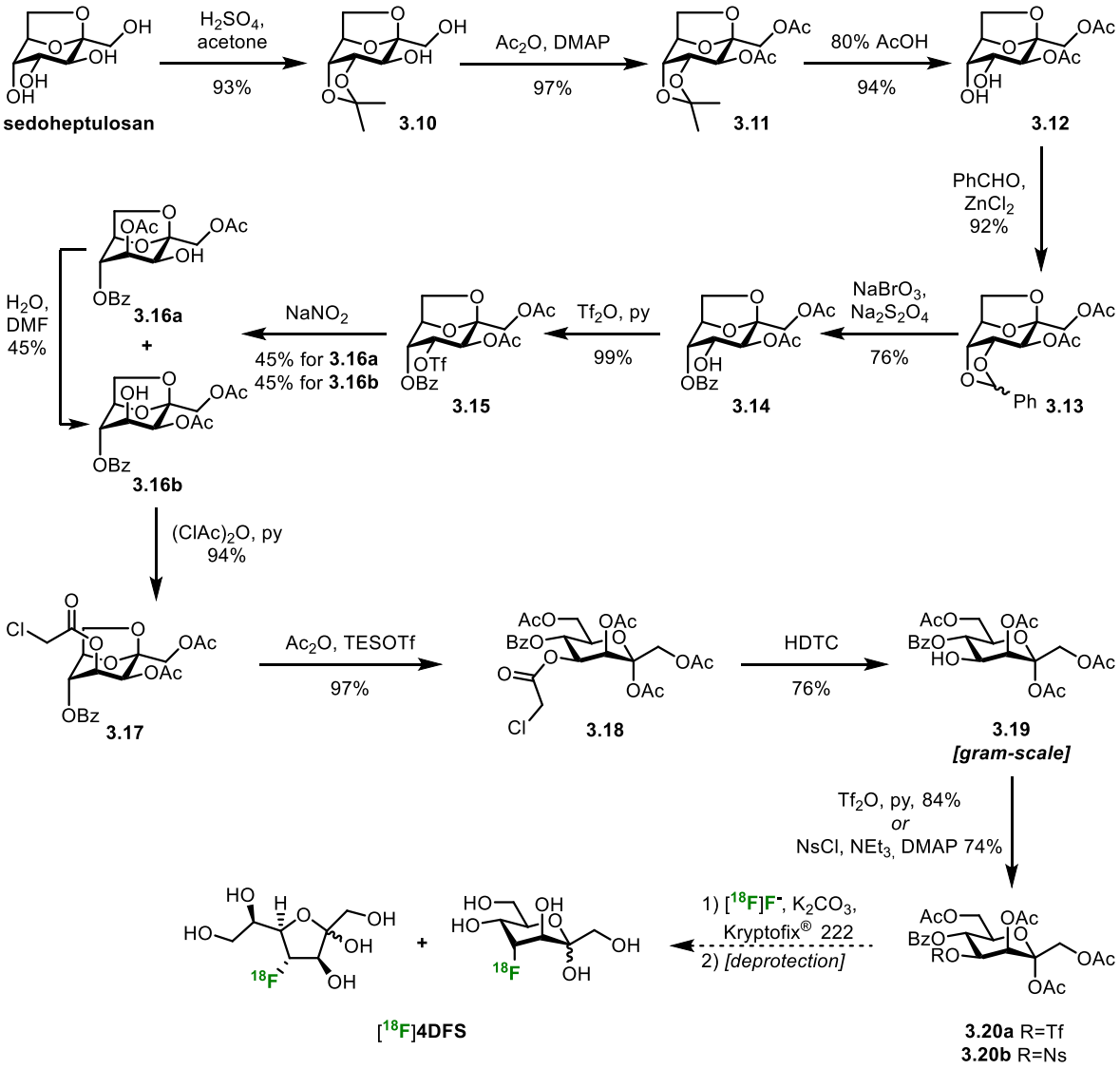


Figure 9: Crystal structure of the active site of TKT (PDB: 4KXX) with **S7P** (light red sticks) covalently bound to ThDP (magenta sticks). Only protein residues in close proximity (<5 Å) to **S7P** are shown in green sticks, the rest of the protein is represented as grey cartoons. Hydrogen bonds of the OH-3 and OH-4 groups of **S7P** are indicated by dashed, yellow lines. Oxygen atoms are shown in red, sulfur atoms in yellow, phosphorus atoms in orange and nitrogen atoms in blue. Water molecules are represented as red spheres. Visualization was generated with PyMOL.

In summary, the results of these first biochemical evaluations make **4DFS** a promising new candidate to expand the principle of metabolic trapping to heptuloses for imaging purposes.

3.1.3 Synthesis of Potential Radiolabeling Precursors for [^{18}F]4DFS

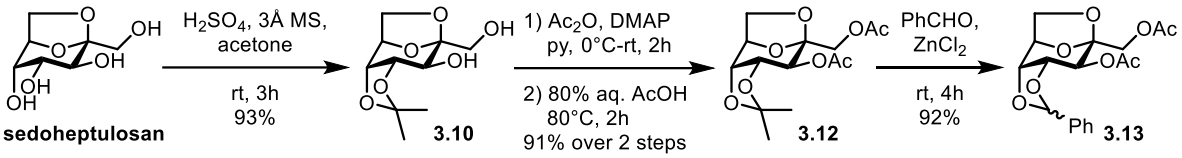
Encouraged by the results of the stability assays, a synthetic route for two potential radiolabeling precursors for **4DFS** was devised. The final synthesis of 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.20a**) and 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-*para*-nitrobenzenesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.20b**) is summarized in Scheme 35 and will be discussed in detail in the following chapter.



Scheme 35: Synthesis of potential radiolabeling precursors **3.20a** and **3.20b** from sedoheptulosan. Dashed arrows indicate reactions that have not been performed yet.

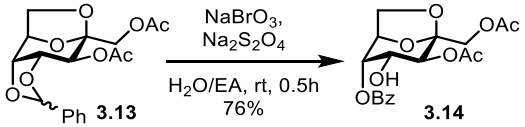
The synthesis started with sedoheptulosan (2,7-anhydro-D-sedoheptulose) monohydrate which is commercially available or can be synthesized from D-sedoheptulose contained in plant extracts of *Sedum maximum*.[103,104] The first 4

synthetic steps were literature-known (Scheme 36) and could be performed on a >10 gram scale: Sedoheptulosan was first selectively isopropylidene protected at position 4 and 5 followed by a standard acetylation of diol **3.11**.[105,106] Then, the acetonide was removed with aqueous acetic acid and replaced with a benzylidene acetal under Lewis acid catalysis.[107,108] Remaining benzaldehyde was removed at 80°C on a rotary evaporator since chromatographic purification on silica gel led to partial decomposition of the product. Using this reaction sequence, over 20 grams of 1,3-di-*O*-acetyl-2,7-anhydro-4,5-*O*-benzylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.13**) were produced in a yield of 78% over 4 steps with only one recrystallization step and without any chromatographic purification steps.



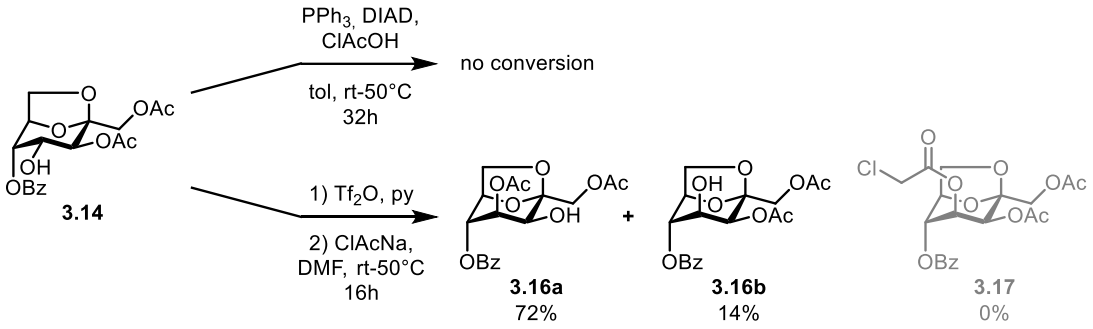
Scheme 36: Multi-gram synthesis of 1,3-di-*O*-acetyl-2,7-anhydro-4,5-*O*-benzylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.13**) from sedoheptulosan.

The benzylidene acetal in **3.13** was then oxidatively opened at the equatorial position with sodium bromate and sodium dithionite in a biphasic mixture of water and ethyl acetate to yield the key synthetic intermediate **3.14** in 76% yield (Scheme 37).[109]



Scheme 37: Oxidative opening of benzylidene acetal to give **3.14**.

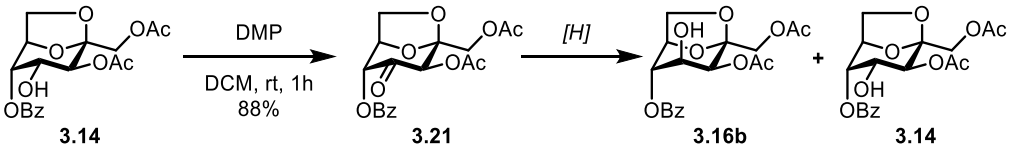
In order to fluorinate – the now unprotected – position 4 with overall retention of configuration, an inversion of the stereocenter was necessary. Several methods for the epimerization of position 4 were examined (Scheme 38): A Mitsunobu approach with chloroacetic acid, diisopropyl azodicarboxylate and triphenylphosphine did not lead to any conversion of **3.14**.[110,111] A S_N2-reaction with sodium chloroacetate and triflate **3.15** gave a 1:5 mixture of the desired product **3.16b** and the migration product **3.16a** but the chloroacetylated product **3.17** was not formed.[112]



Scheme 38: Attempts to invert the stereocenter of position 4 in compound **3.14**.

Another method to invert a stereocenter on sugar scaffolds is to oxidize the alcohol to the respective ketone followed by a diastereoselective reduction of the ketone to the corresponding epimer of the starting alcohol. The results of the tested conditions for this oxidation-reduction approach are summarized in Table 2: Oxidation of alcohol **3.14** to the corresponding ketone **3.21** worked smoothly with DMP. Several simple metal hydrides were tested for the following reduction. The best results were obtained by a Luche reduction (entry 4) giving a 1.6:1 mixture of desired compound **3.16b** and undesired epimer **3.14**.[113,114] Switching to sterically more demanding and more reactive reductants (entries 6-8) was not successful and mainly led to decomposition.

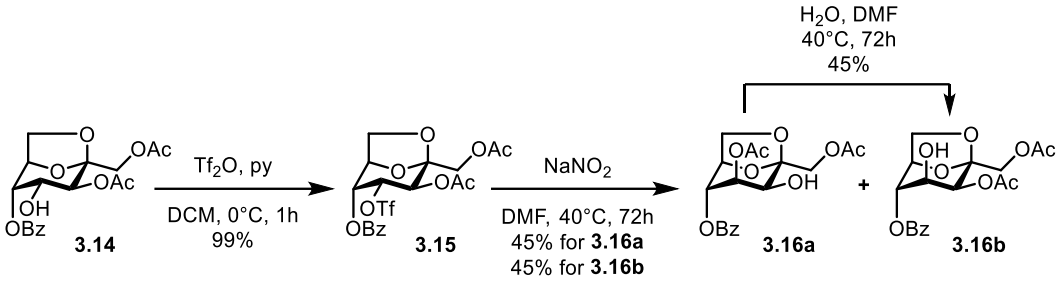
Table 2: Results of the tested oxidation-reduction approaches for inversion of the stereocenter at position 4 in **3.14** (n.d. = not determined).



entry	reductant	solvent	temperature	ratio **3.16b**:**3.14**
1	$NaBH_3CN$	AcOH	rt	1.5:1
2	$NaBH_3CN$	AcOH/MeOH	-20°C to rt	1.5:1
3	$NaBH_4$	DCM/MeOH	-20°C	1:1.6
4	$NaBH_4/CeCl_3{\cdot}7H_2O$	DCM/EtOH	-78 to -20°C	1.6:1
5	$BH_3{\cdot}THF$	THF	0°C-rt	1:1.9
6	DIBAL-H	THF	-78°C	n.d.
7	L-Selectride®	THF	-78°C	n.d.
8	$LiAlH(O\mathit{t}Bu)_3$	THF	0°C to rt	n.d.

Although there were still plenty of additional reduction methods left to test for ketone **3.21**, the oxidation-reduction approach was abandoned because epimers **3.16b** and **3.14** were inseparable with conventional chromatographic methods even after chloroacetylation or benzylation (data not shown).

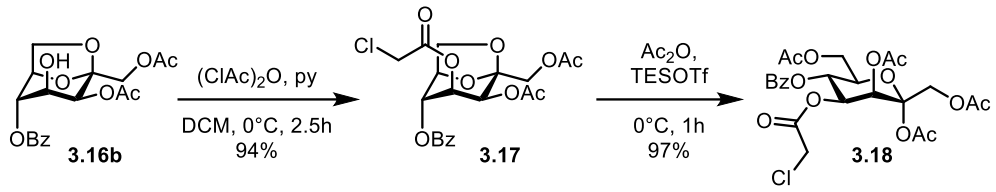
The best results for the stereo inversion of position 4 in compound **3.14** were obtained by a Latrell-Dax-epimerization (Scheme 39).[115,116] For this, **3.14** was treated with triflic anhydride and pyridine in DCM for 1 h to give triflate **3.15** in an excellent yield of 99%.



Scheme 39: Synthesis of triflate **3.15** and subsequent Latrell-Dax epimerization to give migration product **3.16a** and desired product **3.16b**.

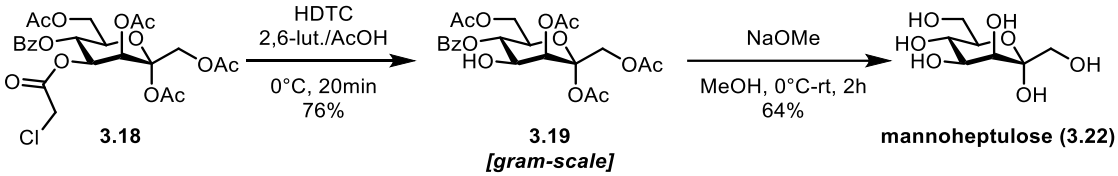
The subsequent reaction with sodium nitrite always led to a 1:1 mixture of desired compound **3.16b** and undesired migration product **3.16a**. Monitoring the reaction by NMR spectroscopy revealed that **3.16a** is actually formed first and then the acetate at position 4 migrates back to position 3 over the course of the reaction until a final 1:1 equilibrium of **3.16a** and **3.16b** is reached. Neither the solvent (DMF, MeCN, DCM or toluene) nor the nitrite source ($NaNO_2$, KNO_2 or $TBANO_2$) had any influence on the outcome of the reaction. Fortunately, compounds **3.16a** and **3.16b** could be separated chromatographically in 2-gram portions with a gradient elution (12%-46% EA in toluene). Pure compound **3.16a** was then stirred in wet DMF to again reach the 1:1 equilibrium with desired alcohol **3.16b**. Thereby, it was possible to push the equilibrium to the side of the desired product. In case of the Latrell-Dax epimerization as well as the re-equilibration reaction, NMR spectroscopy was used to monitor the reaction progress.

After the successful epimerization, a chloroacetyl group was introduced at position 4 as an orthogonal protecting group (Scheme 40). Subsequent acetolysis of the 2,7-anhydro bridge with triethylsilyl triflate in acetic anhydride gave fully protected heptulose **3.18** as a single anomer.[117] This reaction was monitored with NMR spectroscopy because the starting material and the product essentially had the same R_f-value: 0.37 and 0.36 (1:1 *n*-heptane/EA).



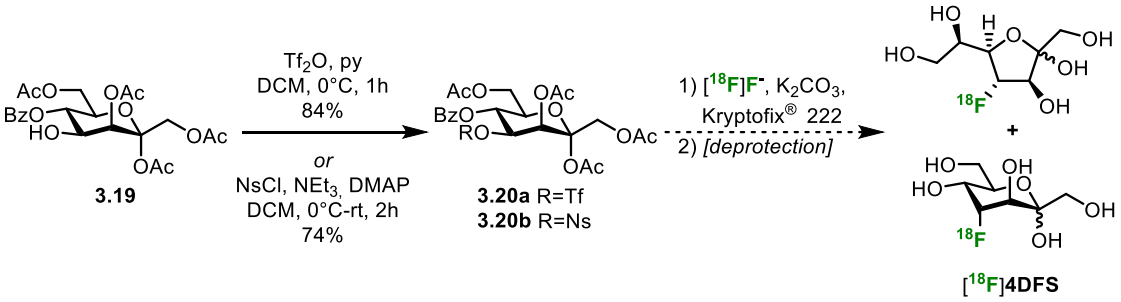
Scheme 40: Synthesis of heptulose **3.18** from 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulose (**3.16b**).

The chloroacetyl protecting group was then removed with freshly prepared hydrazine dithiocarbonate (HDTC) at 0°C to give heptulose **3.19** on a multi-gram scale in 76% yield.[118] As a control experiment heptulose **3.19** was also subjected to a Zemplén deprotection yielding, as expected, D-mannoheptulose (Scheme 41).[119,120]



Scheme 41: Selective deprotection of **3.18** giving heptulose **3.19**, followed by Zemplén deprotection of **3.19** yielding α-D-mannoheptulose (**3.22**).

Installation of good leaving groups for radiolabeling experiments worked well at this stage. Triflate **3.20a** could be accessed in 84% yield after purification (Scheme 42). It is worth noting that **3.20a** always had to be co-evaporated thrice with diethyl ether to yield a foam instead of an oil. Treatment of heptulose **3.19** with nosyl chloride, triethylamine and DMAP in DCM gave 74% of nosylate **3.20b** as a white solid after chromatography.[121] The yield of **3.20a** and **3.20b** over the 11-step synthesis was 15% and 14%, respectively.

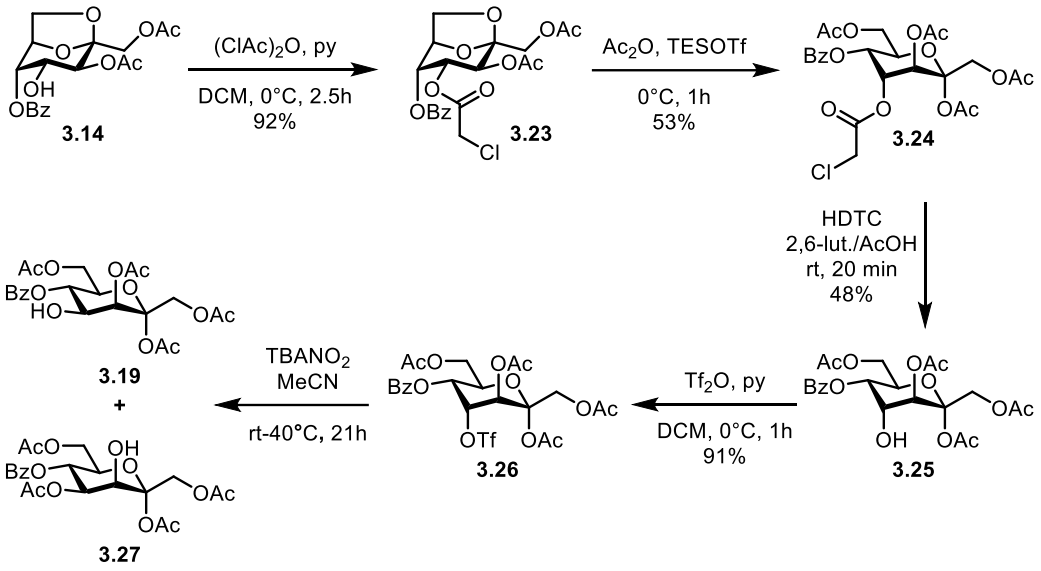


Scheme 42: Final step to access potential radiolabeling precursors **3.20a** and **3.20b**. A possible radio-fluorination strategy for the synthesis of [^{18}F]**4DFS** (obtained after deprotection under basic conditions). Dashed arrows indicate experiments that have not been performed yet.

Compound **3.20a** is currently under investigation for radio-fluorinations with fluoride-18 at the Department of Biomedical Imaging and Image-guided Therapy (Medical

University of Vienna) to access 4-deoxy-4-[^{18}F]fluoro-D-sedoheptulose ([^{18}F]**4DFS**) after deprotection of the obtained intermediate under basic conditions.

Scheme 43 summarizes an additional approach to perform the aforementioned Latrell-Dax-epimerization at a later stage of the synthetic sequence. The initial steps are essentially the same: First, chloroacetylation of compound **3.14** gave **3.23**, then acetolysis gave **3.24** which was followed by removal of the chloroacetate and installation of a triflate group in intermediate **3.25** to give heptulose **3.26**. After treatment with tetrabutylammonium nitrite, ^{1}H NMR spectroscopy of the crude residue unfortunately again showed two substances: the desired heptulose **3.19** and the undesired migration product **3.27** which showed a downfield chemical shift for H-4 consistent with geminal acetates (5.47 ppm, dd, $^{3}J_{4,5}$ = 10.0 Hz, $^{3}J_{4,5}$ = 3.1 Hz) compared to the chemical shift of H-4 in compound **3.19** (4.31 ppm, ddd, $^{3}J_{4,5}$ = 10.0 Hz, $^{3}J_{4,OH}$ = 5.3 Hz, $^{3}J_{4,3}$ = 3.5 Hz).



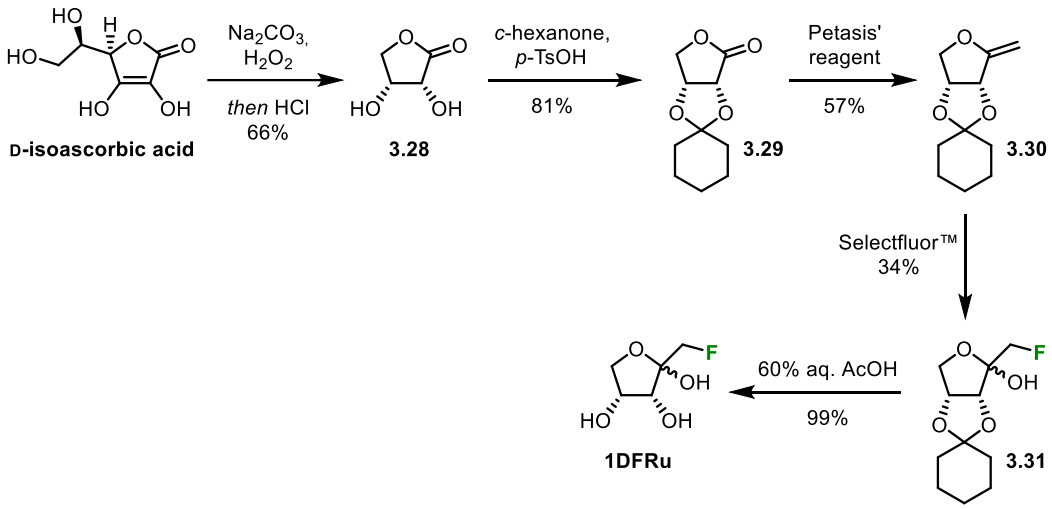
Scheme 43: Alternative approach to perform the Latrell-Dax epimerization with triflate **3.26**.

3.2 1-Deoxy-1-fluoro-D-ribulose

The results in this chapter were obtained together with Kaja Liepert.[122]

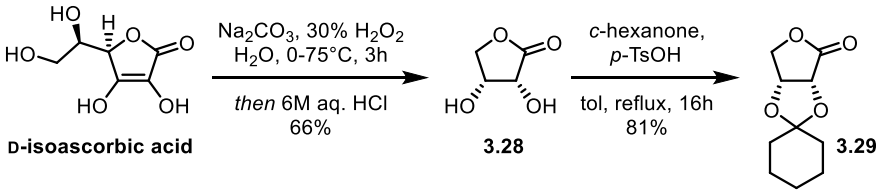
3.2.1 Synthesis of 1-Deoxy-1-fluoro-D-ribulose

The final synthesis of 1-deoxy-1-fluoro-D-ribulose (**1DFRu**) is summarized in Scheme 44 and will be discussed in detail in the following chapter.



Scheme 44: Synthesis of 1-deoxy-1-fluoro-D-ribulose from D-isoascorbic acid.

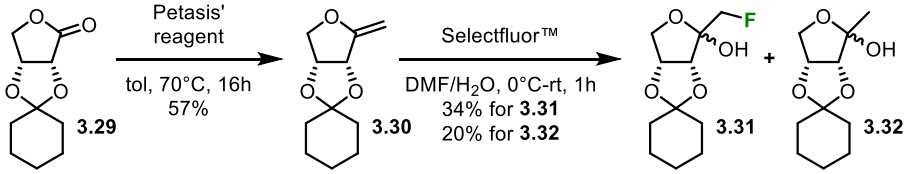
The synthetic route towards **1DFRu** started with two literature-known steps : First, D-isoascorbic acid was oxidized with hydrogen peroxide under basic conditions giving D-erythronic acid which was then heated in the presence of 6 M aq. HCl to yield D-*erythrono* lactone (**3.28**, Scheme 45).[123] Then, the diol was protected as its cyclohexylidene ketal under Dean-Stark-conditions to give lactone **3.29** in 54% yield over 2 steps.[124]



Scheme 45: Synthesis of 2,3-O-cyclohexylidene-D-*erythrono*-1,4-lactone (**3.29**) from D-isoascorbic acid.

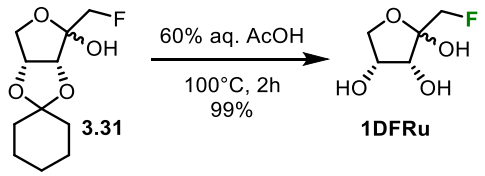
Substance **3.29** was then methylenated using Petasis' reagent to yield exocyclic enol ether **3.30** in 57% yield (Scheme 46).[83,125] Here, the cyclohexylidene protecting group was crucial since the corresponding isopropylidene analog of **3.30** proved to be volatile which hampered isolation and purification.[122]

The resulting electron-rich double bond could then be used in an electrophilic fluorination of position 1 with Selectfluor™ in a 1:1 mixture (v/v) of DMF and water.[74] Unfortunately, this procedure was low yielding (34%) for 3,4-*O*-cyclohexylidene-1-deoxy-1-fluoro-D-ribulose (**3.30**) and substantial amounts (20%) of 3,4-*O*-cyclohexylidene-1-deoxy-D-ribulose (**3.32**) were also formed. The anomeric ratio of **3.31** was 7.7:1 (β:α).



Scheme 46: Methylenation of lactone **3.29** with Petasis' reagent and subsequent electrophilic fluorination of compound **3.30**.

Final deprotection of ribulose **3.31** in 60% aqueous acetic acid at 100°C for 2 hours gave smooth access to 1-deoxy-1-fluoro-D-ribulose in 99% yield (Scheme 47).[126] The anomeric ratio was 2.3:1. However, NOESY experiments were inconclusive for assigning the α- or β-anomer.

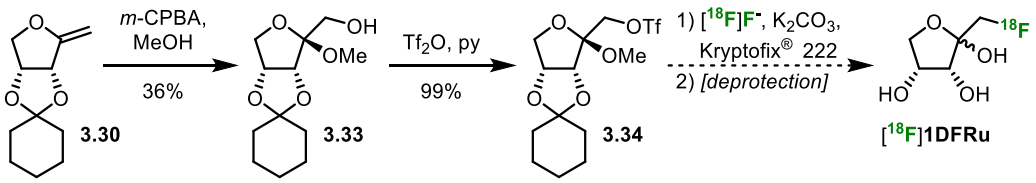


Scheme 47: Final acidic deprotection of compound **3.31** to give 1-deoxy-1-fluoro-D-ribulose (**1DFRu**).

The overall yield for **1DFRu** was 10% over 5 steps.

3.2.2 Synthesis of a potential radiolabeling precursor for [^{18}F]1DFRu

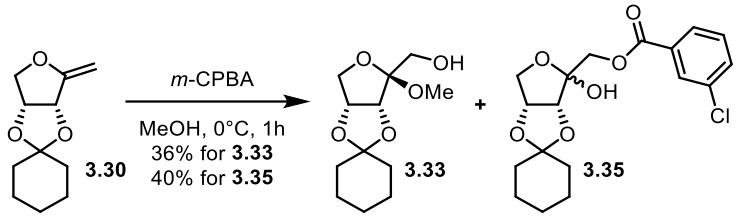
The final synthesis of methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside (**3.34**) is summarized in Scheme 48.



Scheme 48: Synthesis of a potential radiolabeling precursor **3.34** for **1DFRu** from exocyclic enol ether **3.30**. Dashed reaction arrows indicate experiments that have not been performed yet.

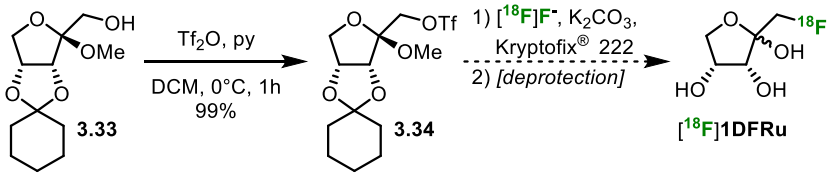
Synthetic intermediate **3.30** from the previous route, could be used to access a potential radiolabeling precursor for [^{18}F]**1DFRu** in a convergent approach. The

exocyclic double bond of **3.30** was subjected to an epoxidation-alcoholysis protocol with *meta*-chloroperbenzoic acid (*m*-CPBA) in methanol yielding methyl 3,4-*O*-cyclohexylidene-β-D-*ribulo*-furanoside (**3.33**) in a low yield of 36% (Scheme 49).[127] **3.33** was obtained as a single anomer and NOESY experiments confirmed a β-configuration at the anomeric center. Unfortunately, 40% of 1-*O*-*meta*-chlorobenzoyl-3,4-*O*-cyclohexylidene-D-ribulose (**3.35**) were also formed.



Scheme 49: Epoxidation-alcoholysis reaction of enol ether **3.30** with *m*-CPBA in methanol yielding desired methyl furanoside **3.33** and undesired 1-*O*-protected ribulose **3.35**.

The primary hydroxy group at position 1 was then triflated (Scheme 50) giving **3.34** in 99% yield. **3.34** might serve as a precursor in radiolabeling experiments with fluoride-18 to access 1-deoxy-1-fluoro-D-ribulose ([^{18}F]**1DFRu**) after acidic deprotection.



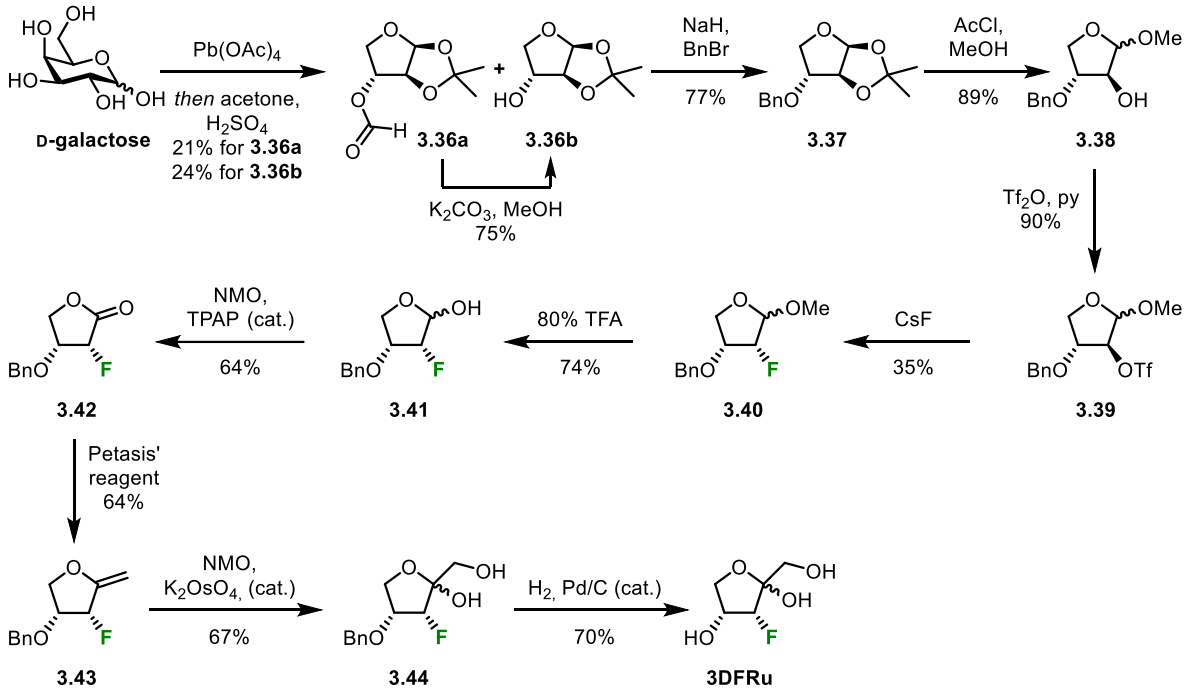
Scheme 50: Final step in the synthesis of potential radiolabeling precursor **3.34**. Dashed arrows indicate experiments that have not been performed yet.

The yield for methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside (**3.34**) was 11% over 5 steps.

3.3 3-Deoxy-3-fluoro-D-ribulose

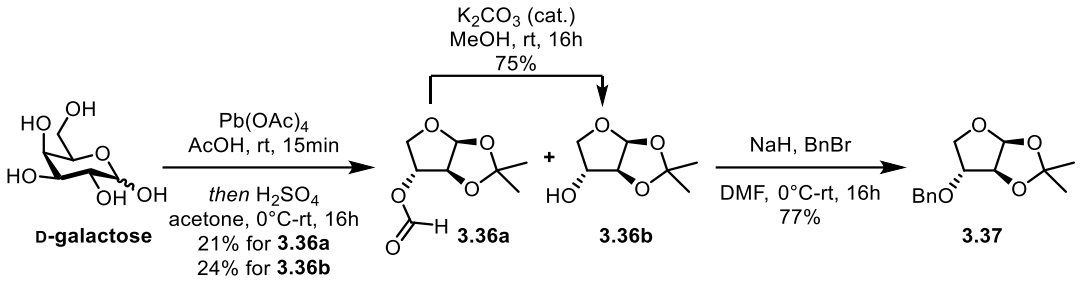
3.3.1 Synthesis of 3-Deoxy-3-fluoro-D-ribulose

The final synthesis of 3-deoxy-3-fluoro-D-ribulose (**3DFRu**) is summarized in Scheme 51 and will be discussed in detail in the following chapter.



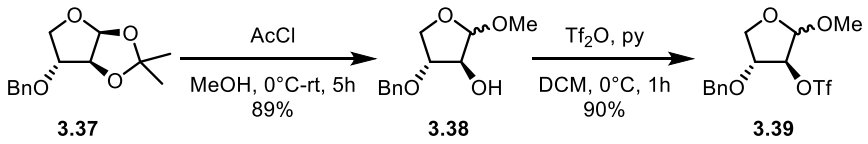
Scheme 51: Synthesis of 3-deoxy-3-fluoro-D-ribulose (**3DFRu**) from D-galactose.

The synthetic route for **3DFRu** started with three literature-known transformations: First, D-galactose was trimmed down to D-threose by a Criegee oxidation followed by a treatment with sulfuric acid in acetone to give threose **3.36b** (Scheme 52).[128,129] The yield for this transformation was low (24%) as the 3-*O*-formyl protected derivative **3.36a** was also formed. The formyl group could, however, be cleaved easily by treating **3.36a** with potassium carbonate in methanol. 1,2-*O*-Isopropylidene-D-threose was then benzylated under standard conditions with sodium hydride and benzyl bromide in dimethylformamide to give compound **3.37**.[130]



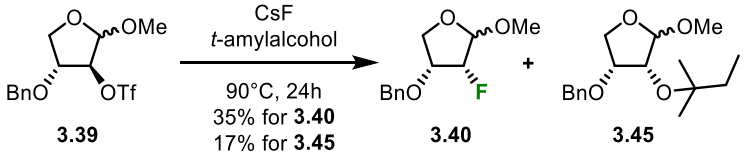
Scheme 52: Synthetic steps to access 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-threose (**3.37**) from D-galactose.

The isopropylidene ketal was then cleaved with *in situ* generated HCl in methanol yielding an anomeric mixture of methyl furanoside **3.38** (Scheme 53).[130,131] Subsequent treatment with triflic anhydride and pyridine in DCM gave triflate **3.39**.



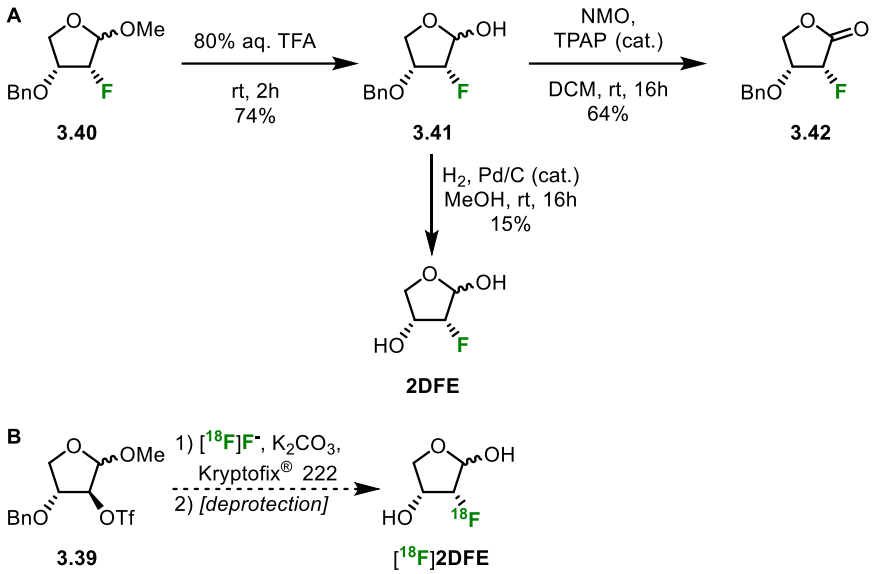
Scheme 53: Synthesis of triflate **3.39** from 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-threose (**3.37**).

Fluorination could be achieved with a protocol from Van der Vorm *et al.* who used cesium fluoride in *tert*-amyl alcohol at elevated temperatures to fluorinate a similar substrate (methyl 3,5-di-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-D-arabinose).[55,132] Unfortunately, yields of the fluorination were low (35%). Despite the steric hindrance of the tertiary alcohol, alcohol substitution product **3.45** was also formed in 17% yield (Scheme 54).



Scheme 54: Fluorination of triflate **3.39** with cesium fluoride giving desired fluorinated furanoside **3.40** and undesired compound **3.45**.

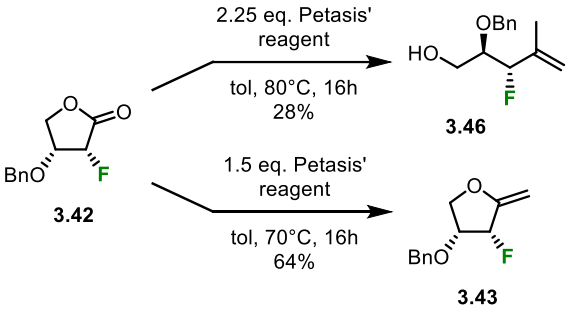
The synthesis continued with an acidic hydrolysis of the methyl glycoside using 80% aqueous trifluoroacetic acid (Scheme 55A).[133] The anomeric mixture was then oxidized to the corresponding lactone **3.42** with tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine-*N*-oxide.[93,134]



Scheme 55: A: Acidic hydrolysis of methyl furanoside **3.40** and subsequent oxidation giving 3-*O*-benzyl-2-deoxy-2-fluoro-D-*erythrono*-1,4-lactone (**3.42**). Benzyl deprotection of erythrose **3.41** yielding 2-deoxy-2-fluoro-D-erythrose (**2DFE**). **B:** Possible radio-fluorination of triflate **3.39** to access 2-deoxy-2-[^{18}F]fluoro-D-erythrose ([^{18}F]**2DFE**) after deprotection. Dashed arrows indicate experiments that have not been performed yet.

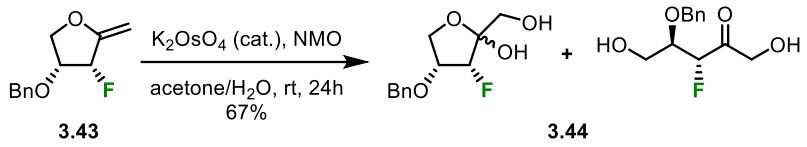
From compound **3.41** it was also possible to synthesize another fluorinated analogue to a sugar of the pentose phosphate pathway: D-erythrose. Debenzylation directly gave rise to 2-deoxy-2-fluoro-D-erythrose (**2DFE**). Triflate **3.39** could therefore serve as a potential radiolabeling precursor to access 2-deoxy-2-[^{18}F]fluoro-D-erythrose ([^{18}F]**2DFE**) after deprotection (Scheme 55B).[48] The applicability of this sugar, however, could be severely hampered by its volatility.

Methylenation of lactone **3.42** with 2.25 equivalents of Petasis' reagent at 80°C mainly gave compound **3.46** (Scheme 56).[83,125] Presumably through, first, an addition of a methyl group to open the lactone followed by a methylenation of the newly formed ketone.



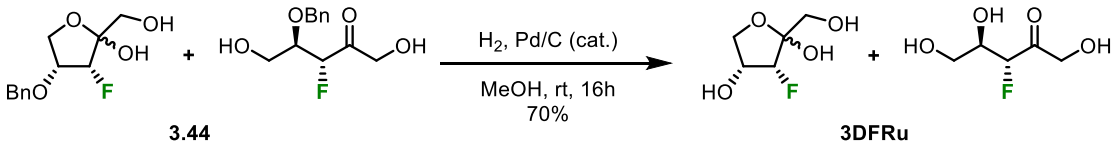
Scheme 56: Methylenation conditions giving either undesired compound **3.46** or desired enol ether **3.43** from lactone **3.42**.

Reducing the equivalents of the methylenation reagent and the temperature furnished desired enol ether **3.43** in 64% yield. **3.43** then underwent a dihydroxylation with potassium osmate and NMO giving desired ribulose **3.44** in 67% yield and as a 7.6:3.3:1 mixture of both anomers and its open chain conformation (Scheme 57).[97]



Scheme 57: Dihydroxylation of compound **3.43** with potassium osmate and NMO giving ribulose **3.44** as a mixture of its α- and β-furanoses and its open-chain conformation.

Final deprotection of ribulose **3.44** with hydrogen gas using catalytic amounts of palladium on charcoal yielded 70% 3-deoxy-3-fluoro-D-ribulose (**3DFRu**, Scheme 58) as a 2.1:2:1 mixture of both anomeric furanoses and the corresponding open chain conformation.

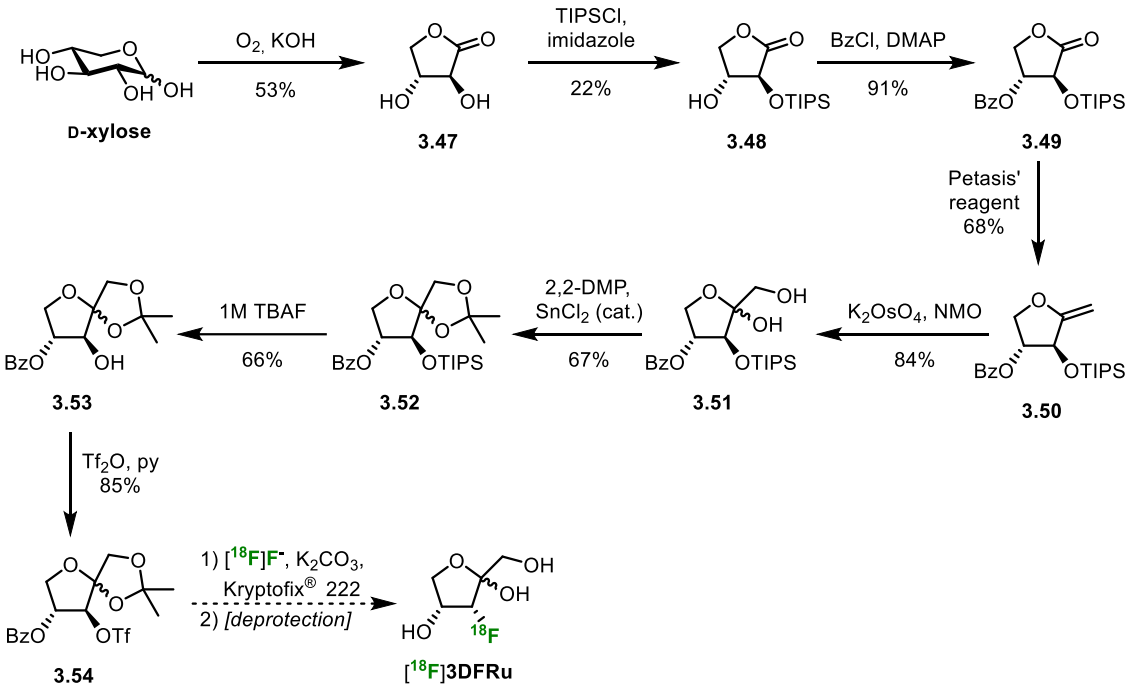


Scheme 58: Final deprotection of **3.44** giving 3-deoxy-3-fluoro-D-ribulose (**3DFRu**) as a mixture of α- and β-furanoses and open-chain conformation.

3DFRu was obtained in an overall yield of 1% over 10-steps.

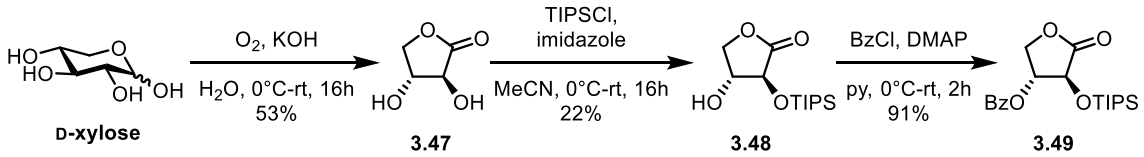
3.3.2 Synthesis of a Potential Radiolabeling Precursor for [^{18}F]3DFRu

The final synthesis of 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (**3.54**) is summarized in Scheme 59 and will be discussed in detail in the following chapter.



Scheme 59: Synthesis of 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (**3.54**) from D-xylose. Dashed arrows indicate experiments that have not been performed yet.

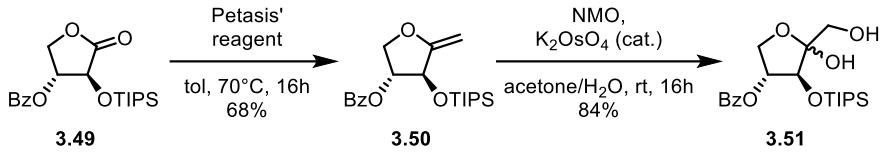
The used reaction sequence for a potential radiolabeling precursor for [^{18}F]**3DFRu** started with a known Spengler-Pfannenstiel oxidation of D-xylose to give D-*threono*-1,4-lactone (**3.47**) in a moderate yield of 53% (Scheme 60).[135,136] Selective protection at position 2 with chlorotriisopropylsilane and imidazole gave mono-protected lactone **3.48** in a poor yield of 22%.[137] This can be explained by the anti-orientation of the two hydroxyl groups not providing enough steric hindrance to avoid di-protection.



Scheme 60: Three-step synthesis of 3-*O*-benzoyl-2-*O*-triisopropylsilyl-D-*threono*-1,4-lactone (**3.49**) from D-xylose.

Subsequent benzoylation of **3.48** under standard conditions furnished fully protected lactone **3.49** in 91% yield which then underwent the above described methylenation

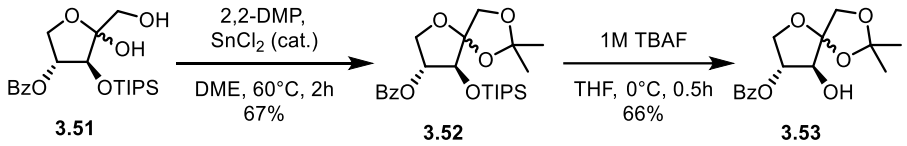
and dihydroxylation protocol to give xylulose **3.51** in 57% yield over 2 steps (Scheme 61).



Scheme 61: Methylenation of **3.49** and subsequent dihydroxylation of **3.50** yielding xylulose **3.51**.

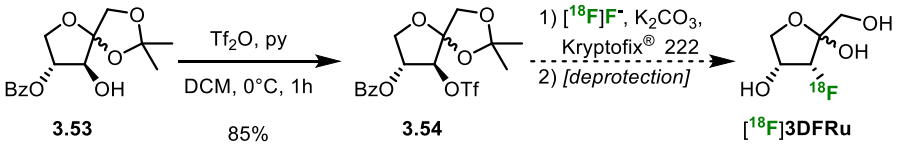
Here, the TIPS-ether was crucial since TES, TBS and even TBDPS groups migrated to position 1 after the dihydroxylation (data not shown).

Protection of the diol with 2,2-dimethoxypropane under Lewis acid catalysis gave fully protected pentulose **3.52** in a moderate yield of 67% (Scheme 62).[138] The silyl-ether at position 3 was then removed with TBAF in THF at 0°C to give compound **3.53**.[139]



Scheme 62: Isopropylidene protection of diol **3.51** and silyl-ether removal giving xylulose **3.53**.

Triflation of position 3 worked smoothly with triflic anhydride and pyridine in DCM at 0°C within 1 hour (Scheme 63).[140] Triflate **3.54** might serve as a precursor for radio-fluorinations with fluoride-18 to access [^{18}F]**3DFRu** after deprotection.



Scheme 63: Triflation of **3.53** giving potential radiolabeling precursor **3.54**. Dashed arrows indicate experiments that have not been performed yet.

The overall yield of 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (**3.54**) was 2% over 8 steps.

4 Summary & Outlook

The first synthesis of 4-deoxy-4-fluoro-D-sedoheptulose was achieved: key steps in the synthetic route involved the installation of the fluorine atom via an epoxide opening approach as reported by Yan *et al.*[60] and the C-1 methylenation and dihydroxylation approach published by Waschke *et al*.[96] **4DFS** was taken up by human fibroblasts and was phosphorylated by SHPK. Furthermore, **4DFS** was no substrate for transaldolase or transketolase making it a promising new sugar to apply the principle of metabolic trapping for biomedical imaging purposes. Additionally, potential radiolabeling precursors for [^{18}F]**4DFS** were synthesized, one of which is currently undergoing first radiolabeling experiments with fluorine-18 at the Department of Biomedical Imaging and Image-guided Therapy (Medical University of Vienna).

Furthermore, synthetic routes to access 1-deoxy-1-fluoro-D-ribulose and 3-deoxy-3-fluoro-D-ribulose were developed. Future biochemical experiments will reveal if the fluorinated pentuloses are taken up by cells, phosphorylated by ribulokinase and if the chosen fluorination site effectively halts the enzymatic degradation by ribose-5-phosphate isomerase and ribulose-5-phosphate epimerase. Nevertheless, syntheses for potential radiolabeling precursors for [^{18}F]**1DFRu** and [^{18}F]**3DFRu** were already developed.

5 Experimental Section

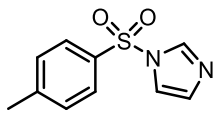
5.1 Synthetic Chemistry

General Experimental Details

All chemicals and solvents were purchased from commercial vendors and used without further purification unless stated. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on either a Bruker AV III HD 700 (^{1}H: 700.40 MHz, ^{13}C: 176.12 MHz, ^{19}F: 659.03 MHz), AV III 600 (^{1}H: 600.25 MHz, ^{13}C: 150.93 MHz, ^{19}F: 564.80 MHz), AV NEO 500 (^{1}H: 500.32 MHz, ^{13}C: 125.81 MHz) or AV NEO 400 (^{1}H: 400.27 MHz, ^{13}C: 100.65 MHz, ^{19}F: 377 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and were referenced to residual solvent signals for proton NMR spectra: $CDCl_3$: δ_H ($CHCl_3$) 7.26 ppm, *d_6*-DMSO: δ_H [$(CD_2H)SO(CD_3)$] 2.50 ppm, *d_4*-MeOH: δ_H (CHD_2OD) 3.31 ppm and D_2O: δ_H (H_2O) 4.79 ppm , ^{13}C NMR spectra were referenced to $CDCl_3$ (δ_C 77.16 ppm), *d_6*-DMSO (δ_C 39.52 ppm) or *d_4*-MeOH (δ_C 49.00 ppm). ^{13}C NMR spectra in D_2O were referenced indirectly to the ^{1}H NMR frequency of the sample with the ”xiref”-command in Bruker Topspin. External CCl_3F (δ_F 0.00) served as reference for ^{19}F NMR spectra. Coupling constants (*J*) are given in Hz. Signal multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet). High resolution mass spectra (HRMS) were recorded on a Bruker maXis ultrahigh resolution - time-of-flight (UHR-TOF) instrument with electrospray ionization (ESI) in positive ion mode. Optical rotations were measured on a Schmidt-Haensch Digital Polarimeter Unipol L 2000 and are given in 10^{-1} deg cm^2 g^{-1}. Chromatographic separations (MPLC) were carried out on a Biotage Isolera Prime (Biotage, Uppsala, Sweden) flash purification system using Macherey-Nagel silica gel 60 (0.04-0.063 mm) in self-packed cartridges. Thin layer chromatography (TLC) was carried out on precoated Macherey-Nagel ALUGRAM Xtra SIL G UV254 aluminum plates. Compounds were visualized with ultra-violet light (254 nm) and/or by treatment with one of the following staining reagents followed by heating: Cerium ammonium molybdate solution(CAM, 46 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 2 g $Ce(SO_4)_2\cdot 4H_2O$) in 1 L 10% (w/w) aq. H_2SO_4), $KMnO_4$ solution (9 g $KMnO_4$ and 60 g K_2CO_3 in 900 mL H_2O and 15 mL 5% (w/w) aq. NaOH) or vanillin solution (60 g vanillin in 1 L EtOH and 10 mL conc. H_2SO_4).

5.1.1 Synthesis of 4-Deoxy-4-fluoro-D-sedoheptulose (4DFS)

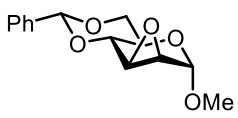
5.1.1.1 1-(*para*-Toluenesulfonyl)imidazole (*p*-TsIm)



***p*-TsIm**
$C_{10}H_{10}N_2O_2S$
222.26 g/mol

para-Toluenesulfonylchloride (3.000 g, 15.74 mmol, 1 equiv.) was dissolved in dry DCM (11 mL) and added dropwise to a solution of imidazole (2.464 g, 36.19 mmol, 2.3 eq) in dry DCM (11 mL) at 0 °C under argon. After the addition was complete the reaction mixture was stirred at room temperature for 2.5 h. The suspension was filtered through a pad of silica and eluted with a 1:1 mixture (v/v) of EA and cyclohexane (38 mL). The filtrate was concentrated and dissolved in EA (1.8 mL) and cyclohexane (18 mL). Precipitation was induced by sonication and storage over 2 days at 4°C. Filtration of the product yielded 1-(*para*-toluenesulfonyl)imidazole as a white solid (3.000 g, 86%). R_f = 0.4 (*n*-heptane/EA 1:1, UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.00 (s, 1H, H^{imid}), 7.82 (d, $^3J_{H,H}$ = 8.4 Hz, 2H, H^{Ar}), 7.35 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, H^{Ar}), 7.28 (t, *J* = 1.4 Hz, 1H, H^{imid}), 7.07 (bs, 1H, H^{imid}), 2.43 (s, 1H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 146.45 (C^{Ar}), 136.78 (CH^{imid}), 135.10 (C^{Ar}), 131.56 (CH^{imid}), 130.56 (2 CH^{Ar}), 127.50 (2 CH^{Ar}), 117.55 (CH-imid.), 21.85 (CH_3). HRMS (ESI+): *m/z* calc. for $C_{10}H_{11}N_2O_2S^+$ $[M+H]^+$: 223.0536, found: 223.0541.

5.1.1.2 Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-*manno*-pyranoside (3.1)

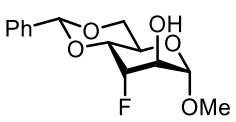


3.1
$C_{14}H_{16}O_5$
264.28 g/mol

Methyl 4,6-*O*-benzylidene-α-D-*gluco*-pyranoside (**3.0**, 97% purity, 5.000 g, 17.18 mmol. 1 equiv.) was dissolved in dry DMF (100 mL) under argon. A suspension of sodium hydride (90% purity, 1.054 g, 39.52 mmol, 2.3 equiv.) in dry DMF (200 mL) was added dropwise and the reaction mixture was stirred at room temperature for 45 min. 1-(*para*-Toluenesulfonyl)imidazole (4.010 g, 18.04 mmol, 1.05 equiv.), dissolved in dry DMF (140 mL), was added dropwise via a syringe pump over 2 h. After the addition was completed the reaction mixture was stirred at room temperature for 1 h. The reaction was poured into ice-cold H_2O (850 mL) with stirring. The white precipitate was collected by filtration, washed once with cold H_2O and dried under high vacuum. The mother liquor was combined with the filtrate of the wash and extracted thrice with EA. The combined organic layers were washed twice with water and once with brine, dried over $MgSO_4$, filtered and evaporated yielding a white solid. The combined crude solids were purified by recrystallization from methanol to give 3.284 g of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-*manno*-pyranoside (**3.1**) as white needles. The mother liquor of

the recrystallization was evaporated and the remaining solid was recrystallized again from methanol to give another 726 mg of white needles (combined yield: 4.010 g, 88%). R_f = 0.29 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = +100.2 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.51-7.49 (m, 2H, H^{Ar}), 7.41-7.37 (m, 3H, H^{Ar}), 5.57 (s, 1H, H^{Bn}), 4.90 (s, 1H, H-1), 4.29-4.24 (m, 1H, H-6a), 3.75-3.67 (m, 3H, H-4, H-5 & H-6b), 3.48 (d, $^3J_{3,2}$ = 3.7 Hz, 1H, H-3), 3.47 (s, 3H, OCH_3), 3.17 (d, $^3J_{2,3}$ = 3.6 Hz, 1H, H-2). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 137.21 (C^{Ar}), 129.45 (CH^{Ar}), 128.54 (2 CH^{Ar}), 126.34 (2 CH^{Ar}), 102.61 (CH^{Bn}), 97.05 (C-1), 75.05 (C-4), 69.59 (C-6), 61.83 (C-5), 55.94 (OCH_3), 54.00 (C-3), 50.72 (C-2). HRMS (ESI+): *m/z* calc. for $C_{14}H_{16}O_5Na^+$ $[M+Na]^+$: 287.0890, found: 287.0889.

5.1.1.3 Methyl 4,6-*O*-benzylidene-3-deoxy-3-fluoro-α-D-*altro*-pyranoside (3.2)

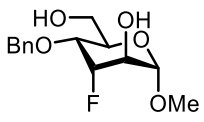


3.2
$C_{14}H_{17}FO_5$
284.28 g/mol

Tetrabutylammonium fluoride trihydrate (23.313 g, 73.83 mmol, 8 equiv.) and KHF_2 (2.886 g, 36.95 mmol, 4 equiv.) were added to 2,3-anhydro-4,6-*O*-benzylidene-α-D-*manno*-pyranoside (**3.1**, 2.441 g, 9.24 mmol, 1 equiv.) in a PFA-flask. The flask was flushed with argon, sealed with a septum and an argon balloon was inserted. The reaction mixture was stirred at 130°C for 3 h (reagents began to melt at 70°C). The brown liquid was then cooled to room temperature and diluted with EA (80 mL) and water (20 mL) and neutralized by the addition of sat. aq. $NaHCO_3$-solution (140 mL). The layers were separated and the aqueous layer was extracted thrice with EA. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (50 g silica gel, 5-40% EA in *n*-heptane) to give methyl 4,6-*O*-benzylidene-3-deoxy-3-fluoro-α-D-*altro*-pyranoside as a white solid (**3.2**, 1.990 g, 76%). R_f = 0.10 (*n*-heptane/EA 4:1, UV & CAM). $[\alpha]_D^{20}$ = +110.7 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.52-7.49 (m, 2H, H^{Ar}), 7.39-7.34 (m, 3H, H^{Ar}), 5.61 (s, 1H, H^{Bn}), 4.86 (dt, $^2J_{3,F}$ = 49.8 Hz, $^3J_{3,2}$ = 3.2 Hz, $^3J_{3,4}$ = 2.6 Hz, 1H, H-3), 4.67 (s, 1H, H-1), 4.36 (dd, $^2J_{6a,6b}$ = 10.1 Hz, $^3J_{6a,5}$ = 5.3 Hz, 1H, H-6a), 4.31 (td, $^3J_{5,4}$ = $^3J_{5,6b}$ = 10.1 Hz, $^3J_{5,6a}$ = 5.3 Hz, 1H, H-5), 4.15 (td, $^3J_{2,OH}$ = $^3J_{2,F}$ = 6.2 Hz, $^3J_{2,3}$ = 3.2 Hz, 1H, H-2), 3.99 (ddd, $^3J_{4,F}$ = 30.2 Hz, $^3J_{4,5}$ = 9.7, $^3J_{4,3}$ = 2.6 Hz, 1H, H-4), 3.80 (td, $^2J_{6b,6a}$ = $^3J_{6b,5}$ = 10.1 Hz, $^5J_{6b,F}$ =1.0 Hz, 1H, H-6b), 3.44 (s, 3H, OCH_3), 1.96 (d, $^3J_{OH,2}$ = 6.2 Hz, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.25 (C^{Ar}), 129.41 (CH^{Ar}), 128.50 (2 CH^{Ar}), 126.45 (2 CH^{Ar}), 102.76 (CH^{Bn}), 101.58 (C-1), 87.10 (d, $^1J_{3,F}$ = 185.6 Hz, C-3), 74.99 (d, $^2J_{4,F}$ = 16.6 Hz, C-4), 69.36 (C-6), 69.29 (d,

$^{2}J_{2,F}$ = 26.5 Hz, C-2), 58.53 (d, $^{3}J_{5,F}$ = 3.1 Hz, C-5), 55.82 (OCH_3). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -205.71 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -205.71 (ddd, $^{2}J_{F,3}$ = 49.8 Hz, $^{3}J_{F,4}$ = 30.2 Hz, $^{3}J_{F,2}$ = 6.2 Hz). HRMS (ESI+): *m/z* calc. for $C_{14}H_{17}FO_5Na^+$ $[M+Na]^+$: 307.0952, found: 307.0964.

5.1.1.4 Methyl 4-*O*-benzyl-3-deoxy-3-fluoro-α-D-*altro*-pyranoside (3.3)

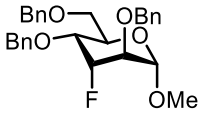


3.3
$C_{14}H_{19}FO_5$
286.30 g/mol

Borane THF complex (1 M in THF, 52 mL, 52.00 mmol, 5 equiv.) was slowly added to methyl 4,6-*O*-benzylidene-3-deoxy-3-fluoro-α-D-*altro*-pyranoside (**3.2**, 2.956 g, 10.40 mmol, 1 equiv.) under argon and the reaction mixture was stirred at room temperature for 10 min. $Cu(OTf)_2$ (376 mg, 1.04 mmol, 0.1 equiv.) was added and stirring was continued for 1.5 h. The black suspension was then cooled to 0°C and triethylamine (1.052 g, 1.45 mL, 1.04 mmol, 1 equiv.) was added dropwise followed by methanol (36 mL). The mixture was warmed to room temperature and co-evaporated thrice with methanol. The crude residue was purified by MPLC (100 g silica gel, 20-100% EA in *n*-heptane) to give methyl 4-*O*-benzyl-3-deoxy-3-fluoro-α-D-*altro*-pyranoside as a colorless oil (**3.3**, 2.950 g, 99%). R_f = 0.34 (*n*-heptane/EA 1:3, UV & vanillin). $[\alpha]_D^{20}$ = +106.1 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.38-7.33 (m, 4H, H^{Ar}), 7.33-7.29 (m, 1H, H^{Ar}), 4.86 (dt, $^{2}J_{3,F}$ = 49.1 Hz, $^{3}J_{3,2}$ = $^{3}J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.73 (d, $^{2}J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.65 (s, 1H, H-1), 4.58 (d, $^{2}J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.09-4.04 (m, 2H, H-2 & H-5), 3.84 (ddd, $^{3}J_{4,F}$ = 27.2 Hz, $^{3}J_{4,5}$ = 9.8 Hz, $^{3}J_{4,3}$ = 2.9 Hz, 1H, H-4), 3.85-3.82 (m, 2H, H-6a & H-6b), 3.40 (s, 3H, OCH_3), 2.36 (d, $^{3}J_{OH,2}$ = 7.2 Hz, 1H, OH-2), 1.97 (dd, $^{3}J_{OH,6a\ or\ 6b}$ = 6.6 Hz, $^{3}J_{OH,6a\ or\ 6b}$ = 6.0 Hz, 1H, OH-6). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.71 (C^{Ar}), 128.69 (2 CH^{Ar}), 128.21 (CH^{Ar}), 128.14 (2 CH^{Ar}), 101.30 (C-1), 87.03 (d, $^{1}J_{3,F}$ = 183.8 Hz, C-3), 71.54 (CH_2^{Bn}) 70.25 (d, $^{2}J_{4,F}$ = 16.8 Hz, C-4), 68.98 (d, $^{2}J_{2,F}$ = 25.3 Hz, C-2), 67.26 (d, $^{3}J_{5,F}$ = 2.9 Hz, C-5), 62.19 (C-6), 55.74 (OCH_3). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -207.40 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -207.39 (ddd, $^{2}J_{F,3}$ = 49.1 Hz, $^{3}J_{F,4}$ = 27.2 Hz, $^{3}J_{F,2}$ = 6.5 Hz). HRMS (ESI+): *m/z* calc. for $C_{14}H_{19}FO_5Na^+$ $[M+Na]^+$: 309.1109, found: 309.1115.

5.1.1.5 Methyl 2,4,6-tri-*O*-benzyl-3-deoxy-3-fluoro-α-D-*altro*-pyranoside (3.4)

Methyl 4-*O*-benzyl-3-deoxy-3-fluoro-α-D-*altro*-pyranoside (**3.3**, 2.925 g, 10.22 mmol, 1 equiv.) was dissolved in dry DMF (29 mL) under argon and cooled to 0°C. Sodium hydride (90% purity, 817 mg, 30.65 mmol, 3 equiv.) was added in small portions and

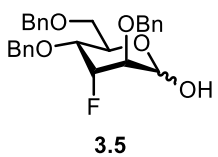


3.4
$C_{28}H_{31}FO_5$
466.55 g/mol

the reaction mixture was stirred at 0°C for 30 min. Benzyl bromide (5.242 g, 3.6 mL, 30.65 mmol, 3 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched by the dropwise addition of methanol (45 mL) at 0°C, followed by water (45 mL) and EA (45 mL). After the reaction mixture reached room temperature the layers were separated and the aq. layer was extracted twice with EA. The combined org. layers were washed twice with water and once with brine. The org. layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 5-31% EA in *n*-heptane) to give methyl 2,4,6-tri-*O*-benzyl-3-deoxy-3-fluoro-α-D-*altro*-pyranoside as a colorless oil (**3.4**, 3.824 g, 80%). R_f = 0.26 (*n*-heptane/EA 4:1, UV & CAM). $[\alpha]_D^{20}$ = +47.9 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.36-7.26 (m, 15H, 15 H^{Ar}), 4.79 (dt, $^2J_{3,F}$ = 49.1 Hz, $^3J_{3,2}$ = 3.1 Hz, $^3J_{3,4}$ = 2.7 Hz, 1H, H-3), 4.74 (s, 1H, H-1), 4.67 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.65 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.61 (d, $^2J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.55 (d, $^2J_{H,H}$ = 11.4 Hz, 1H, H^{Bn}), 4.53 (d, $^2J_{H,H}$ = 11.4 Hz, 1H, H^{Bn}), 4.51 (d, $^2J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.15 (ddd, $^3J_{5,4}$ = 9.4 Hz, $^3J_{5,6a}$ = 4.0 Hz, $^3J_{5,6b}$ = 2.6 Hz, 1H, H-5), 3.90 (ddd, $^3J_{4,F}$ = 27.1 Hz, $^3J_{4,5}$ = 9.4 Hz, $^3J_{4,3}$ = 2.7 Hz, 1H, H-4), 3.78 (dd, $^3J_{2,F}$ = 7.4 Hz, $^3J_{2,3}$ = 3.1 Hz, 1H, H-2), 3.76 (dd, $^2J_{6a,6b}$ = 10.9 Hz, $^3J_{6a,5}$ = 4.0 Hz, 1H, H-6a), 3.73 (dd, $^2J_{6b,6a}$ = 10.9 Hz, $^3J_{6b,6a}$ = 2.6 Hz, 1H, H-6b), 3.39 (s, 3H, OCH_3). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 138.42 (C^{Ar}), 137.99 (C^{Ar}), 137.57 (C^{Ar}), 128.66 (2 CH^{Ar}), 128.52 (2 CH^{Ar}), 128.46 (2 CH^{Ar}), 128.18 (CH^{Ar}), 128.09 (2 CH^{Ar}), 127.95 (2 CH^{Ar}), 127.94 (CH^{Ar}), 127.88 (2 CH^{Ar}), 127.68 (CH^{Ar}), 99.51 (C-1), 86.56 (d, $^1J_{3,F}$ = 183.1 Hz, C-3), 75.74 (d, $^2J_{2,F}$ = 24.5 Hz, C-2), 73.65 (CH_2^{Bn}), 72.94 (CH_2^{Bn}), 71.82 (CH_2^{Bn}), 71.41 (d, $^2J_{4,F}$ = 16.6 Hz, C-4), 69.34 (C-6), 67.01 (d, $^3J_{5,F}$ = 3.8 Hz, C-5), 55.51 (OCH_3). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -207.65 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -207.65 (ddd, $^2J_{F,3}$ = 49.1 Hz, $^3J_{F,4}$ = 27.1 Hz, $^3J_{F,2}$ = 7.8 Hz). HRMS (ESI+): *m/z* calc. for $C_{28}H_{31}FO_5Na^+$ $[M+Na]^+$: 489.2048, found: 489.2051.

5.1.1.6 2,4,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-D-altrose (3.5)

Methyl 2,4,6-tri-*O*-benzyl-3-deoxy-3-fluoro-α-D-*altro*-pyranoside (**3.4**, 3.804 g, 8.15 mmol, 1 equiv.) was dissolved in acetic acid (82 mL) and 1 M aq. H_2SO_4 (18.5 mL, 81.53 mmol, 10 equiv.) was added dropwise under stirring. The flask was equipped with a reflux condenser, heated to 100°C and stirred for 15 h. The reaction was cooled



3.5
$C_{27}H_{29}FO_5$
452.52 g/mol

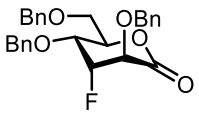
to room temperature and ice-cold water (300 mL) was slowly added. The mixture was extracted thrice with DCM and the combined org. layers were washed twice with sat. aq. $NaHCO_3$-sol. and once with brine. The org. layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 0-4% EA in DCM) to give 2,4,6-tri-*O*-benzyl-3-deoxy-3-fluoro-D-altrose as a colorless oil and as a mixture of anomers (**3.5**, α/β = 1:4, 1.770 g, 48%). R_f = 0.14 (*n*-heptane/EA 4:1, UV & CAM). $[\alpha]_D^{20}$ = +21.5 (c 1.0, $CHCl_3$).

β-Pyranose: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.39-7.22 (m, 15H, H^{Ar}), 5.01 (dt, $^3J_{1,OH}$ = 11.7 Hz, $^3J_{1,2}$ = $^4J_{1,F}$ = 2.0 Hz, 1H, H-1), 4.74 (ddd, $^2J_{3,F}$ = 48.7 Hz, $^3J_{3,2}$ = 4.0 Hz, $^3J_{3,4}$ = 2.2 Hz, 1H, H-3), 4.68 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.64 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.56 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, H^{Bn}), 4.54 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, H^{Bn}), 4,47 (s, 2H, CH_2^{Bn}), 3.94 (dd, $^3J_{5,4}$ = 9.5 Hz, $^3J_{5,6}$ = 1.5 Hz 1H, H-5), 3.86 (ddd, $^3J_{4,F}$ = 29.0 Hz, $^3J_{4,5}$ = 9.5 Hz, $^3J_{4,3}$ = 2.2 Hz, 1H, H-4), 3.77-3.70 (m, 3H, H-2, H-6a & H-6b), 3.57 (d, $^3J_{1,OH}$ = 11.7 Hz, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.30 (C^{Ar}), 137.71 (C^{Ar}), 137.23 (C^{Ar}), 128.90 (2 CH^{Ar}), 128.62 (CH^{Ar}), 128.60 (2 CH^{Ar}), 128.48 (2 CH^{Ar}), 128.30 (2 CH^{Ar}), 128.24 (2 CH^{Ar}), 128.12 (CH^{Ar}), 128.09 (2 CH^{Ar}), 127.75 (CH^{Ar}), 91.89 (C-1), 86.77 (d, $^1J_{3,F}$ = 178.7 Hz, C-3), 76.05 (d, $^2J_{2,F}$ = 25.9 Hz, C-2), 74.10 (CH_2^{Bn}), 73.78 (CH_2^{Bn}), 72.37 (d, $^3J_{5,F}$ = 3.6 Hz, C-5), 72.15 (CH_2^{Bn}), 71.20 (d, $^2J_{4,F}$ = 16.5 Hz, C-4), 69.15 (C-6). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -209.84 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -209.84 (dddd, $^2J_{F,3}$ = 48.7 Hz, $^3J_{F,4}$ = 29.1 Hz, $^3J_{F,2}$ = $^4J_{F,1}$ = 2.2 Hz).

α-Pyranose: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.38-7.22 (m, 15H, H^{Ar}), 5.20 (d, $^3J_{1,OH}$ = 7.9 Hz, 1H, H-1), 4.84 (ddd, $^2J_{3,F}$ = 49.3 Hz, $^3J_{3,2}$ = 4.0 Hz, $^3J_{3,4}$ = 2.6 Hz, 1H, H-3), 4.68 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.64 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.60 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.56 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.54 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.53 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.28 (dt, $^3J_{5,4}$ = 8.6 Hz, $^3J_{5,6a}$ = $^3J_{5,6b}$ = 4.2 Hz, 1H, H-5), 3.94 (ddd, $^3J_{4,F}$ = 27.1 Hz, $^3J_{4,5}$ = 8.6 Hz, $^3J_{4,3}$ = 2.6 Hz, 1H, H-4), 3.82 (ddd, $^3J_{2,F}$ = 8.0 Hz, $^3J_{2,3}$ = 4.0 Hz, $^3J_{2,1}$ = 0.9 Hz, 1H, H-2), 3.77-3.69 (m, 2H, H-6a & H-6b), 3.27 (dd, $^3J_{OH,1}$ = 7.9 Hz, $J_{OH,F}$ = 5.2 Hz, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.26 (C^{Ar}), 137.68 (C^{Ar}), 137.43 (C^{Ar}), 128.70 (2 CH^{Ar}), 128.62 (CH^{Ar}), 128.60 (2 CH^{Ar}), 128.50 (2 CH^{Ar}), 128.24 (CH^{Ar}), 128.17 (2 CH^{Ar}), 128.01 (2 CH^{Ar}), 127.95 (2 CH^{Ar}), 127.77 (CH^{Ar}), 93.29 (C-1), 88.40 (d, $^1J_{3,F}$ = 179.2 Hz, C-3), 75.94 (d, $^2J_{2,F}$ = 22.5 Hz, C-2), 73.73 (CH_2^{Bn}), 72.80 (CH_2^{Bn}), 72.20 (CH_2^{Bn}), 71.60 (d, $^2J_{4,F}$ = 16.4 Hz, C-4), 69.35 (C-6), 67.80 (d, $^3J_{5,F}$ = 4.4 Hz, C-5). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -205.48 (s).

^{19}F NMR (659 MHz, $CDCl_3$) δ = -205.48 (dddd, $^2J_{F,3}$ = 49.3 Hz, $^3J_{F,4}$ = 27.3 Hz, $^3J_{F,2}$ = 7.0 Hz, $J_{F,OH}$ = 5.2 Hz). HRMS (ESI+): *m/z* calc. for $C_{27}H_{29}FO_5Na^+$ [M+Na]$^+$: 475.1891, found: 475.1881.

5.1.1.7 2,4,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-D-*altrono*-1,5-lactone (3.6)



3.6
$C_{27}H_{27}FO_5$
450.51 g/mol

2,4,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-D-altrose (**3.5**, 1.745 g, 3.86 mmol, 1 equiv.) was dissolved in dry DCM (45 mL) under argon. Dess-Martin-Periodinane (3.271 g, 7.99 mmol, 2 equiv.) was added and the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of a sat. aq. $NaHCO_3$-sol. (160 mL) and a sat. aq. $Na_2S_2O_3$-sol. (160 mL). The mixture was extracted thrice with DCM and the combined org. layers were dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 4-40% EA in *n*-heptane) to give 2,4,6-tri-*O*-benzyl-3-deoxy-3-fluoro-D-*altrono*-1,5-lactone as a colorless oil (**3.6**, 1.663 g, 96%). R_f = 0.34 (*n*-heptane/EA 4:1, UV & CAM). $[\alpha]_D^{20}$ = -25.2 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.41-7.26 (m, 15H, H^{Ar}), 5.14 (ddd, $^2J_{3,F}$ = 49.8 Hz, $^3J_{3,2}$ = 7.5 Hz, $^3J_{3,4}$ = 3.1 Hz, 1H, H-3), 5.04 (d, $^2J_{H,H}$ = 11.5 Hz, 1H, H^{Bn}), 4.74 (d, $^2J_{H,H}$ = 11.5 Hz, 1H, H^{Bn}), 4.74 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.62 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.58 (d, $^2J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.58 (m, 1H, H-5), 4.48 (d, $^2J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.44 (dd, $^3J_{2,F}$ = 14.5 Hz, $^3J_{2,3}$ = 7.5 Hz, 1H, H-2), 4.17 (ddd, $^3J_{4,F}$ = 14.0 Hz, $^3J_{4,5}$ = 4.2 Hz, $^3J_{4,3}$ = 3.1 Hz, 1H, H-4), 3.67 (dd, $^2J_{6a,6b}$ = 11.0 Hz, $^3J_{6a,5}$ = 3.8 Hz, 1H, H-6a), 3.64 (dd, $^2J_{6b,6a}$ = 11.9 Hz, $^3J_{6b,5}$ = 2.7 Hz, 1H, H-6b). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.51 (d, $^3J_{1,F}$ = 10.4 Hz, C-1), 137.23 (C^{Ar}), 137.16 (2 C^{Ar}), 128.71 (2 CH^{Ar}), 128.67 (2 CH^{Ar}), 128.58 (2 CH^{Ar}), 128.39 (2 CH^{Ar}), 128.33 (CH^{Ar}), 128.19 (CH^{Ar}), 128.10 (3 CH^{Ar}), 127.90 (2 CH^{Ar}), 88.84 (d, $^1J_{3,F}$ = 186.5 Hz, C-3), 78.17 (d, $^3J_{5,F}$ = 6.5 Hz, C-5), 74.83 (d, $^2J_{2,F}$ = 24.3 Hz, C-2), 74.05 (CH_2^{Bn}), 73.94 (CH_2^{Bn}), 73.34 (CH_2^{Bn}), 73.30 (d, $^2J_{4,F}$ = 17.3 Hz, C-4), 68.81 (C-6). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -199.38 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -199.38 (dt, $^2J_{F,3}$ = 49.8 Hz, $^3J_{F,2}$ = 14.5 Hz, $^3J_{F,4}$ = 14.0 Hz). HRMS (ESI+): *m/z* calc. for $C_{27}H_{27}FO_5Na^+$ [M+Na]$^+$: 473.1735, found: 473.1739.

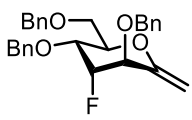
5.1.1.8 Bis(cyclopentadienyl)dimethyltitanium (Petasis' reagent)

This reaction is light sensitive and was carried out in the dark. Bis(cyclopentadienyl)titanium dichloride (3.500 g, 14.06 mmol, 1 equiv.) was suspended in dry Et_2O (70 mL) in a flame-dried flask under argon and cooled to 10°C.

Petasis' reagent
$C_{12}H_{16}Ti$
208.13 g/mol

Methyl lithium (1.6 M in Et_2O, 21 mL, 33.74 mmol, 2.4 equiv.) was added dropwise and the reaction mixture was stirred at room temperature for 15 min. The reaction was quenched by the drop-wise addition of ice-cold H_2O (30 mL) at 0°C. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, evaporated at 25°C to give bis(cyclopentadienyl)dimethyltitanium as an orange solid (2.900 g, 99%). The product was stored as a 0.5 M solution in dry toluene under argon at -20°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.06 (s, 10H, Cp-CH), -0.15 (s, 6H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 113.23 (10 CH^{Cp}), 45.61 (2 CH_3).

5.1.1.9 2,6-Anhydro-3,5,7-tri-*O*-benzyl-1,4-dideoxy-4-fluoro-D-*altro*-hept-1-enitol (3.7)

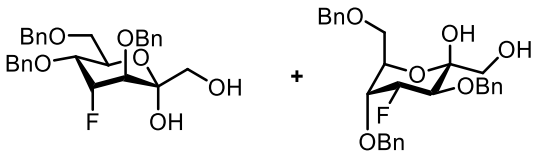


3.7
$C_{28}H_{29}FO_4$
448.53 g/mol

2,4,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-D-*altrono*-1,5-lactone (**3.6**, 1.639 g, 3.64 mmol, 1 equiv.) was dissolved in dry toluene (18 mL) under argon and the flask was wrapped in aluminum foil. Bis(cyclopentadienyl)dimethyltitanium (0.5 M in dry toluene, 18 mL, 9.10 mmol, 2.5 equiv.) was added dropwise and the flask was equipped with a reflux condenser. The mixture was stirred at 70°C for 16 h before being cooled to room temperature. The dark red solution was diluted with *n*-heptane (60 mL) and stirring was continued for 30 min. The orange suspension was filtered through a pad of Celite® and the filtrate was evaporated. The crude residue was purified by MPLC (100 g silica gel, 2-20% EA in *n*-heptane) to give 2,6-anhydro-3,5,7-tri-*O*-benzyl-1,4-dideoxy-4-fluoro-D-*altro*-hept-1-enitol as an orange oil (**3.7**, 1.215 g, 74%). R_f = 0.32 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = +48.0 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.36-7.26 (m, 15H, H^{Ar}), 4.95 (s, 1H, H-1a), 4.91 (ddd, $^2J_{4,F}$ = 50.6 Hz, $^3J_{4,3}$ = 4.6 Hz, $^3J_{4,5}$ = 2.1 Hz, 1H, H-4), 4.70 (d, $^2J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.69 (d, $^2J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.66 (d, $^2J_{H,H}$ = 11.5 Hz, 1H, H^{Bn}), 4.56 (s, 1H, H-1b), 4.55 (d, $^2J_{H,H}$ = 11.5 Hz, 1H, H^{Bn}), 4.54 (d, $^2J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.37 (d, $^2J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.17 (ddd, $^3J_{5,F}$ = 28.4 Hz, $^3J_{5,6}$ = 9.5 Hz, $^3J_{5,4}$ = 2.1 Hz, 1H, H-5), 4.10 (dd, $^3J_{3,F}$ = 5.7 Hz, $^3J_{3,4}$ = 4.6 Hz, 1H, H-3), 4.06 (ddd, $^3J_{6,5}$ = 9.5 Hz, $^3J_{6,7a}$ = 3.7 Hz, $^3J_{6,7b}$ = 2.5 Hz, 1H, H-6), 3.82 (dd, $^2J_{7a,7b}$ = 11.1 Hz, $^3J_{7a,6}$ = 3.7 Hz, 1H, H-7a), 3.79 (dd, $^2J_{7b,7a}$ = 11.1 Hz, $^3J_{7b,6}$ = 2.5 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 153.32 (C-2), 138.38 (C^{Ar}), 137.77 (C^{Ar}), 137.71 (C^{Ar}), 128.57 (2 CH^{Ar}), 128.55 (2 CH^{Ar}), 128.48 (2 CH^{Ar}),

128.10 (2 CH^{Ar}), 128.01 (CH^{Ar}), 127.95 (2 CH^{Ar}), 127.93 (CH^{Ar}), 127.88 (2 CH^{Ar}), 127.70 (CH^{Ar}), 101.91 (C-1), 87.02 (d, $^{1}J_{4,F}$ = 178.1 Hz, C-4), 76.34 (d, $^{3}J_{6,F}$ = 3.0 Hz, C-6), 75.25 (d, $^{2}J_{3,F}$ = 28.6 Hz, C-3), 73.67 (CH_2^{Bn}), 72.14 (CH_2^{Bn}), 71.16 (d, $^{2}J_{5,F}$ = 16.6 Hz, C-5), 70.06 (CH_2^{Bn}), 69.24 (C-7). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -206.16 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -206.16 (ddd, $^{2}J_{F,4}$ = 50.6 Hz, $^{3}J_{F,5}$ = 28.4 Hz, $^{3}J_{F,3}$ = 5.3 Hz). HRMS (ESI+): *m/z* calc. for $C_{28}H_{29}FO_4Na^+$ $[M+H_2O+Na]^+$: 471.1942, found: 471.1936.

5.1.1.10 3,5,7-Tri-*O*-benzyl-4-deoxy-4-fluoro-D-*glycero*-D-*arabino*-hept-2-ulopyranose (3.8)



3.8
$C_{28}H_{31}FO_6$
482.55 g/mol

2,6-Anhydro-3,5,7-tri-*O*-benzyl-1,4-dideoxy-4-fluoro-D-*altro*-hept-1-enitol (**3.7**, 1.202 g, 2.68 mmol, 1 equiv.) was dissolved in a 4:1 (v/v) mixture of acetone and water (54 mL) and *N*-methylmorpholine-*N*-oxide (628 mg, 5.36 mmol, 2 equiv.) and potassium osmate dihydrate (49 mg, 0.13 mmol, 0.05 equiv.) were added. The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with EA and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 12-84% EA in *n*-heptane) to give 3,5,7-tri-*O*-benzyl-4-deoxy-4-fluoro-D-*glycero*-α/β-D-*arabino*-hept-2-ulopyranose as a brown oil and as a mixture of anomers (**3.8**, α/β = 4.6:1, 1.126 g, 87%). R_f = 0.28 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = +32.4 (c 1.0, $CHCl_3$).

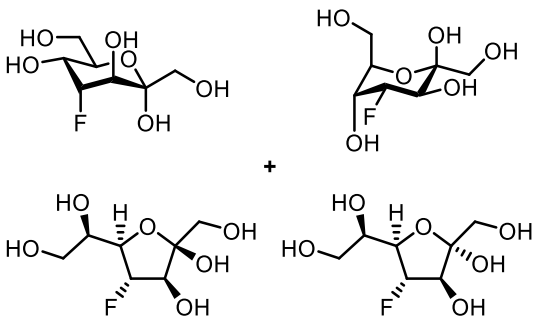
<u>α-Pyranose ($^{5}C_2$):</u> ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.37-7.24 (m, 15H, H^{Ar}), 4.78 (ddd, $^{2}J_{4,F}$ = 49.5 Hz, $^{3}J_{4,3}$ = 3.7 Hz, $^{3}J_{4,5}$ = 2.5 Hz, 1H, H-4), 4.65 (d, $^{2}J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.59 (d, $^{2}J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.55 (d, $^{2}J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.53 (d, $^{2}J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.53 (d, $^{2}J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.52 (d, $^{2}J_{H,H}$ = 11.6 Hz, 1H, H^{Bn}), 4.25 (ddd, $^{3}J_{6,5}$ = 9.8 Hz, $^{3}J_{6,7a}$ = 4.4 Hz, $^{3}J_{6,7b}$ = 2.1 Hz, 1H, H-6), 3.90 (ddd, $^{3}J_{5,F}$ = 30.1 Hz, $^{3}J_{5,6}$ = 9.8 Hz, $^{3}J_{5,4}$ = 2.5 Hz, 1H, H-5), 3.80 (dd, $^{3}J_{3,F}$ = 5.7 Hz, $^{3}J_{3,4}$ = 3.7 Hz, 1H, H-3), 3.80 (d, $J_{OH,F}$ = 6.9 Hz, 1H, OH-2), 3.78 (dd, $^{2}J_{7a,7b}$ = 11.1 Hz, $^{3}J_{7a,6}$ = 4.4 Hz, 1H, H-7a), 3.71 (dd, $^{2}J_{7b,7a}$ = 11.1 Hz, $^{3}J_{7b,6}$ = 2.1 Hz, 1H, H-7b), 3.69 (dd, $^{2}J_{1a,1b}$ = 11.5 Hz, $^{3}J_{1a,OH}$ = 3.5 Hz, 1H, H-1a), 3.55 (t, $^{2}J_{1b,1a}$ = $^{3}J_{1b,OH}$ = 11.1 Hz, 1H, H-1b), 2.01 (dd, $^{3}J_{OH,1b}$ = 11.1 Hz, $^{3}J_{OH,1a}$ = 3.5 Hz, 1H, OH-1). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 138.39 (C^{Ar}), 137.75 (C^{Ar}), 137.24 (C^{Ar}), 128.77 (2 CH^{Ar}), 128.61 (2 CH^{Ar}), 128.48 (2

CH^{Ar}), 128.45 (CH^{Ar}), 128.29 (4 CH^{Ar}), 128.13 (CH^{Ar}), 128.05 (2 CH^{Ar}), 127.76 (CH^{Ar}), 96.91 (C-2), 87.22 (d, $^{1}J_{4,F}$ = 181.0 Hz, C-4), 75.35 (d, $^{2}J_{3,F}$ = 21.5 Hz, C-3), 73.77 (CH_2^{Bn}), 73.68 (CH_2^{Bn}), 71.99 (CH_2^{Bn}), 70.81 (d, $^{2}J_{5,F}$ = 16.5 Hz, C-5), 69.21 (C-7), 67.85 (d, $^{3}J_{6,F}$ = 3.4 Hz, C-6), 65.77 (C-1). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -204.33 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -204.33 (ddt, $^{2}J_{F,4}$ = 49.5 Hz, $^{3}J_{F,5}$ = 30.1 Hz, $^{3}J_{F,3}$ = $J_{F,OH}$ = 6.9 Hz).

β-Pyranose ($^{2}C_5$): ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.37-7.24 (m, 15H, H^{Ar}), 5.00 (ddd, $^{2}J_{4,F}$ = 49.3 Hz, $^{3}J_{4,3}$ = 7.7 Hz, $^{3}J_{4,5}$ = 3.2 Hz, 1H, H-4), 4.80 (d, $^{2}J_{H,H}$ = 11.0 Hz, 1H, H^{Bn}), 4.68 (d, $^{2}J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.66 (d, $^{2}J_{H,H}$ = 11.0 Hz, 1H, H^{Bn}), 4.62 (d, $^{2}J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.55 (d, $^{2}J_{H,H}$ = 12.3 Hz, 1H, H^{Bn}), 4.50 (d, $^{2}J_{H,H}$ = 12.3 Hz, 1H, H^{Bn}), 4.15 (dq, $^{3}J_{6,7a}$ = 6.2 Hz, $^{3}J_{6,5}$ = $^{3}J_{6,7b}$ = $^{4}J_{6,F}$ = 4.2 Hz, 1H, H-6), 4.09 (dd, $^{3}J_{3,F}$ = 10.1 Hz, $^{3}J_{3,4}$ = 7.7 Hz, 1H, H-3), 4.07 (ddd, $^{3}J_{5,F}$ = 14.9 Hz, $^{3}J_{5,6}$ = 4.2, $^{3}J_{5,4}$ = 3.2 Hz, 1H, H-5), 3.79 (s, 1H, OH-2), 3.68 (dd, $^{2}J_{7a,7b}$ = 10.4 Hz, $^{3}J_{7a,6}$ = 6.2 Hz, 1H, H-7a), 3.64 (dd, $^{2}J_{7b,7a}$ = 10.4 Hz, $^{3}J_{7b,6}$ = 4.2 Hz, 1H, H-7b), 3.58 (dd, $^{2}J_{1a,1b}$ = 11.6 Hz, $^{3}J_{1a,OH}$ = 7.2 Hz, 1H, H-1a), 3.57 (dd, $^{2}J_{1b,1a}$ = 11.6 Hz, $^{3}J_{1b,OH}$ = 6.9 Hz, 1H, H-1b), 1.96 (t, $^{3}J_{OH,1a}$ = 7.2 Hz, $^{3}J_{OH,1b}$ = 6.9 Hz, 1H, OH-1). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 137.96 (C^{Ar}), 137.73 (C^{Ar}), 137.43 (C^{Ar}), 128.72 (2 CH^{Ar}), 128.64 (2 CH^{Ar}), 128.57 (2 CH^{Ar}), 128.56 (2 CH^{Ar}), 128.38 (CH^{Ar}), 128.03 (CH^{Ar}), 128.02 (2 CH^{Ar}), 127.99 (CH^{Ar}), 127.93 (2 CH^{Ar}), 98.25 (d, $^{3}J_{2,F}$ = 6.4 Hz, C-2), 89.76 (d, $^{1}J_{4,F}$ = 184.6 Hz, C-4), 74.87 (d, $^{4}J_{C,F}$ = 2.1 Hz, CH_2^{Bn}), 74.56 (d, $^{2}J_{3,F}$ = 20.0 Hz, C-3), 74.41 (d, $^{3}J_{6,F}$ = 5.8 Hz, C-6), 74.17 (d, $^{2}J_{5,F}$ = 15.8 Hz, C-5), 73.59 (CH_2^{Bn}), 72.75 (d, $^{4}J_{C,F}$ = 1.8 Hz, CH_2^{Bn}), 70.29 (C-7), 65.32 (d, $^{4}J_{1,F}$ = 3.4 Hz, C-1). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -205.36 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -205.36 (dddd, $^{2}J_{F,4}$ = 49.3 Hz, $^{3}J_{F,5}$ = 14.2 Hz, $^{3}J_{F,3}$ = 10.4, $^{4}J_{F,6}$ = 4.2 Hz). HRMS (ESI+): *m/z* calc. for $C_{28}H_{31}FO_6Na^+$ $[M+Na]^+$: 505.1997, found: 505.1998.

5.1.1.11 4-Deoxy-4-fluoro-D-sedoheptulose/ 4-Deoxy-4-fluoro-D-*glycero*-D-*arabino*-hept-2-ulopyranose & 4-deoxy-4-fluoro-D-*glycero*-D-*arabino*-hept-2-ulofuranose (4DFS)

3,5,7-Tri-*O*-benzyl-4-deoxy-4-fluoro-D-*glycero*-α/β-D-*arabino*-hept-2-ulopyranose (**3.8**, 170 mg, 0.35 mmol, 1 equiv.) was dissolved in methanol (5 mL) and Pd/C (10% Pd, 60 mg, 0.04 mmol, 0.1 equiv.) was added. The black suspension was degassed (3 freezing/thawing cycles with liquid N_2) and subsequently stirred at room temperature for 24 h until NMR indicated completion (absence of aromatic signals in *d_4*-methanol after drying a small sample on high vacuum). The mixture was filtered, evaporated and purified by reversed-phase chromatography (C_{18}-silica gel, H_2O) to give 4-deoxy-4-



4DFS
$C_7H_{13}FO_6$
212.17 g/mol

fluoro-D-sedoheptulose as a colorless oil and as a mixture of its α- and β-furanoses and pyranoses (1.3:4:4:1, 60 mg, 80%). R_f = 0.7 (1-BuOH/acetone/H_2O 5:4:1, CAM). $[\alpha]_D^{20}$ = +23.4 (c 1.0, H_2O).

β-Furanose: ^{1}H NMR (700 MHz, D_2O) δ = 5.17 (dt, $^2J_{4,F}$ = 56.4 Hz, $^3J_{4,3}$ = 6.1 Hz, $^3J_{4,5}$ = 5.1 Hz, 1H, H-4), 4.42 (dd, $^3J_{3,F}$ = 22.7 Hz, $^3J_{3,4}$ = 6.1 Hz, 1H, H-3), 4.00 (ddd, $^3J_{5,F}$ = 21.4 Hz, $^3J_{5,6}$ = 7.8 Hz, $^3J_{5,4}$ = 5.1 Hz, 1H, H-5), 3.82 (ddd, $^3J_{6,5}$ = 7.8 Hz, $^3J_{6,7b}$ = 6.2 Hz, $^3J_{6,7a}$ = 3.3 Hz, 1H, H-6), 3.76 (dd, $^2J_{7a,7b}$ = 11.9 Hz, $^3J_{7a,6}$ = 3.3 Hz, 1H, H-7a), 3.62 (dd, $^2J_{7b,7a}$ = 11.9 Hz, $^3J_{7b,6}$ = 6.2 Hz, 1H, H-7b), 3.59 (dd, $^2J_{1a,1b}$ = 12.1 Hz, $^5J_{1a,F}$ = 0.7 Hz, 1H, H-1a), 3.55 (dd, $^2J_{1b,1a}$ = 12.1 Hz, $^5J_{1b,F}$ = 1.7 Hz, 1H, H-1b). ^{13}C NMR (176 MHz, D_2O) δ = 105.30 (d, $^3J_{2,F}$ = 10.0 Hz, C-2), 101.15 (d, $^1J_{4,F}$ = 182.28 Hz, C-4), 81.07 (d, $^2J_{5,F}$ = 24.4 Hz, C-5), 77.11 (d, $^2J_{3,F}$ = 22.3 Hz, C-3), 74.99 (d, $^3J_{6,F}$ = 3.6 Hz, C-6), 65.04 (C-1), 64.94 (C-7). ^{19}F{^{1}H} NMR (659 MHz, D_2O) δ = -192.63 (s). ^{19}F NMR (659 MHz, D_2O) δ = -192.63 (dt, $^2J_{F,4}$ = 56.4 Hz, $^3J_{F,3}$ = $^3J_{F,5}$ = 22.0 Hz).

α-Pyranose ($^5C_2$): ^{1}H NMR (700 MHz, D_2O) δ = 4.83 (dt, $^2J_{4,F}$ = 48.9 Hz, $^3J_{4,3}$ = $^3J_{4,5}$ = 3.2 Hz, 1H, H-4), 4.10 (ddd, $^3J_{6,5}$ = 10.5 Hz, $^3J_{6,7b}$ = 5.8 Hz, $^3J_{6,7a}$ = 2.4 Hz, 1H, H-6), 4.06 (dd, $^3J_{3,F}$ = 6.0 Hz, $^3J_{3,4}$ = 3.2 Hz, 1H, H-3), 3.88 (ddd, $^3J_{5,F}$ = 31.1 Hz, $^3J_{5,6}$ = 10.5 Hz, $^3J_{5,4}$ = 3.2 Hz, 1H, H-5), 3.87 (dd, $^2J_{7a,7b}$ = 12.2 Hz, $^3J_{7a,6}$ = 2.4 Hz, 1H, H-7a), 3.75 (dd, $^2J_{7b,7a}$ = 12.2 Hz, $^3J_{7b,6}$ = 5.8 Hz, 1H, H-7b), 3.70 (d, $^2J_{1a,1b}$ = 11.7 Hz, 1H, H-1a), 3.53 (d, $^2J_{1b,1a}$ = 11.7 Hz, 1H, H-1b). ^{13}C NMR (176 MHz, D_2O) δ = 99.27 (C-2), 93.43 (d, $^1J_{4,F}$ = 179.6 Hz, C-4), 71.20 (d, $^3J_{6,F}$ = 2.4 Hz, C-6), 70.00 (d, $^2J_{3,F}$ = 23.4 Hz, C-3), 67.31 (C-1), 65.67 (d, $^2J_{5,F}$ = 17.5 Hz, C-5), 63.76 (C-7). ^{19}F{^{1}H} NMR (659 MHz, D_2O) δ = -202.12 (s). ^{19}F NMR (659 MHz, D_2O) δ = -202.12 (ddd, $^2J_{F,4}$ = 48.9 Hz, $^3J_{F,5}$ = 31.1 Hz, $^3J_{F,3}$ = 6.0 Hz).

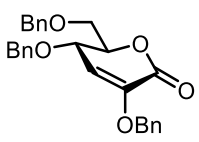
α-Furanose: ^{1}H NMR (700 MHz, D_2O) δ = 5.03 (ddd, $^2J_{4,F}$ = 52.9 Hz, $^3J_{4,5}$ = 3.8 Hz, $^3J_{4,3}$ = 2.2 Hz, 1H, H-4), 4.33 (dd, $^3J_{3,F}$ = 16.2 Hz, $^3J_{3,4}$ = 2.2 Hz, 1H, H-3), 4.24 (ddd, $^3J_{5,F}$ = 24.0 Hz, $^3J_{5,6}$ = 6.7 Hz, $^3J_{5,4}$ = 3.8 Hz, 1H, H-5), 3.80 (td, $^3J_{6,5}$ = $^3J_{6,7b}$ = 6.7 Hz, $^3J_{6,7a}$ = 3.6 Hz, 1H, H-6), 3.74 (ddd, $^2J_{7a,7b}$ = 12.0 Hz, $^3J_{7a,6}$ = 3.6 Hz, $^5J_{7a,F}$ = 0.4 Hz, 1H, H-7a), 3.72 (d, $^2J_{1a,1b}$ = 12.0 Hz, 1H, H-1a), 3.66 (d, $^2J_{1b,1a}$ = 12.0 Hz, 1H, H-1b), 3.62 (dd, $^2J_{7b,7a}$ = 12.0 Hz, $^3J_{7b,6}$ = 6.7 Hz, 1H, H-7b). ^{13}C NMR (176 MHz, D_2O) δ = 108.28 (d, $^3J_{2,F}$ = 4.2 Hz, C-2), 100.47 (d, $^1J_{4,F}$ = 183.0 Hz, C-4), 84.08 (d, $^2J_{5,F}$ = 25.7

Hz, C-5), 81.32 (d, $^2J_{3,F}$ = 23.1 Hz, C-3), 73.73 (d, $^3J_{6,F}$ = 5.5 Hz, C-6), 65.06 (C-1), 65.02 (C-7). $^{19}F\{^1H\}$ NMR (659 MHz, D_2O) δ = -182.45 (s). ^{19}F NMR (659 MHz, D_2O) δ = -182.45 (ddd, $^2J_{F,4}$ = 52.9 Hz, $^3J_{F,5}$ = 24.0 Hz, $^3J_{F,3}$ = 16.2 Hz).

β-Pyranose ($^2C_5$): ^1H NMR (700 MHz, D_2O) δ = 4.93 (ddd, $^2J_{4,F}$ = 48.9 Hz, $^3J_{4,3}$ = 8.3 Hz, $^3J_{4,5}$ = 3.5 Hz, 1H, H-4), 4.27 (dt, $^3J_{5,F}$ = 13.8 Hz, $^3J_{5,4}$ = $^3J_{5,6}$ = 3.5 Hz, 1H, H-5), 4.14 (dd, $^3J_{3,F}$ = 10.9 Hz, $^3J_{3,4}$ = 8.3 Hz, 1H, H-3), 3.99 (dddd, $^3J_{6,7a}$ = 6.3 Hz, $^3J_{6,7b}$ = 6.0 Hz, $^4J_{6,F}$ = 4.3 Hz, $^3J_{6,5}$ = 3.5 Hz, 1H, H-6), 3.80 (dd, $^2J_{7a,7b}$ = 12.0 Hz, $^3J_{7a,6}$ = 6.3 Hz, 1H, H-7a), 3.77 (dd, $^2J_{7b,7a}$ = 12.0 Hz, $^3J_{7b,6}$ = 6.0 Hz, 1H, H-7b), 3.71 (dd, $^2J_{1a,1b}$ = 11.9 Hz, $^5J_{1a,F}$ = 1.0 Hz, 1H, H-1a), 3.57 (dd, $^2J_{1b,1a}$ = 11.9 Hz, $^5J_{1b,F}$ = 1.9 Hz, 1H, H-1b). ^{13}C NMR (176 MHz, D_2O) δ = 101.58 (d, $^3J_{2,F}$ = 6.5 Hz, C-2), 92.94 (d, $^1J_{4,F}$ = 178.3 Hz, C-4), 80.52 (d, $^3J_{6,F}$ = 5.6 Hz, C-6), 69.03 (d, $^2J_{5,F}$ = 16.6 Hz, C-5), 68.64 (d, $^2J_{3,F}$ = 20.5 Hz, C-3), 65.81 (d, $^5J_{1,F}$ = 3.4 Hz, C-1), 64.74 (C-7). $^{19}F\{^1H\}$ NMR (659 MHz, D_2O) δ = -205.02 (s). ^{19}F NMR (659 MHz, D_2O) δ = -205.02 (dtd, $^2J_{F,4}$ = 48.9 Hz), $^3J_{F,5}$ = 13.8 Hz, $^3J_{F,3}$ = 10.9 Hz, $^4J_{F,6}$ = 4.3 Hz). HRMS (ESI+): *m/z* calc. for $C_7H_{13}FO_6Na^+$ $[M+Na]^+$: 235.0588, found: 235.0593.

5.1.2 Additional Experiments in the Synthesis of 4DFS

5.1.2.1 2,4,6-Tri-O-benzyl-D-erythro-hex-2-enonolactone (3.9)



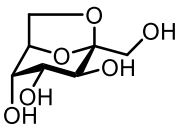
3.9
$C_{27}H_{26}O_5$
430.50 g/mol

2,4,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-D-*altro*-pyranose (**3.5**, 40 mg, 0.09 mmol, 1 equiv.) was dissolved in dry DCM (740 µL) under argon. *N*-Methylmorpholine-*N*-oxide (24 mg, 0.20 mmol, 2.3 equiv.) and 3 Å molecular sieves (40 mg) were added and the reaction mixture was stirred at room temperature for 15 min before TPAP (3 mg, 9 µmol, 0.1 equiv.) was added. The mixture was stirred at room temperature for 4 h. TLC indicated complete consumption of the starting material and the mixture was filtered over a short plug of silica gel with EA. The filtrate was evaporated and the crude residue was purified by MPLC (10 g silica gel, 5-40% EA in *n*-heptane) to give 2,4,6-tri-*O*-benzyl-D-*erythro*-hex-2-enonolactone as a colorless oil (**3.9**). R_f = 0.26 (4:1 *n*-heptane/EA, UV & CAM). ^1H NMR (700 MHz, $CDCl_3$) δ = 7.39-7.24 (m, 15H, H^{Ar}), 5.64 (d, $^3J_{3,4}$ = 4.1 Hz, 1H, H-3), 4.90 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.87 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.57 (ddd, $^3J_{5,4}$ = 5.8 Hz, $^3J_{5,6b}$ = 4.7 Hz, $^3J_{5,6a}$ = 3.8 Hz, 1H, H-5), 4.56 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.54 (d, $^2J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.51 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.51 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, H^{Bn}), 4.48 (dd, $^3J_{4,5}$ = 5.8 Hz, $^3J_{4,3}$ = 4.1 Hz, 1H, H-4), 3.74 (dd, $^2J_{6a,6b}$ = 10.7 Hz, $^3J_{6a,5}$ = 3.8 Hz, 1H, H-6a), 3.66 (dd, $^2J_{6b,6a}$ = 10.7 Hz,

$^{3}J_{6b,5}$ = 4.7 Hz, 1H, H-6b). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 159.60 (C-1), 144.23 (C-2), 137.62 (C^{Ar}), 137.47 (C^{Ar}), 135.37 (C^{Ar}), 128.82 (2 CH^{Ar}), 128.72 (2 CH^{Ar}), 128.63 (2 CH^{Ar}), 128.43 (CH^{Ar}), 128.27 (CH^{Ar}), 128.10 (2 CH^{Ar}), 128.05 (CH^{Ar}), 127.90 (2 CH^{Ar}), 127.55 (2 CH^{Ar}), 110.36 (C-3), 79.95 (C-5), 73.76 (CH_2^{Bn}), 71.34 (CH_2^{Bn}), 70.54 (CH_2^{Bn}), 69.55 (C-4), 68.47 (C-6). HRMS (ESI+): *m/z* calc. for $C_{27}H_{26}O_5Na^+$ $[M+Na]^+$: 453.1672, found: 453.1669.

5.1.3 Synthesis of Potential Rabiolabeling Precursors for 4DFS

5.1.3.1 2,7-Anhydro-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose/2,7-Anhydro-β-D-sedoheptulose (sedoheptulosan)

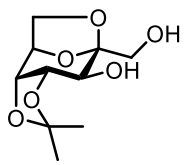


sedoheptulosan
$C_7H_{12}O_6$
192.17 g/mol

Plant extracts from *Sedum maximum* containing D-sedoheptulose were previously generated[103] and kindly provided by Prof. Kosma (University of Natural Resources and Life Sciences, Vienna). The plant extract (500 g) was thawed at room temperature overnight. The orange solution was diluted with water (1.2 L) and conc. H_2SO_4 (20 mL) was slowly added under stirring at room temperature. The mixture was then heated to 60°C for 16 h. Reaction control was done as follows: 500 µL of the reaction mixture were neutralized with $BaCO_3$, filtered over cotton, evaporated and redissolved in D_2O. As soon as ^{1}H NMR spectroscopy indicated a 1:4 ratio of the doublet of sedoheptulose at 4.09 ppm ($^{3}J_{3,4}$ = 7.9 Hz) and the dd of sedoheptulosan at 4.69 ppm ($^{3}J_{6,7b}$ = 5.0 Hz, $^{3}J_{6,5}$ = 1.9 Hz), the reaction mixture was cooled to room temperature and solid $BaCO_3$ (540 g) was added to pH 5. $BaSO_4$ was removed by filtration over a frit with additional filter paper and the filtrate was evaporated. The residue was dissolved in 100 mL water and filtered again over a Büchner funnel. The filtrate was then subjected to cation exchange chromatography (DOWEX 50W x8/ H^+-form, 450 mL resin, 3.5 cm diameter column). Five fractions (5x250 mL) were collected. Fraction 2 and 3 contained sedoheptulosan and were pooled and evaporated. The resulting oil was dissolved in water (20 mL) and subjected to anion exchange chromatography (DOWEX monosphere 550A/ OH^--form, 340 mL resin, 2.5 cm diameter column). 17 Fractions (17x100 mL) were collected. Fractions 4-13 contained sedoheptulosan and were pooled and evaporated. The resulting oil crystallized upon standing to give 2,7-anhydro-β-D-sedoheptulose/sedoheptulosan as a white solid (14.436 g). R_f = 0.5 (1-BuOH/acetone/H_2O 5:4:1, CAM). $[\alpha]_D^{20}$ = -133.5 (c 1.0, H_2O). ^{1}H NMR (700 MHz, D_2O) δ = 4.69 (dd, $^{3}J_{6.7b}$ = 5.2 Hz, $^{3}J_{6.5}$ = 2.2 Hz, 1H, H-6), 4.00 (dd, $^{3}J_{5,4}$ = 4.5 Hz, $^{3}J_{5,6}$ = 2.2 Hz, 1H, H-5), 3.90 (d, $^{2}J_{7a,7b}$ = 8.2 Hz, 1H, H-7a), 3.87 (dd, $^{2}J_{7b,7a}$ = 8.2 Hz, $^{3}J_{7b,6}$ = 5.2

Hz, 1H, H-7b), 3.85 (d, $^2J_{1a,1b}$ = 12.6 Hz, 1H, H-1a), 3.81 (d, $^2J_{1a,1b}$ = 12.6 Hz, 1H, H-1b), 3.76 (dd, $^3J_{4,3}$ = 8.8 Hz, $^3J_{4,5}$ = 4.5 Hz, 1H, H-4), 3.67 (d, $^3J_{3,4}$ = 8.8 Hz, 1H, H-3). ^{13}C NMR (176 MHz, D_2O) δ = 110.22 (C-2), 80.46 (C-6), 74.92 (C-3), 72.75 (C-4 or 5), 72.75 (C-4 or 5), 69.17 (C-7), 62.38 (C-1). HRMS (ESI+): *m/z* calc. for $C_7H_{12}O_6Na^+$ $[M+Na]^+$: 215.0527, found: 215.0527.

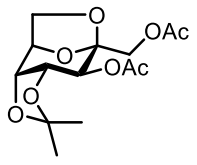
5.1.3.2 2,7-Anhydro-4,5-*O*-isopropylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.10)



3.10
$C_{10}H_{16}O_6$
232.23 g/mol

Sedoheptulosan monohydrate (11.3 g, 58.77 mmol, 1 equiv.) and 3 Å molecular sieves (2.8 g) were suspended in dry acetone (117 mL) containing sulfuric acid (2.1 g, 1.15 mL, 21.45 mmol, 0.37 equiv.). The suspension was stirred under argon at room temperature for 3 h. Over the course of the reaction, the suspension of colorless crystals of sedoheptulosan monohydrate turned into a white suspension. The suspension was filtered and washed twice with cold acetone to give 2,7-anhydro-4,5-*O*-isopropylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a white solid which was used without further purification (**3.10**, 11.6 g, 93%). R_f = 0.25 (EA, CAM). $[\alpha]_D^{20}$ = -126.4 (c 1.0, H_2O). ^{1}H NMR (700 MHz, *d*$_6$-DMSO) δ = 5.13 (d, $^3J_{OH,3}$ = 6.7 Hz, 1H, OH-3), 4.72 (dd, $^3J_{OH,1a}$ = 7.0 Hz, $^3J_{OH,1b}$ = 5.7 Hz, 1H, OH-1), 4.71 (d, $^3J_{6,7b}$ = 5.3 Hz, 1H, H-6), 4.19 (dd, $^3J_{5,4}$ = 6.2 Hz, $^3J_{5,6}$ = 1.1 Hz, 1H, H-5), 3.99 (t, $^3J_{4,5}$ = 6.2 Hz, $^3J_{4,3}$ = 6.0 Hz, 1H, H-4), 3.76 (d, $^2J_{7a,7b}$ = 7.5 Hz, 1H, H-7a), 3.68 (dd, $^2J_{7b,7a}$ = 7.5 Hz, $^3J_{7b,6}$ = 5.3 Hz, 1H, H-7b), 3.59 (dd, $^2J_{1a,1b}$ = 11.9 Hz, $^3J_{1a,OH}$ = 7.0 Hz, 1H, H-1a), 3.53 (dd, $^3J_{3,OH}$ = 6.7 Hz, $^3J_{3,4}$ = 6.0 Hz, 1H, H-3), 3.34 (dd, $^2J_{1b,1a}$ = 11.9 Hz, $^3J_{1b,OH}$ = 5.7 Hz, 1H, H-1b), 1.39 (s, 3H, CH_3^{isopr}), 1.27 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, *d*$_6$-DMSO) δ = 109.13 (C^{isopr}), 107.76 (C-2), 78.95 (C-4), 75.86 (C-5), 73.65 (C-6), 71.88 (C-3), 66.64 (C-7), 60.59 (C-1), 27.81 (CH_3^{isopr}), 26.18 (CH_3^{isopr}). HRMS (ESI+): *m/z* calc. for $C_{10}H_{16}O_6Na^+$ $[M+Na]^+$: 255.0839, found: 255.0840.

5.1.3.3 1,3-Di-*O*-acetyl-2,7-anhydro-4,5-*O*-isopropylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.11)

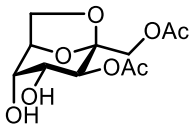


3.11
$C_{14}H_{20}O_8$
316.31 g/mol

2,7-Anhydro-4,5-*O*-isopropylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.10**, 16.3 g, 70.24 mmol, 1 equiv.) was dissolved in dry pyridine (141 mL) under argon and cooled to 0°C. Acetic anhydride (28.7 g, 26.6 mL, 281 mmol, 4 equiv.) was added dropwise followed by 4-(dimethylamino)pyridine (429 mg, 3.51 mmol, 0.05 equiv.). The

reaction mixture was stirred at room temperature for 2 h. The solution was then co-evaporated thrice with toluene. The residue was dissolved in EA and washed twice with water and once with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 1,3-di-*O*-acetyl-2,7-anhydro-4,5-*O*-isopropylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a white solid which was used without further purification (**3.11**, 21.45 g, 97%). R_f = 0.24 (*n*-heptane/EA 2:1, CAM). $[\alpha]_D^{20}$ = -133.5 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 5.13 (d, $^3J_{3,4}$ = 5.8 Hz, 1H, H-3), 4.89 (d, $^3J_{6,7a}$ = 5.1 Hz, 1H, H-6), 4.40 (d, $^2J_{1a,1b}$ = 12.2 Hz, 1H, H-1a), 4.27 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 5.8 Hz, 1H, H-4), 4.22 (dd, $^3J_{5,4}$ = 5.8 Hz, $^3J_{5,6}$ = 1.3 Hz, 1H, H-5), 3.97 (d, $^2J_{1b,1a}$ = 12.2 Hz, 1H, H-1b), 3.95 (dd, $^2J_{7a,7b}$ = 7.9 Hz, $^3J_{7a,6}$ = 5.1 Hz, 1H, H-7a), 3.91 (d, $^2J_{7b,7a}$ = 7.9 Hz, 1H, H-7b), 2.12 (s, 3H, $CH_3^{Ac\text{-}3}$), 2.08 (s, 3H, $CH_3^{Ac\text{-}1}$), 1.59 (s, 3H, CH_3^{isopr}), 1.37 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 170.43 ($C^{Ac\text{-}1}$), 169.89 ($C^{Ac\text{-}3}$), 111.52 (C^{isopr}), 105.56 (C-2), 76.90 (C-4), 76.49 (C-5), 75.12 (C-6), 73.43 (C-3), 67.89 (C-7), 61.83 (C-1), 27.80 ($CH_3^{Ac\text{-}3}$), 26.39 ($CH_3^{Ac\text{-}1}$), 21.08 (CH_3^{isopr}), 20.84 (CH_3^{isopr}). HRMS (ESI+): *m/z* calc. for $C_{14}H_{20}O_8Na^+$ [M+Na]$^+$: 339.1050, found: 339.1052.

5.1.3.4 1,3-Di-*O*-acetyl-2,7-anhydro-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.12)

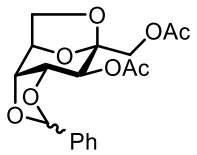


3.12
$C_{11}H_{16}O_8$
276.24 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-4,5-*O*-isopropylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.11**, 21.5 g, 67.81 mmol, 1 equiv.) was dissolved in acetic acid (424 mL) and water (106 mL) was added. The reaction mixture was stirred at 80°C for 2 h. The solution was then cooled to room temperature and co-evaporated thrice with toluene. The crude residue was recrystallized from ethanol to give 1,3-di-*O*-acetyl-2,7-anhydro-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a white solid (**3.12**, 17.7 g, 94%). R_f = 0.24 (EA, CAM). $[\alpha]_D^{20}$ = -94.7 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.97 (d, $^3J_{3,4}$ = 8.3 Hz, 1H, H-3), 4.77 (dd, $^3J_{6,7a}$ = 5.4 Hz, $^3J_{6,5}$ = 2.0 Hz, 1H, H-6), 4.53 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.00 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 3.96 (td, $^3J_{5,4}$ = $^3J_{5,OH}$ = 4.8 Hz, $^3J_{5,6}$ = 2.0 Hz, 1H, H-5), 3.93 (dd, $^2J_{7a,7b}$ = 8.1 Hz, $^3J_{7a,6}$ = 5.4 Hz, 1H, H-7a), 3.88 (ddd, $^3J_{4,3}$ = 8.8 Hz, $^3J_{4,OH}$ = 6.3 Hz, $^3J_{4,5}$ = 4.8 Hz, 1H, H-4), 3.84 (d, $^2J_{7b,7a}$ = 8.1 Hz, 1H, H-7b), 3.25 (d, $^3J_{OH,4}$ = 6.3 Hz, 1H, OH-4), 2.77 (d, $^3J_{OH,5}$ = 4.8 Hz, 1H, OH-5), 2.16 (s, 3H, $CH_3^{Ac\text{-}3}$), 2.09 (s, 3H, $CH_3^{Ac\text{-}1}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.32 ($C^{Ac\text{-}3}$), 170.32 ($C^{Ac\text{-}1}$), 105.50 (C-2), 77.57 (C-6), 74.75 (C-3), 70.53 (C-5), 69.99 (C-4), 66.58

(C-7), 61.70 (C-1), 21.08 (CH_3^{Ac-3}), 20.84 (CH_3^{Ac-3}). HRMS (ESI+): ***m/z*** calc. for $C_{11}H_{16}O_8Na^+$ $[M+Na]^+$: 299.0737, found: 299.0737.

5.1.3.5 1,3-Di-*O*-acetyl-2,7-anhydro-4,5-*O*-benzylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.13)

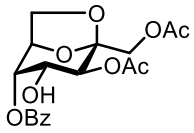


3.13
$C_{18}H_{20}O_8$
364.35 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.12**, 17.7 g, 64.05 mmol, 1 equiv.) was suspended in benzaldehyde (101 mL) under argon and zinc chloride (10.5 g, 76.86 mmol, 1.2 equiv.), freshly molten with a Bunsen burner and grinded in a mortar, was added. The reaction mixture was stirred at room temperature for 4 h and was then diluted with DCM and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. Remaining benzaldehyde was removed under reduced pressure at 80°C for 4 h on a rotary evaporator to yield 1,3-di-*O*-acetyl-2,7-anhydro-4,5-*O*-benzylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a 1:1 mixture of exo- and endo-stereoisomers and as a yellow oil which was used without further purification (**3.13**, 21.1 g, 92%). $[\alpha]_D^{20}$ = -119.8 (c 1.0, $CHCl_3$). Exo: R_f = 0.13 (*n*-heptane/EA 2:1, UV & CAM). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.62 (m, 1H, H^{Ar}), 7.50-7.46 (m, 2H, H^{Ar}), 7.39-7.37 (m, 2H, H^{Ar}), 6.23 (s, 1H, H^{Bn}), 5.30 (d, $^3J_{3,4}$ = 6.0 Hz, 1H, H-3), 4.96 (d, $^3J_{6,7a}$ = 4.9 Hz, 1H, H-6), 4.60 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 6.0 Hz, 1H, H-4), 4.46 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.26 (dd, $^3J_{5,4}$ = 6.0 Hz, $^3J_{5,6}$ = 1.3 Hz, 1H, H-5), 4.01 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 3.95 (dd, $^2J_{7a,7b}$ = 7.9 Hz, $^3J_{7a,6}$ = 4.9 Hz, 1H, H-7a), 3.92 (dd, $^2J_{7b,7a}$ = 7.9 Hz, $^3J_{7b,6}$ = 0.9 Hz, 1H, H-7b), 2.15 (s, 3H, CH_3^{Ac-3}), 2.12 (s, 3H, CH_3^{Ac-1}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.32 (C^{Ac-1}), 169.77 (C^{Ac-3}), 137.39 (C^{Ar}), 133.76 (CH^{Ar}), 128.47 (2 CH^{Ar}), 126.36 (2 CH^{Ar}), 105.19 (C-2), 104.08 (CH^{Bn}), 77.87 (C-4), 76.39 (C-5), 75.60 (C-6), 70.97 (C-3), 67.42 (C-7), 61.69 (C-1), 20.91 (CH_3^{Ac-3}), 20.74 (CH_3^{Ac-1}). Endo: R_f = 0.24 (*n*-heptane/EA 2:1, UV & CAM). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.64-7.61 (m, 1H, H^{Ar}), 7.58-7.55 (m, 2H, H^{Ar}), 7.42-7.39 (m, 2H, H^{Ar}), 5.93 (s, 1H, H^{Bn}), 5.19 (d, $^3J_{3,4}$ = 5.1 Hz, 1H, H-3), 5.02-5.00 (m, 1H, H-6), 4.41 (dd, $^3J_{4,5}$ = 6.8 Hz, $^3J_{4,3}$ = 5.1 Hz, 1H, H-4), 4.39 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.30 (dd, $^3J_{5,4}$ = 6.8 Hz, $^3J_{5,6}$ = 1.2 Hz, 1H, H-5), 4.02 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 3.99-3.98 (m, 2H, H-7a & H-7b), 2.12 (s, 3H, CH_3^{Ac-3}), 2.07 (s, 3H, CH_3^{Ac-1}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.28 (C^{Ac-1}), 169.65 (C^{Ac-3}), 136.31 (C^{Ar}), 129.71 (CH^{Ar}), 128.50 (2 CH^{Ar}), 126.92 (2 CH^{Ar}), 105.50 (CH^{Bn}), 105.47 (C-2), 78.24 (C-5), 76.74 (C-4), 74.86 (C-6), 73.25 (C-3), 67.78 (C-7), 61.75 (C-1), 20.92 (CH_3^{Ac-3}),

20.69 (CH_3^{Ac-1}). HRMS (ESI+): *m/z* calc. for $C_{18}H_{20}O_8Na^+$ $[M+Na]^+$: 387.1050, found: 387.1050.

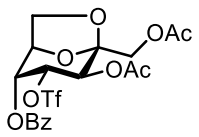
5.1.3.6 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.14)



3.14
$C_{18}H_{20}O_9$
380.35 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-4,5-*O*-benzylidene-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.13**, 21.1 g, 57.91 mmol, 1 equiv.) was dissolved in EA (772 mL) and sodium bromate (26.2 g, 173.73 mmol, 3 equiv.), dissolved in 386 mL water, was added. To the biphasic system, sodium dithionite (85% pure, 29.660 g, 144.78 mmol, 2.5 equiv.), dissolved in 772 mL water, was added dropwise over 10 min. The reaction was stirred at room temperature for 35 min before dilution with EA. The layers were separated and the aqueous layer was extracted twice with EA. The combined organic layers were washed with sat. aq. $Na_2S_2O_3$-solution, water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was recrystallized from MeOH to give 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a white solid (**3.14**, 16.7 g, 76%). R_f = 0.18 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = -177.9 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.10 (d, $^3J_{H,H}$ = 8.4 Hz, 2H, H^{Ar}), 7.63 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.50 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.35 (dd, $^3J_{5,4}$ = 4.8 Hz, $^3J_{5,6}$ = 2.6 Hz, 1H, H-5), 5.22 (d, $^3J_{3,4}$ = 9.0 Hz, 1H, H-3), 4.93 (dd, $^3J_{6,7a\text{ or }7b}$ = 5.6 Hz, $^3J_{6,5}$ = 2.6 Hz, 1H, H-6), 4.55 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.16 (m, 1H, H-4), 4.05 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1a), 3.98-3.94 (m, 2H, H-7a & H-7b), 2.28 (s, 1H, OH), 2.17 (s, 3H, CH_3^{Ac-3}), 2.11 (s, 3H, CH_3^{Ac-1}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.29 (C^{Ac-3}), 170.34 (C^{Ac-3}), 166.30 (C^{Bz}), 133.88 (CH^{Ar}), 130.10 (2 CH^{Ar}), 129.30 (C^{Ar}), 128.76 (2 CH^{Ar}), 106.01 (C-2), 76.15 (C-6), 74.12 (C-3), 72.88 (C-5), 68.64 (C-4), 66.95 (C-7), 61.60 (C-1), 21.09 (CH_3^{Ac-3}), 20.84 (CH_3^{Ac-1}). HRMS (ESI+): *m/z* calc. for $C_{18}H_{20}O_9Na^+$ $[M+Na]^+$: 403.1000, found: 403.1003.

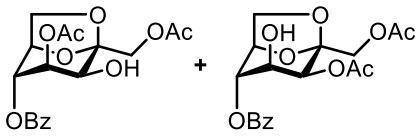
5.1.3.7 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.15)



3.15
$C_{19}H_{19}F_3O_{11}S$
512.41 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.14**, 10.0 g, 26.29 mmol, 1 equiv.) was dissolved in dry DCM (131 mL) under argon. The solution was cooled to 0°C and pyridine (17.7 g, 18 mL, 223.50 mmol, 8.5 equiv.) and trifluoromethanesulfonic anhydride (14.8 g, 8.8 mL, 52.58 mmol, 2 equiv.) were added dropwise. The reaction mixture was stirred at 0°C for 1 h before it was diluted with DCM (200 mL) and quenched by the dropwise addition of ice-cold 1 M aq. HCl (125 mL). The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with cold water, cold sat. aq. $NaHCO_3$-solution and cold brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was dried under high vacuum to give 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a white foam which was used without further purification (**3.15**, 13.4 g, 99%). R_f = 0.66 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = -143.7 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.11 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, H^{Ar}), 7.64 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, H^{Ar}), 7.51 (t, $^3J_{H,H}$ = 7.9 Hz, 2H, H^{Ar}), 5.58 (d, $^3J_{3,4}$ = 9.0 Hz, 1H, H-3), 5.58 (dd, $^3J_{5,4}$ = 4.7 Hz, $^3J_{5,6}$ = 2.5 Hz, 1H, H-5), 5.18 (dd, $^3J_{4,3}$ = 9.0 Hz, $^3J_{4,5}$ = 4.7 Hz, 1H, H-4), 5.00 (dd, $^3J_{6,7b}$ = 5.2 Hz, $^3J_{6,5}$ = 2.2 Hz, 1H, H-6), 4.56 (d, $^2J_{1a,1b}$ = 12.3 Hz, 1H, H-1a), 4.04 (dd, $^2J_{7a,7b}$ = 8.5 Hz, $^3J_{7a,6}$ = 0.7 Hz, 1H, H-7a), 4.02 (d, $^2J_{1b,1a}$ = 12.3 Hz, 1H, H-1b), 4.00 (dd, $^2J_{7b,7a}$ = 8.5 Hz, $^3J_{7b,6}$ = 5.2 Hz, 1H, H-7b), 2.16 (s, 3H, CH_3^{Ac-3}), 2.11 (s, 3H, CH_3^{Ac-1}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 170.23 (C^{Ac-1}), 169.42 (C^{Ac-3}), 165.71 (C^{Bz}), 134.16 (CH^{Ar}), 130.25 (2 CH^{Ar}), 128.84 (2 CH^{Ar}), 128.60 (C^{Ar}), 118.39 (q, $^1J_{C,F}$ = 319.6 Hz, C^{Tf}), 106.52 (C-2), 81.31 (C-4), 76.20 (C-6), 70.77 (C-5), 70.13 (C-3), 66.88 (C-7), 61.16 (C-1), 20.79 (CH_3^{Ac-1}), 20.60 (CH_3^{Ac-3}). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -75.25 (s). HRMS (ESI+): *m/z* calc. for $C_{19}H_{19}F_3O_{11}SNa^+$ $[M+Na]^+$: 535.0492, found: 535.0490, *m/z* calc. for $C_{18}H_{19}O_8^+$ $[M-OTf]^+$: 363.1074, found: 363.1076.

5.1.3.8 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (3.16a) & 1,4-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (3.16b)



3.16a
$C_{18}H_{20}O_9$
380.35 g/mol

3.16b
$C_{18}H_{20}O_9$
380.35 g/mol

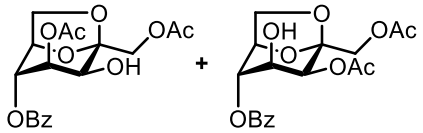
Crude 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.15**, 13. g, 26.29 mmol, 1 equiv.) was dissolved in dry DMF (263 mL) under argon and sodium nitrite (18.1 g, 262.92 mmol, 10 equiv.). The reaction mixture was stirred at 40°C for 72 h. The reaction was then diluted with EA and washed twice with water. The combined aqueous layers were extracted thrice with EA. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified in 2 g portions by MPLC (340 g silica gel, 12-46% EA in toluene) to give 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose as a white foam (**3.16a**, 4.5 g, 45%) and 1,4-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose as a white foam (**3.16b**, 4.5 g, 45%).

3.16a: R_f = 0.16 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = -118.9 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.07 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, H^{Ar}), 7.61 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.47 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.37 (dt, $^3J_{4,3}$ = 6.0 Hz, $^3J_{4,5}$ = $^4J_{4,6}$ = 1.7 Hz, 1H, H-4), 5.06 (t, $^3J_{5,4}$ = $^3J_{5,6}$ = 1.7 Hz, 1H, H-5), 4.79 (d, $^3J_{6,7b}$ = 5.3 Hz, 1H, H-6), 4.49 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.34 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 4.21 (dd, $^2J_{7a,7b}$ = 7.8 Hz, $^3J_{7a,6}$ = 0.7 Hz, 1H, H-7a), 4.11 (dd, $^3J_{3,OH}$ = 10.2 Hz, $^3J_{3,4}$ = 6.0 Hz, 1H, H-3), 3.97 (dd, $^2J_{7b,7a}$ = 7.8 Hz, $^3J_{7b,6}$ = 5.3 Hz, 1H, H-7b), 2.45 (d, $^3J_{OH,3}$ = 10.2 Hz, 1H, OH), 2.20 (s, 3H, $CH_3^{Ac\text{-}4}$), 2.15 (s, 3H, $CH_3^{Ac\text{-}1}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.70 ($C^{Ac\text{-}1}$), 170.03 ($C^{Ac\text{-}4}$), 165.47 (C^{Bz}), 133.82 (CH^{Ar}), 130.11 (2 CH^{Ar}), 129.24 (C^{Ar}), 128.67 (2 CH^{Ar}), 106.27 (C-2), 75.37 (C-6), 72.76 (C-5), 69.90 (C-4), 66.54 (C-7), 65.94 (C-3), 62.37 (C-1), 21.13 ($CH_3^{Ac\text{-}1\text{ or }4}$), 20.99 ($CH_3^{Ac\text{-}1\text{ or }4}$). HRMS (ESI+): *m/z* calc. for $C_{18}H_{20}O_9Na^+$ $[M+Na]^+$: 403.1000, found: 403.1002.

3.16b: R_f = 0.21 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = -114.9 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.09 (d, $^3J_{H,H}$ = 7.2 Hz, 2H, H^{Ar}), 7.61 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.48 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.21 (t, $^3J_{5,4}$ = $^3J_{5,6}$ = 1.4 Hz, 1H, H-5), 5.17 (d, $^3J_{3,4}$ = 5.2 Hz, 1H, H-3), 4.85 (d, $^3J_{6,7b}$ = 5.3 Hz, 1H, H-6), 4.54 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.44 (d, $^2J_{7a,7b}$ = 7.5 Hz, 1H, H-7a), 4.33 (tt, $^3J_{4,3}$ = $^3J_{4,OH}$ = 5.2 Hz, $^3J_{4,5}$ = $^4J_{4,6}$ = 1.4 Hz, 1H, H-4), 4.09 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 3.95 (dd, $^2J_{7b,7a}$ = 7.5 Hz, $^3J_{7b,6}$

= 5.6 Hz, 1H, H-7b), 2.75 (d, $^{3}J_{OH,4}$ = 5.2 Hz, 1H, OH), 2.18 (s, 3H, CH_3^{Ac-3}), 2.11 (s, 3H, CH_3^{Ac-1}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.37 (C^{Ac-1}), 169.58 (C^{Ac-1}), 165.66 (C^{Bz}), 133.75 (CH^{Ar}), 130.13 (2 CH^{Ar}), 129.39 (C^{Ar}), 128.66 (2 CH^{Ar}), 105.82 (C-2), 76.26 (C-6), 74.21 (C-5), 68.75 (C-4), 68.35 (C-3), 66.70 (C-7), 62.05 (C-1), 20.92 ($CH_3^{Ac-1\ or\ 3}$), 20.87 ($CH_3^{Ac-1\ or\ 3}$). HRMS (ESI+): *m/z* calc. for $C_{18}H_{20}O_9Na^+$ $[M+Na]^+$: 403.1000, found: 403.1005.

5.1.3.9 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (3.16b) from 3.16a

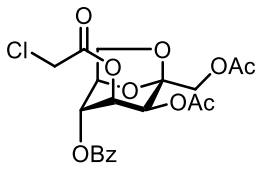


3.16a
$C_{18}H_{20}O_9$
380.35 g/mol

3.16b
$C_{18}H_{20}O_9$
380.35 g/mol

1,4-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (**3.16a**, 5.933 g, 15.60 mmol, 1 equiv.) was dissolved in dry DMF (156 mL) and water (2.810 g, 156.11 mmol, 10 equiv.) was added. The solution warmed to 40°C for 72 h. After NMR indicated a 1:1 ratio of starting material and product the solution was co-evaporated thrice with *n*-heptane. The crude residue was purified in 2 g portions by MPLC (340 g silica gel, 12-46% EA in toluene) to give 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose as a white foam (**3.16b**, 2.650 g, 45%) and 1,4-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose as a white foam (**3.16a**, 2.690 g, 45%). Analytical data for **3.16a** and **3.16b** were identical as in chapter 5.1.3.8.

5.1.3.10 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (3.17)

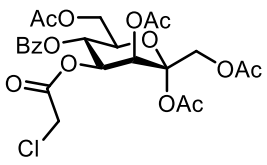


3.17
$C_{20}H_{21}ClO_{10}$
456.83 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.16b**, 4.268 g, 11.22 mmol, 1 equiv.) was dissolved in dry DCM (75 mL) under argon and cooled to 0°C. Pyridine (3.550 g, 3.6 mL, 44.89 mmol, 4 equiv.) was added dropwise followed by chloroacetic anhydride (3.837 g, 22.44 mmol, 2 equiv.), dissolved in dry DCM (37 mL). The reaction mixture was stirred at 0°C for 2.5 h. Water (75 mL) was added at 0°C and stirring was continued for 5 min. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with 1 M HCl, water and brine, dried over $MgSO_4$, filtered and evaporated to give 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose as a white foam

which was used without further purification (**3.17**, 4.843 g, 94%). R_f = 0.37 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = -149.8 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.10 (d, $^3J_{H,H}$ = 7.3 Hz, 2H, H^{Ar}), 7.63 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.49 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.54 (dt, $^3J_{4,3}$ = 5.4 Hz, $^3J_{4,5}$ = $^4J_{4,6}$ = 1.5 Hz, 1H, H-4), 5.36 (d, $^3J_{3,4}$ = 5.4 Hz, 1H, H-3), 5.13 (t, $^3J_{5,4}$ = $^3J_{5,6}$ = 1.5 Hz, 1H, H-5), 4.86 (d, $^3J_{6,7b}$ = 5.5 Hz, 1H, H-6), 4.54 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.39 (d, $^2J_{7a,7b}$ = 7.8 Hz, 1H, H-7a), 4.17 (s, 2H, CH_2^{ClAc}), 4.05 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 4.03 (dd, $^2J_{7b,7a}$ = 7.8 Hz, $^3J_{7b,6}$ = 5.5 Hz, 1H, H-7b), 2.10 (s, 3H, $CH_3^{Ac\text{-}1}$), 2.04 (s, 3H, $CH_3^{Ac\text{-}1}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.28 ($C^{Ac\text{-}1}$), 169.53 ($C^{Ac\text{-}3}$), 166.38 (C^{ClAc}), 165.47 (C^{Bz}), 134.03 (CH^{Ar}), 130.23 (2 CH^{Ar}), 128.88 (C^{Ar}), 128.74 (2 CH^{Ar}), 105.50 (C-2), 75.96 (C-6), 72.59 (C-5), 70.07 (C-4), 66.58 (C-7), 65.91 (C-3), 61.96 (C-1), 40.66 (CH_2^{ClAc}), 20.84 ($CH_3^{Ac\text{-}1}$), 20.63 ($CH_3^{Ac\text{-}3}$). HRMS (ESI+): *m/z* calc. for $C_{20}H_{21}ClO_{10}Na^+$ $[M+Na]^+$: 479.0715, found: 479.0725.

5.1.3.11 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (3.18)

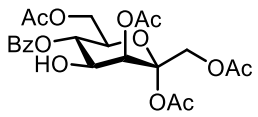


3.18
$C_{24}H_{27}ClO_{13}$
558.92 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (**3.17**, 4.746 g, 10.39 mmol, 1 equiv.) was dissolved in acetic anhydride (104 mL) under argon and cooled to 0°C. Triethylsilyltrifluoromethanesulfonate (2.746 g, 2.35 mL, 19.39 mmol, 1 equiv.) was added dropwise and the reaction mixture was stirred at 0°C for 1 h. After NMR indicated completion of the reaction it was quenched by the slow addition of sat. aq. $NaHCO_3$-sol. (2 L) at 0°C. The mixture was diluted with DCM and the layers were separated. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with sat. aq. $NaHCO_3$-sol. and brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 12-63% EA in *n*-heptane) to give 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose as a white foam (**3.18**, 5.643 g, 97%). R_f = 0.36 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = +23.4 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.99 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, H^{Ar}), 7.60 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.46 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.59 (dd, $^3J_{4,5}$ = 10.5 Hz, $^3J_{4,3}$ = 2.6 Hz, 1H, H-4), 5.57 (t, $^3J_{5,4}$ = $^3J_{5,6}$ = 10.5 Hz, 1H, H-5), 5.52 (d, $^3J_{3,4}$ = 2.6 Hz, 1H, H-3), 4.88 (d, $^2J_{1a,1b}$ = 12.3 Hz, 1H, H-1a), 4.49 (d, $^2J_{1b,1a}$ = 12.3 Hz, 1H, H-1b), 4.29 (dd, $^2J_{7a,7b}$ = 12.3 Hz, $^3J_{7a,6}$ = 5.7 Hz, 1H, H-7a), 4.21 (dd, $^2J_{7b,7a}$ = 12.3 Hz, $^3J_{7b,6}$ = 3.0 Hz, 1H, H-7b), 4.10 (ddd, $^3J_{6,5}$ = 9.7 Hz, $^3J_{6,7a}$ =

5.7 Hz, $^{3}J_{6,7b}$ = 3.0 Hz, 1H, H-6), 3.90 (d, $^{2}J_{H,H}$ = 15.2 Hz, 1H, H^{ClAc}), 3.87 (d, $^{2}J_{H,H}$ = 15.2 Hz, 1H, H^{ClAc}), 2.21 (s, 3H, CH_3^{Ac-2}), 2.19 (s, 3H, $CH_3^{Ac-1\ or\ 3}$), 2.04 (s, 3H, $CH_3^{Ac-1\ or\ 3}$), 2.02 (s, 3H, CH_3^{Ac-7}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 170.74 (C^{Ac-7}), 169.97 ($C^{Ac-1\ or\ 3}$), 169.90 ($C^{Ac-1\ or\ 3}$), 167.69 (C^{Ac-2}), 166.73 (C^{ClAc}), 165.47 (C^{Bz}), 134.01 (CH^{Ar}), 130.02 (2 CH^{Ar}), 128.80 (2 CH^{Ar}), 128.72 (C^{Ar}), 102.05 (C-2), 71.23 (C-4), 71.03 (C-6), 67.12 (C-3), 66.06 (C-5), 62.42 (C-7), 60.15 (C-1), 40.46 (CH_2^{ClAc}), 22.04 (CH_3^{Ac-2}), 20.86 ($CH_3^{Ac-1,3\ or\ 7}$), 20.76 ($CH_3^{Ac-1,3\ or\ 7}$), 20.70 ($CH_3^{Ac-1,3\ or\ 7}$). HRMS (ESI+): *m/z* calc. for $C_{24}H_{27}ClO_{13}Na^{+}$ $[M+Na]^{+}$: 581.1032, found: 581.1017.

5.1.3.12 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (3.19)

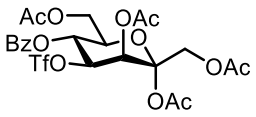


3.19
$C_{22}H_{26}O_{12}$
482.44 g/mol

Hydrazine hydrate (1.700 g, 1.65 mL, 33.96 mmol, 1 equiv.) was dissolved in a 2:1 (v/v) mixture of ethanol and water (68 mL) and cooled to 0°C. *N,N*-Diisopropyl-*N*-ethylamine (4.389 g, 5.9 mL, 33.96 mmol, 1 equiv.) was slowly added followed by carbon disulfide (2.586 g, 2.0 mL, 33.96 mmol, 1 equiv.) in dioxane (14 mL). The mixture was stirred at 0°C for 10 min and was used immediately in the next step. 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.18**, 5.643 g, 10.10 mmol, 1 equiv.) was dissolved in a 3:1 (v/v) mixture of 2,6-lutidine and acetic acid (101 mL) and cooled to 0°C. The freshly prepared hydrazine dithiocarbonate solution (~0.375 M, 81 mL, 30.29 mmol, 3 equiv.) was added dropwise. The reaction was stirred at 0°C for 20 min before a sat. aq. $NaHCO_3$-sol. (250 mL) was added. The mixture was extracted thrice with DCM. The combined organic layers were washed with sat. aq. $NaHCO_3$-sol., 0.5 M HCl, sat. aq. $NaHCO_3$-sol. and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (340 g silica gel, 12-83% EA in *n*-heptane) to give 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose as a white solid (**3.19**, 3.685 g, 76%). R_f = 0.23 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = +44.0 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.05 (d, $^{3}J_{H,H}$ = 7.3 Hz, 2H, H^{Ar}), 7.61 (t, $^{3}J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.47 (t, $^{3}J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.53 (d, $^{3}J_{3,4}$ = 3.6 Hz, 1H, H-3), 5.31 (t, $^{3}J_{5,4}$ = $^{3}J_{5,6}$ = 10.0 Hz, 1H, H-5), 4.82 (d, $^{2}J_{1a,1b}$ = 12.2 Hz, 1H, H-1a), 4.46 (d, $^{2}J_{1b,1a}$ = 12.2 Hz, 1H, H-1b), 4.31 (ddd, $^{3}J_{4,5}$ = 10.0 Hz, $^{3}J_{4,OH}$ = 5.3 Hz, $^{3}J_{4,3}$ = 3.6 Hz, 1H, H-4), 4.29-4.25 (m, 2H, H-7a & H-7b), 4.07 (ddd, $^{3}J_{6,5}$ = 10.0 Hz, $^{3}J_{6,7a}$ = 4.7 Hz, $^{3}J_{6,7b}$ = 3.8 Hz 1H, H-6), 2.48 (d, $^{3}J_{OH,4}$ = 5.3 Hz, 1H, OH), 2.20 (s,

3H, CH_3^{Ac-3}), 2.16 (s, 3H, CH_3^{Ac-2}), 2.06 (s, 3H, CH_3^{Ac-1}), 2.03 (s, 3H, CH_3^{Ac-7}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.85 (C^{Ac-7}), 170.31 (C^{Ac-3}), 170.08 (C^{Ac-1}), 167.78 (C^{Ac-2}), 166.92 (C^{Bz}), 133.97 (CH^{Ar}), 130.08 (2 CH^{Ar}), 129.03 (C^{Ar}), 128.74 (2 CH^{Ar}), 102.31 (C-2), 70.77 (C-6), 69.86 (C-5), 69.36 (C-3 or C-4), 69.35 (C-3 or C-4), 62.65 (C-7), 60.54 (C-1), 21.99 (CH_3^{Ac-2}), 20.96 ($CH_3^{Ac-1,3\ or\ 7}$), 20.82 ($CH_3^{Ac-1,3\ or\ 7}$), 20.75 ($CH_3^{Ac-1,3\ or\ 7}$). HRMS (ESI+): *m/z* calc. for $C_{22}H_{26}O_{12}Na^+$ [M+Na]$^+$: 505.1316, found: 505.1297.

5.1.3.13 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (3.20a)

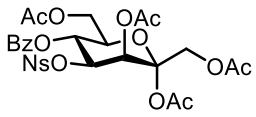


3.20a
$C_{23}H_{25}F_3O_{14}S$
614.49 g/mol

1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.19**, 300 mg, 0.62 mmol, 1 equiv.) was dissolved in dry DCM (3 mL) under argon and cooled to 0°C. Dry pyridine (418 mg, 430 µL, 5.29 mmol, 8.5 equiv.) and trifluoromethanesulfonic anhydride (351 mg, 210 µL, 1.24 mmol, 2 equiv.) were added dropwise. The reaction mixture was stirred at 0°C for 1h before it was diluted with DCM (3 mL) and quenched by the dropwise addition of ice-cold 1 M aq. HCl (5 mL). The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with ice-cold water, ice-cold sat. aq. $NaHCO_3$-solution and ice-cold brine. The organic layer was dried over $MgSO_4$, filtered and evaporated at 25°C. The crude residue was purified by MPLC (25 g silica gel, 8-66% EA in *n*-heptane) to give a colorless oil. Co-evaporating the oil thrice with Et_2O yielded 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose as a white foam (**3.20a**, 320 mg, 84%). R_f = 0.37 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = +0.62 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.06 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, H^{Ar}), 7.62 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, H^{Ar}), 7.47 (t, $^3J_{H,H}$ = 7.9 Hz, 2H, H^{Ar}), 5.74 (d, $^3J_{3,4}$ = 3.5 Hz, 1H, H-3), 5.69 (t, $^3J_{5,4}$ = $^3J_{5,6}$ = 10.1 Hz, 1H, H-5), 5.35 (dd, $^3J_{4,5}$ = 10.1 Hz, $^3J_{4,3}$ = 3.5 Hz, 1H, H-4), 4.86 (d, $^2J_{1a,1b}$ = 12.4 Hz, 1H, H-1a), 4.45 (d, $^2J_{1b,1a}$ = 12.4 Hz, 1H, H-1b), 4.28 (dd, $^2J_{7a,7b}$ = 12.3 Hz, $^3J_{7a,6}$ = 5.5 Hz, 1H, H-7a), 4.20 (dd, $^2J_{7b,7a}$ = 12.3 Hz, $^3J_{7b,6}$ = 3.2 Hz, 1H, H-7b), 4.08 (ddd, $^3J_{6,5}$ = 10.1 Hz, $^3J_{6,7a}$ = 5.5 Hz, $^3J_{6,7b}$ = 3.2 Hz, 1H, H-6), 2.22 (s, 3H, CH_3^{Ac-3}), 2.22 (s, 3H, CH_3^{Ac-2}), 2.07 (s, 3H, CH_3^{Ac-1}), 2.00 (s, 3H, CH_3^{Ac-7}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.64 (C^{Ac-7}), 169.96 (C^{Ac-1}), 168.84 (C^{Ac-3}), 167.43 (C^{Ac-2}), 165.11 (C^{Bz}), 134.20 (CH^{Ar}), 130.16 (2 CH^{Ar}), 128.78 (2 CH^{Ar}), 128.25 (C^{Ar}), 118.31 (q, $^1J_{C,F}$ = 319.6 Hz, C^{Tf}), 102.31 (C-2), 82.17 (C-4), 70.96 (C-6), 67.33 (C-3), 65.89 (C-5), 62.20 (C-7),

59.88 (C-1), 22.02 (CH_3^{Ac-2}), 20.71 ($CH_3^{Ac-1,3\ or\ 7}$), 20.69 ($CH_3^{Ac-1,3\ or\ 7}$), 20.60 ($CH_3^{Ac-1,3\ or\ 7}$). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -75.30 (s). HRMS (ESI+): *m/z* calc. for $C_{23}H_{25}F_3O_{14}SNa^+$ $[M+Na]^+$: 637.0809, found: 637.0794.

5.1.3.14 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-*para*-nitrobenzenesulfonyl-D-*glycero*-α-D-*lxyo*-hept-2-ulopyranose (3.20b)

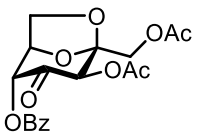


3.20b
$C_{28}H_{29}NO_{16}S$
667.59 g/Mol

1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.19**, 100 mg, 0.21 mmol, 1 equiv.) was dissolved in dry DCM (2 mL) under argon and cooled to 0°C. DMAP (3 mg, 0.02 mmol, 0.1 equiv.) was added followed by triethylamine (59 mg, 80 µL, 0.58 mmol, 2.8 equiv.). *para*-Nitrobenzenesulfonyl chloride (92 mg, 0.41 mmol, 2 equiv.), dissolved in 1 mL dry DCM, was added dropwise. The ice bath was removed and stirring was continued at room temperature for 2 h. The reaction mixture was then cooled again to 0°C and quenched by the dropwise addition of a 5% aq. $NaHCO_3$-solution (3 mL). The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (25 g silica gel, 12-95% EA in *n*-heptane) to give 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-*para*-nitrobenzenesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose as a white solid (**3.20b**, 102 mg, 74%). R_f = 0.33 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = -32.5 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.01 (d, $^3J_{H,H}$ = 8.8 Hz, 2H, H^{Ar}), 7.90 (d, $^2J_{H,H}$ = 8.8 Hz, 2H, H^{Ar}), 7.78 (d, $^3J_{H,H}$ = 7.2 Hz, 2H, H^{Ar}), 7.56 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, H^{Ar}), 7.37 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.72 (d, $^3J_{3,4}$ = 3.5 Hz, 1H, H-3), 5.53 (t, $^3J_{5,4}$ = $^3J_{5,6}$ = 10.1 Hz, 1H, H-5), 5.23 (dd, $^3J_{4,5}$ = 10.1 Hz, $^3J_{4,3}$ = 3.5 Hz, 1H, H-4), 4.84 (d, $^2J_{1a,1b}$ = 12.4 Hz, 1H, H-1a), 4.44 (d, $^2J_{1b,1a}$ = 12.4 Hz, 1H, H-1b), 4.21 (dd, $^2J_{7a,7b}$ = 12.3 Hz, $^3J_{7a,6}$ = 5.6 Hz, 1H, H-7a), 4.14 (dd, $^2J_{7b,7a}$ = 12.3 Hz, $^3J_{7b,6}$ = 3.1 Hz, 1H, H-7b), 4.05 (ddd, $^3J_{6,5}$ = 10.1 Hz, $^3J_{6,7a}$ = 5.6 Hz, $^3J_{6,7b}$ = 3.1 Hz, 1H, H-6), 2.24 (s, 3H, CH_3^{Ac-2}), 2.17 (s, 3H, CH_3^{Ac-3}), 2.07 (s, 3H, CH_3^{Ac-1}), 1.97 (s, 3H, CH_3^{Ac-7}). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.64 (C^{Ac-7}), 170.01 (C^{Ac-1}), 168.89 (C^{Ac-3}), 167.56 (C^{Ac-2}), 164.74 (C^{Bz}), 150.49 (C^{Ar}), 141.75 (C^{Ar}), 134.30 (CH^{Ar}), 129.82 (2 CH^{Ar}), 128.94 (2 CH^{Ar}), 128.64 (2 CH^{Ar}), 128.17 (C^{Ar}), 124.34 (2 CH^{Ar}), 102.35 (C-2), 77.58 (C-4), 70.81 (C-6), 67.93 (C-3), 65.82 (C-5), 62.22 (C-7), 59.99 (C-1), 22.11 (CH_3^{Ac-2}), 20.74 ($CH_3^{Ac-1,3\ or\ 7}$), 20.71 ($CH_3^{Ac-1,3\ or\ 7}$), 20.68 ($CH_3^{Ac-1,3\ or\ 7}$). HRMS (ESI+): *m/z* calc. for $C_{28}H_{29}NO_{16}SNa^+$ $[M+Na]^+$: 690.1099, found: 690.1097.

5.1.4 Additional Experiments in the Precursor Synthesis for 4DFS

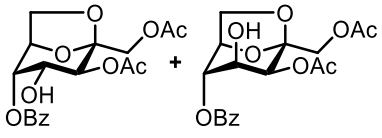
5.1.4.1 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hepto-2,4-diulopyranose (3.21)



3.21
$C_{18}H_{18}O_9$
378.33 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.14**, 225 mg, 0.59 mmol, 1 equiv.) was dissolved in dry DCM (2.4 mL) under argon and Dess-Martin-Periodinane (376 mg, 0.89 mmol, 1.5 equiv.) was added followed by *tert*-butanol (66 mg, 84 µL, 0.89 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with DCM and washed thrice with a 1:1 mixture of a sat. aq. $Na_2S_2O_3$-solution and a sat. aq. $NaHCO_3$-solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (25 g silica gel, 2-20% EA in *n*-heptane) to give 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hepto-2,4-diulopyranose as a white solid (**3.21**, 198 mg, 88%). R_f = 0.25 (*n*-heptane/EA 2:1, UV & CAM). $[\alpha]_D^{20}$ = -123.5 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.08 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, H^{Ar}), 7.63 (t, $^3J_{H,H}$ = 7.3 Hz, 1H, H^{Ar}), 7.49 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, H^{Ar}), 5.68 (s, 1H, H-3), 5.30 (s, 1H, H-5), 5.13 (d, $^3J_{6,7a}$ = 5.8 Hz, 1H, H-6), 4.56 (d, $^2J_{1a,1b}$ = 12.2 Hz, 1H, H-1a), 4.17 (d, $^2J_{1b,1a}$ = 12.2 Hz, 1H, H-1b), 4.07 (dd, $^2J_{7a,7b}$ = 8.0 Hz, $^3J_{7a,6}$ = 5.8 Hz, 1H, H-7a), 3.97 (d, $^2J_{7b,7a}$ = 8.0 Hz, 1H, H-7b), 2.23 (s, 3H, $CH_3^{Ac\text{-}3}$), 2.12 (s, 3H, $CH_3^{Ac\text{-}1}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 194.55 (C-4), 170.11 ($C^{Ac\text{-}1}$), 169.50 ($C^{Ac\text{-}3}$), 165.27 (C^{Bz}), 134.15 (CH^{Ar}), 130.30 (2 CH^{Ar}), 128.79 (2 CH^{Ar}), 128.56 (C^{Ar}), 107.99 (C-2), 77.31 (C-5), 76.90 (C-6), 75.52 (C-3), 66.97 (C-7), 61.62 (C-1), 20.81 ($CH_3^{Ac\text{-}1}$), 20.52 ($CH_3^{Ac\text{-}3}$). HRMS (ESI+): *m/z* calc. for $C_{18}H_{18}O_9Na^+$ $[M+Na]^+$: 401.0843, found: 401.0825.

5.1.4.2 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.14) & 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (3.16b) from 3.21



3.14
$C_{18}H_{20}O_9$
380.35 g/mol

3.16b
$C_{18}H_{20}O_9$
380.35 g/mol

<u>$NaBH_3CN$ in acetic acid:</u> 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hepto-2,4-diulopyranose (**3.21**, 25 mg, 0.07 mmol, 1 equiv.) was dissolved in acetic acid (380 µL) under argon. Sodium cyanoborohydride (4 mg, 0.07 mmol, 1.05 equiv.) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction was poured into a sat. aq. $NaHCO_3$-solution and EA was added. The layers were separated and the aqueous layer was extracted twice with EA. The combined organic

layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. ^1H NMR of the crude residue indicated a 1.5:1 mixture of desired **3.16b** and undesired **3.14**. Analytical data were identical as in chapter 5.1.3.8 and 5.1.3.6.

<u>$NaBH_3CN$ in acetic acid/methanol:</u> **3.21** (17 mg, 0.04 mmol, 1 equiv.) was dissolved in a 1:1 mixture (v/v) of acetic acid and methanol (670 µL) under argon and cooled to -20°C. Sodium cyanoborohydride (3 mg, 0.05 mmol, 1.05 equiv.) was added and stirring was continued at -20°C for 1 h. The reaction was poured into a sat. aq. $NaHCO_3$-solution and EA was added. The layers were separated and the aqueous layer was extracted twice with EA. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. ^1H NMR of the crude residue indicated a 1.5:1 mixture of desired **3.16b** and **3.14**.

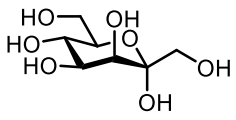
<u>$NaBH_4$:</u> **3.21** (20 mg, 0.05 mmol, 1 equiv.) was dissolved in a 1:1 mixture (v/v) of DCM and MeOH (880 µL) and cooled to -20°C. Sodium borohydride (2 mg, 0.05 mmol, 1 equiv.) was added and the reaction mixture was stirred for 5 min at -20°C. The reaction was quenched by the addition of acetone (100 µL) and sat. aq. NH_4Cl-solution (880 µL). After the addition of EA (3 mL), the layers were separated and the organic layer was dried over $MgSO_4$, filtered and evaporated. ^1H NMR of the crude residue indicated a 1:1.6 mixture of desired **3.16b** and **3.14**.

<u>$NaBH_4/CeCl_3{\cdot}7H_2O$:</u> **3.21** (23 mg, 0.06 mmol, 1 equiv.) was dissolved in a 1:1 mixture (v/v) of DCM and EtOH (1.9 mL) under argon and $CeCl_3{\cdot}7H_2O$ (23 mg, 0.06 mmol, 1 equiv.) was added. The solution was cooled to -78°C, sodium borohydride (2 mg, 0.06 mmol, 1 equiv.) was added and the reaction mixture was stirred at -78°C for 10 min followed by 15 min at -20°C. The reaction was then quenched by the addition of a sat. aq. $NaHCO_3$-solution (1.9 mL) and the mixture was extracted thrice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. ^1H NMR of the crude residue indicated a 1.6:1 mixture of desired **3.16b** and **3.14**.

<u>$BH_3{\cdot}THF$:</u> **3.21** (20 mg, 0.05 mmol, 1 equiv.) was dissolved in THF (150 µL) under argon and cooled to 0°C. $BH_3{\cdot}THF$ complex (1 M in THF, 50 µL, 0.05 mmol, 1 equiv.) was added dropwise and the reaction mixture was stirred at 0°C for 1 h. As TLC indicated incomplete conversion, the solution was warmed to room temperature and stirred for another 2 h. TLC still indicated incomplete conversion and another equivalent of $BH_3{\cdot}THF$ was added before stirring was continued for 16 h. TLC still indicated incomplete conversion and another equivalent of $BH_3{\cdot}THF$ was added before. stirring was continued at room temperature for 1 h. The reaction was quenched at 0°C

by the addition of methanol (500 µL) and subsequently co-evaporated thrice with methanol. ^{1}H NMR of the crude residue indicated a 1:1.9 mixture of desired **3.16b** and **3.14**.

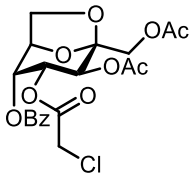
5.1.4.3 D-*Glycero*-α-D-*lyxo*-hept-2-ulopyranose/ α-D-mannoheptulose (3.22)



3.22
$C_7H_{14}O_7$
210.18 g/mol

1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-β-D-*lyxo*-hept-2-ulopyranose (**3.19**, 50 mg, 0.1 mmol, 1 equiv.) was dissolved in dry MeOH (4 mL) under argon. The solution was cooled to 0°C and a freshly prepared 1 M solution of NaOMe (26 µL, 0.026 mmol, 0.25 equiv.) in dry MeOH was added. The mixture was stirred at room temperature for 2 h. After TLC indicated completion of the reaction, it was neutralized by the addition of a spatula tip of DOWEX 50W x8/ H^+-resin. The resin was removed by filtration and washed thrice with MeOH. The filtrate was evaporated and the crude residue was purified by reversed-phase chromatography (C_{18}-silica gel, H_2O) to give D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.22**, α-D-mannoheptulose) as a colorless oil (14 mg, 64%). R_f = 0.4 (1-BuOH/acetone/H_2O 5:4:1, CAM). $[\alpha]_D^{20}$ = +34.6 (c 1.0, H_2O). ^{1}H NMR (600 MHz, D_2O) δ = 3.93 (dd, $^3J_{4,5}$ = 9.6, $^3J_{4,3}$ = 3.4 Hz, 1H, H-4), 3.91 (d, $^3J_{3,4}$ = 3.4 Hz, 1H, H-3), 3.88 (dd, $^2J_{7a,7b}$ = 11.9, $^3J_{7a,6}$ = 2.1 Hz, 1H, H-7a), 3.80 (ddd, $^3J_{6,5}$ = 9.6, $^3J_{6,7b}$ = 6.1, $^3J_{6,7a}$ = 2.1 Hz, 1H, H-6), 3.74 (dd, $^2J_{7b,7a}$ = 11.9, $^3J_{7b,6}$ = 6.1 Hz, 1H, H-7b), 3.73 (d, $^2J_{1a,1b}$ = 11.8 Hz, 1H, H-1a), 3.62 (t, $^3J_{5,4}$ = $^3J_{5,6}$ = 9.6 Hz, 1H, H-5), 3.58 (d, $^2J_{1b,1a}$ = 11.8 Hz, 1H, H-1a). ^{13}C NMR (151 MHz, D_2O) δ = 100.52 (C-2), 75.79 (C-6), 73.66 (C-4), 72.69 (C-3), 69.65 (C-5), 66.84 (C.1), 63.83 (C-7). HRMS (ESI+): *m/z* calc. for $C_7H_{14}O_7Na^+$ $[M+Na]^+$: 233.0631, found: 233.0631.

5.1.4.4 1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (3.23)

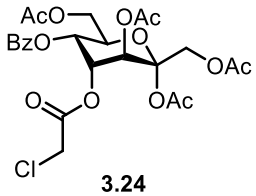


3.23
$C_{20}H_{21}ClO_{10}$
456.83 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.14**, 1.337 g, 3.52 mmol, 1 equiv.) was dissolved in dry DCM (23 mL) under argon and cooled to 0°C. Pyridine (1.308 g, 1.34 mL, 14.06 mmol, 4 equiv.) was added dropwise followed by chloroacetic anhydride (1.202 g, 7.03 mmol, 2 equiv.), dissolved in dry DCM (11.5 mL). The reaction mixture was stirred at 0°C for 2.5 h. Water (23 mL) was added at 0°C and stirring was continued for 5 min. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with 1 M aq. HCl, water and brine, dried over $MgSO_4$,

filtered and evaporated to give 1,3-di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a white solid which was used without further purification (**3.23**, 1.481 g, 92%). R_f = 0.38 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = -147.4 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.10 (d, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 7.63 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.50 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.54 (dd, $^3J_{5,4}$ = 4.7 Hz, $^3J_{5,6}$ = 2.1 Hz, 1H, H-5), 5.46 (d, $^3J_{3,4}$ = 9.1 Hz, 1H, H-3), 5.39 (dd, $^3J_{4,3}$ = 9.1 Hz, $^3J_{4,5}$ = 4.7 Hz, 1H, H-4), 4.89 (dd, $^3J_{6,7b}$ = 5.3 Hz, $^3J_{6,5}$ = 2.1 Hz, 1H, H-6), 4.57 (d, $^2J_{1a,1b}$ = 12.2 Hz, 1H, H-1a), 4.10 (d, $^2J_{7a,7b}$ = 8.3 Hz, 1H, H-7a), 4.04 (d, $^2J_{1b,1a}$ = 12.2 Hz, 1H, H-1b), 4.01 (dd, $^2J_{7b,7a}$ = 8.3 Hz, $^3J_{7b,6}$ = 5.3 Hz, 1H, H-7b), 3.92 (s, 2H, CH_2^{ClAc}), 2.11 (s, 3H, $CH_3^{Ac\text{-}1}$), 2.08 (s, 3H, $CH_3^{Ac\text{-}3}$). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.30 ($C^{Ac\text{-}1}$), 169.92 ($C^{Ac\text{-}3}$), 166.82 (C^{ClAc}), 166.08 (C^{Bz}), 133.93 (CH^{Ar}), 130.19 (2 CH^{Ar}), 129.13 (C^{Ar}), 128.78 (2 CH^{Ar}), 106.30 (C-2), 76.54 (C-6), 70.81 (C-4), 70.44 (C-3), 70.07 (C-5), 66.92 (C-7), 61.44 (C-1), 40.50 (CH_2^{ClAc}), 20.87 ($CH_3^{Ac\text{-}1\text{ or }3}$), 20.82 ($CH_3^{Ac\text{-}1\text{ or }3}$). HRMS (ESI+): *m/z* calc. for $C_{20}H_{21}ClO_{10}Na^+$ [M+Na]$^+$: 479.0715, found: 479.0717.

5.1.4.5 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-α-D-*arabino*-hept-2-ulopyranose (3.24)

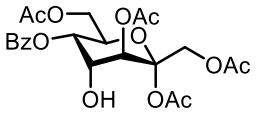


3.24
$C_{24}H_{27}ClO_{13}$
558.92 g/mol

1,3-Di-*O*-acetyl-2,7-anhydro-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.23**, 193 mg, 0.42 mmol, 1 equiv.) was dissolved in acetic anhydride (4.2 mL) under argon and cooled to 0°C. TESOTf (56 mg, 48 µL, 0.5 equiv.) was added and the reaction mixture was stirred at 0°C for 1 h. The reaction was quenched by the addition of a sat. aq. $NaHCO_3$-sol. (10 mL) at 0°C, diluted with DCM and neutralized with more sat. aq. $NaHCO_3$-sol. in a separating funnel. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with a sat. aq. $NaHCO_3$-sol. and brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (50 g silica gel, 8-66% EA in *n*-heptane) to give 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-α-D-*arabino*-hept-2-ulopyranose as a colorless oil (**3.24**, 126 mg, 53%). R_f = 0.14 (*n*-heptane/EA 2:1, UV & CAM). $[\alpha]_D^{20}$ = +34.1 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.94 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, H^{Ar}), 7.59 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, H^{Ar}), 7.45 (t, $^3J_{H,H}$ = 7.7 Hz, 2H, H^{Ar}), 5.52 (t, $^3J_{4,5}$ = $^3J_{4,3}$ = 3.4 Hz, 1H, H-4), 5.49 (d, $^3J_{3,4}$ = 3.4 Hz, 1H, H-3), 5.45 (dd, $^3J_{5,6}$ = 10.3 Hz, $^3J_{5,4}$ = 3.5

Hz, 1H, H-4), 4.79 (d, $^{2}J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.51 (ddd, $^{3}J_{6,5}$ = 10.2 Hz, $^{3}J_{6,7a}$ = 4.9, $^{3}J_{6,7b}$ = 3.0 Hz, 1H, H-6), 4.48 (d, $^{2}J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 4.32 (dd, $^{2}J_{7a,7b}$ = 12.3 Hz, $^{3}J_{7a,6}$ = 5.2 Hz, 1H, H-7a), 4.28 (dd, $^{2}J_{7b,7a}$ = 12.3 Hz, $^{3}J_{7b,6}$ = 2.8 Hz, 1H, H-7b), 4.11 (d, $^{2}J_{H,H}$ = 14.6 Hz, 1H, CH_2^{ClAc}), 4.05 (d, $^{2}J_{H,H}$ = 14.6 Hz, 1H, CH_2^{ClAc}), 2.20 (s, 3H, CH_3^{Ac-3}), 2.17 (s, 3H, CH_3^{Ac-2}), 2.05 (s, 3H, CH_3^{Ac-1}), 2.05 (s, 3H, CH_3^{Ac-7}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.79 (C^{Ac-7}), 170.06 (C^{Ac-1}), 168.70 (C^{Ac-3}), 168.13 (C^{Ac-2}), 165.77 (C^{ClAc}), 165.03 (C^{Bz}), 133.93 (CH^{Ar}), 129.85 (2 CH^{Ar}), 128.82 (C^{Ar}), 128.79 (2 CH^{Ar}), 101.13 (C-2), 68.48 (C-4), 66.89 (C-6), 66.82 (C-3), 64.99 (C-5), 62.54 (C-7), 61.59 (C-1), 40.47 (CH_2^{ClAc}), 22.05 (CH_3^{Ac-2}), 20.86 ($CH_3^{Ac-1or7}$), 20.84 ($CH_3^{Ac-1or7}$), 20.76 (CH_3^{Ac-3}). HRMS (ESI+): *m/z* calc. for $C_{24}H_{27}ClO_{13}Na^{+}$ $[M+Na]^{+}$: 581.1032, found: 581.1032.

5.1.4.6 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*arabino*-hept-2-ulopyranose (3.25)

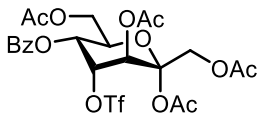


3.25
$C_{22}H_{26}O_{12}$
482.44 g/mol

1,3-Di-*O*-acetyl-5-*O*-benzoyl-4-*O*-chloroacetyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.24**, 540 mg, 0.97 mmol, 1 equiv.) was dissolved in a 3:1 mixture (v/v) of 2,6-lutidine and acetic acid (9.7 mL) and a freshly prepared hydrazine dithiocarbonate solution (~0.375 M, 7.8 mL, 2.90 mmol, 3 equiv.) was added dropwise. The reaction was stirred at room temperature for 20 min before a sat. aq. $NaHCO_3$-sol. (20 mL) was added. The mixture was diluted with DCM and washed with a sat. aq. $NaHCO_3$-sol., 0.2 M HCl, sat. aq. $NaHCO_3$-sol. and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 12-86% EA in *n*-heptane) to give 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*arabino*-hept-2-ulopyranose as a colorless oil (**3.25**, 225 mg, 48%). R_f = 0.26 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = +59.4 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.03 (d, $^{3}J_{H,H}$ = 8.3 Hz, 2H, H^{Ar}), 7.60 (t, $^{3}J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.46 (dd, $^{3}J_{H,H}$ = 8.2 Hz, $^{3}J_{H,H}$ = 7.6 Hz, 2H, H^{Ar}), 5.54 (d, $^{3}J_{3,4}$ = 3.4 Hz, 1H, H-3), 5.29 (dd, $^{3}J_{5,6}$ = 10.3 Hz, $^{3}J_{5,4}$ = 3.4 Hz, 1H, H-5), 4.70 (d, $^{2}J_{1a,1b}$ = 12.0 Hz, 1H, H-1a), 4.59 (ddd, $^{3}J_{6,5}$ = 10.3 Hz, $^{3}J_{6,7a}$ = 5.0 Hz, $^{3}J_{6,7b}$ = 3.1 Hz, 1H, H-6), 4.50 (d, $^{2}J_{1b,1a}$ = 12.0 Hz, 1H, H-1b), 4.33 (dd, $^{2}J_{7a,7b}$ = 12.3 Hz, $^{3}J_{7a,6}$ = 5.0 Hz, 1H, H-7a), 4.30 (dt, $^{3}J_{4,OH}$ = 5.0 Hz, $^{3}J_{4,5}$ = $^{3}J_{4,3}$ = 3.4 Hz, 1H, H-4), 4.30 (dd, $^{2}J_{7b,7a}$ = 12.3 Hz, $^{3}J_{7b,6}$ = 3.1 Hz, 1H, H-7b), 2.40 (d, $^{3}J_{OH,4}$ = 5.0 Hz, 1H, OH), 2.17 (s, 3H, CH_3^{Ac-3}), 2.13 (s, 3H, CH_3^{Ac-2}), 2.06 (s, 3H, CH_3^{Ac-1}), 2.04 (s, 3H, CH_3^{Ac-7}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.89 (C^{Ac-7}), 170.18

(C^{Ac-1}), 169.33 (C^{Ac-3}), 168.43 (C^{Ac-2}), 165.36 (C^{Bz}), 133.90 (CH^{Ar}), 129.93 (2 CH^{Ar}), 129.15 (C^{Ar}), 128.79 (2 CH^{Ar}), 101.55 (C-2), 68.68 (C-3), 67.49 (C-5), 67.11 (C-4), 66.35 (C-6), 62.97 (C-7), 62.17 (C-1), 22.02 (CH_3^{Ac-2}), 20.98 (CH_3^{Ac-3}), 20.87 (CH_3^{Ac-1}), 20.79 (CH_3^{Ac-7}). HRMS (ESI+): *m/z* calc. for $C_{22}H_{26}O_{12}Na^+$ $[M+Na]^+$: 505.1316, found: 505.1314.

5.1.4.7 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*arabino*-hept-2-ulopyranose (3.26)

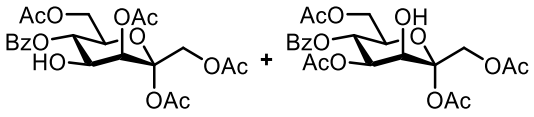


3.26
$C_{23}H_{25}F_3O_{14}S$
614.49 g/mol

1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.25**, 73 mg, 0.15 mmol, 1 equiv.) was dissolved in dry DCM (760 µL) under argon. The solution was cooled to 0°C and pyridine (102 mg, 100 µL, 1.29 mmol, 8.5 equiv.) and trifluoromethanesulfonic anhydride (85 mg, 50 µL, 0.30 mmol, 2 equiv.) were added dropwise. The reaction mixture was stirred at 0°C for 1 h before it was diluted with DCM (3 mL) and quenched by the dropwise addition of ice-cold 1 M HCl (1.5 mL). The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with ice-cold water, an ice-cold sat. aq. $NaHCO_3$-solution and ice-cold brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was dried under high vacuum to give 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose as a yellow oil which was used without further purification (**3.26**, 85 mg, 91%). R_f = 0.46 (*n*-heptane/EA 1:1, UV & CAM). $[\alpha]_D^{20}$ = +42.4 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.04 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, H^{Ar}), 7.62 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.48 (t, $^3J_{H,H}$ = 7.7 Hz, 2H, H^{Ar}), 5.60 (d, $^3J_{3,4}$ = 3.2 Hz, 1H, H-3), 5.48 (dd, $^3J_{5,6}$ = 10.5 Hz, $^3J_{5,4}$ = 3.2 Hz, 1H, H-5), 5.22 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 3.2 Hz, 1H, H-4), 4.78 (d, $^2J_{1a,1b}$ = 12.1 Hz, 1H, H-1a), 4.52 (ddd, $^3J_{6,5}$ = 10.5 Hz, $^3J_{6,7a}$ = 4.8 Hz, $^3J_{6,7b}$ =2.7 Hz, 1H, H-6), 4.50 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 4.35 (dd, $^2J_{7a,7b}$ = 12.4 Hz, $^3J_{7a,6}$ = 4.8 Hz, 1H, H-7a), 4.29 (dd, $^2J_{7b,7a}$ = 12.4 Hz, $^3J_{7b,6}$ = 2.7 Hz, 1H, H-7b), 2.23 (s, 3H, $CH_3^{Ac-2\text{ or }3}$), 2.15 (s, 3H, $CH_3^{Ac-2\text{ or }3}$), 2.07 (s, 3H, CH_3^{Ac-1}), 2.04 (s, 3H, CH_3^{Ac-7}).^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.62 (C^{Ac-7}), 170.03 (C^{Ac-1}), 168.46 ($C^{Ac-2\text{ or }3}$), 168.08 ($C^{Ac-2\text{ or }3}$), 165.04 (C^{Bz}), 134.28 (CH^{Ar}), 130.08 (2 CH^{Ar}), 128.87 (2 CH^{Ar}), 128.24 (C^{Ar}), 118.52 (q, $^1J_{C,F}$ = 318.5 Hz, C^{Tf}), 100.56 (C-2), 79.35 (C-4), 66.43 (C-2 or 6), 66.36 (C-2 or 6), 64.03 (C-5), 62.13 (C-7), 61.39 (C-1), 21.68 ($CH_3^{Ac-2\text{ or }3}$), 20.78 ($CH_3^{Ac-1,2,3\text{ or }7}$), 20.74 ($CH_3^{Ac-1,2,3\text{ or }7}$), 20.72 ($CH_3^{Ac-1,2,3\text{ or }7}$). ^{19}F NMR (659 MHz, $CDCl_3$)

δ = -75.47 (s). HRMS (ESI+): *m/z* calc. for $C_{23}H_{25}F_3O_{14}SNa^+$ [M+Na]$^+$: 637.0809, found: 637.0810.

5.1.4.8 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (3.19) & 1,2,4,7-tetra-*O*-acetyl-5-*O*-benzoyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (3.27)



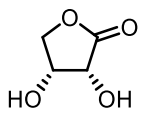
3.19
$C_{22}H_{26}O_{12}$
482.44 g/mol

3.27
$C_{22}H_{26}O_{12}$
482.44 g/mol

Crude 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-β-D-*arabino*-hept-2-ulopyranose (**3.26**, 14 mg, 0.06 mmol, 1 equiv.) was dissolved in dry MeCN (130 µL) under argon and tetrabutylammonium nitrite (57 mg, 0.2 mmol, 8 equiv.) was added. The reaction mixture was stirred at room temperature for 5 h. TLC indicated no conversion. The temperature was elevated to 40°C and stirring was continued at that temperature for 16 h. The reaction was diluted with EA and washed twice with water and once with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. NMR indicated a 1:1 mixture of the desired product **3.19** and the undesired migration product **3.27**.

5.1.5 Synthesis of 1-Deoxy-1-fluoro-D-ribulose (1DFRu)

5.1.5.1 D-*Erythrono*-1,4-lactone (3.28)

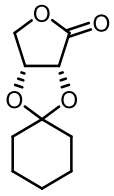


3.28
$C_4H_6O_4$
118.09 g/mol

D-Isoascorbic acid (10.0 g, 56.78 mmol, 1 equiv.) was dissolved in water (142 mL) in a three-necked flask equipped with a thermometer and an addition funnel. The solution was cooled to 0°C and Na_2CO_3 (12.0 g, 113.55 mmol, 2 equiv.) was added in small portions. After the addition was complete 30 % (w/w) aq. H_2O_2 (13 mL, 127.75 mmol, 2.25 equiv.) was added dropwise via an addition funnel at 0°C over 10 min (internal temperature rose to 19°C). The reaction mixture was stirred at 0°C for 5 min and at 42°C for 30 min. Activated charcoal (2.3 g) was added and the reaction mixture was heated to 75°C for 30 min until gas formation has ceased. The mixture was filtered hot over a pad of Celite® which was washed with water (30 mL). The filtrate was carefully acidified with 6 M aq. HCl (43 mL) to pH 1 followed by evaporation of the solvent. The colorless residue was dried under high vacuum with a water bath, refluxed with EA (92 mL) and the liquid was decanted. The refluxing was repeated once with 34 mL EA. The combined organic solutions were left to stand at 4°C overnight. The precipitate was

collected by filtration, washed once with cold EA and dried under high vacuum to give D-*erythrono*-1,4-lactone as white needles (4.450 g, 66%). R_f = 0.19 (EA, $KMnO_4$). $[\alpha]_D^{20}$ = -74.1 (c 1.0, H_2O). ^{1}H NMR (600 MHz, d_6-DMSO): δ = 5.76 (5.76 (bs, 1H, OH), 5.35 (bs, 1H, OH), 4.37 (d, $^3J_{2,3}$ = 4.3 Hz, 1H, H-2), 4.28 (dd, $^2J_{4a,4b}$ = 9.9 Hz, $^3J_{4a,3}$ = 3.1 Hz, 1H, H-4a), 4.23 (dd, $^3J_{3,2}$ = 4.3 Hz, $^3J_{3,4a}$ = 3.1 Hz, 1H, H-3), 4.04 (d, $^2J_{4b,4a}$ = 9.9 Hz, 1H, H-4b). ^{13}C NMR (151 MHz, d_6-DMSO): δ = 176.41 (C-1), 71.78 (C-4), 69.45 (C-2), 68.38 (C-3). HRMS (ESI+): *m/z* calc. for $C_4H_6O_4Na^+$ $[M+Na]^+$: 141.0158, found: 141.0157.

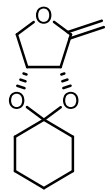
5.1.5.2 2,3-*O*-Cyclohexylidene-D-*erythrono*-1,4-lactone (3.29)



3.29
$C_{10}H_{14}O_4$
198.22 g/mol

D-*Erythrono*-1,4-lactone (**3.28**, 3.000 g, 25.40 mmol, 1 equiv.) was suspended in toluene (150 mL). Cyclohexanone (3.241 g, 3.4 mL, 33.03 mmol, 1.3 equiv.) and *para*-toluenesulfonic acid monohydrate (242 mg, 1.27 mmol, 0.05 equiv.) were added and the resulting mixture was refluxed with a Dean-Stark apparatus for 16 h. After cooling down to room temperature the mixture was poured into a sat. aq. $NaHCO_3$-solution and extracted thrice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was recrystallized from cyclohexane to give 2,3-*O*-cyclohexylidene-D-*erythrono*-1,4-lactone as a white solid (**3.29**, 4.057 g, 81%). R_f = 0.26 (*n*-heptane/EA 2:1, $KMnO_4$). $[\alpha]_D^{20}$ = -113.7 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.86 (dd, $^3J_{3,2}$ = 5.6 Hz, $^3J_{3,4b}$ = 4.0 Hz, 1H, H-3), 4.74 (d, $^3J_{2,3}$ = 5.6 Hz, 1H, H-2), 4.48 (d, $^2J_{4a,4b}$ = 11.0 Hz, 1H, H-4a), 4.40 (dd, $^2J_{4b,4a}$ = 11.0 Hz, $^3J_{4b,3}$ = 4.0 Hz, 1H, H-4b), 1.71-1.56 (m, 8H, CH_2^{cy}), 1.44-1.37 (m, 2H, CH_2^{cy}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.32 (C-1), 114.98 (C^{cy}), 75.17 (C-3), 74.46 (C-2), 70.51 (C-4), 36.54 (CH_2^{cy}), 35.28 (CH_2^{cy}), 24.90 (CH_2^{cy}), 23.97 (CH_2^{cy}), 23.86 (CH_2^{cy}). HRMS (ESI+): *m/z* calc. for $C_{10}H_{14}O_4Na^+$ $[M+Na]^+$: 221.0784, found: 221.0788.

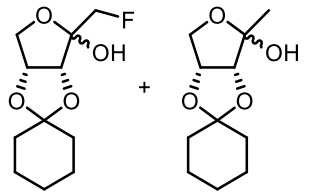
5.1.5.3 2,5-Anhydro-3,4-*O*-cyclohexylidene-1-deoxy-D-*erythro*-pent-1-enitol (3.30)



3.30
$C_{11}H_{16}O_3$
196.25 g/mol

2,3-*O*-Cyclohexylidene-D-*erythrono*-1,4-lactone (**3.29**, 1.000 g, 5.04 mmol, 1 equiv.) was dissolved in dry toluene (25 mL) under argon and Petasis' reagent (0.5 M in toluene, 15 mL, 7.57 mmol, 1.5 equiv.) was slowly added. The flask was equipped with a reflux condenser and the mixture was heated to 70°C for 16 h. After the flask cooled down to room temperature *n*-heptane (80 mL) was added and stirring was continued for 30 min. The orange suspension was filtered over Celite® and the filtrate was evaporated at 25°C. The crude residue was purified by MPLC (100 g silica gel, 2-18% Et_2O in pentane) to give 2,5-anhydro-3,4-*O*-cyclohexylidene-1-deoxy-D-*erythrono*-pent-1-enitol as a yellow oil (**3.30**, 570 mg, 57%). R_f = 0.25 (*n*-heptane/EA 9:1, CAM). $[\alpha]_D^{20}$ = -231.3 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.00 (d, $^3J_{3,4}$ = 5.2 Hz, 1H, H-3), 4.78 (t, $^3J_{4,3}$ = $^3J_{4,5b}$ = 5.2 Hz, 1H, H-4), 4.47 (s, 1H, H-1a), 4.27 (s, 1H, H-1b), 4.24 (d, $^2J_{5a,5b}$ = 10.3 Hz, 1H, H-5a), 4.08 (dd, $^2J_{5b,5a}$ = 10.3 Hz, $^3J_{5b,4}$ = 5.2 Hz, 1H, H-5b), 1.75-1.69 (m, 2H, CH_2^{cy}), 1.67-1.55 (m, 6H, CH_2^{cy}), 1.44-1.35 (m, 2H, CH_2^{cy}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.46 (C-2), 114.10 (C^{cy}), 85.82 (C-1), 79.22 (C-3), 78.29 (C-4), 74.51 (C-5), 36.84 (CH_2^{cy}), 35.48 (CH_2^{cy}), 25.15 (CH_2^{cy}), 24.12 (CH_2^{cy}), 24.01 (CH_2^{cy}). HRMS (ESI+): *m/z* calc. for $C_{11}H_{17}O_3^+$ $[M+H]^+$: 197.1172, found: 197.1170.

5.1.5.4 3,4-*O*-Cyclohexylidene-1-deoxy-1-fluoro-D-ribulose (3.31) & 3,4-*O*-cyclohexylidene-1-deoxy-D-ribulose (3.32)



3.31
$C_{11}H_{17}FO_4$
232.25 g/mol

3.32
$C_{11}H_{18}O_4$
214.26 g/mol

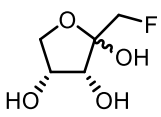
2,5-Anhydro-3,4-*O*-cyclohexylidene-1-deoxy-D-*erythrono*-pent-1-enitol (**3.30**, 200 mg, 1.02 mmol, 1 equiv.) was dissolved in a 1:1 mixture (v/v) of DMF and water (4 mL) and cooled to 0°C. Selectfluor™ (3.610 g, 10.19 mmol, 10 equiv.) was added and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EA and washed twice with water and once with brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (10 g silica gel, 8-60% EA in *n*-heptane) to give 3,4-*O*-cyclohexylidene-1-deoxy-1-fluoro-D-ribulose as a 7.7:1 mixture of the β- and α-anomer and as a colorless oil (**3.31**, 81 mg, 34%) and 44 mg, 3,4-*O*-cyclohexylidene-1-deoxy-D-ribulose as a 4.2:1 mixture of anomers and as a white solid (**3.32**, 20%).

3.31: R_f = 0.19 (*n*-heptane/EA 2:1, CAM). $[\alpha]_D^{20}$ = -60.2 (c 1.0, $CHCl_3$). β-Anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 4.91-4.88 (m, 1H, H-4), 4.64 (dd, $^2J_{1a,F}$ = 47.0 Hz, $^2J_{1a,1b}$ = 9.8 Hz, 1H, H-1a), 4.57 (d, $^3J_{3,4}$ = 5.7 Hz, 1H, H-3), 4.53 (dd, $^2J_{1b,F}$ = 47.0 Hz, $^2J_{1b,1a}$ = 9.8 Hz, 1H, H-1b), 4.07 (dd, $^2J_{5a,5b}$ = 10.3 Hz, $^3J_{5a,4}$ = 3.3 Hz, 1H, H-5a), 4.05 (d, $^2J_{5b,5a}$ = 10.3 Hz, 1H, H-5b), 2.68 (d, $^4J_{OH,F}$ = 2.7 Hz, 1H, OH), 1.70-1.64 (m, 2H, CH_2^{cy}), 1.63-1.58 (m, 2H, CH_2^{cy}), 1.57-1.51 (m, 4H, CH_2^{cy}), 1.45-1.35 (m, 2H, CH_2^{cy}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 113.87 (C^{cy}), 104.26 (d, $^2J_{2,F}$ = 18.1 Hz, C-2), 84.47 (d, $^3J_{3,F}$ = 1.4 Hz, C-3), 84.36 (d, $^1J_{1,F}$ = 170.7 Hz, C-1), 80.33 (C-4), 72.21 (C-5), 36.08 (CH_2^{cy}), 34.47 (CH_2^{cy}), 25.17 (CH_2^{cy}), 24.10 (CH_2^{cy}), 23.85 (CH_2^{cy}). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -232.25 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -232.25 (t, $^2J_{F,1a}$ = $^2J_{F,1b}$ = 47.0Hz).
α-Anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 4.88 (ddd, $^3J_{4,3}$ =6.4 Hz, $^3J_{4,5b}$ = 4.5 Hz, $^3J_{4,5a}$ = 1.7 Hz, 1H, H-4), 4.65 (dd, $^3J_{3,4}$ = 6.4 Hz, $^4J_{3,F}$ = 1.2 Hz, 1H, H-3), 4.44 (dd, $^2J_{1a,1b}$ = 47.0 Hz, $^2J_{1a,1b}$ = 9.6 Hz, 1H, H-1a), 4.40 (dd, $^2J_{1b,F}$ = 47.0 Hz, $^2J_{1b,1a}$ = 9.6 Hz, 1H, H-1b), 4.21 (d, $^4J_{OH,F}$ = 1.6 Hz, 1H, OH), 4.05 (dt, $^2J_{5a,5b}$ = 10.7 Hz, $^3J_{5a,4}$ = $^5J_{5a,F}$ = 1.7 Hz, 1H, H-5a), 3.91 (ddd, $^2J_{5b,5a}$ = 10.7 Hz, $^3J_{5b,4}$ = 4.5 Hz, $^5J_{5b,F}$ = 0.9 Hz, 1H, H-5b), 1.82-1.78 (m, 2H, CH_2^{cy}), 1.71-1.64 (m, 2H, CH_2^{cy}), 1.64-1.59 (m, 2H, CH_2^{cy}), 1.57-1.50 (m, 2H, CH_2^{cy}), 1.45-1.33 (m, 2H, CH_2^{cy}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 115.11 (C^{cy}), 101.64 (C-2), 84.62 (d, $^1J_{1,F}$ = 172.5 Hz, C-1), 80.02 (C-4), 79.17 (d, $^3J_{3,F}$ = 2.0 Hz, C-3), 70.50 (d, $^4J_{5,F}$ = 2.1 Hz, C-5), 36.06 (CH_2^{cy}), 34.32 (CH_2^{cy}), 25.09 (CH_2^{cy}), 24.12 (CH_2^{cy}), 23.72 (CH_2^{cy}). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -239.58 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -239.58 (t, $^2J_{F,1a}$ = $^2J_{F,1b}$ = 47.0 Hz). HRMS (ESI+): *m/z* calc. for $C_{11}H_{17}FO_4Na^+$ $[M+Na]^+$: 255.1003, found: 255.1006.

3.32: R_f = 0.28 (hept/EA 2:1, CAM). $[\alpha]_D^{20}$ = -55.5 (c 0.2, $CDCl_3$). Major anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.86 (dd, $^3J_{4,3}$ = 5.9 Hz, $^3J_{4,5a}$ = 3.9 Hz, 1H, H-4), 4.40 (d, $^3J_{3,4}$ = 5.9 Hz, 1H, H-3), 4.01 (dd, $^2J_{5a,5b}$ = 10.3 Hz, $^3J_{5a,4}$ = 3.9 Hz, 1H, H-5a), 3.93 (d, $^2J_{5b,5a}$ = 10.3 Hz, 1H, H-5b), 1.91 (s, 1H, OH), 1.72-1.35 (m, 10H, CH_2^{cy}), 1.55 (s, 3H, H-1). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 113.34 (C^{cy}), 106.26 (C-2), 84.74 (C-3), 80.68 (C-4), 71.42 (C-5), 36.31 (CH_2^{cy}), 34.79 (CH_2^{cy}), 25.27 (CH_2^{cy}), 24.16 (CH_2^{cy}), 23.95 (CH_2^{cy}), 22.76 (C-1).
Minor anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.79 (ddd, $^3J_{4,3}$ = 6.2 Hz, $^3J_{4,5b}$ = 4.2 Hz, $^3J_{4,5a}$ = 1.4 Hz, 1H, H-4), 4.25 (d, $^3J_{3,4}$ = 6.2 Hz, 1H, H-3), 4.05 (s, 1H, OH), 3.93 (dd, $^2J_{5a,5b}$ = 10.9 Hz, $^3J_{5a,4}$ = 1.4 Hz, 1H, H-5a), 3.63 (dd, $^2J_{5b,5a}$ = 10.9 Hz, $^3J_{5b,4}$ = 4.2 Hz, 1H, H-5b), 1.79-1.33 (m, 10H, CH_2^{cy}), 1.37 (s, 3H, H-1). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 114.34 (C^{cy}), 103.08 (C-2), 81.91 (C-3), 79.87 (C-4), 68.77 (C-5), 36.08 (CH_2^{cy}),

34.54 (CH_2^{cy}), 25.16 (CH_2^{cy}), 24.15 (CH_2^{cy}), 23.80 (CH_2^{cy}), 22.20 (C-1). HRMS (ESI+): *m/z* calc. for $C_{11}H_{18}O_4Na^+$ $[M+Na]^+$: 237.1097, found: 237.1109.

5.1.5.5 1-Deoxy-1-fluoro-D-ribulose (1DFRu)



1DFRu
$C_5H_9FO_4$
152.12 g/mol

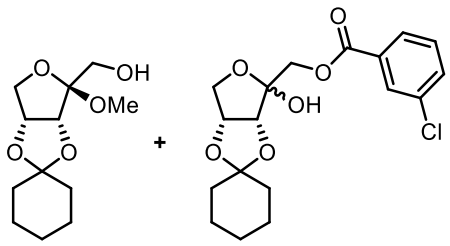
3,4-*O*-Cyclohexylidene-1-deoxy-1-fluoro-D-ribulose (**3.31**, 73 mg, 0.31 mmol, 1 equiv.) was dissolved in 60% (v/v) aq. acetic acid and the mixture was heated at 100°C for 2 h. The mixture was cooled down to room temperature and co-evaporated thrice with toluene. The crude residue was purified by reversed-phase chromatography (C_{18}-silica gel, H_2O) to give 1-deoxy-1-fluoro-D-ribulose as a 2.3:1 mixture of anomers and as a white solid (**1DFRu**, 44 mg, 92%). R_f = 0.27 (EA, CAM). $[\alpha]_D^{20}$ = -14.9 (c 1.0, H_2O).

Major anomer: ^{1}H NMR (700 MHz, D_2O) δ = 4.43 (dd, $^2J_{1a,F}$ = 46.6 Hz, $^2J_{1a,1b}$ = 10.0 Hz, 1H, H-1a), 4.39 (dd, $^2J_{1b,F}$ = 46.6 Hz, $^2J_{1b,1a}$ = 10.0 Hz, 1H, H-1b), 4.37 (td, $^3J_{4,3}$ = $^3J_{4,5a}$ = 5.0 Hz, $^3J_{4,5b}$ = 2.5 Hz, 1H, H-4), 4.18 (d, $^3J_{3,4}$ = 5.0 Hz, 1H, H-3), 4.08 (dd, $^2J_{5a,5b}$ = 10.1 Hz, $^3J_{5a,4}$ = 5.0 Hz, 1H, H-5a), 3.99 (dd, $^2J_{5b,5a}$ = 10.1 Hz, $^3J_{5b,4}$ = 2.5 Hz, 1H, H-5b). ^{13}C NMR (176 MHz, D_2O) δ = 103.41 (d, $^2J_{2,F}$ = 19.7 Hz, C-2), 85.38 (d, $^1J_{1,F}$ = 172.5 Hz, C-1), 74.43 (C-5), 73.47 (d, $^3J_{3,F}$ = 1.7 Hz, C-3), 72.64 (C-4). ^{19}F{^{1}H} NMR (659 MHz, D_2O) δ = -228.06 (s). ^{19}F NMR (659 MHz, D_2O) δ = -228.06 (t, $^2J_{F,1a}$ = $^2J_{F,1b}$ = 46.6 Hz).

Minor anomer: ^{1}H NMR (700 MHz, D_2O) δ = 4.63 (dd, $^2J_{1a,F}$ = 46.6 Hz, $^2J_{1a,1b}$ = 10.1 Hz, 1H, H-1a), 4.59 (q, $^3J_{4,3}$ = $^3J_{4,5a}$ = $^3J_{4,5b}$ = 5.4 Hz, 1H, H-4), 4.47 (dd, $^2J_{1b,F}$ = 46.6 Hz, $^2J_{1b,1a}$ = 10.1 Hz, 1H, H-1b), 4.23 (ddd, $^2J_{5a,5b}$ = 9.5 Hz, $^3J_{5a,4}$ = 5.4, $^5J_{5a,F}$ = 1.0 Hz, 1H, H-5a), 4.16 (d, $^3J_{3,4}$ = 4.9 Hz, 1H, H-3), 3.82 (dd, $^2J_{5b,5a}$ = 9.5 Hz, $^3J_{5b,4}$ = 5.4 Hz, 1H, H-5b). ^{13}C NMR (176 MHz, D_2O) δ = 106.58 (d, $^2J_{2,F}$ = 19.4 Hz, C-2), 85.64 (d, $^1J_{1,F}$ = 169 Hz, C-1), 78.66 (C-3), 73.61 (C-5), 73.06 (C-4). ^{19}F{^{1}H} NMR (659 MHz, D_2O) δ = -231.46 (s). ^{19}F NMR (659 MHz, D_2O) δ = -231.46 (t, $^2J_{F,1a}$ = $^2J_{F,1b}$ = 46.6 Hz). HRMS (ESI+): *m/z* calc. for $C_5H_9FO_4Na^+$ $[M+Na]^+$: 175.0377, found: 175.0378.

5.1.6 Synthesis of a Potential Radiolabeling Precursor for 1DFRu

5.1.6.1 Methyl 3,4-*O*-cyclohexylidene-β-D-*ribulo*-furanoside (3.33) & 1-*O*-meta-chlorobenzoyl-3,4-*O*-cyclohexylidene-D-ribulose (3.35)



3.33
$C_{12}H_{20}O_5$
244.29 g/mol

3.35
$C_{18}H_{21}ClO_6$
368.81 g/mol

Purification of *m*-CPBA:[141] A 0.1 M aq. NaOH-sol. (41 mL) was added to a 0.2 M aq. KH_2PO_4-sol. (25 mL) and filled up to 100 mL with water. The solution was stirred for 5 min and the pH was adjusted to 7.5. Commercial *m*-CPBA (3.000 g, 70−75%) was dissolved in Et_2O (20 mL) and washed thrice with the prepared buffer solution (3x15 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to yield *m*-CPBA (1.83 g) as a white solid which was stored at +4°C. 2,5-Anhydro-3,4-*O*-cyclohexylidene-1-deoxy-D-*erythrono*-pent-1-enitol (**3.30**, 184 mg, 0.94 mmol, 1 equiv.) was dissolved in a dry methanol (3.75 mL) and cooled to 0°C. *m*-CPBA (243 mg, 1.41 mmol, 1.5 equiv.) was added and stirring was continued at 0°C for 1 h. The mixture was diluted with DCM and washed twice with 1 M NaOH and once with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (10 g silica gel, 12-100% EA in *n*-heptane) to give methyl 3,4-*O*-cyclohexylidene-β-D-*ribulo*-furanoside as a single anomer and as a colorless oil (**3.33**, 82 mg, 36%) and 1-*O*-*meta*-chlorobenzoyl-3,4-*O*-cyclohexylidene-D-ribulose 3:1 mixture of anomers and as a colorless oil (**3.35**, 138 mg, 40%).

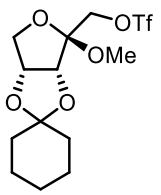
3.33: R_f = 0.17 (*n*-heptane/EA 2:1, CAM). $[\alpha]_D^{20}$ = -99.2 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 4.84 (dd, $^3J_{4,3}$ = 5.9 Hz, $^3J_{4,5b}$ = 3.9 Hz, 1H, H-4), 4.50 (d, $^3J_{3,4}$ = 5.9 Hz, 1H, H-3), 4.01 (d, $^2J_{5a,5b}$ = 10.3 Hz, 1H, H-5a), 3.87 (dd, $^2J_{1a,1b}$ = 12.1 Hz, $^3J_{1a,OH}$ = 2.6 Hz, 1H, H-1a), 3.81 (dd, $^2J_{5b,5a}$ = 10.3 Hz, $^3J_{5b,4}$ = 3.9 Hz, 1H, H-5b), 3.79 (d, $^2J_{1b,1a}$ = 12.1 Hz, 1H, H-1b), 3.24 (s, 3H, OCH_3), 2.09 (bs, 1H, OH), 1.74-1.67 (m, 2H, CH_2^{cy}), 1.66-1.60 (m, 2H, CH_2^{cy}), 1.60-1.50 (m, 4H, CH_2^{cy}), 1.45-1.39 (m, 1H, CH_2^{cy}), 1.39-1.33 (m, 1H, CH_2^{cy}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 113.68 (C^{cy}), 108.82 (C-2), 84.65 (C-3), 80.12 (C-4), 71.83 (C-5), 59.03 (C-1), 48.60 (OCH_3), 36.09 (CH_2^{cy}), 34.35 (CH_2^{cy}), 25.20 (CH_2^{cy}), 24.17 (CH_2^{cy}), 23.85 (CH_2^{cy}). HRMS (ESI+): *m/z* calc. for $C_{12}H_{20}O_5Na^+$ $[M+Na]^+$: 267.1203, found: 267.1213.

3.35: R_f = 0.25 (*n*-heptane/EA 2:1, UV & $KMnO_4$). Major anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.05 (s, 1H, H^{Ar}), 7.97 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, H^{Ar}), 7.55 (d, $^3J_{H,H}$ = 8.0 Hz, 1H, H^{Ar}), 7.40 (t, $^3J_{H,H}$ = 7.9 Hz, 1H, H^{Ar}), 4.92 (dd, $^3J_{4,3}$ = 5.9 Hz, $^3J_{4,5a}$ = 3.5 Hz, 1H,

H-4), 4.64 (d, $^{2}J_{1a,1b}$ = 11.7 Hz, 1H, H-1a), 4.59 (d, $^{3}J_{3,4}$ = 5.9 Hz, 1H, H-3), 4.58 (d, $^{2}J_{1b,1a}$ = 11.7 Hz, 1H, H-1b), 4.10 (dd, $^{2}J_{5a,5b}$ = 10.4, $^{3}J_{4,5a}$ = 3.5 Hz, 1H, H-5a), 4.05 (d, $^{2}J_{5b,5a}$ = 10.4 Hz, 1H, H-5b), 2.81 (s, 1H, OH), 1.75-1.35 (m, 10H, CH_2^{cy}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.65 (C^{mClBz}), 134.63 (C^{Ar}), 133.35 (CH^{Ar}), 131.42 (C^{Ar}), 129.87 (CH^{Ar}), 129.79 (CH^{Ar}), 128.01 (CH^{Ar}), 113.80 (C^{cy}), 104.75 (C-2), 84.31 (C-3), 80.23 (C-4), 72.06 (C-5), 66.34 (C-1), 36.08 (CH_2^{cy}), 34.51 (CH_2^{cy}), 25.07 (CH_2^{cy}), 24.01 (CH_2^{cy}), 23.78 (CH_2^{cy}).

Minor anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.01 (s, 1H, H^{Ar}), 7.93 (d, $^{3}J_{H,H}$ = 7.8 Hz, 1H, H^{Ar}), 7.55 (d, $^{3}J_{H,H}$ = 8.0 Hz, 1H, H^{Ar}), 7.40 (t, $^{3}J_{H,H}$ = 7.9 Hz, 1H, H^{Ar}), 4.89 (d, $^{3}J_{4,5b}$ = 4.5 Hz, $^{3}J_{4,3}$ = 1.7 Hz, 1H, H-4), 4.57 (d, $^{3}J_{3,4}$ = 1.7 Hz, 1H, H-3), 4.44 (d, $^{2}J_{1a,1b}$ = 11.6 Hz, 1H, H-1a), 4.36 (d, $^{2}J_{1b,1a}$ = 11.6 Hz, 1H, H-1b), 4.30 (s, 1H, OH), 4.05 (d, $^{2}J_{5a,5b}$ = 10.8 Hz, 1H, H-5a), 3.91 (dd, $^{2}J_{5b,5a}$ = 10.8 Hz, $^{3}J_{5b,4}$ = 4.5 Hz, 1H, H-5b), 1.83-1.35 (m, 10H, CH_2^{cy}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.96 (C^{mClBz}), 134.69 (C^{Ar}), 133.37 (CH^{Ar}), 131.34 (C^{Ar}), 129.83 (CH^{Ar}), 129.82 (CH^{Ar}), 127.89 (CH^{Ar}), 115.14 (C^{cy}), 102.08 (C-2), 79.71 (C-4), 79.44 (C-3), 70.04 (C-5), 65.77 (C-1), 35.95 (CH_2^{cy}), 34.28 (CH_2^{cy}), 24.94 (CH_2^{cy}), 23.98 (CH_2^{cy}), 23.60 (CH_2^{cy}). HRMS (ESI+): *m/z* calc. for $C_{18}H_{21}ClO_6Na^+$ $[M+Na]^+$: 391.0919, found: 391.0920.

5.1.6.2 Methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside (3.34)



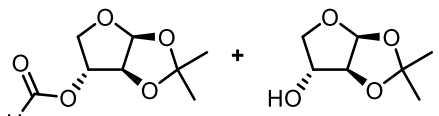
3.34
$C_{13}H_{19}F_3O_7S$
376.34 g/mol

Methyl 3,4-*O*-cyclohexylidene-β-D-*ribulo*-furanoside (**3.33**, 36 mg, 0.15 mmol, 1 equiv.) was dissolved in dry DCM (740 µL) under argon. The solution was cooled to 0°C and dry pyridine (99 mg, 100 µL, 1.25 mmol, 8.5 equiv.) and trifluoromethanesulfonic anhydride (83 mg, 49 µL, 0.29 mmol, 2 equiv.) were added dropwise. The reaction mixture was stirred at 0°C for 1 h before it was quenched by the addition of MeOH (100 µL) and the mixture partitioned between DCM and water. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed twice with ice-cold water and once with an ice-cold sat. aq. $NaHCO_3$-solution and once with ice-cold brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was dried under high vacuum to give methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside as yellow oil (**3.34**, 55 mg, 99%). R_f = 0.53 (*n*-heptane/EA 2:1, CAM). $[\alpha]_D^{20}$ = -71.5 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.86 (dd, $^{3}J_{4,3}$ = 5.7 Hz, $^{3}J_{4,5b}$ = 4.0 Hz, 1H,

H-4), 4.65 (d, $^{2}J_{1a,1b}$ = 10.4 Hz, 1H, H-1a), 4.59 (d, $^{2}J_{1b,1a}$ = 10.4 Hz, 1H, H-1b), 4.48 (d, $^{3}J_{3,4}$ = 5.7 Hz, 1H, H-3), 4.03 (d, $^{2}J_{5a,5b}$ = 10.3 Hz, 1H, H-5a), 3.83 (dd, $^{2}J_{5b,5a}$ = 10.3 Hz, $^{3}J_{5b,4}$ = 4.0 Hz, 1H, H-5b), 3.26 (s, 3H, OCH_3), 1.73-1.50 (m, 8H, CH_2^{cy}), 1.47-1.34 (m, 2H, CH_2^{cy}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 118.77 (q, $^{1}J_{C,F}$ = 319.6 Hz, C^{Tf}), 114.08 (C^{cy}), 106.50 (C-2), 84.03 (C-3), 80.00 (C-4), 72.71 (C-5), 69.26 (C-1), 48.95 (OCH_3), 36.13 (CH_2^{cy}), 34.42 (CH_2^{cy}), 25.19 (CH_2^{cy}), 24.00 (CH_2^{cy}), 23.80 (CH_2^{cy}). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -74.83 (s). HRMS (ESI+): *m/z* calc. for $C_{13}H_{19}F_3O_7SNa^+$ $[M+Na]^+$: 399.0696, found: 399.0687.

5.1.7 Synthesis of 3-Deoxy-3-fluoro-D-ribulose (3DFRu)

5.1.7.1 3-*O*-Formyl-1,2-*O*-isopropylidene-β-D-threose (3.36a) & 1,2-*O*-isopropylidene-β-D-threose (3.36b)



3.36a
$C_8H_{12}O_5$
188.18 g/mol

3.36b
$C_7H_{12}O_4$
160.17 g/mol

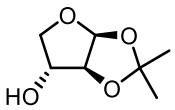
A suspension of D-galactose (8.000 g, 44.4 mmol, 1 equiv.) in water (44 mL) was added to acetic acid (590 mL) and the mixture was heated to dissolution with a hotgun. Thereafter, the solution was cooled to 16°C and $Pb(OAc)_4$ (39.376 g, 88.81 mmol, 2 equiv., previously dried on high vacuum) was added in small portions over 10 min and the reaction mixture was stirred at room temperature for 15 min. Oxalic acid dihydrate (10.077 g, 79.93 mmol, 1.8 equiv.), dissolved in 80 mL acetic acid, was added and stirring was continued for 30 min. The suspension was filtered over Celite® and the filtrate was evaporated at 50°C on a rotary evaporator followed by drying under high vacuum. The remaining solid was suspended in EA (240 mL) and the suspension was washed twice with ice cold water (2x16 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The remaining yellow oil was dissolved in acetone (160 mL), cooled to 0°C under argon and sulfuric acid (830 µL, 1.524 g, 15.54 mmol, 0.35 equiv.) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was neutralized by the addition of a sat. aq. $NaHCO_3$-solution (80 mL) and EA (80 mL) was added. The layers were separated and the org. layer was extracted with 8x50 mL sat. aq. $NaHCO_3$-sol. The org. layer was dried over $MgSO_4$, filtered and evaporated to give 3-*O*-formyl-1,2-*O*-isopropylidene-β-D-threose as a yellow oil which was used without further purification (**3.36a**, 1.740 g, 21%). To the combined aq. layers was added NaCl (100 g) and they were extracted thrice with EA. The combined org. layers were dried over $MgSO_4$, filtered and evaporated to give

1,2-*O*-isopropylidene-β-D-threose as a white solid which was used without further purification (**3.36b**, 1.678 g, 24%).

3.36a: R_f = 0.59 (*n*-heptane/EA 2:1, CAM). $[\alpha]_D^{20}$ = -28.0 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.04 (s, 1H, H^{formyl}), 5.97 (d, $^3J_{1,2}$ = 3.7 Hz, 1H, H-1), 5.26 (d, $^3J_{3,4a}$ = 2.9 Hz, 1H, H-3), 4.60 (d, $^3J_{2,1}$ = 3.7 Hz, 1H, H-2), 4.19 (dd, $^2J_{4a,4b}$ = 10.9 Hz, $^3J_{4a,3}$ = 2.9 Hz, 1H, H-4a), 3.99 (d, $^2J_{4b,4a}$ = 10.9 Hz, 1H, H-4b), 1.51 (s, 3H, CH_3^{isopr}), 1.33 (s, 3H, CH_3^{isopr}). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.93 (C^{formyl}), 112.41 (C^{isopr}), 105.50 (C-1), 83.05 (C-2), 76.84 (C-3), 70.53 (C-4), 26.83 (CH_3^{isopr}), 26.40 (CH_3^{isopr}).

3.36b: R_f = 0.22 (*n*-heptane/EA 2:1, CAM). $[\alpha]_D^{20}$ = -7.6 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 5.96 (d, $^3J_{1,2}$ = 3.6 Hz, 1H, H-1), 4.50 (d, $^3J_{2,1}$ = 3.6 Hz, 1H, H-2), 4.28 (bs, 1H, H-3), 4.10 (dd, $^2J_{4a,4b}$ = 10.2 Hz, $^3J_{4a,3}$ = 2.7 Hz, 1H, H-4a), 3.88 (dd, $^2J_{4b,4a}$ = 10.2 Hz, $^3J_{4b,3}$ = 1.0 Hz, 1H, H-4b), 1.76 (d, $^3J_{OH,3}$ = 4.5 Hz, 1H, OH), 1.48 (s, 3H, CH_3^{isopr}), 1.32 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 111.92 (C^{isopr}), 105.33 (C-1), 85.11 (C-2), 75.48 (C-3), 73.04 (C-4), 26.85 (CH_3^{isopr}), 26.35 (CH_3^{isopr}). HRMS (ESI+): *m/z* calc. for $C_7H_{12}O_4Na^+$ $[M+Na]^+$: 183.0628, found: 183.0628.

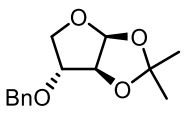
5.1.7.2 1,2-*O*-Isopropylidene-β-D- threose (3.36b) from 3.36a



3.36b
$C_7H_{12}O_4$
160.17 g/mol

3-*O*-Formyl-1,2-*O*-isopropylidene-β-D-threose (**3.36a**, 3.071 g, 16.32 mmol, 1 equiv.) was dissolved in methanol (8.33 mL) and K_2CO_3 (23 mg, 0.16 mmol, 0.01 equiv.) was added. The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated and the crude residue was purified by MPLC (50 g silica gel, 12-100% EA in *n*-heptane) to give 1,2-*O*-isopropylidene-β-D-threose as a white solid (1.969 g, 75%). Analytical data was identical as for **3.36b** in chapter 5.1.7.1.

5.1.7.3 3-*O*-Benzyl-1,2-*O*-isopropylidene-β-D-threose (3.37)

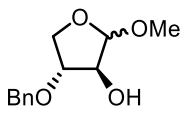


3.37
$C_{14}H_{18}O_4$
250.29 g/mol

1,2-*O*-Isopropylidene-β-D-threose (**3.36b**, 4.660 g, 29.09 mmol, 1 equiv.) was dissolved in dry DMF (291 mL) under argon and cooled to 0°C. Sodium hydride (1.746 g, 72.74 mmol, 2.5 equiv.) was added and the reaction mixture was stirred at 0°C for 1 h. Benzyl bromide (12.441 g, 8.6 mL, 72.74 mmol, 2.5 equiv.) was added dropwise and the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched by the dropwise addition of methanol (120 mL) at 0°C, followed by water (50 mL) and diluted with EA. After the reaction mixture reached room temperature the layers were separated and the aq. layer was extracted twice with EA. The combined

org. layers were washed twice with water and once with brine. The org. layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 5-20% EA in *n*-heptane) to give 3-*O*-benzyl-1,2-*O*-isopropylidene-β-D-threose as a colorless oil (**3.37**, 5.627 g, 77%). R_f = 0.24 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = -24.2 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.37-7.32 (m, 4H, H^{Ar}), 7.31-7.28 (m, 1H, H^{Ar}), 5.96 (d, $^3J_{1,2}$ = 3.7 Hz, 1H, H-1), 4.62 (d, $^3J_{2,1}$ = 3.8 Hz, 1H, H-2), 4.57 (s, 2H, H^{Bn}), 4.05-4.03 (m, 2H, H-4a & H-4b), 4.03-4.02 (m, 1H, H-3), 1.48 (s, 3H, CH_3^{isopr}), 1.32 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 137.54 (C^{Ar}), 128.67 (2 CH^{Ar}), 128.06 (CH^{Ar}), 127.84 (2 CH^{Ar}), 111.74 (C^{isopr}), 105.69 (C-1), 83.09 (C-2), 82.05 (C-3), 71.36 (CH_2^{Bn}), 70.53 (C-4), 26.96 (CH_3^{isopr}), 26.41 (CH_3^{isopr}). HRMS (ESI+): *m/z* calc. for $C_{14}H_{18}O_4Na^+$ $[M+Na]^+$: 273.1097, found: 273.1098.

5.1.7.4 Methyl 3-*O*-benzyl-D-*threo*-furanoside (3.38)



3.38
$C_{12}H_{16}O_4$
224.26 g/mol

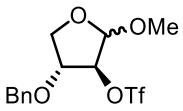
3-*O*-Benzyl-1,2-*O*-isopropylidene-β-D-threose (**3.37**, 5.577 g, 22.28 mmol, 1 equiv.) was dissolved in methanol (290 mL) under argon and cooled to 0°C. Acetyl chloride (12.715 g, 11.6 mL, 161.99 mmol, 7.27 equiv.) was added dropwise and the reaction was stirred at room temperature for 5 h. The reaction was quenched and neutralized by the addition of sat. aq. $NaHCO_3$-sol. The mixture was then evaporated, redissolved in DCM and washed with a sat. aq. $NaHCO_3$-sol. and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 10-55% EA in *n*-heptane) to give methyl 3-*O*-benzyl-D-*threo*-furanoside as a mixture of anomers and as a colorless oil (**3.38**, 4.445 g, 89%). R_f = 0.06 & 0.14 (*n*-heptane/EA 3:1, UV & CAM). $[\alpha]_D^{20}$ = +13.3 (c 1.0, $CHCl_3$).

Major anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37-7.28 (m, 5H, H^{Ar}), 4.81 (s, 1H, H-1), 4.64 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.57 (d, $^2J_{H,H}$ = 12.1 Hz, 1H, H^{Bn}), 4.20 (bs, 1H, H-2), 4.19 (dd, $^2J_{4a,4b}$ = 9.5 Hz, $^3J_{4a,3}$ = 6.1 Hz, 1H, H-4a), 3.96 (td, $^3J_{3,4a}$ = $^3J_{3,4b}$ = 6.13 Hz, $^3J_{3,2}$ = 2.2 Hz, 1H, H-3), 3.84 (dd, $^2J_{4b,4a}$ = 9.5 Hz, $^3J_{4b,3}$ = 6.1 Hz, 1H, H-4b), 3.39 (s, 3H, OCH_3). (α-anomer). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.84 (C^{Ar}), 128.67 (2 CH^{Ar}), 128.09 (3 CH^{Ar}), 109.54 (C-1), 84.29 (C-3), 80.62 (C-2), 72.46 (CH_2^{Bn}), 70.75 (C-4), 55.20 (OCH_3).

Minor anomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.36-7.27 (m, 5H, H^{Ar}), 4.95 (d, $^3J_{1,2}$ = 4.6 Hz, 1H, H-1), 4.70 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.56 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.23 (t, $^3J_{2,1}$ = $^3J_{2,3}$ = 3.8 Hz, 1H, H-2), 4.09 (dd, $^2J_{4a,4b}$ = 9.6 Hz, $^3J_{4a,3}$ = 6.0 Hz, 1H, H-

4a), 4.04 (dt, $^3J_{3,4a}$ = 6.0 Hz, $^3J_{3,2}$ = $^3J_{3,4b}$ = 3.8 Hz, 1H, H-3), 3.80 (dd, $^2J_{4b,4a}$ = 9.6 Hz, $^3J_{4b,3}$ = 3.8 Hz, 1H, H-4b), 3.46 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.96 (C^{Ar}), 128.60 (2 CH^{Ar}), 127.96 (2 CH^{Ar}), 127.94 (CH-Ar), 102.93 (C-1), 83.75 (C-3), 77.84 (C-2), 71.69 (CH_2^{Bn}), 69.97 (C-4), 55.63 (OCH_3). HRMS (ESI+): *m/z* calc. for $C_{12}H_{16}O_4Na^+$ $[M+Na]^+$: 247.0941, found: 247.0941.

5.1.7.5 Methyl 3-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-D-*threo*-furanoside (3.39)



3.39
$C_{13}H_{15}F_3O_6S$
356.31 g/mol

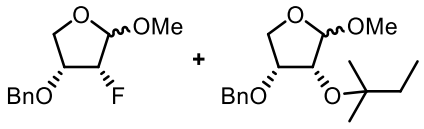
Methyl 3-*O*-benzyl-D-*threo*-furanoside (**3.38**, 1.533 g, 6.84 mmol, 1 equiv.) was dissolved in dry DCM (34 mL) under argon and cooled to 0°C. Dry pyridine (4.596 g, 4.7 mL, 58.10 mmol, 8.5 equiv.) and trifluoromethanesulfonic anhydride (3.857 g, 2.3 mL, 13.67 mmol, 2 equiv.) were added dropwise. The reaction mixture was stirred at 0°C for 1 h before being quenched by the dropwise addition of ice-cold 1 M aq. HCl (34 mL). The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with an ice-cold sat. aq. $NaHCO_3$-sol., ice-cold water and ice-cold brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give methyl 3-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-D-*threo*-furanoside as a red oil which was used without further purification (**3.39**, 2.191 g, 90%). R_f = 0.37 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = +2.6 (c 1.0, $CHCl_3$).

Major anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.38-7.35 (m, 2H, H^{Ar}), 7.34-7.29 (m, 3H, H^{Ar}), 5.19 (s, 1H, H-2), 5.08-5.05 (m, 1H, H-1), 4.72 (d, $^2J_{H,H}$ = 12.2 Hz, 1H, H^{Bn}), 4.54 (d, $^2J_{H,H}$ = 12.2 Hz, 1H, H^{Bn}), 4.26-4.22 (m, 2H, H-3 & H-4a), 3.85 (dd, $^2J_{4b,4a}$ = 12.5 Hz, $^3J_{4b,3}$ = 8.9 Hz, 1H, H-4b), 3.41 (s, 3H, OCH_3). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 136.73 (C^{Ar}), 128.80 (3 CH^{Ar}), 128.10 (2 CH^{Ar}), 106.04 (C-1), 92.12 (C-2), 81.43 (C-3), 72.75 (CH_2^{Bn}), 70.69 (C-4), 55.19 (OCH_3). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -75.26 (s).

Minor anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.39-7.35 (m, 2H, H^{Ar}), 7.34-7.30 (m, 3H, H^{Ar}), 5.08-5.04 (m, 2H, H-1 & H-2), 4.64 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.53 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.44 (dt, $^3J_{3,4a}$ = 6.9 Hz, $^3J_{3,2}$ = $^3J_{3,4b}$ = 4.0 Hz, 1H, H-3), 4.11 (dd, $^2J_{4a,4b}$ = 9.7 Hz, $^3J_{4a,3}$ = 6.9 Hz, 1H, H-4a), 3.79 (dd, $^2J_{4b,4a}$ = 9.7 Hz, $^3J_{4b,3}$ = 4.0 Hz, 1H, H-4b), 3.43 (s, 3H, OCH_3). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 136.83 (C^{Ar}), 128.45 (2 CH^{Ar}), 128.42 (CH^{Ar}), 128.00 (2 CH^{Ar}), 100.99 (C-1), 88.58 (C-2), 79.56 (C-3), 72.53

(CH_2^{Bn}), 68.84 (C-4), 55.74 (OCH_3). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -75.16 (s). HRMS (ESI+): *m/z* calc. for $C_{13}H_{15}F_3O_6SNa^+$ $[M+Na]^+$: 379.0434, found: 379.0437.

5.1.7.6 Methyl 3-*O*-benzyl-2-deoxy-2-fluoro-D-*erythro*-furanoside (3.40) & methyl 3-*O*-benzyl-2-*O*-*tert*-amyl-D-*erythro*-furanoside (3.45)



3.40
$C_{12}H_{15}FO_3$
226.25 g/mol

3.45
$C_{17}H_{26}O_4$
294.39 g/mol

The crude triflate **3.39** was dissolved in *tert*-amylalcohol (20 mL) and evenly distributed across two 20 mL microwave vials. To each vial cesium fluoride (3.150 g, 20.05 mmol, 4 equiv.) was added and the vial was flushed with argon and sealed. The mixture was stirred at 90°C for 24 h. After the mixture cooled to room temperature the two solutions were pooled and diluted with 200 mL water and extracted thrice with Et_2O. The combined organic layers were washed with water, sat. aq. $NaHCO_3$-sol. and brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 2-20% EA in *n*-heptane) to give methyl 3-*O*-benzyl-2-deoxy-2-fluoro-D-*erythro*-furanoside as a mixture of anomers and as a colorless oil (**3.40**, 543 mg, 35%) and methyl 3-*O*-benzyl-2-*O*-*tert*-amyl-D-*erythro*-furanoside as a mixture of anomers and as a colorless oil (**3.45**, 343 mg, 17%).

3.40: Major anomer: R_f = 0.25 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = -54.9 (c 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ = 7.38-7.34 (m, 4H, H^{Ar}), 7.34-7.29 (m, 1H, H^{Ar}), 5.03 (d, $^3J_{1,F}$ = 10.1 Hz, 1H, H-1), 4.78 (dd, $^2J_{2,F}$ = 52.5 Hz, $^3J_{2,3}$ = 4.0 Hz, 1H, H-2), 4.69 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.55 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.31 (dtd, $^3J_{3,F}$ = 20.7 Hz, $^3J_{3,4a}$ = $^3J_{3,4b}$ = 6.9 Hz, $^3J_{3,2}$ = 4.0 Hz, 1H, H-3), 4.10 (dd, $^2J_{4a,4b}$ = 8.7 Hz, $^3J_{4a,3}$ = 6.9 Hz, 1H, H-4a), 3.90 (dd, $^2J_{4b,4a}$ = 8.7, $^3J_{4b,3}$ =6.9 Hz, 1H, H-4b), 3.34 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.50 (C^{Ar}), 128.69 (2 CH^{Ar}), 128.23 (CH^{Ar}), 128.09 (2 CH^{Ar}), 106.20 (d, $^2J_{1,F}$ = 29.8 Hz, C-1), 91.39 (d, $^1J_{2,F}$ = 186.4 Hz, C-2), 76.65 (d, $^2J_{3,F}$ = 15.2 Hz, C-3), 72.94 (CH_2^{Bn}), 69.36 (C-4), 55.21 (OCH_3). $^{19}F\{^1H\}$ NMR (659 MHz, $CDCl_3$) δ = -210.80 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -210.80 (ddd, $^2J_{F,2}$ = 52.5 Hz, $^3J_{F,3}$ = 20.7 Hz, $^3J_{F,1}$ = 10.1 Hz).

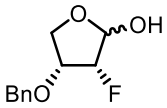
Minor anomer: R_f = 0.08 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = +162.6 (c 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ = 7.38-7.33 (m, 4H, H^{Ar}), 7.31-7.28 (m, 1H, H^{Ar}), 4.98 (dd, $^3J_{1,2}$ = 4.3 Hz, $^3J_{1,F}$ = 3.1 Hz, 1H, H-1), 4.82 (ddd, $^2J_{2,F}$ = 50.9 Hz, $^3J_{2,3}$ = 5.6 Hz, $^3J_{2,1}$ = 4.3 Hz, 1H, H-2), 4.80 (d, $^2J_{H,H}$ = 12.4 Hz, 1H, H^{Bn}), 4.59 (d, $^2J_{H,H}$ = 12.4 Hz, 1H, H^{Bn}), 4.08-4.02 (m, 2H, H-3 & H-4a), 3.96-3.91 (m, 1H, H-4b), 3.50 (s, 3H, OCH_3). ^{13}C

NMR (151 MHz, $CDCl_3$) δ = 137.83 (C^{Ar}), 128.64 (2 CH^{Ar}), 128.06 (CH^{Ar}), 128.03 (2 CH^{Ar}), 101.27 (d, $^2J_{1,F}$ = 15.8 Hz, C-1), 88.51 (d, $^1J_{2,F}$ = 203.8 Hz, C-2), 73.50 (d, $^2J_{3,F}$ = 14.8 Hz, C-3), 72.90 (d, $^4J_{H,F}$ = 2.5 Hz, CH_2-Bn), 69.81 (d, $^3J_{4,F}$ = 2.4 Hz, C-4), 55.97 (OCH_3). $^{19}F\{^1H\}$ NMR (659 MHz, $CDCl_3$) δ = -218.15 (s). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -218.15 (ddd, $^2J_{F,2}$ = 50.9 Hz, $^3J_{F,3}$ = 6.7 Hz, $^3J_{F,1}$ = 3.1 Hz). HRMS (ESI+): *m/z* calc. for $C_{12}H_{15}FO_3Na^+$ $[M+Na]^+$: 249.0897, found: 249.0897.

3.45: Major anomer: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41-7.27 (m, 5H, H^{Ar}), 5.28 (d, $^3J_{1,2}$ = 4.2 Hz, 1H, H-1), 4.71 (d, $^2J_{H,H}$ = 12.5 Hz, 1H, H^{Bn}), 4.57 (d, $^2J_{H,H}$ = 12.5 Hz, 1H, H^{Bn}), 4.04 (ddd, $^3J_{3,4b}$ = 6.4 Hz, $^3J_{3,2}$ = 6.1 Hz, $^3J_{3,4a}$ = 4.8 Hz, 1H, H-3), 3.93 (dd, $^2J_{4a,4b}$ = 9.2 Hz, $^3J_{4a,3}$ = 4.8 Hz, 1H, H-4a), 3.88 (dd, $^2J_{4b,4a}$ = 9.2 Hz, $^3J_{4b,3}$ = 6.4 Hz, 1H, H-4b), 3.55 (dd, $^3J_{2,3}$ = 6.1 Hz, $^3J_{2,1}$ = 4.2 Hz, 1H, H-2), 3.49 (s, 3H, OCH_3), 1.59 (q, $^3J_{H,H}$ = 7.5 Hz, 2H, CH_2*t*-amyl), 1.25 (s, 3H, CH_3 *t*-amyl), 1.23 (s, 3H, CH_3 *t*-amyl), 0.93 (t, $^3J_{H,H}$ = 7.5 Hz, 3H, CH_3 *t*-amyl).

Minor anomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, H^{Ar}), 5.29 (d, $^3J_{1,2}$ = 2.7 Hz, 1H, H-1), 4.72 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, H^{Bn}), 4.65 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, H^{Bn}), 4.18 (dt, $^3J_{3,4a}$ = 5.6 Hz, $^3J_{3,4b}$ = $^3J_{3,2}$ = 4.7 Hz, 1H, H-3), 4.04 (dd, $^2J_{4a,4b}$ = 9.2 Hz, $^3J_{4a,3}$ = 5.6 Hz, 1H, H-4a), 3.86 (dd, $^2J_{4b,4a}$ = 9.2 Hz, $^3J_{4b,3}$ = 4.7 Hz, 1H, H-4b), 3.59 (dd, $^3J_{2,3}$ = 4.7 Hz, $^3J_{2,1}$ = 2.7 Hz, 1H, H-2), 3.46 (s, 3H, OCH_3), 1.52 (q, $^3J_{H,H}$ = 7.4 Hz, 2H, CH_2*t*-amyl), 1.19 (s, 6H, 2 CH_3*t*-amyl), 0.87 (t, $^3J_{H,H}$ = 7.4 Hz, 3H, CH_3*t*-amyl).

5.1.7.7 3-*O*-Benzyl-2-deoxy-2-fluoro-D-erythrose (3.41)



3.41
$C_{11}H_{13}FO_3$
212.22 g/mol

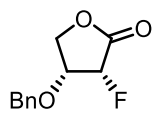
Methyl 3-*O*-benzyl-2-deoxy-2-fluoro-D-*erythro*-furanoside (**3.40**, 546 mg, 2.41 mmol, 1 equiv.) was dissolved in 80% (v/v) aq. TFA. The solution was stirred at room temperature for 2 h. After TLC indicated completion of the reaction, volatiles were evaporated under reduced pressure. The crude residue was purified by MPLC (25 g silica gel, 5-40% EA in *n*-heptane) to give 3-*O*-benzyl-2-deoxy-2-fluoro-D-erythrose as a white solid (**3.41**, 380 mg, 74%). R_f = 0.23 (*n*-heptane/EA 2:1, UV & CAM). $[\alpha]_D^{20}$ = +10.2 (c 1.0, $CHCl_3$).

Major anomer: ^1H NMR (600 MHz, $CDCl_3$) δ = 7.39-7.30 (m, 5H, H^{Ar}), 5.50 (dd, $^3J_{1,F}$ = 10.2 Hz, $^3J_{1,OH}$ = 3.0 Hz, 1H, H-1), 4.83 (dd, $^2J_{2,F}$ = 52.5 Hz, $^3J_{2,3}$ = 3.8 Hz, 1H, H-2), 4.70 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.57 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.39 (dtd, $^3J_{3,F}$ = 21.5 Hz, $^3J_{3,4a}$ = $^3J_{3,4b}$ = 7.3 Hz, $^3J_{3,2}$ = 3.8 Hz, 1H, H-3), 4.22 (dd, $^2J_{4a,4b}$ = 8.6 Hz, $^3J_{4a,3}$ = 7.3 Hz, 1H, H-4a), 3.91 (dd, $^2J_{4b,4a}$ = 8.6 Hz, $^3J_{4b,3}$ = 7.3 Hz, 1H, H-4b), 2.50 (t, $^3J_{OH,1}$ = $^4J_{OH,F}$ = 3.0 Hz, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.43 (C^{Ar}), 128.71 (2

CH^{Ar}), 128.28 (CH^{Ar}), 128.11 (2 CH^{Ar}), 100.23 (d, $^2J_{1,F}$ = 30.5 Hz, C-1), 91.83 (d, $^1J_{2,F}$ = 186.4 Hz, C-2), 76.35 (d, $^2J_{3,F}$ = 15.3 Hz, C-3), 73.00 (CH_2^{Bn}), 69.52 (C-4). $^{19}F\{^1H\}$ NMR (659 MHz, $CDCl_3$) δ = -210.79 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -210.79 (ddd, $^1J_{F,2}$ = 52.5 Hz, $^2J_{F,3}$ = 21.5 Hz, $^2J_{F,1}$ = 10.2 Hz).

Minor anomer: ^1H NMR (600 MHz, $CDCl_3$) δ = 7.39-7.30 (m, 5H, H^{Ar}), 5.27 (dd, $^3J_{1,OH}$ = 12.2 Hz, $^3J_{1,2}$ = 3.4 Hz, 1H, H-1), 4.87 (dt, $^2J_{2,F}$ = 50.9 Hz, $^3J_{2,1}$ = $^3J_{2,3}$ = 4.3 Hz, 1H, H-2), 4.77 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.66 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.17 (qd, $^3J_{3,2}$ = $^3J_{3,4b}$ = $^3J_{3,F}$ = 4.3 Hz, $^3J_{3,4a}$ = 2.5 Hz, 1H, H-3), 4.13 (dt, $^2J_{4a,4b}$ = 9.6 Hz, $^3J_{4a,3}$ = $^4J_{4a,F}$ =2.5 Hz, 1H), 3.97 (dd, $^2J_{4b,4a}$ = 9.6 Hz, $^3J_{4b,3}$ = 4.3 Hz, 1H, H-4b), 3.95 (dd, $^3J_{OH,1}$ = 12.2 Hz, $^4J_{OH,F}$ = 1.6 Hz, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 137.002 (C^{Ar}), 128.80 (2 CH^{Ar}), 128.40 (CH^{Ar}), 128.02 (2 CH^{Ar}), 95.24 (d, $^2J_{1,F}$ = 18.8 Hz, C-1), 89.29 (d, $^1J_{2,F}$ = 200.3 Hz, C-2), 75.71 (d, $^2J_{3,F}$ = 14.6 Hz, C-3), 73.21 (d, $^4J_{C,F}$ = 2.3 Hz, CH_2^{Bn}), 69.50 (d, $^3J_{4,F}$ = 3.1 Hz, C-4). $^{19}F\{^1H\}$ NMR (659 MHz, $CDCl_3$) δ = -217.81 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -217.82 (ddd, $^2J_{F,2}$ = 50.9 Hz, $^3J_{F,3}$ = 4.3 Hz, $^4J_{F,OH}$ = 1.6 Hz). HRMS (ESI+): *m/z* calc. for $C_{11}H_{13}FO_3Na^+$ $[M+Na]^+$: 235.0741, found: 235.0742, *m/z* calc. for $C_{12}H_{17}FO_4Na^+$ $[M+MeOH+Na]^+$: 267.1003, found: 267.1007.

5.1.7.8 3-*O*-Benzyl-2-deoxy-2-fluoro-D-*erythrono*-1,4-lactone (3.42)

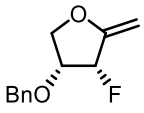


3.42
$C_{11}H_{11}FO_3$
210.20 g/mol

3-*O*-Benzyl-2-deoxy-2-fluoro-D-erythrose (**3.41**, 580 mg, 2.73 mmol, 1 equiv.) was dissolved in dry DCM (23 mL) under argon. NMO (480 mg, 4.10 mmol, 1.5 equiv.) was added and the mixture was stirred for at room temperature 10 min before TPAP (48 mg, 0.14 mmol, 0.05 equiv.) was added. The reaction mixture was stirred at room temperature for 16 h. The mixture was filtered over a short plug of silica gel and eluted with EA. The filtrate was evaporated and the crude residue was purified by MPLC (50 g silica gel, 8-58% EA in *n*-heptane) to give 3-*O*-benzyl-2-deoxy-2-fluoro-D-*erythrono*-1,4-lactone as a white solid (**3.42**, 366 mg, 64%). R_f = 0.17 (*n*-heptane/EA 2:1, CAM). $[\alpha]_D^{20}$ = +9.6 (c 1.0, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$) δ = 7.39-7.31 (m, 5H, H-Ar), 5.20 (dd, $^2J_{2,F}$ = 48.5 Hz, $^3J_{2,3}$ = 4.4 Hz, 1H, H-2), 4.83 (d, $^2J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.65 (d, $^2J_{H,H}$ = 11.9 Hz, 1H, H^{Bn}), 4.42 (ddd, $^2J_{4a,4b}$ = 10.6 Hz, $^4J_{4a,F}$ = 4.2 Hz, $^3J_{4a,3}$ = 0.7 Hz, 1H, H-4a), 4.39 (td, $^3J_{3,2}$ = $^3J_{3,4b}$ = 4.4 Hz, $^3J_{3,4a}$ = 0.7 Hz, 1H, H-3), 4.31 (ddd, $^2J_{4b,4a}$ = 10.6, $^3J_{4b,3}$ = 4.4, $^4J_{4b,F}$ = 1.3 Hz, 1H, H-4b). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 169.92 (d, $^2J_{1,F}$ = 22.7 Hz, C-1), 136.83 (C^{Ar}), 128.79 (2 CH^{Ar}), 128.45 (CH^{Ar}), 128.02 (2 CH^{Ar}), 86.16 (d, $^1J_{2,F}$ = 206.0 Hz, C-2), 73.24 (d, $^2J_{3,F}$ = 14.3 Hz, C-3), 73.04 (d, $^4J_{C,F}$ = 3.2 Hz, CH_2^{Bn}), 69.67

(d, $^{3}J_{4,F}$ = 5.3 Hz, C-4). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -217.91 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -217.91 (dd, $^{2}J_{F,2}$ = 48.5 Hz, $^{4}J_{F,4a}$ = 4.2 Hz). HRMS (ESI+): *m/z* calc. for $C_{11}H_{11}FO_3Na^+$ $[M+Na]^+$: 233.0584, found: 233.0583, *m/z* calc. for $C_{12}H_{15}FO_4Na^+$ $[M+MeOH+Na]^+$: 265.0847, found: 265.0846.

5.1.7.9 2,5-Anhydro-4-*O*-benzyl-3-deoxy-3-fluoro-D-*erythro*-pent-1-enitol (3.43)

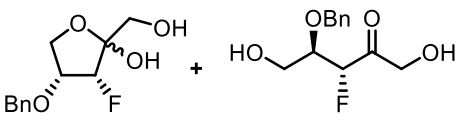


3.43
$C_{12}H_{13}FO_2$
208.23 g/mol

This reaction was carried out in the dark. 3-*O*-Benzyl-2-deoxy-2-fluoro-D-*erythro*-1,4-lactone (**3.42**, 366 mg, 1.74 mmol, 1 equiv.) was suspended in dry toluene (8.7 mL) under argon and Petasis' reagent (0.5 M in toluene, 5.2 mL, 544 mg, 2.61 mmol, 1.5 equiv.) was added dropwise. The flask was equipped with a reflux condenser and the solution was stirred at 70°C for 16 h in the dark. The reaction mixture was cooled to room temperature and diluted with pentane (40 mL) and stirring was continued for 30 min. The orange suspension was filtered through Celite® and the filtrate was evaporated. The crude residue was purified by MPLC (100 g silica gel, 1-10% Et_2O in pentane) to give 2,5-anhydro-4-*O*-benzyl-3-deoxy-3-fluoro-D-*erythro*-pent-1-enitol as a yellow oil (**3.43**, 233 mg, 64%) which was immediately used in the next step: R_f = 0.24 (9:1 *n*-heptane/EA, UV & CAM). $[\alpha]_D^{20}$ = +70.7 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.39-7.35 (m, 4H, H^{Ar}), 7.35-7.31 (m, 1H, H^{Ar}), 5.12 (dd, $^{2}J_{3,F}$ = 55.4 Hz, $^{3}J_{3,4}$ = 3.9 Hz, 1H, H-3), 4.76 (d, $^{2}J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.62 (d, $^{2}J_{H,H}$ = 11.8 Hz, 1H, H^{Bn}), 4.55 (dd, $^{4}J_{1a,F}$ = 5.4 Hz, $^{2}J_{1a,1b}$ = 2.1 Hz, 1H, H-1a), 4.36 (dd, $^{4}J_{1b,F}$ = 5.8 Hz, $^{2}J_{1b,1a}$ = 2.1 Hz, 1H, H-1b), 4.17 (dd, $^{2}J_{5a,5b}$ = 7.6 Hz, $^{3}J_{5a,4}$ = 5.9 Hz, 1H, H-5a), 4.12 (dddd, $^{3}J_{4,F}$ = 16.7 Hz, $^{3}J_{4,5b}$ = 7.6 Hz, $^{3}J_{4,5a}$ = 5.9 Hz, $^{3}J_{4,3}$ = 3.9 Hz, 1H, H-4), 4.08 (td, $^{2}J_{5b,5a}$ = $^{3}J_{5b,4}$ = 7.6 Hz, $^{4}J_{5b,F}$ = 1.8 Hz, 1H, H-5b). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.68 (d, $^{2}J_{2,F}$ = 14.5 Hz, C-2), 137.27 (C^{Ar}), 128.76 (2 CH^{Ar}), 128.37 (CH^{Ar}), 128.12 (2 CH^{Ar}), 88.15 (d, $^{3}J_{1,C}$ = 8.3 Hz, C-1), 88.08 (d, $^{1}J_{3,F}$ = 187.5 Hz, C-3), 76.22 (d, $^{2}J_{4,F}$ = 16.5 Hz, C-4), 72.72 (CH_2^{Bn}), 70.55 (d, $^{3}J_{5,F}$ = 1.5 Hz, C-5). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -193.65 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -193.65 (ddt, $^{2}J_{F,3}$ = 55.4 Hz, $^{3}J_{F,4}$ = 16.7 Hz, $^{4}J_{F,1a}$ = $^{4}J_{F,1b}$ = 5.5 Hz). HRMS (ESI+): *m/z* calc. for $C_{12}H_{13}FO_2Na^+$ $[M+Na]^+$: 231.0792, found: 231.0789.

5.1.7.10 4-O-Benzyl-3-deoxy-3-fluoro-D-ribulose (3.44)

2,5-Anhydro-4-*O*-benzyl-3-deoxy-3-fluoro-D-*erythro*-pent-1-enitol (**3.43**, 207 mg, 0.99 mmol, 1 equiv.) was dissolved in a 4:1 mixture (v/v) of acetone and H_2O (20 mL) and *N*-methylmorpholine *N*-oxide (233 mg, 1.99 mmol, 2 equiv.) was added. Potassium



3.44
$C_{12}H_{15}FO_4$
242.25 g/mol

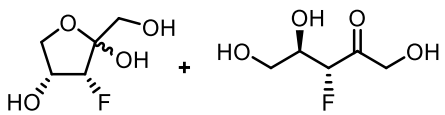
osmate dihydrate (18 mg, 0.05 mmol, 0.05 equiv.) was added and the mixture was stirred at room temperature for 24 h. After TLC indicated completion, the mixture was diluted with EA and the organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (25 g silica gel, 16-100% EA in *n*-heptane) to give 4-*O*-benzyl-3-deoxy-3-fluoro-D-ribulose as a colorless oil and as a 7.6:3.3:1 mixture of anomers and open chain conformation (**3.44**, 161 mg, 67%). R_f = 0.21 (*n*-heptane/EA 1:2, UV & CAM). $[\alpha]_D^{20}$ = +9.4 (c 1.0, $CHCl_3$).

Major anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.39-7.30 (m, 5H, H^{Ar}), 5.01 (dd, $^2J_{3,F}$ = 50.7 Hz, $^3J_{3,4}$ = 4.5 Hz, 1H, H-3), 4.79 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.67 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.33 (d, $^4J_{OH,F}$ = 2.7 Hz, 1H, OH-2), 4.23 (qd, $^3J_{4,3}$ = $^3J_{4,F}$ = $^3J_{4,5b}$ = 4.3 Hz, $^3J_{4,5a}$ = 2.8 Hz, 1H, H-4), 4.14 (dt, $^2J_{5a,5b}$ = 10.2 Hz, $^3J_{5a,4}$ = $^4J_{5a,F}$ = 2.5 Hz, 1H, H-5a), 3.97 (ddd, $^2J_{5b,5a}$ = 10.2 Hz, $^3J_{5b,4}$ = 4.6 Hz, $^4J_{5b,F}$ = 1.3 Hz, 1H, H-5b), 3.69 (ddd, $^2J_{1a,1b}$ = 12.0 Hz, $^3J_{1a,OH}$ = 9.1 Hz, $^4J_{1a,F}$ = 0.7 Hz, 1H, H-1a), 3.62 (dd, $^2J_{1b,1a}$ = 12.0 Hz, $^3J_{1b,OH}$ = 4.8 Hz, 1H, H-1b), 1.81 (dd, $^3J_{OH,1a}$ = 9.1 Hz, $^3J_{OH,1b}$ = 4.9 Hz, 1H, OH-1). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 136.83 (C^{Ar}), 128.66 (2 CH^{Ar}), 128.26 (CH^{Ar}), 127.85 (2 CH^{Ar}), 101.65 (d, $^2J_{2,F}$ = 17.9 Hz, C-2), 88.36 (d, $^1J_{3,F}$ = 200.6 Hz, C-3), 76.33 (d, $^2J_{4,F}$ = 14.5 Hz, C-4), 73.07 (d, $^4J_{C,F}$ = 2.4 Hz, CH_2^{Bn}), 69.32 (d, $^3J_{5,F}$ = 5.3 Hz, C-5), 63.25 (C-1). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -216.52 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -216.52 (d, $^2J_{F,3}$ = 50.7 Hz).

Minor anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.39-7.30 (m, 5H, H^{Ar}), 4.83 (dd, $^2J_{3,F}$ = 53.5 Hz, $^3J_{3,4}$ = 3.9 Hz, 1H, H-3), 4.69 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.57 (d, $^2J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.47 (dtd, $^3J_{4,F}$ = 20.9 Hz, $^3J_{4,5a}$ = $^3J_{4,5b}$ = 7.2 Hz, $^3J_{4,3}$ = 3.9 Hz, 1H, H-4), 4.21 (dd, $^2J_{5a,5b}$ = 8.7 Hz, $^3J_{5a,4}$ = 7.2 Hz, 1H, H-5a), 3.91 (dd, $^2J_{5b,5a}$ = 8.7 Hz, $^3J_{5b,4}$ = 7.2 Hz, 1H, H-5b), 3.84-3.80 (m, 2H, H-1a & H-1b), 3.37 (d, $^4J_{OH,F}$ = 3.1 Hz, 1H, OH-2), 1.94 (dd, $^3J_{OH,1a\ or\ 1b}$ = 7.2 Hz, $^3J_{OH,1a\ or\ 1b}$ = 6.0 Hz, 1H, OH-1). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 137.39 (C^{Ar}), 128.82 (CH^{Ar}), 128.72 (2 CH^{Ar}), 128.10 (2 CH^{Ar}), 104.69 (d, $^2J_{2,F}$ = 24.6 Hz, C-2), 91.75 (d, $^1J_{3,F}$ = 189.5 Hz, C-3), 76.96 (d, $^2J_{4,F}$ = 15.8 Hz, C-4), 72.98 (CH_2^{Bn}), 69.62 (C-5), 64.10 (d, $^3J_{1,F}$ = 6.2 Hz, C-1). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -214.85 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -214.85 (dd, $^2J_{F,3}$ = 53.5 Hz, $^3J_{F,4}$ = 20.9 Hz).

Open chain: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.39-7.31 (m, 5H, H^{Ar}), 5.18 (dd, $^{2}J_{3,F}$ = 47.9 Hz, $^{3}J_{3,4}$ = 2.8 Hz, 1H, H-3), 4.72 (d, $^{2}J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.64 (d, $^{2}J_{H,H}$ = 11.7 Hz, 1H, H^{Bn}), 4.55 (dd, $^{3}J_{1,OH}$ = 5.1 Hz, $^{4}J_{1,F}$ = 1.8 Hz, 2H, CH_2-1), 4.04 (dddd, $^{3}J_{4,F}$ = 20.9 Hz, $^{3}J_{4,5a\ or\ 5b}$ = 6.7 Hz, $^{3}J_{4,5a\ or\ 5b}$ = 6.2 Hz, $^{3}J_{4,3}$ = 2.8 Hz, 1H, H-4), 3.80-3.75 (m, 2H, H-5a & H-5b), 2.85 (t, $^{3}J_{OH,1}$ = 5.1 Hz, 1H, OH-1), 1.75 (dd, $^{3}J_{OH,5a\ or\ 5b}$ = 6.5 Hz, $^{3}J_{OH,5a\ or\ 5b}$ = 5.4 Hz, 1H, OH-5). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 207.82 (d, $^{2}J_{2,F}$ = 26.4 Hz, C-2), 137.16 (C^{Ar}), 128.44 (CH^{Ar}), 128.30 (2 CH^{Ar}), 128.08 (2 CH^{Ar}), 94.37 (d, $^{1}J_{3,F}$ = 186.7 Hz, C-3), 79.72 (d, $^{2}J_{4,F}$ = 19.8 Hz, C-4), 73.48 (CH_2^{Bn}), 67.38 (d, $^{3}J_{1,F}$ = 4.2 Hz, C-1), 60.14 (d, $^{3}J_{5,F}$ = 8.4 Hz, C-5). ^{19}F{^{1}H} NMR (659 MHz, $CDCl_3$) δ = -210.53 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -210.52 (dd, $^{2}J_{F,3}$ = 47.9 Hz, $^{3}J_{F,4}$ = 20.9 Hz). HRMS (ESI+): *m/z* calc. for $C_{12}H_{15}FO_4Na^+$ $[M+Na]^+$: 265.0847, found: 265.0853.

5.1.7.11 3-Deoxy-3-fluoro-D-ribulose (3DFRu)



3DFRu
$C_5H_9FO_4$
152.12 g/mol

4-*O*-Benzyl-3-deoxy-3-fluoro-D-ribulose (**3.44**, 156 mg, 0.64 mmol, 1 equiv.) was dissolved in methanol (8.5 mL) and palladium on charcoal (10% Pd, 69 mg, 0.06 mmol, 0.1 equiv.) was added. The mixture was degassed (3 freezing/thawing cycles with liquid N_2 under vacuum) and stirred under atmospheric pressure of H_2 at room temperature for 16 h. The suspension was filtered and evaporated. The crude residue was purified by reversed-phase chromatography (C_{18}-silica gel, H_2O) to give 3-deoxy-3-fluoro-D-ribulose as a colorless oil and as a 2.1:2:1 mixture of anomers and open chain conformation (**3DFRu**, 69 mg, 70%). R_f = 0.19 (EA, CAM). $[\alpha]_D^{20}$ = -16.1 (c 1.0, H_2O).

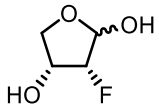
Major anomer: ^{1}H NMR (700 MHz, D_2O) δ = 4.93 (dd, $^{2}J_{3,F}$ = 52.2 Hz, $^{3}J_{3,4}$ = 4.9 Hz, 1H, H-3), 4.50 (dq, $^{3}J_{4,F}$ = 12.4 Hz, $^{3}J_{4,3}$ = $^{3}J_{4,5a}$ = $^{3}J_{4,5b}$ = 5.8 Hz, 1H, H-4), 4.11 (dd, $^{2}J_{5a,5b}$ = 9.4 Hz, $^{3}J_{5a,4}$ = 5.8 Hz, 1H, H-5a), 3.94 (ddd, $^{2}J_{5b,5a}$ = 9.4 Hz, $^{3}J_{5b,4}$ = 5.8 Hz, $^{4}J_{5b,F}$ = 1.4 Hz, 1H, H-5b), 3.64 (dd, $^{2}J_{1a,1b}$ = 12.1 Hz, $^{4}J_{1a,F}$ = 1.4 Hz, 1H, H-1a), 3.57 (d, $^{2}J_{1b,1a}$ = 12.1 Hz, 1H, H-1b). ^{13}C NMR (176 MHz, D_2O) δ = 105.22 (d, $^{2}J_{2,F}$ = 16.2 Hz, C-2), 92.51 (d, $^{1}J_{3,F}$ = 193.1 Hz, C-3), 72.78 (d, $^{3}J_{5,F}$ = 3.0 Hz, C-5), 71.60 (d, $^{2}J_{4,F}$ = 16.0 Hz, C-4), 66.06 (C-1). ^{19}F NMR (659 MHz, D_2O) δ = -213.53 (dd, $^{2}J_{F,3}$ = 52.2 Hz, $^{3}J_{F,4}$ = 12.3 Hz).

Minor anomer: ^{1}H NMR (700 MHz, D_2O) δ = 4.86 (dd, $^{2}J_{3,F}$ = 53.4 Hz, $^{3}J_{3,4}$ = 4.3 Hz, 1H, H-3), 4.75 (dtd, $^{3}J_{4,F}$ = 21.0 Hz, $^{3}J_{4,5a}$ = $^{3}J_{4,5b}$ = 7.1 Hz, $^{3}J_{4,3}$ = 4.3 Hz, 1H, H-4), 4.30

(dd, $^{2}J_{5a,5b}$ = 9.0 Hz, $^{3}J_{5a,4}$ = 7.1 Hz, 1H, H-5a), 3.85 (dd, $^{2}J_{1a,1b}$ = 12.1 Hz, $^{4}J_{1a,F}$ = 2.6 Hz, 1H, H-1a), 3.80 (dd, $^{2}J_{5b,5a}$ = 9.0 Hz, $^{3}J_{5b,4}$ = 7.1 Hz, 1H, H-5b), 3.65 (dd, $^{2}J_{1b,1a}$ = 12.1 Hz, $^{4}J_{1b,F}$ = 4.4 Hz, 1H, H-1b). ^{13}C NMR (176 MHz, D_2O) δ = 107.63 (d, $^{2}J_{2,F}$ = 23.2 Hz, C-2), 96.03 (d, $^{1}J_{3,F}$ = 186.9 Hz, C-3), 72.93 (d, $^{3}J_{5,F}$ = 1.5 Hz, C-5), 72.13 (d, $^{2}J_{4,F}$ = 16.1 Hz, C-4), 64.58 (d, $^{3}J_{1,F}$ = 5.2 Hz, C-1). ^{19}F{^{1}H} NMR (659 MHz, D_2O) δ = -210.50 (s). ^{19}F NMR (659 MHz, D_2O) δ = -210.50 (dd, $^{2}J_{F,3}$ = 53.4 Hz, $^{3}J_{F,4}$ = 21.0 Hz). Open chain: ^{1}H NMR (700 MHz, D_2O) δ = 5.22 (dd, $^{2}J_{3,F}$ = 47.7 Hz, $^{3}J_{3,4}$ = 3.0 Hz, 1H, H-3), 4.65 (dd, $^{2}J_{1a,1b}$ = 19.8 Hz, $^{4}J_{1a,F}$ = 1.4 Hz, 1H, H-1a), 4.61 (dd, $^{2}J_{1b,1a}$ = 19.8 Hz, $^{4}J_{1b,F}$ = 1.0 Hz, 1H, H-1b), 4.22 (dtd, $^{3}J_{4,F}$ = 23.3 Hz, $^{3}J_{4,5a}$ = $^{3}J_{4,5b}$ = 6.5 Hz, $^{3}J_{4,3}$ = 3.0 Hz, 1H, H-3), 3.70 (d, $^{3}J_{5a\ \&\ b,4}$ = 6.5 Hz, 2H, H-5a & H-5b). ^{13}C NMR (176 MHz, D_2O) δ = 211.33 (d, $^{2}J_{2,F}$ = 23.8 Hz, C-2), 98.18 (d, $^{1}J_{3,F}$ = 184.1 Hz, C-3), 74.43 (d, $^{2}J_{4,F}$ = 20.5 Hz, C-4), 68.82 (d, $^{3}J_{1,F}$ = 4.3 Hz, C-1), 62.72 (d, $^{3}J_{5,F}$ = 7.7 Hz, C-5). ^{19}F{^{1}H} NMR (659 MHz, D_2O) δ = -210.13 (s). ^{19}F NMR (659 MHz, D_2O) δ = -210.13 (dd, $^{2}J_{F,3}$ = 47.7 Hz, $^{3}J_{F,4}$ = 23.3 Hz). HRMS (ESI+): *m/z* calc. for $C_5H_9FO_4Na^+$ $[M+Na]^+$: 175.0377, found: 175.0375, *m/z* calc. for $C_{10}H_{16}F_2O_7Na^+$ $[M_2-H_2O+Na]^+$: 309.0756, found: 309.0370, *m/z* calc. for $C_{10}H_{16}F_2O_8Na^+$ $[M_2-2H+Na]^+$: 325.0706, found: 325.0686.

5.1.8 Additional Experiments in the Synthesis of 3DFRu

5.1.8.1 2-Deoxy-2-fluoro-D-erythrose (2DFE)



2DFE
$C_4H_7FO_3$
122.10 g/mol

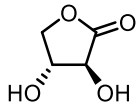
3-*O*-Benzyl-2-deoxy-2-fluoro-D-erythrose (**3.41**, 45 mg, 0.21 mmol, 1 equiv.) was dissolved in dry methanol (3 mL). Pd/C (10% Pd, 23 mg, 0.02 mmol, 0.1 equiv. Pd) was added and the mixture was degassed (3 freezing/thawing cycles with liquid N_2 under vacuum). The black reaction mixture was stirred under atmospheric pressure of H_2 for 16 h. After NMR indicated completion of the reaction, the mixture was filtered and evaporated. The crude residue was purified by MPLC (10 g silica gel, 18-100% EA in *n*-heptane) to give 2-deoxy-2-fluoro-D-erythrose as a 1.1:1 mixture of anomers and as a volatile colorless oil (**2DFE**, 4 mg, 15%). R_f = 0.16 (1:3 *n*-heptane/EA, CAM). $[\alpha]_D^{20}$ = -8.0 (c 0.2, $CDCl_3$). Major anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 5.52 (dd, $^{3}J_{1,F}$ = 11.0 Hz, $^{3}J_{1,OH}$ = 2.9 Hz, 1H, H-1), 4.80 (dd, $^{2}J_{2,F}$ = 52.9 Hz, $^{3}J_{2,3}$ = 4.4 Hz, 1H, H-2), 4.62 (ddddd, $^{3}J_{3,F}$ = 17.0 Hz, $^{3}J_{3,OH}$ = 8.9 Hz, $^{3}J_{3,4a}$ = 6.7 Hz, $^{3}J_{3,4b}$ = 5.9 Hz, $^{3}J_{3,2}$ = 4.4 Hz, 1H, H-3), 4.29 (dd, $^{2}J_{4a,4b}$ = 9.3 Hz, $^{3}J_{4a,3}$ = 6.7 Hz, 1H, H-4a), 3.80 (ddd, $^{2}J_{4b,4a}$ = 9.3 Hz, $^{3}J_{4b,3}$ = 5.9 Hz, $^{4}J_{4b,F}$ = 0.7 Hz, 1H, H-4b), 2.68 (t, $^{3}J_{OH,1}$ = $J_{OH,F}$ = 3.0 Hz, 1H, OH-1), 2.07 (dd, $^{3}J_{OH,3}$ = 8.9 Hz, $J_{OH,F}$ = 4.3 Hz, 1H, OH-3). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 99.81 (d,

$^{2}J_{1,F}$ = 31.3 Hz, C-1), 94.37 (d, $^{1}J_{2,F}$ = 181.8 Hz, C-2), 71.77 (d, $^{3}J_{4,F}$ = 1.5 Hz, C-4), 70.42 (d, $^{2}J_{3,F}$ = 16.5 Hz, C-3). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -211.99 (s). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -211.99 (ddd, $^{2}J_{F,2}$ = 52.9 Hz, $^{3}J_{F,3}$ = 17.0 Hz, $^{3}J_{F,1}$ = 11.0 Hz).

Minor anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 5.33 (ddd, $^{3}J_{1,OH}$ = 10.1 Hz, $^{3}J_{1,2}$ = 4.3 Hz, $^{3}J_{1,F}$ = 0.8 Hz, 1H, H-1), 4.83 (dt, $^{2}J_{2,F}$ = 51.3 Hz, $^{3}J_{2,1}$ = $^{3}J_{2,3}$ = 4.3 Hz, 1H, H-2), 4.45-4.41 (m, 1H, H-3), 4.11-4.07 (m, 2H, H-4a & H-4b), 3.65 (dd, $^{3}J_{OH,1}$ = 10.1 Hz, $J_{OH,F}$ = 1.5 Hz, 1H, OH-1), 2.55 (dd, $^{3}J_{OH,3}$ = 5.4 Hz, $J_{OH,F}$ = 1.9 Hz, 1H, OH-3). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 95.01 (d, $^{2}J_{1,F}$ = 18.1 Hz, C-1), 89.54 (d, $^{1}J_{2,F}$ = 196.8 Hz, C-2), 71.56 (d, $^{3}J_{4,F}$ = 4.6 Hz, C-4), 69.66 (d, $^{2}J_{3,F}$ = 16.3 Hz, C-3). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -218.20 (s). $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) δ = -218.20 (d, $^{2}J_{F,2}$ = 51.3 Hz).

5.1.9 Synthesis of a Potential Radiolabeling Precursor of 3DFRu

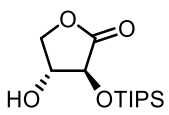
5.1.9.1 D-*Threono*-1,4-lactone (3.47)



3.47
$C_4H_6O_4$
118.09 g/mol

D-Xylose (30.0 g, 199.8 mmol, 1 equiv.) was dissolved in water (1 L) and cooled to 0°C. An ice-cold 0.6 M aq. KOH-solution (1 L, 600 mmol, 3 equiv.) was added and the flask was evacuated at 0°C for 3 min. The flask was vented with an O_2-balloon and the mixture was warmed to room temperature and stirred under an atmospheric pressure of O_2 for 16 h. The solution was passed through DOWEX 50W X8 H^+-resin (750 mL) and the filtrate was evaporated. The oil was dissolved in MeCN (333 mL) and *para*-toluenesulfonic acid monohydrate (253 mg, 1.33 mmol, 0.02 equiv.) was added. The mixture was refluxed for 5 h, cooled to room temperature, filtered and evaporated. The crude residue was recrystallized from EA to give D-*threono*-1,4-lactone as a white solid (**3.47**, 12.5 g, 53%). R_f = 0.46 (EA, $KMnO_4$). $[\alpha]_D^{20}$ = -32.1 (c 1.0, H_2O). ^{1}H NMR (600 MHz, d_6-DMSO) δ = 6.12 (d, $^{3}J_{OH,2}$ = 6.3 Hz, 1H, OH-2), 5.77 (d, $^{3}J_{OH,3}$ = 4.8 Hz, 1H, OH-3), 4.33 (dd, $^{2}J_{4a,4b}$ = 8.8 Hz, $^{3}J_{4a,3}$ = 6.7 Hz, 1H, H-4a), 4.14 (qd, $^{3}J_{3,2}$ = $^{3}J_{3,4a}$ = $^{3}J_{3,4b}$ = 6.7 Hz, $^{3}J_{3,OH}$ = 4.8 Hz, 1H, H-3), 4.07 (t, $^{3}J_{2,3}$ = $^{3}J_{2,OH}$ = 6.7 Hz, 1H, H-2), 3.84 (dd, $^{2}J_{4b,4a}$ = 8.8 Hz, $^{3}J_{4b,3}$ = 6.7 Hz, 1H, H-4b). ^{13}C NMR (151 MHz, d_6-DMSO) δ = 175.63 (C-1), 73.02 (C-2), 72.21 (C-3), 69.80 (C-4). HRMS (ESI+): *m/z* calc. for $C_4H_6O_4Na^+$ $[M+Na]^+$: 141.0158, found: 141.0158, *m/z* calc. for $C_5H_{10}O_5Na^+$ $[M+MeOH+Na]^+$: 173.0420, found: 173.0420.

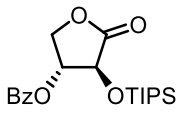
5.1.9.2 2-*O*-Triisopropylsilyl-D-*threono*-1,4-lactone (3.48)



3.48
$C_{13}H_{26}O_4Si$
274.43 g/mol

D-*Threono*-1,4-lactone (**3.47**, 8.936 g, 75.67 mmol, 1 equiv.) was dissolved in dry MeCN (204 mL) under argon and imidazole (12.364 g, 181.61 mmol, 2.4 equiv.) was added. The solution was cooled to 0°C and TIPSCl (17.500 g, 90.81 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 16 h. The volatiles were evaporated under reduced pressure and the residue was partitioned between EA and water. The layers were separated and the aqueous layer was extracted twice with EA. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 6-50% EA in *n*-heptane) to give 2-*O*-triisopropylsilyl-D-*threono*-1,4-lactone as a colorless oil (**3.48**, 3.900 g, 22%). R_f = 0.19 (*n*-heptane/EA 3:1, $KMnO_4$). $[\alpha]_D^{20}$ = -39.8 (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.48 (dd, $^2J_{4a,4b}$ = 8.9, $^3J_{4a,3}$ = 6.0 Hz, 1H, H-4a), 4.44 (qd, $^3J_{3,2}$ = $^3J_{3,4a}$ = $^3J_{3,4b}$ = 6.0, $^3J_{3,OH}$ = 4.3 Hz, 1H, H-3), 4.36 (d, $^3J_{2,3}$ = 6.0 Hz, 1H, H-2), 4.02 (dd, $^2J_{4b,4a}$ = 9.0 Hz, $^3J_{4b,3}$ = 6.0 Hz, 1H, H-4b), 2.09 (d, $^3J_{OH,3}$ = 4.3 Hz, 1H, OH), 1.23-1.15 (m, 3H, CH^{TIPS}), 1.10 (d, $^3J_{H,H}$ = 7.0 Hz, 18H, CH_3^{TIPS}). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.72 (C-1), 74.99 (C-2), 74.59 (C-3), 70.08 (C-4), 17.95 (3 CH_3^{TIPS}), 17.91 (3 CH_3^{TIPS}), 12.34 (3 CH^{TIPS}). HRMS (ESI+): *m/z* calc. for $C_{13}H_{26}O_4SiNa^+$ $[M+Na]^+$: 297.1493, found: 297.1492.

5.1.9.3 3-*O*-Benzoyl-2-*O*-triisopropylsilyl-D-*threono*-1,4-lactone (3.49)

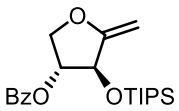


3.49
$C_{20}H_{30}O_5Si$
378.54 g/mol

2-*O*-Triisopropylsilyl-D-*threono*-1,4-lactone (**3.48**, 3.900 g, 14.21 mmol, 1 equiv.) was dissolved in dry pyridine (28 mL) under argon and cooled to 0°C. 4-(Dimethylamino)pyridine (87 mg, 0.71 mmol, 0.05 equiv.) was added followed by the dropwise addition of benzoyl chloride (3.7 mL, 4.495 g, 31.98 mmol, 2.25 equiv.). The mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of water (10 mL) and the mixture was extracted thrice with EA. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was purified my MPLC (100 g silica gel, 1-9% EA in *n*-heptane) to give 3-*O*-benzoyl-2-*O*-triisopropylsilyl-D-*threono*-1,4-lactone as a colorless oil (**3.49**, 4.900 g, 91%). R_f = 0.22 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = -102.5 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.02 (d, $^3J_{H,H}$ = 7.0 Hz, 2H, H^{Ar}), 7.62 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.47 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.43 (dt, $^3J_{3,4a}$ = 5.4 Hz, $^3J_{3,2}$ = $^3J_{3,4b}$ = 4.2 Hz, 1H, H-3), 4.81

(dd, $^{2}J_{4a,4b}$ = 10.2 Hz, $^{3}J_{4a,3}$ = 5.4 Hz, 1H, H-4a), 4.62 (d, $^{3}J_{2,3}$ = 4.2 Hz, 1H, H-2), 4.26 (dd, $^{2}J_{4b,4a}$ = 10.2 Hz, $^{3}J_{4b,3}$ = 4.2 Hz, 1H, H-4b), 1.24-1.17 (m, 3H, CH^{TIPS}), 1.11 (d, $^{3}J_{H,H}$ = 7.2 Hz, 9H, CH_3^{TIPS}), 1.10 (d, $^{3}J_{H,H}$ = 7.3 Hz, 9H, CH_3^{TIPS}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 173.01 (C-1), 165.76 (C^{Bz}), 134.00 (CH^{Ar}), 129.89 (2 CH^{Ar} & C^{Ar}), 128.77 (2 CH^{Ar}), 76.37 (C-3), 72.02 (C-2), 69.81 (C-4), 17.89 (3 CH_3^{TIPS}), 17.85 (3 CH_3^{TIPS}), 12.28 (3 CH^{TIPS}). HRMS (ESI+): *m/z* calc. for $C_{20}H_{30}O_5SiNa^+$ $[M+Na]^+$: 401.1755, found: 401.1745.

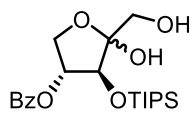
5.1.9.4 2,5-Anhydro-4-*O*-benzoyl-1-deoxy-3-*O*-triisopropylsilyl-D-*threo*-pent-1-enitol (3.50)



3.50
$C_{21}H_{32}O_4Si$
376.57 g/mol

This reaction was carried out in the dark. Bis(cyclopentadienyl)-dimethyltitanium (0.5 M in dry toluene, 12.5 mL, 6.26 mmol, 2.3 equiv.) was added dropwise to 3-*O*-benzoyl-2-*O*-triisopropylsilyl-D-*threono*-1,4-lactone (**3.49**, 1.031 g, 2.72 mmol, 1 equiv.) under argon in the dark. The flask was equipped with a reflux condenser and the mixture was heated to 70°C for 16 h. The reaction mixture was cooled to room temperature, diluted with *n*-heptane (50 mL) and stirring was continued for 30 min. The orange suspension was filtered through Celite® and the filtrate was evaporated. The crude residue was purified by MPLC (100 g silica gel, 1-5% EA in *n*-heptane) to give 2,5-anhydro-4-*O*-benzoyl-1-deoxy-3-*O*-triisopropylsilyl-D-*threo*-pent-1-enitol as a yellow oil (**3.50**, 700 mg, 68%) which was immediately used in the next step: R_f = 0.37 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = -61.1 (c 1.0, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.02 (d, $^{3}J_{H,H}$ = 7.1 Hz, 2H, H^{Ar}), 7.58 (t, $^{3}J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.44 (t, $^{3}J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.28-5.27 (m, 1H, H-4), 4.70 (d, $^{3}J_{3,4}$ = 1.3 Hz, 1H, H-3), 4.54 (dd, $^{2}J_{5a,5b}$ = 10.4 Hz, $^{3}J_{5a,4}$ = 3.7 Hz, 1H, H-5a), 4.49 (d, $^{2}J_{1a,1b}$ = 1.8 Hz, 1H, H-1a), 4.22 (d, $^{2}J_{1b,1a}$ = 1.8 Hz, 1H, H-1b), 4.21 (d, $^{2}J_{5b,5a}$ = 10.4 Hz, 1H, H-5b), 1.20-1.14 (m, 3H, CH^{TIPS}), 1.10 (d, $^{3}J_{H,H}$ = 7.1 Hz, 18H, CH_3^{TIPS}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 165.87 (C^{Bz}), 162.66 (C-2), 133.55 (CH^{Ar}), 129.95 (2 CH^{Ar}), 129.59 (C^{Ar}), 128.60 (2 CH^{Ar}), 85.01 (C-1), 78.61 (C-4), 74.97 (C-3), 72.93 (C-5), 18.13 (6 CH_3^{TIPS}), 12.47 (3 CH^{TIPS}). HRMS (ESI+): *m/z* calc. for $C_{21}H_{32}O_4SiNa^+$ $[M+Na]^+$: 399.1962, found: 399.1962, *m/z* calc. for $C_{21}H_{34}O_5SiNa^+$ $[M+H_2O+Na]^+$: 417.2068, found: 417.2083.

5.1.9.5 4-*O*-Benzoyl-3-*O*-triisopropylsilyl-D-xylulose (3.51)



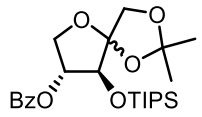
3.51
$C_{21}H_{34}O_6Si$
410.58 g/mol

2,5-Anhydro-4-*O*-benzoyl-1-deoxy-3-*O*-triisopropylsilyl-D-*threo*-pent-1-enitol (**3.50**, 700 mg, 1.86 mmol, 1 equiv.) was dissolved in a 4:1 mixture (v/v) of acetone and water (37 mL) and *N*-methylmorpholine-*N*-oxide (436 mg, 3.72 mmol, 2 equiv.) and potassium osmate dihydrate (34 mg, 0.09 mmol, 0.05 equiv.) were added. The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with EA and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (100 g silica gel, 6-42% EA in *n*-heptane) to give 4-*O*-benzoyl-3-*O*-triisopropylsilyl-D-xylulose as a mixture of anomers and as a colorless oil (**3.51**, 642 mg, 84%). R_f = 0.2 (*n*-heptane/EA 3:1, UV & CAM). $[\alpha]_D^{20}$ = -47.1 (c 1.0, $CHCl_3$).

Major anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.02 (d, $^3J_{H,H}$ = 7.0 Hz, 2H, H^{Ar}), 7.60 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.46 (t, $^3J_{H,H}$ = 7.7 Hz, 2H, H^{Ar}), 5.31 (d, $^3J_{4,5a}$ = 3.7 Hz, 1H, H-4), 4.61 (bs, 2H, H-3 & OH-2), 4.33 (dd, $^2J_{5a,5b}$ = 10.8 Hz, , $^3J_{5a,4}$ = 3.7 Hz, 1H, H-5a), 3.95 (d, $^2J_{5b,5a}$ = 10.8 Hz, 1H, H-5b), 3.74 (dd, $^2J_{1a,1b}$ = 11.8 Hz, $^3J_{1a,OH}$ = 7.3 Hz, 1H, H-1a), 3.70 (dd, $^2J_{1b,1a}$ = 11.8 Hz, $^3J_{1b,OH}$ = 7.3 Hz, 1H, H-1b), 1.93 (t, $^3J_{OH,1a}$ = $^3J_{OH,1b}$ = 7.3 Hz, 1H, OH-1), 1.28-1.21 (m, 3H, CH^{TIPS}), 1.11 (d, $^3J_{H,H}$ = 7.4 Hz, 9H, CH_3^{TIPS}), 1.11 (d, $^3J_{H,H}$ = 7.5 Hz, 9H, CH_3^{TIPS}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 165.77 (C^{Bz}), 133.69 (CH^{Ar}), 129.86 (2 CH^{Ar}), 129.41 (C^{Ar}), 128.74 (2 CH^{Ar}), 104.16 (C-2), 80.51 (C-4), 76.53 (C-3), 70.10 (C-5), 65.00 (C-1), 17.97 (3 CH_3^{TIPS}), 17.92 (3 CH_3^{TIPS}), 12.20 (3 CH^{TIPS}). HRMS (ESI+): *m/z* calc. for $C_{21}H_{34}O_6SiNa^+$ $[M+Na]^+$: 433.2017, found: 433.2015.

Only the signals of the major anomer could be interpreted by NMR spectroscopy.

5.1.9.6 4-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*O*-triisopropylsilyl-D-xylulose (3.52)



3.52
$C_{24}H_{38}O_6Si$
450.65 g/mol

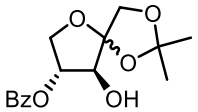
4-*O*-Benzoyl-3-*O*-triisopropylsilyl-D-xylulose (**3.51**, 348 mg, 0.85 mmol, 1 equiv.) was dissolved in 2,2-dimethoxypropane (520 µL, 441 mg, 4.24 mmol, 5 equiv.) and $SnCl_2$ (3 mg, 0.02 mmol, 0.02 equiv.), dissolved in 1,2-dimethoxyethane (170 µL) was added. The mixture was heated to 60°C for 2 h. The mixture cooled down to room temperature and evaporated under reduced pressure. The crude residue was purified by MPLC (50 g silica gel, 2-20% EA in *n*-heptane) to give 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-triisopropylsilyl-D-xylulose as a mixture of anomers and as a

colorless oil (**3.52**, 255 mg, 67%). R_f = 0.45 (*n*-heptane/EA 9:1, UV & CAM). $[\alpha]_D^{20}$ = -48.0 (c 1.0, $CHCl_3$).

Major anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.06 (d, $^3J_{H,H}$ = 8.2 Hz, 2H, H^{Ar}), 7.59 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.46 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.20 (ddd, $^3J_{4,5a}$ = 6.0 Hz, $^3J_{4,5b}$ = 4.1, $^3J_{4,3}$ = 2.5 Hz, 1H, H-4), 4.56 (d, $^3J_{3,4}$ = 2.5 Hz, 1H, H-3), 4.41 (dd, $^2J_{5a,5b}$ = 10.1 Hz, $^3J_{5a,4}$ = 6.0 Hz, 1H, H-5a), 4.37 (d, $^2J_{1a,1b}$ = 9.4 Hz, 1H, H-1a), 4.04 (d, $^2J_{1b,1a}$ = 9.4 Hz, 1H, H-1b), 3.92 (dd, $^2J_{5b,5a}$ = 10.1 Hz, $^3J_{5b,4}$ = 4.1 Hz, 1H, H-5b), 1.51 (s, 3H, CH_3^{isopr}), 1.42 (s, 3H, CH_3^{isopr}), 1.19-1.13 (m, 3H, CH^{TIPS}), 1.08 (d, $^3J_{H,H}$ = 6.3 Hz, 9H, CH_3^{TIPS}), 1.08 (d, $^3J_{H,H}$ = 7.2 Hz, 9H, CH_3^{TIPS}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 166.18 (C^{Bz}), 133.44 (CH^{Ar}), 129.97 (2 CH^{Ar}), 129.79 (C^{Ar}), 128.57 (2 CH^{Ar}), 113.52 (C-2), 111.37 (C^{isopr}), 80.63 (C-3), 79.53 (C-4), 70.12 (C-5), 69.63 (C-1), 26.71 (CH_3^{isopr}), 26.47 (CH_3^{isopr}), 18.11 (3 CH_3^{TIPS}), 18.03 (3 CH_3^{TIPS}), 12.46 (3 CH_3^{TIPS}).

Minor anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.03 (d, $^3J_{H,H}$ = 8.2 Hz, 2H, H^{Ar}), 7.59 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.46 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.34 (ddd, $^3J_{4,5a}$ = 6.4 Hz, $^3J_{4,3}$ = 5.2 Hz, $^3J_{4,5b}$ = 3.3 Hz, 1H, H-4), 4.51 (d, $^3J_{3,4}$ = 5.0 Hz, 1H, H-3), 4.50 (dd, $^2J_{5a,5b}$ = 10.5 Hz, $^3J_{5a,4}$ = 6.4 Hz, 1H, H-5a), 4.13 (d, $^2J_{1a,1b}$ = 8.8 Hz, 1H, H-1a), 4.11 (d, $^2J_{1b,1a}$ = 8.8 Hz, 1H, H-1b), 3.76 (dd, $^2J_{5b,5a}$ = 10.5 Hz, $^3J_{5b,4}$ = 3.3 Hz, 1H, H-5b), 1.53 (s, 3H, CH_3^{isopr}), 1.46 (s, 3H, CH_3^{isopr}), 1.20-1.13 (m, 3H, CH^{TIPS}), 1.08 (d, $^3J_{H,H}$ = 6.3 Hz, 9H, CH_3^{TIPS}), 1.08 (d, $^3J_{H,H}$ = 7.2 Hz, 9H, CH_3^{TIPS}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 166.39 (C^{Bz}), 133.55 (CH^{Ar}), 129.75 (2 CH^{Ar}), 129.50 (C^{Ar}), 128.65 (2 CH^{Ar}), 111.82 (C^{isopr}), 110.07 (C-2), 80.02 (C-4), 76.15 (C-3), 70.85 (C-1), 69.88 (C-5), 26.93 (CH_3^{isopr}), 26.48 (CH_3^{isopr}), 18.17 (3 CH_3^{TIPS}), 18.08 (3 CH_3^{TIPS}), 12.69 (3 CH^{TIPS}). HRMS (ESI+): *m/z* calc. for $C_{24}H_{38}O_6SiNa^+$ $[M+Na]^+$: 473.2330, found: 473.2327.

5.1.9.7 4-*O*-Benzoyl-1,2-*O*-isopropylidene-D-xylulose (3.53)



3.53
$C_{15}H_{18}O_6$
294.30 g/mol

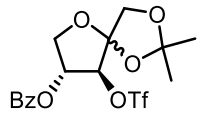
4-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*O*-triisopropylsilyl-D-xylulose (**3.52**, 328 mg, 0.73 mmol, 1 equiv.) was dissolved in dry THF (3.6 mL) under argon and cooled to 0°C. Tetrabutylammonium fluoride (1 M in THF, 1.2 mL, 1.16 mmol, 1.6 equiv.) was added dropwise. The mixture was stirred at 0°C for 0.5 h before being quenched by the dropwise addition of a sat. aq. $NaHCO_3$-solution (7.7 mL). The mixture was extracted thrice with DCM and the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by MPLC (25 g silica gel, 6-43% EA in *n*-heptane) to give 4-*O*-benzoyl-1,2-*O*-isopropylidene-D-xylulose as a mixture of

anomers and as a colorless oil (**3.53**, 141 mg, 66%). R_f = 0.17 (*n*-heptane/EA 3:1, UV & CAM). $[\alpha]_D^{20}$ = +7.9 (c 1.0, $CHCl_3$).

Major anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.05 (d, $^3J_{H,H}$ = 8.1 Hz, 2H, H^{Ar}), 7.60 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, H^{Ar}), 7.46 (t, $^3J_{H,H}$ = 7.8 Hz, 2H, H^{Ar}), 5.10 (ddd, $^3J_{4,5a}$ = 6.8, $^3J_{4,5b}$ = 6.2, $^3J_{4,3}$ = 3.0 Hz, 1H, H-4), 4.39 (dd, $^2J_{5a,5b}$ = 9.8 Hz, $^3J_{5a,4}$ = 6.8 Hz, 1H, H-5a), 4.37 (d, $^2J_{1a,1b}$ = 9.6 Hz, 1H, H-1a), 4.35 (t, $^3J_{3,4}$ = $^3J_{3,OH}$ = 3.0 Hz, 1H, H-3), 4.06 (d, $^2J_{1b,1a}$ = 9.6 Hz, 1H, H-1b), 4.05 (dd, $^2J_{5b,5a}$ = 9.8 Hz, $^3J_{5b,4}$ = 6.2 Hz, 1H, H-5b), 2.95 (d, $^3J_{OH,3}$ = 3.0 Hz, 1H, OH), 1.51 (s, 3H, CH_3^{isopr}), 1.40 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 167.45 (C^{Bz}), 133.74 (CH^{Ar}), 130.01 (2 CH^{Ar}), 129.35 (C^{Ar}), 128.66 (2 CH^{Ar}), 112.82 (C-2), 111.47 (C^{isopr}), 80.77 (C-3), 80.72 (C-4), 69.24 (C-1), 68.32 (C-5), 26.56 (CH_3^{isopr}), 26.55 (CH_3^{isopr}).

Minor anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.04 (d, $^3J_{H,H}$ = 8.2 Hz, 2H, H^{Ar}), 7.59 (t, $^3J_{H,H}$ = 7.9 Hz, 1H, H^{Ar}), 7.46 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, H^{Ar}), 5.30 (ddd, $^3J_{4,5a}$ = 6.3 Hz, $^3J_{4,3}$ = 4.5 Hz, $^3J_{4,5b}$ =3.4 Hz, 1H, H-4), 4.42 (dd, $^2J_{5a,5b}$ = 10.5 Hz, $^3J_{5a,4}$ = 6.3 Hz, 1H, H-5a), 4.26 (dd, $^3J_{3,OH}$ = 8.0 Hz, $^3J_{3,4}$ = 4.5 Hz, 1H, H-3), 4.18 (d, $^2J_{1a,1b}$ = 9.2 Hz, 1H, H-1a), 4.14 (d, $^2J_{1b,1a}$ = 9.2 Hz, 1H, H-1b), 3.89 (dd, $^2J_{5b,5a}$ = 10.5 Hz, $^3J_{5b,4}$ = 3.4 Hz, 1H, H-5b), 2.73 (d, $^3J_{OH,3}$ = 8.0 Hz, 1H, OH), 1.55 (s, 3H, CH_3^{isopr}), 1.47 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 166.62 (C^{Bz}), 133.62 (CH^{Ar}), 129.90 (2 CH^{Ar}), 129.44 (C^{Ar}), 128.64 (2 CH^{Ar}), 111.95 (C^{isopr}), 109.88 (C-2), 79.75 (C-4), 76.77 (C-3), 70.90 (C-1), 69.85 (C-5), 26.51 (CH_3^{isopr}), 26.41 (CH_3^{isopr}). HRMS (ESI+): *m/z* calc. for $C_{15}H_{18}O_6Na^+$ $[M+Na]^+$: 317.0996, found: 317.1002.

5.1.9.8 4-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (3.54)



3.54
$C_{16}H_{17}F_3O_8S$
426.36 g/mol

4-*O*-Benzoyl-1,2-*O*-isopropylidene-D-xylulose (**3.53**, 39 mg, 0.13 mmol, 1 equiv.) was dissolved in dry DCM (660 µL) under argon. The solution was cooled to 0°C and dry pyridine (89 mg, 90 µL, 1.13 mmol, 8.5 equiv.) and trifluoromethanesulfonic anhydride (75 mg, 50 µL, 0.27 mmol, 2 equiv.) were added dropwise. The reaction mixture was stirred at 0°C for 1 h before it was quenched by the addition of MeOH (90 µL) and the mixture partitioned between DCM and water. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed twice with ice-cold water, once with an ice-cold sat. aq. $NaHCO_3$-solution and once with ice-cold brine. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-

trifluoromethanesulfonyl-D-xylulose as a mixture of anomers and as a yellow oil (**3.54**, 48 mg, 85%). R_f = 0.42 (*n*-heptane/EA 3:1, UV & CAM). $[\alpha]_D^{20}$ = -55.4 (c 1.0, $CHCl_3$).
Major anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.06 (d, $^3J_{H,H}$ = 8.2 Hz, 2H, H^{Ar}), 7.62 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.48 (t, $^3J_{H,H}$ = 7.9 Hz, 2H, H^{Ar}), 5.51 (ddd, $^3J_{4,5a}$ = 7.0 Hz, $^3J_{4,5b}$ = 5.4 Hz, $^3J_{4,3}$ = 2.2 Hz, 1H, H-4), 5.41 (d, $^3J_{3,4}$ = 2.2 Hz, 1H, H-3), 4.56 (dd, $^2J_{5a,5b}$ = 10.1 Hz, $^3J_{5a,4}$ = 7.0 Hz, 1H, H-5a), 4.27 (d, $^2J_{1a,1b}$ = 10.0 Hz, 1H, H-1a), 4.18 (d, $^2J_{1b,1a}$ = 10.0 Hz, 1H, H-1b), 3.97 (dd, $^2J_{5b,5a}$ = 10.1 Hz, , $^3J_{5b,4}$ = 5.4 Hz, 1H, H-5b), 1.52 (s, 3H, CH_3^{isopr}), 1.46 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 165.54 (C^{Bz}), 134.00 (CH^{Ar}), 130.11 (2 CH^{Ar}), 128.76 (2 CH^{Ar}), 128.72 (C^{Ar}), 113.15 (C^{isopr}), 118.57 (q, $^1J_{C,F}$ = 319.8 Hz, C^{Tf}), 110.35 (C-2), 91.37 (C-3), 76.03 (C-4), 69.75 (C-5), 69.38 (C-1), 26.31 (CH_3^{isopr}), 26.26 (CH_3^{isopr}). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -74.79 (s).
Minor anomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.03 (d, $^3J_{H,H}$ = 8.2 Hz, 2H, H^{Ar}), 7.62 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, H^{Ar}), 7.48 (t, $^3J_{H,H}$ = 7.9 Hz, 2H, H^{Ar}), 5.66 (ddd, $^3J_{4,5a}$ = 6.7 Hz, $^3J_{4,3}$ = 5.2 Hz, $^3J_{4,5b}$ = 3.7 Hz, 1H, H-4), 5.27 (d, $^3J_{3,4}$ = 5.2 Hz, 1H, H-3), 4.54 (dd, $^2J_{5a,5b}$ = 10.3 Hz, $^3J_{5a,4}$ = 6.7 Hz, 1H, H-5a), 4.28 (d, $^2J_{1a,1b}$ = 9.7 Hz, 1H, H-1a), 4.20 (d, $^2J_{1b,1a}$ = 9.7 Hz, 1H, H-1b), 3.91 (dd, $^2J_{5b,5a}$ = 10.3 Hz, $^3J_{5b,4}$ = 3.7 Hz, 1H, H-5b), 1.54 (s, 3H, CH_3^{isopr}), 1.49 (s, 3H, CH_3^{isopr}). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 165.87 (C^{Bz}), 134.05 (CH^{Ar}), 129.94 (2 CH^{Ar}), 128.83 (2 CH^{Ar}), 128.60 (C^{Ar}), 113.11 (C^{isopr}), 107.72 (C-2), 85.78 (C-3), 75.82 (C-4), 70.14 (C-1), 69.42 (C-5), 26.19 (CH_3^{isopr}), 25.97 (CH_3^{isopr}). ^{19}F NMR (659 MHz, $CDCl_3$) δ = -75.07 (s). HRMS (ESI+): *m/z* calc. for $C_{16}H_{17}F_3O_8SNa^+$ $[M+Na]^+$: 449.0488, found: 449.0491.

5.2 Biochemical Assays

5.2.1 HPAEC-PAD

High performance anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) was carried out on an ICS-5000+-System (Dionex/Thermo Fisher) equipped with an amperometric detector (Thermo Fisher) and pre-columns Dionex BorateTrap (50 mm), Dionex AminoTrap (30 mm), Dionex CarboPac PA20 (30 mm), and a Dionex CarboPac PA20 (150 mm) column for separation. Mobile phase **A** was water, mobile phase **B** was 200 mM NaOH in water and mobile phase **C** was 100 mM NaOH and 0.5 mM NaOAc in water. The following gradient was used at a flow rate of 0.4 mL/min: 0-18 min 7.5% **B**, 18-35 min 7.5%-50% **B**, 35-36 min 50% **B** and 0%-10% **C**, 36-40 min 50%-25% **B** and 10%-75% **C**, 40-43 min 25% **B** and 75% **C**,

43-44 min 25%-100% **B** and 75%-0% **C**, 44-46 min 100% **B**, 46-47 min 100%-8% **B**, 47-60 min 8% **B**.

5.2.2 HILIC-MS

All used solvents were of MS-grade. Water and MeCN were purchased from Honeywell (Seelze, Germany). Ammonium bicarbonate as well as ammonium hydroxide were obtained from Sigma Aldrich (St. Louis, Missouri, USA). Hydrophilic interaction liquid chromatography (HILIC) was performed using an Atlantis Premier BEH Z-HILIC Column (2.1 mm x 150 mm; 1.7 µm) (Waters, Milford, MA, USA) on a Vanquish Horizon HPLC system (Thermo Fisher Scientific, Waltham, MA, USA). The used mobile phases consisted of: mobile phase **A**:15 mM ammonium bicarbonate in water (pH = 9.00); mobile phase **B**: 15 mM ammonium bicarbonate in a 9:1 mixture (v/v) of MeCN and H_2O (pH = 9.00). The separation was achieved using a 15 min gradient as follows: 0-2 min 100%-85% **B**, 2-7 min 85% **B**, 7-10 min 85-40% **B**, 10-11 min 40% **B**. The system was re-equilibrated 100% **B** from 11-15 min. The column temperature was 30°C and the flow rate 250 µL/min throughout the entire chromatographic run. Mass spectrometry analysis was performed on Thermo Scientific™ Orbitrap ID-X™ Tribrid™ mass spectrometer with electrospray ionization (ESI) in negative ion mode. ESI source parameters were set as follows: spray voltage 2900 V, sheath gas 40, auxiliary gas 8, ion transfer tube temperature 275°C. A full MS scan was conducted in the range of 200-600 *m/z* at a resolution of 60 000. Chromatographic data was analyzed with FreeStyle™.

5.2.3 Cellular Uptake Assay

An aqueous solution of sugar **4DFS** (0.1 M) was added to adherent human dermal fibroblasts cultured in DMEM medium containing 10% FBS to reach a final concentration of 1 mM for the sugar. No fluorinated sugar was added to the control sample. Cells were incubated at 37°C for 10 min, then the culture medium was removed and cells were thoroughly washed (3x5 mL water). The cells were shock-frozen with liquid nitrogen in the plates and stored at -80°C. Directly before HILIC-MS analysis, the cells were taken from the freezer and instantly lysed by the addition of an 8:2 mixture (v/v) of methanol and water (300 µL), scraped off the plates and transferred into an Eppendorf tube. The suspension was centrifuged (18 000 g, 20 min, 12°C) to clear from precipitates. The supernatant was then collected and evaporated at 45°C

with a SpeedVac™. The remaining small molecule extract was dissolved in a 1:1 mixture (v/v) of MeCN and water (160 µL) and subjected to HILIC-MS-analysis.

5.2.4 Kinase Assay

Recombinant sedoheptulose kinase (SHPK) was expressed in *E.coli* and purified as previously described.[24] An ADP-Quest™ Assay kit was obtained from DisoverX and used according to the manufacturer's instructions. In short: 20 µL SHPK (0.009 µg/µl in assay buffer), 10 µL sugar solution (sedoheptulose (**sedo**) *or* **4DFS**; 10 mM in water each), 20 µL reagent **A**, 40 µL reagent **B** and 10 µL ATP solution (2 mM in 10 mM HEPES pH 7.6) were mixed in a 96 well plate. Fluorescence was measured on a BioTek Synergy 2 plate reader (excitation wavelength: 530 nm, emission wavelength: 590 nm) for 10 min (fluorescence was read every 2 min, Table 3). All experiments were performed in triplicates. RFU mean of negative control (sedoheptulose with no ATP added) was subtracted from all other values for analysis. The shown graph (Figure 7, chapter 3.1.2) represents the observed change in signal intensity from starting- to endpoint compared to the positive control (**sedo**) which was normalized to 100%. Statistical analysis was done with GraphPad Prism.

Table 3: Measured relative fluorescence units during sedoheptulose kinase assay.

time [min]	sedo			4DFS			sedo no SHK			no sugar			sedo no ATP		
00:03	23908	18552	16844	18110	19984	23988	6845	7668	7925	15839	16601	16069	13634	19726	18726
02:03	26081	20340	18493	20079	22309	26610	7000	7856	8181	16376	17178	16614	13973	20184	19080
04:03	27823	22006	19936	21768	24345	28790	7083	7952	8245	16712	17539	16838	14175	20441	19266
06:03	29169	23442	21240	23157	25870	30395	7091	7969	8260	16937	17783	17057	14263	20565	19335
08:03	29941	24206	22329	23593	26412	30572	7188	7972	8271	17099	17935	17229	14320	20508	19428
10:03	30160	24531	22903	23616	26560	30282	7213	7963	8230	17221	18040	17352	14366	20520	19407

5.2.5 Stability Assays[49]

Human transaldolase (TALDO1) was purchased from ProSpecBio (Rehovot, Israel) and used as received. Transaldolase stability assays contained the following components in water: 1 mM sugar (**sedo** or **4DFS**), 1 mM ATP, 10 mM HEPES pH 7.6, 20 mM KCl, 10 mM $MgCl_2$, 1 mM G3P, 0.045 µg SHPK & 1 µg TALDO1 in a final volume of 25 µL. The reactions were incubated at 30°C for 1.5 h, then diluted 1:100 with MeCN/water 1:1 (v/v) and subjected to HILIC-MS analysis. The shown graph (Figure 8A, chapter 3.1.2) represents the peak area of the respective sugar phosphate compared to the negative control (no TALDO1 added) which was normalized to 100%. All experiments were performed in triplicates. Statistical analysis was done with GraphPad Prism.

Human transketolase (TKT) was purchased from ProSpecBio (Rehovot, Israel) and used as received. Transketolase stability assays contained the following components in water: 1 mM sugar (**sedo** or **4DFS**), 1 mM ATP, 10 mM HEPES pH 7.6, 20 mM KCl, 10 mM $MgCl_2$, 1 mM G3P, 0.5 mM ThDP, 0.045 µg SHPK & 1 µg TKT in a final volume of 25 µL. The reactions were incubated at 30°C for 0.5h, then diluted 1:100 with MeCN/water 1:1 (v/v) and subjected to HILIC-MS analysis. The shown graph (Figure 8B, chapter 3.1.2) represents the peak area of the respective sugar phosphate compared to the negative control (no TKT added) which was normalized to 100%. All experiments were performed in triplicates. Statistical analysis was done with GraphPad Prism.

6 Appendix

6.1 Chromatograms

6.1.1 Uptake Assay

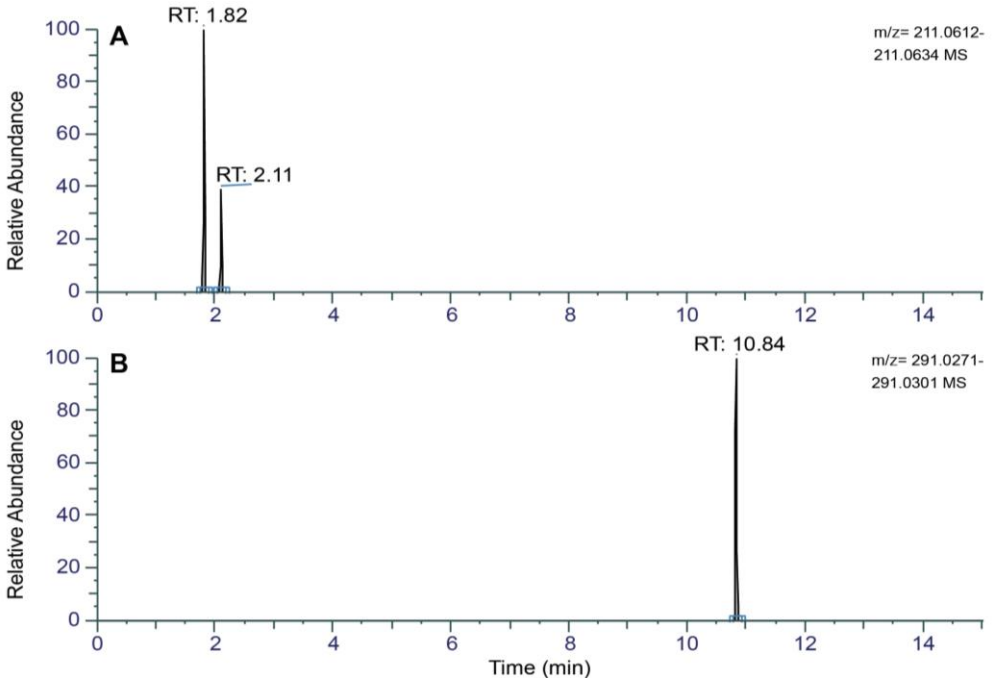


Figure 10: Extracted-ion chromatograms (**A**: *m/z* = 211.0623, **B**: *m/z* = 291.0286; mass tolerance = 5 ppm) of uptake assay control sample (no fluorinated sugar added). *m/z* calc. for $C_7H_{12}FO_6^-$ [M-H]$^-$: 211.0623 (**4DFS**). *m/z* calc. for $C_7H_{13}FO_9P^-$ [M-H]$^-$: 291.0286 (**4DFS**-phosphate).

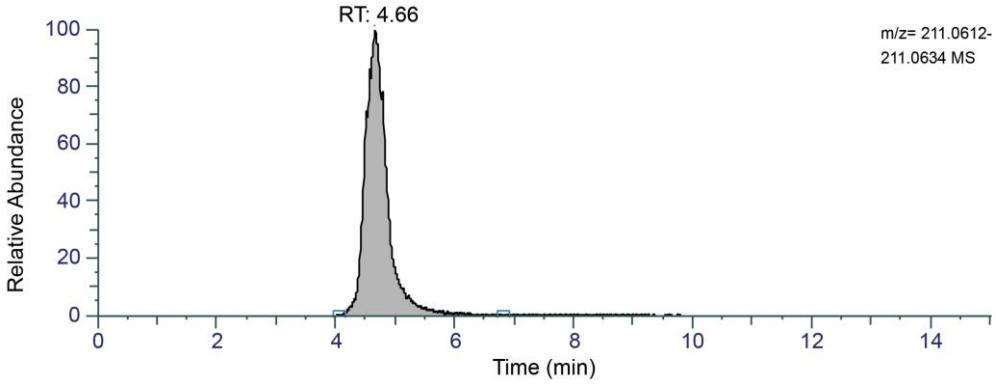


Figure 11: Extracted-ion chromatogram (*m/z* = 211.0623; mass tolerance = 5 ppm) of **4DFS** standard. *m/z* calc. for $C_7H_{12}FO_6^-$ [M-H]$^-$: 211.0623 (**4DFS**).

6.1.2 Stability Assay - TALDO1

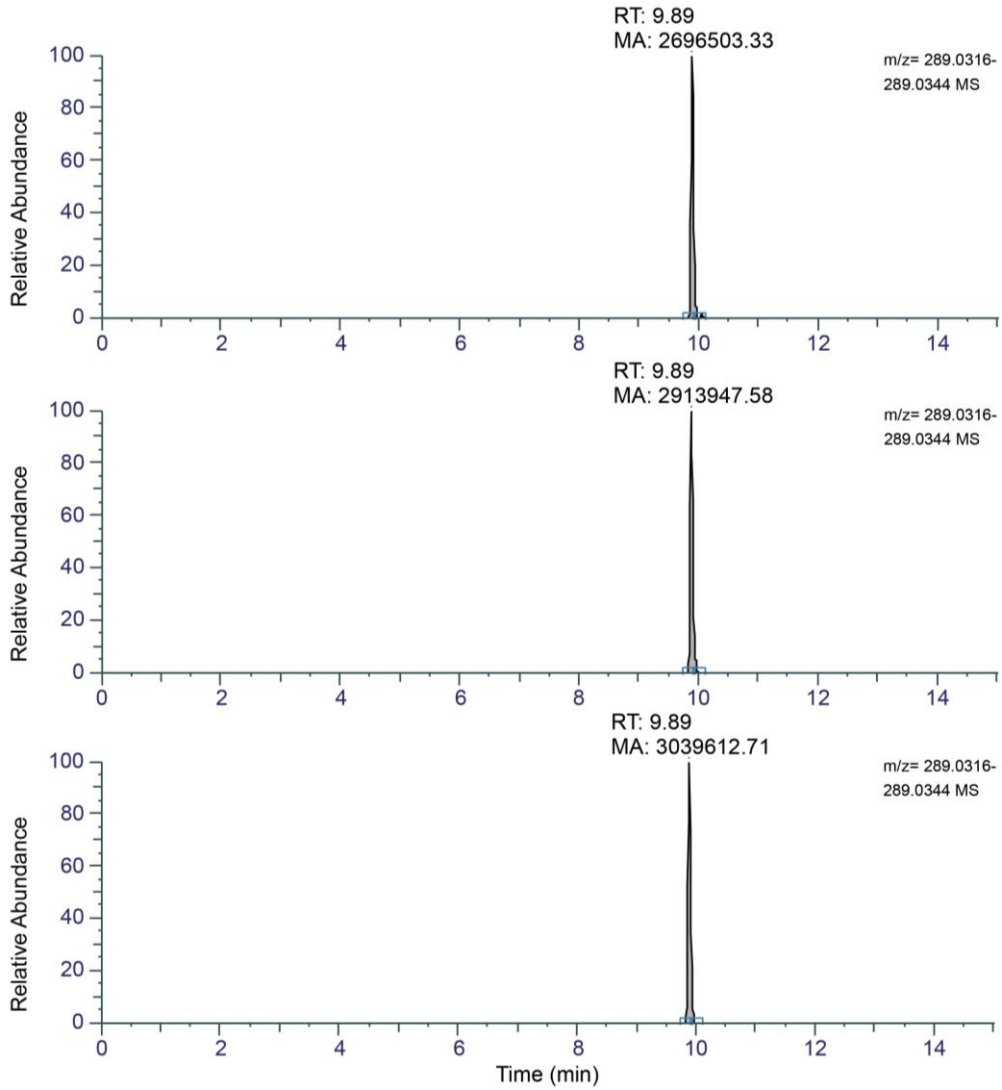


Figure 12: Extracted-ion chromatograms (*m/z* = 289.0330; mass tolerance = 5 ppm) of **sedo** triplicate control samples for TALDO1-stability assay (no TALDO1 added). *m/z* calc. for $C_7H_{14}O_{10}P^-$ $[M-H]^-$: 289.0330 (**S7P**).

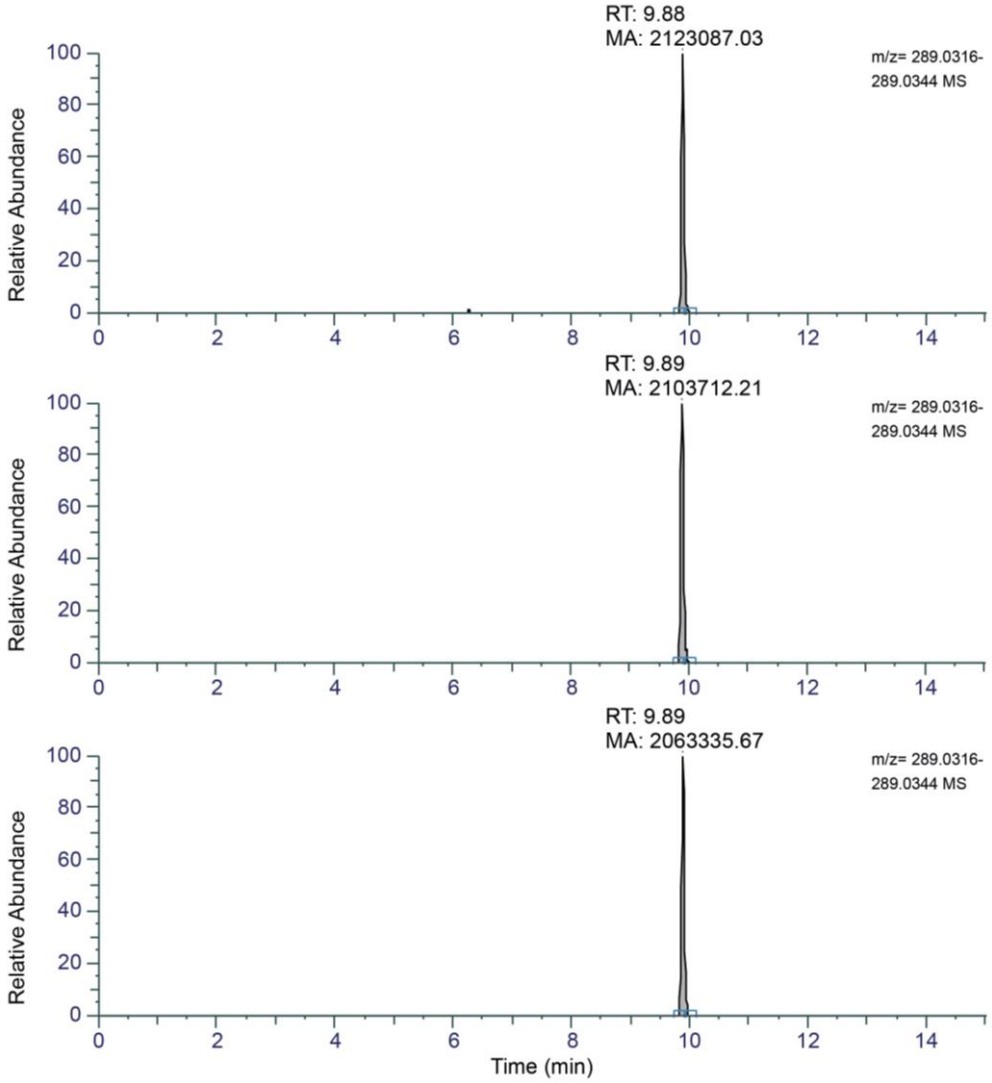


Figure 13: Extracted-ion chromatograms (*m/z* = 289.0330; mass tolerance = 5 ppm) of **sedo** triplicate samples for TALDO1-stability assay. *m/z* calc. for $C_7H_{14}O_{10}P^-$ $[M-H]^-$: 289.0330 (**S7P**).

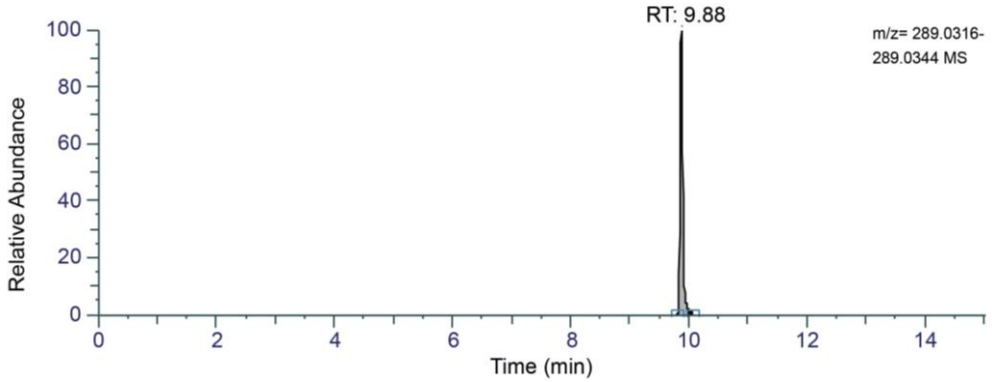


Figure 14: Extracted-ion chromatogram (*m/z* = 289.0330; mass tolerance = 5 ppm) of **S7P** standard. *m/z* calc. for $C_7H_{14}O_{10}P^-$ $[M-H]^-$: 289.0330 (**S7P**).

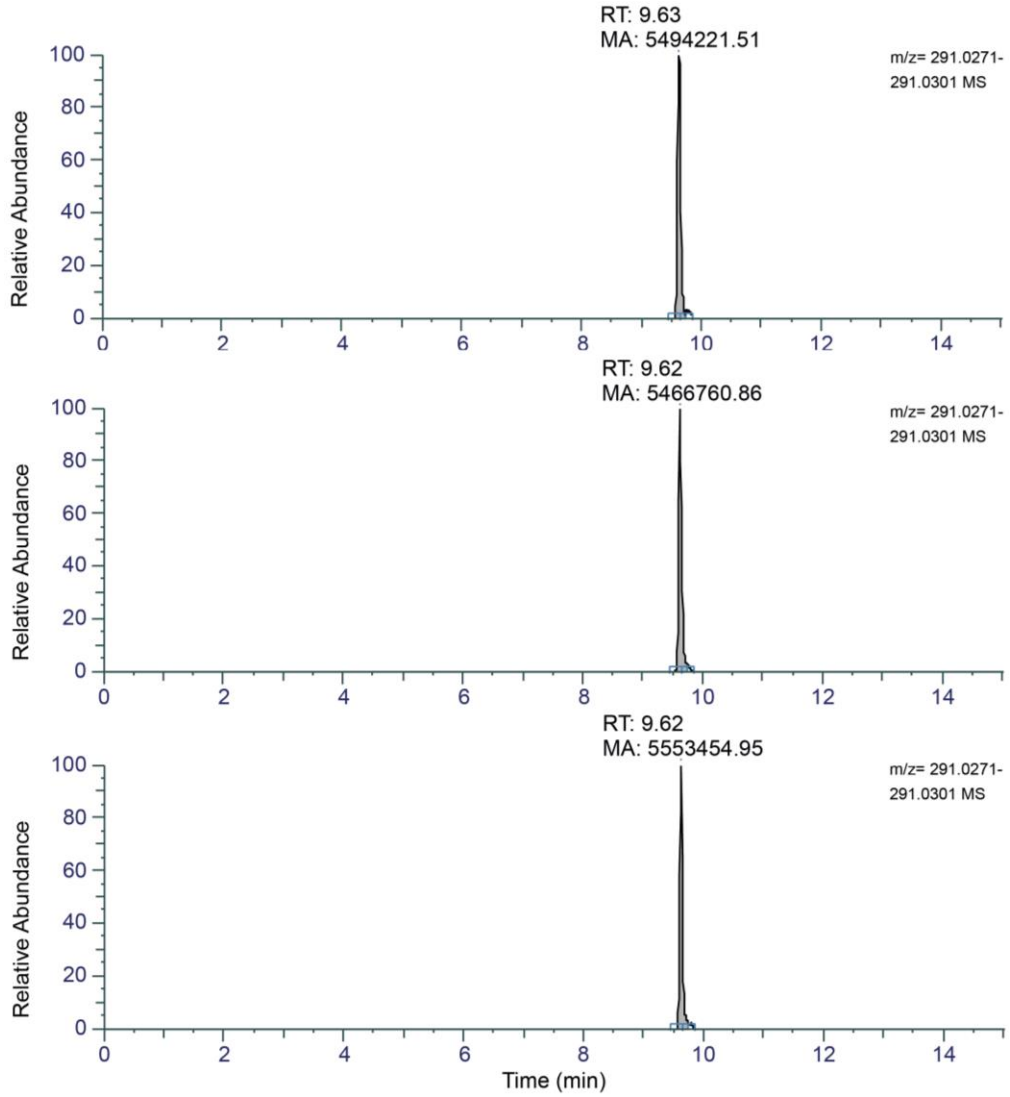


Figure 15: Extracted-ion chromatograms (*m/z* = 291.0286; mass tolerance = 5 ppm) of **4DFS** triplicate control samples for TALDO1-stability assay (no TALDO1 added). *m/z* calc. for $C_7H_{13}FO_9P^-$ $[M-H]^-$: 291.0286 (**4DFS**-phosphate).

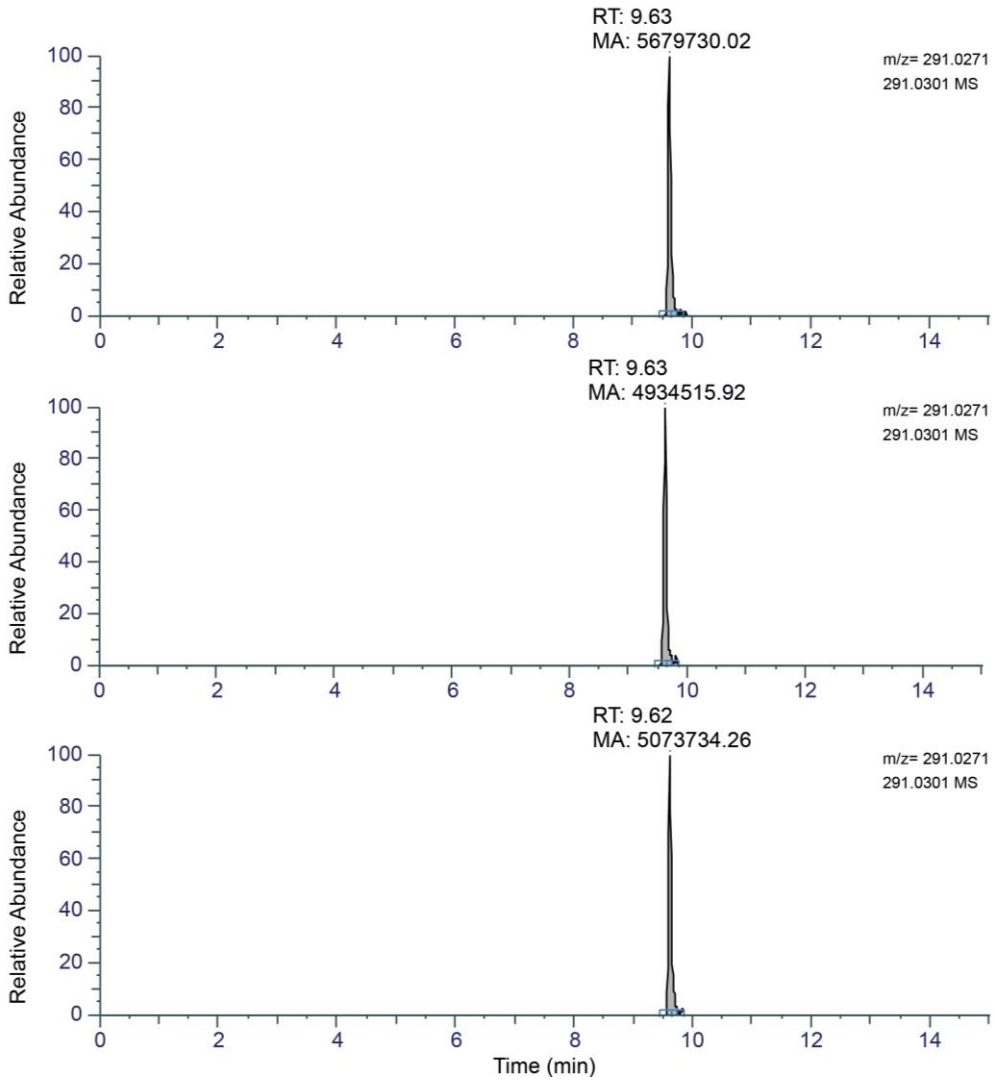


Figure 16: Extracted-ion chromatograms (*m/z* = 291.0286; mass tolerance = 5 ppm) of **4DFS** triplicate samples for TALDO1-stability assay. *m/z* calc. for $C_7H_{13}FO_9P^-$ $[M-H]^-$: 291.0286 (**4DFS**-phosphate).

6.1.3 Stability Assay – TKT

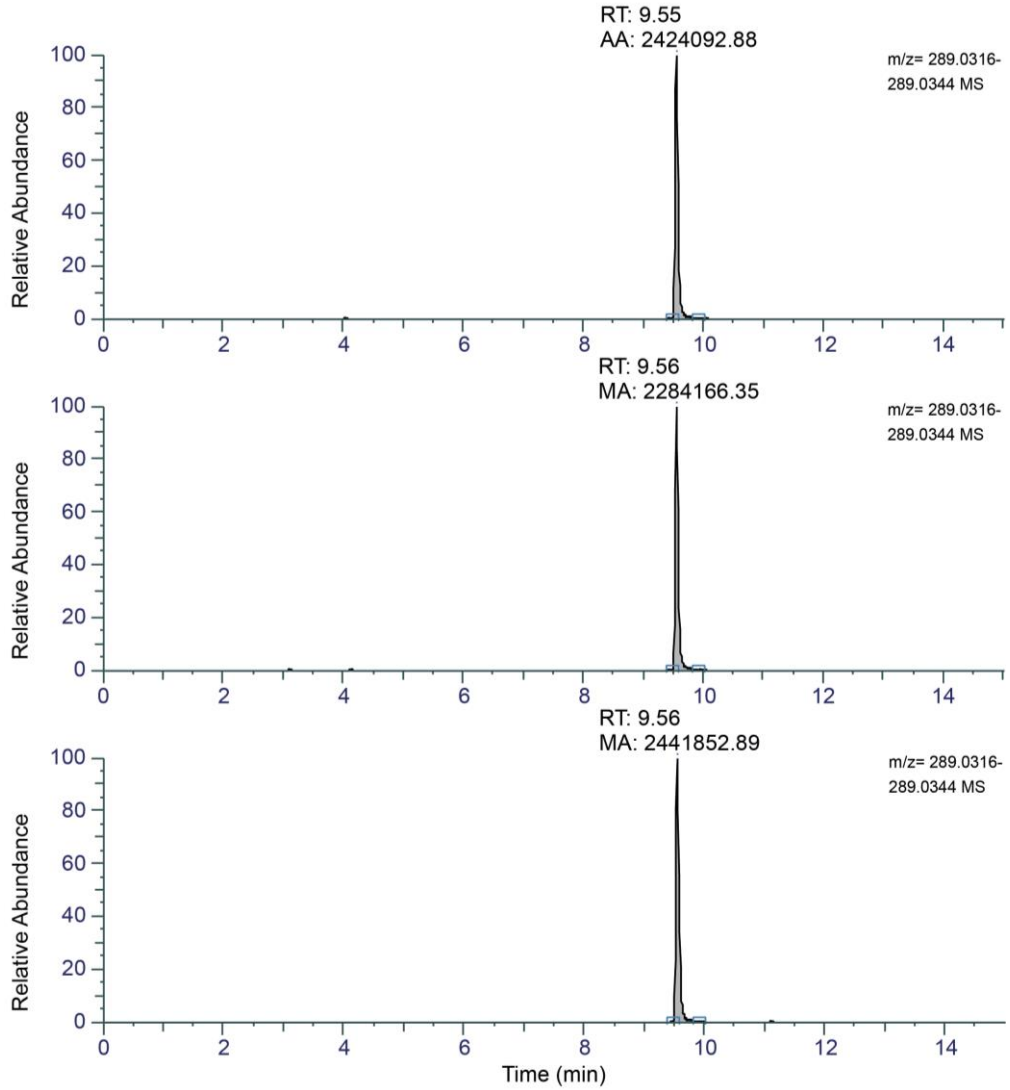


Figure 17: Extracted-ion chromatograms (*m/z* = 289.0330; mass tolerance = 5 ppm) of **sedo** triplicate control samples for TKT-stability assay (no TKT added). *m/z* calc. for $C_7H_{14}O_{10}P^-$ $[M-H]^-$: 289.0330 (**S7P**).

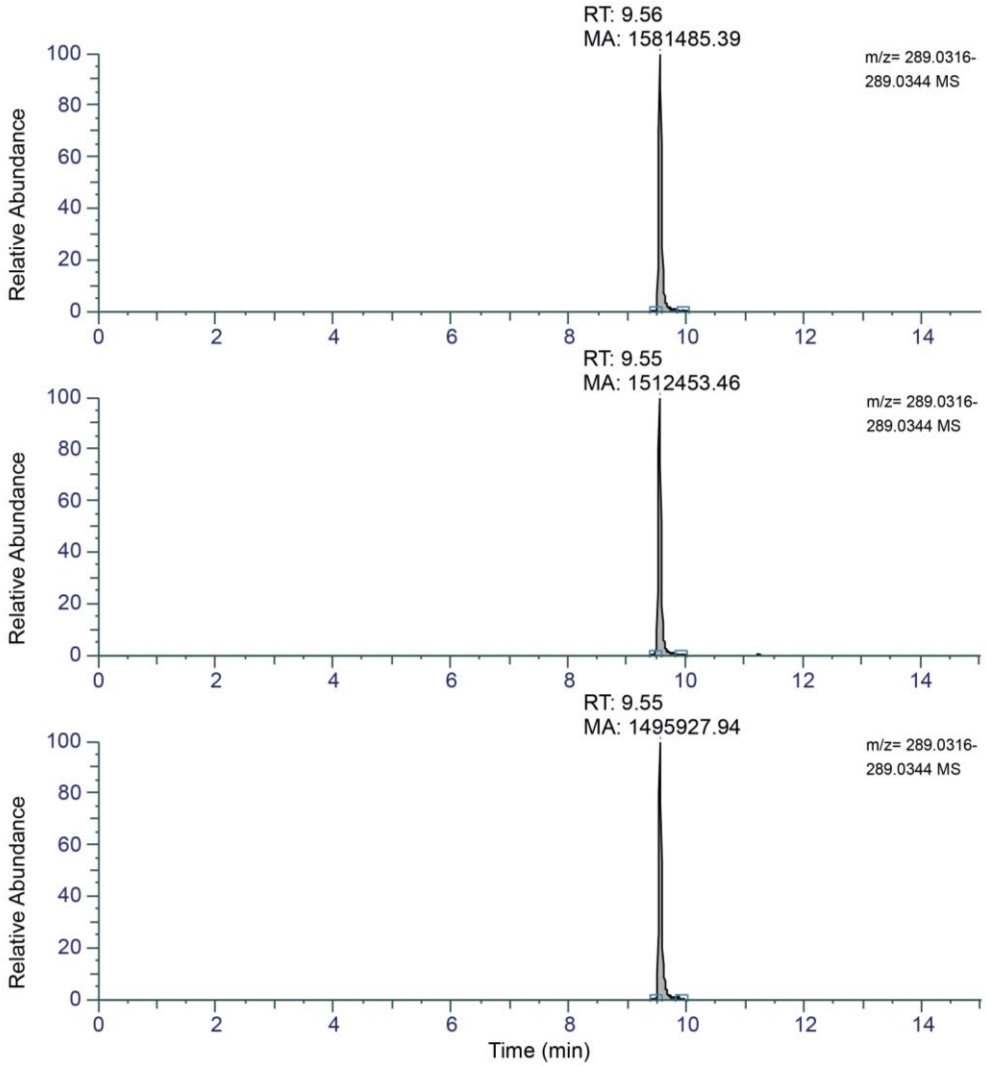


Figure 18: Extracted-ion chromatograms (*m/z* = 289.0330; mass tolerance = 5 ppm) of **sedo** triplicate samples for TKT-stability assay. *m/z* calc. for $C_7H_{14}O_{10}P^-$ $[M-H]^-$: 289.0330 (**S7P**).

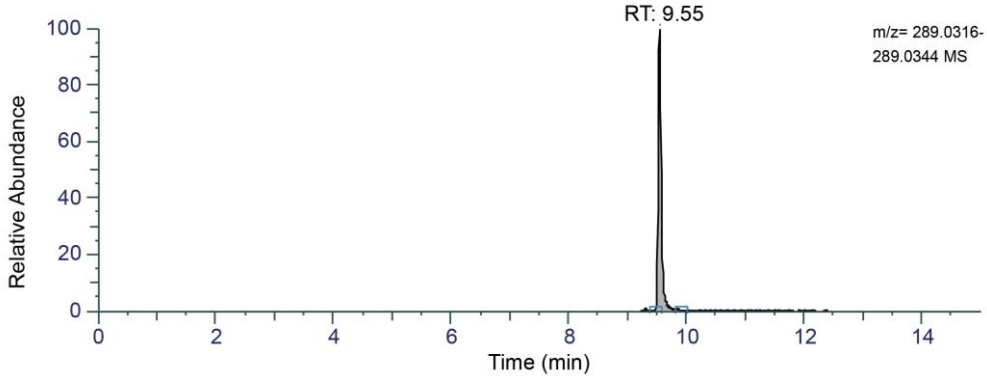


Figure 19: Extracted-ion chromatogram (*m/z* = 289.0330; mass tolerance = 5 ppm) of **S7P** standard. *m/z* calc. for $C_7H_{14}O_{10}P^-$ $[M-H]^-$: 289.0330 (**S7P**).

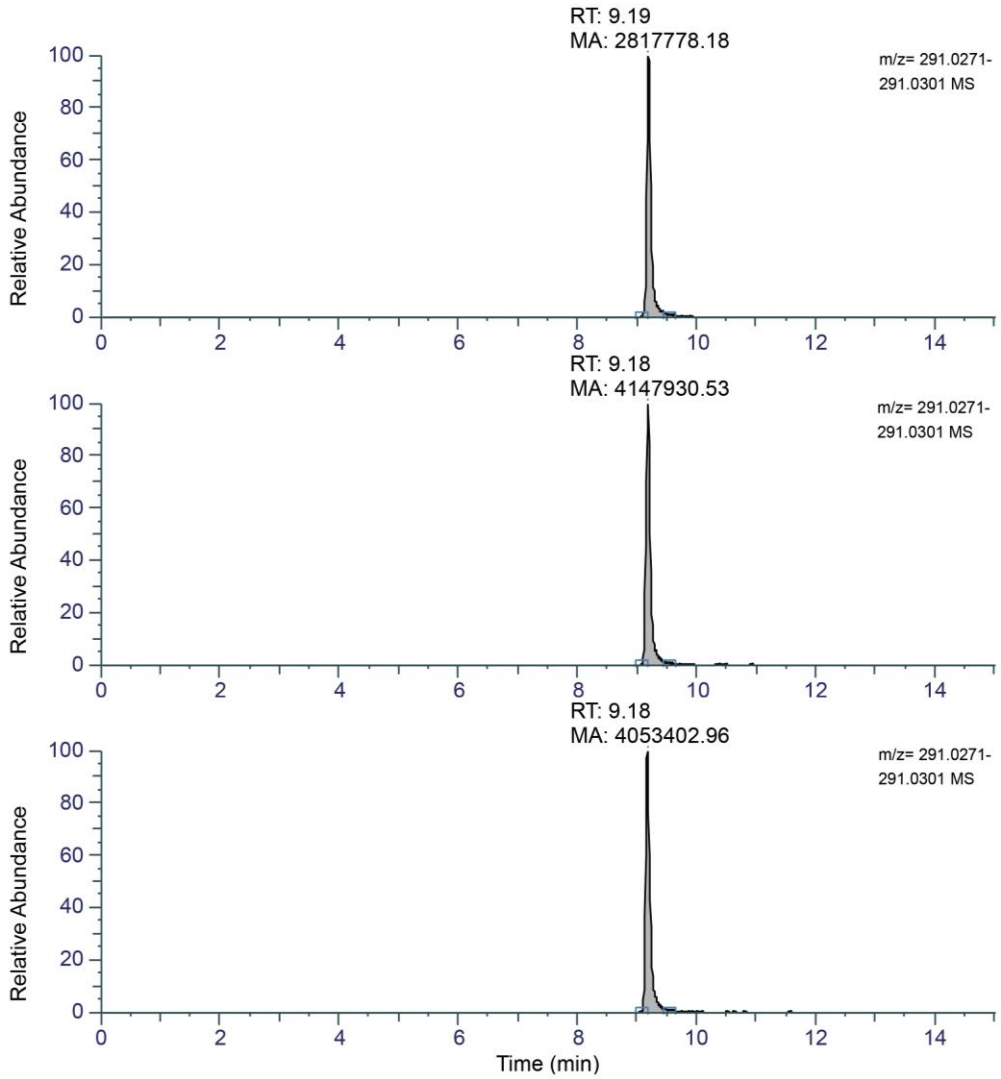


Figure 20: Extracted-ion chromatograms (*m/z* = 291.0286; mass tolerance = 5 ppm) of **4DFS** triplicate control samples for TKT-stability assay (no TKT added). *m/z* calc. for $C_7H_{13}FO_9P^-$ $[M-H]^-$: 291.0286 (**4DFS**-phosphate).

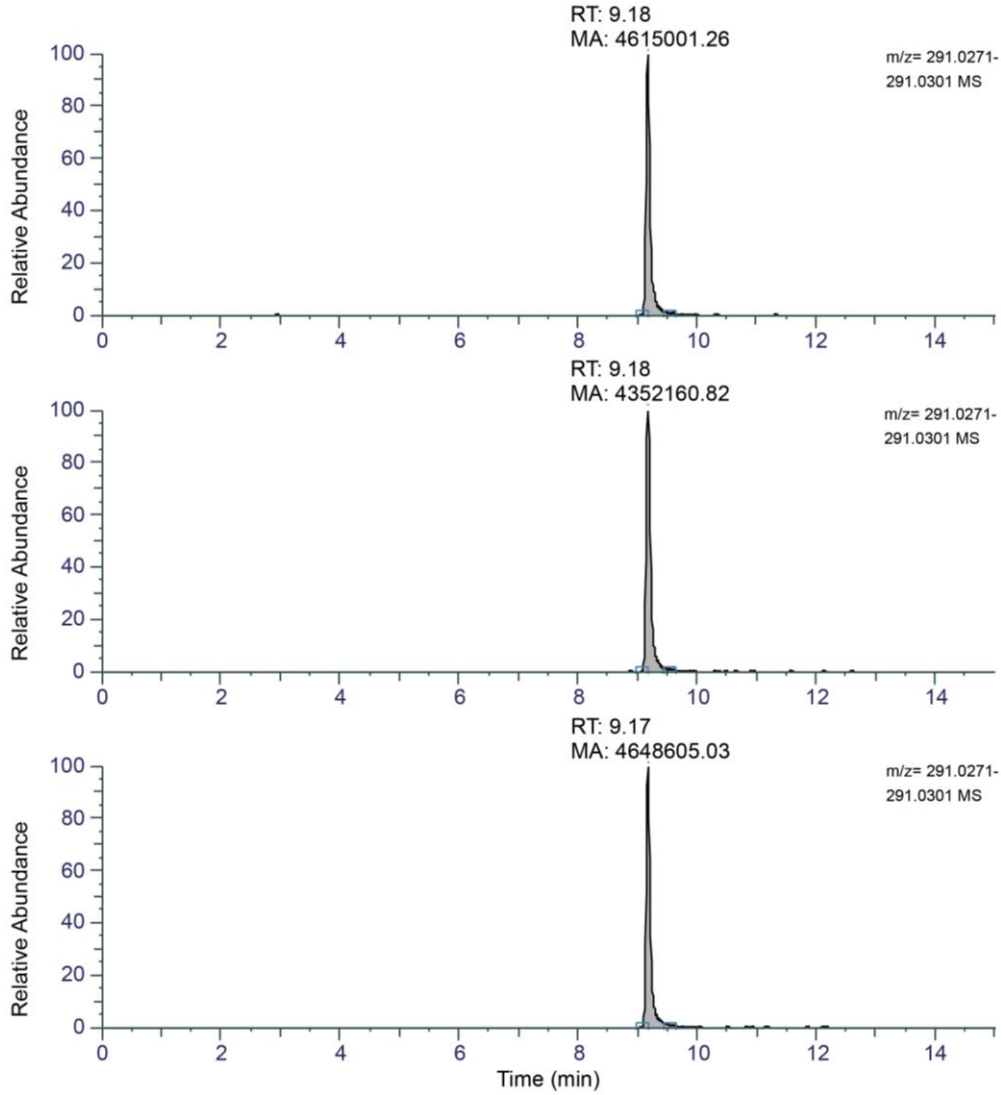


Figure 21: Extracted-ion chromatograms (*m/z* = 291.0286; mass tolerance = 5 ppm) of **4DFS** triplicate samples for TKT-stability assay. *m/z* calc. for $C_7H_{13}FO_9P^-$ $[M-H]^-$: 291.0286 (**4DFS**-phosphate).

6.2 NMR Spectra

^{1}H, ^{13}C & ^{19}F (if applicable) NMR spectra of all synthesized target compounds are shown in this chapter: **4DFS**, compounds **3.20a** & **3.20b**, **1DFRu**, compound **3.34**, **3DFRu**, **2DFE** & compound **3.54**.

6.2.1 4-Deoxy-4-fluoro-D-sedoheptulose/ 4-deoxy-4-fluoro-D-*glycero*-D-*arabino*-hept-2-ulopyranose & 4-deoxy-4-fluoro-D-*glycero*-D-*arabino*-hept-2-ulofuranose (4DFS)

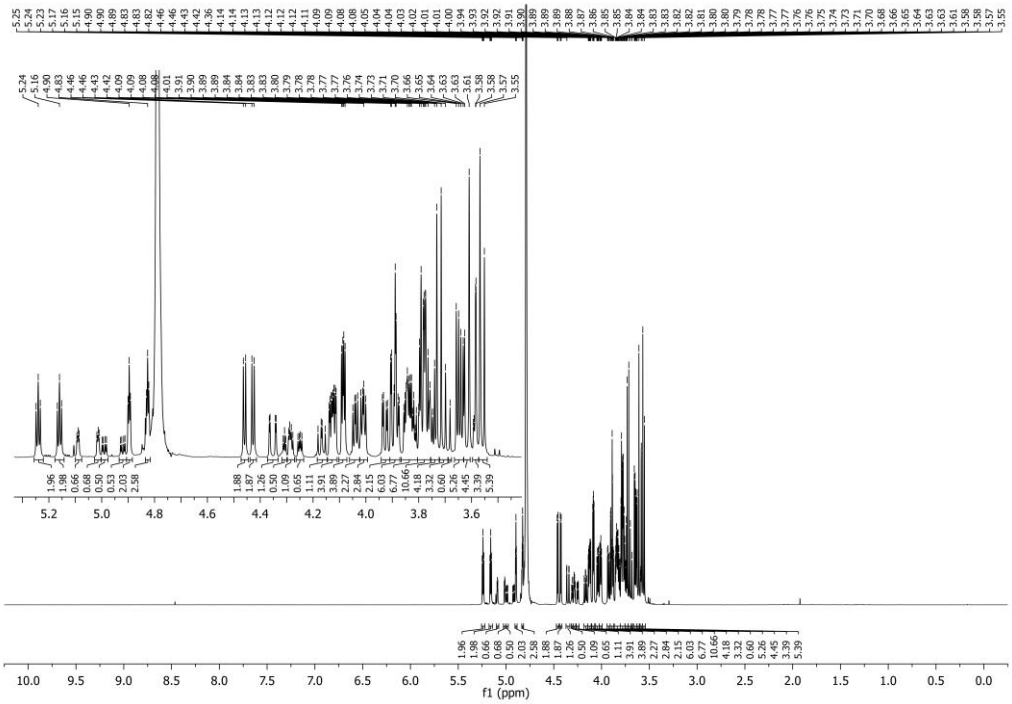


Figure 22: ^{1}H NMR (700 MHz, D_2O) of 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**).

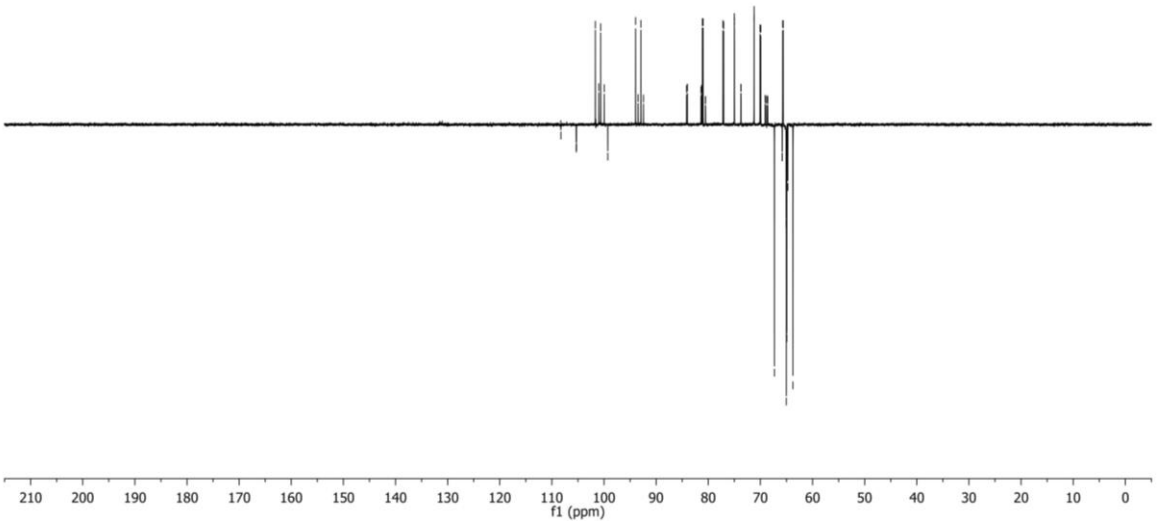


Figure 23: ^{13}C NMR (176 MHz, D_2O) of 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**).

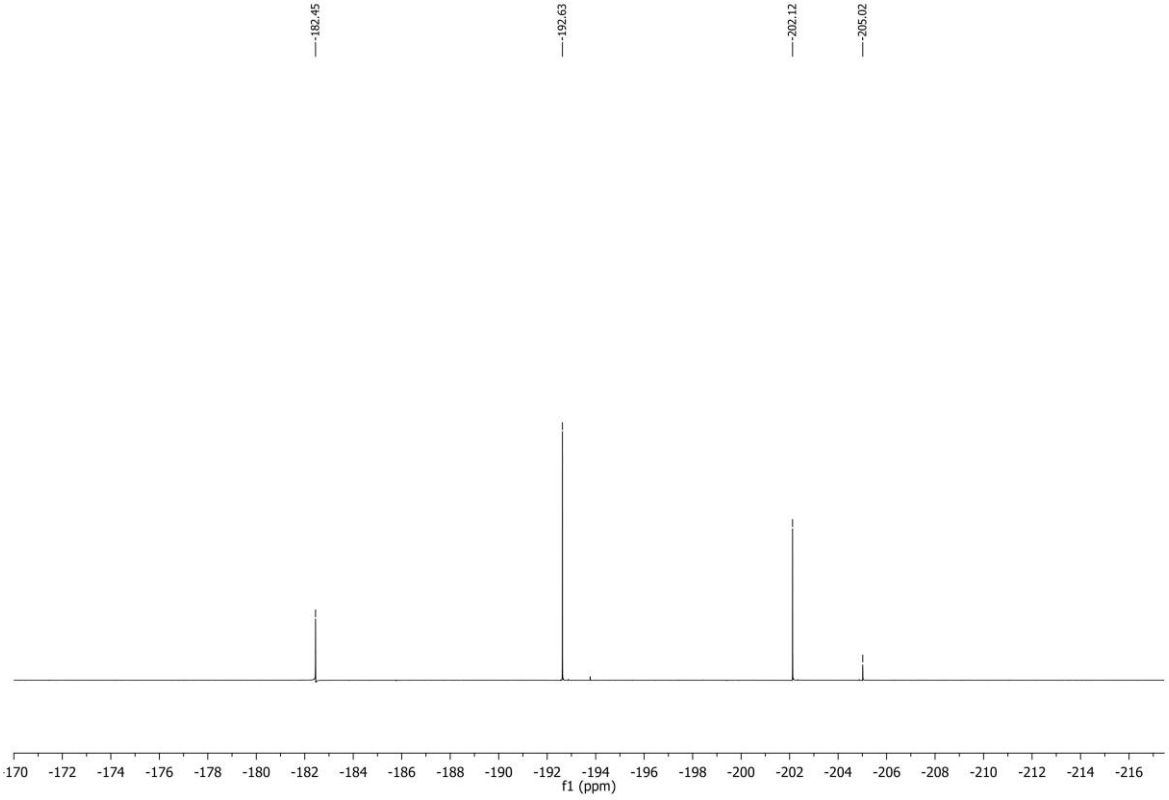


Figure 24: $^{19}F\{^{1}H\}$ NMR (659 MHz, D_2O) of 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**).

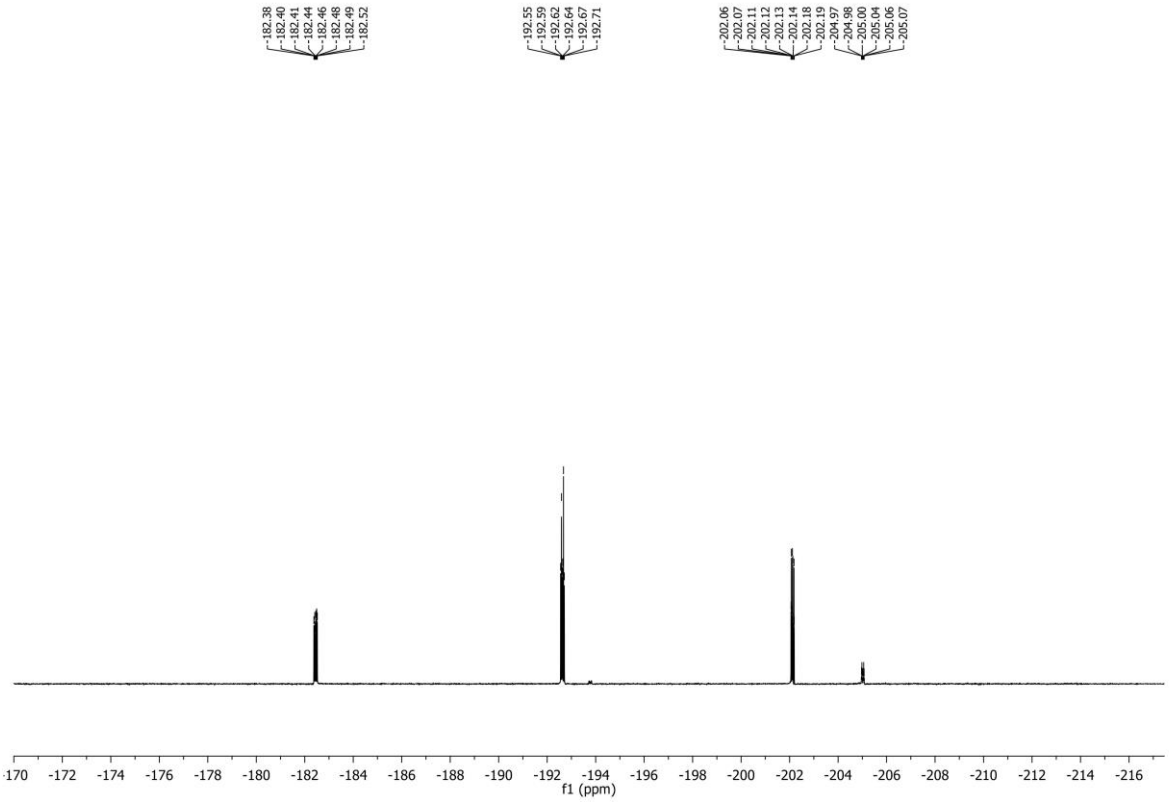


Figure 25: ^{19}F NMR (659 MHz, D_2O) of 4-deoxy-4-fluoro-D-sedoheptulose (**4DFS**).

6.2.2 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (3.20a)

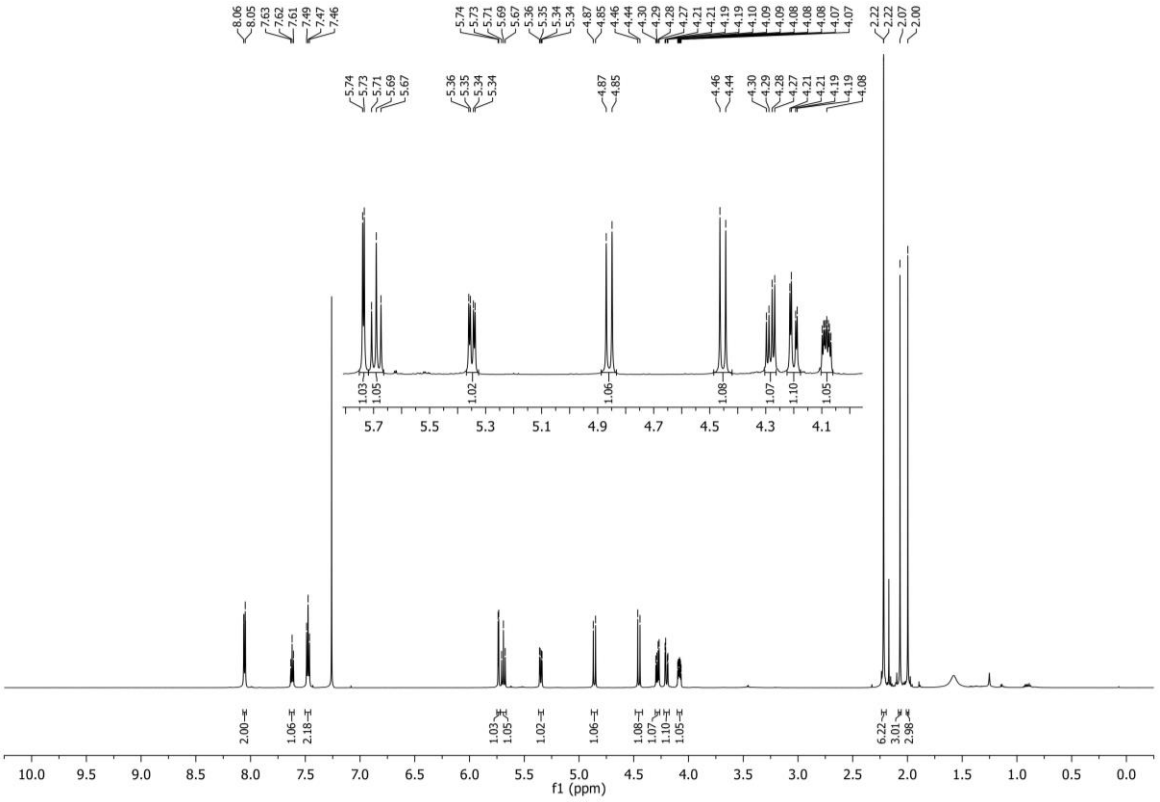


Figure 26: ^{1}H NMR (600 MHz, $CDCl_3$) of 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.20a**).

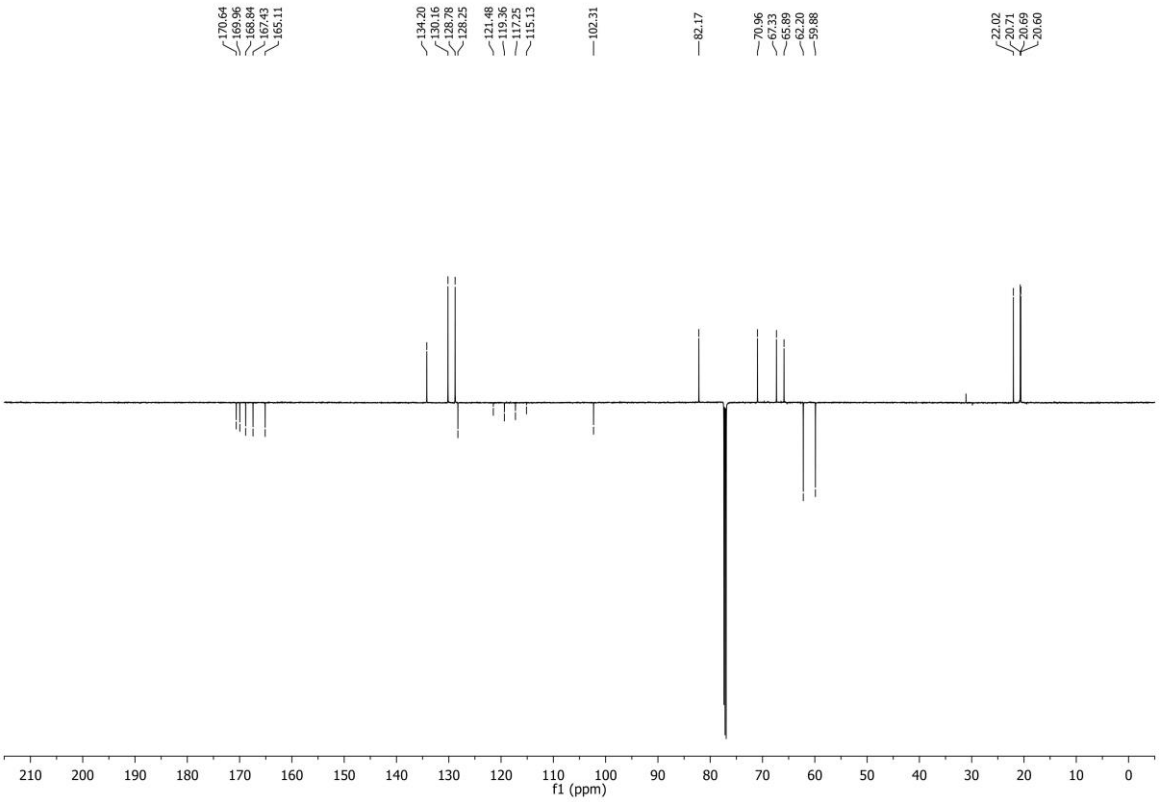


Figure 27: ^{13}C NMR (151 MHz, $CDCl_3$) of 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.20a**).

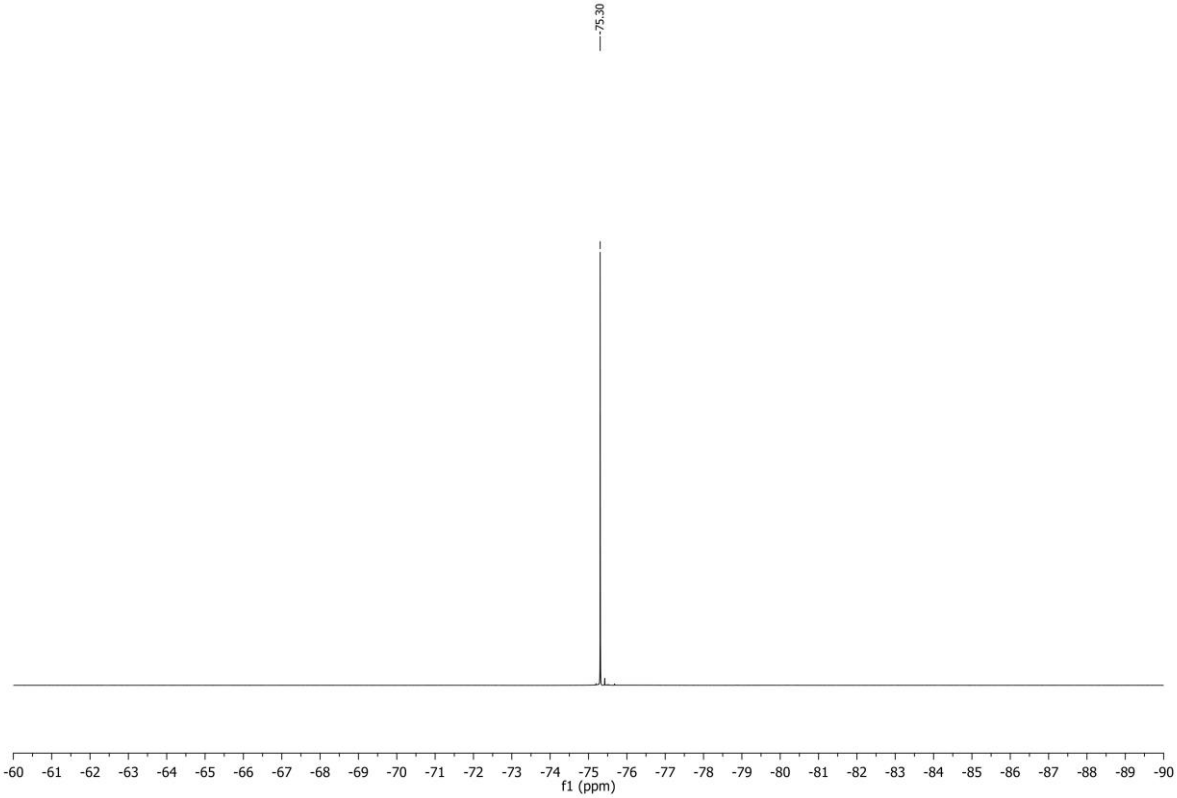


Figure 28: ^{19}F NMR (659 MHz, $CDCl_3$) of 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-trifluoromethanesulfonyl-D-*glycero*-α-D-*lyxo*-hept-2-ulopyranose (**3.20a**).

6.2.3 1,2,3,7-Tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-*para*-nitrobenzenesulfonyl-D-*glycero*-α-D-*lxyo*-hept-2-ulopyranose (3.20b)

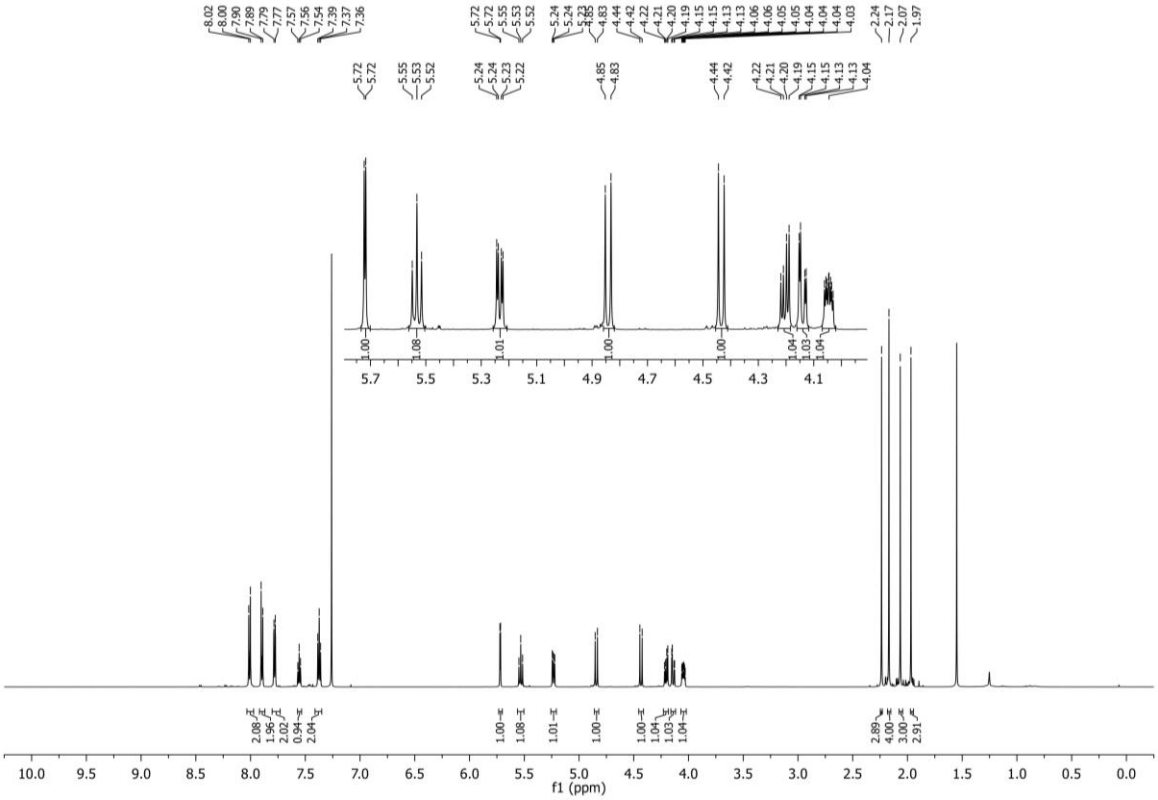


Figure 29: ^{1}H NMR (600 MHz, $CDCl_3$) of 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-*para*-nitrobenzenesulfonyl-D-*glycero*-α-D-*lxyo*-hept-2-ulopyranose (**3.20b**).

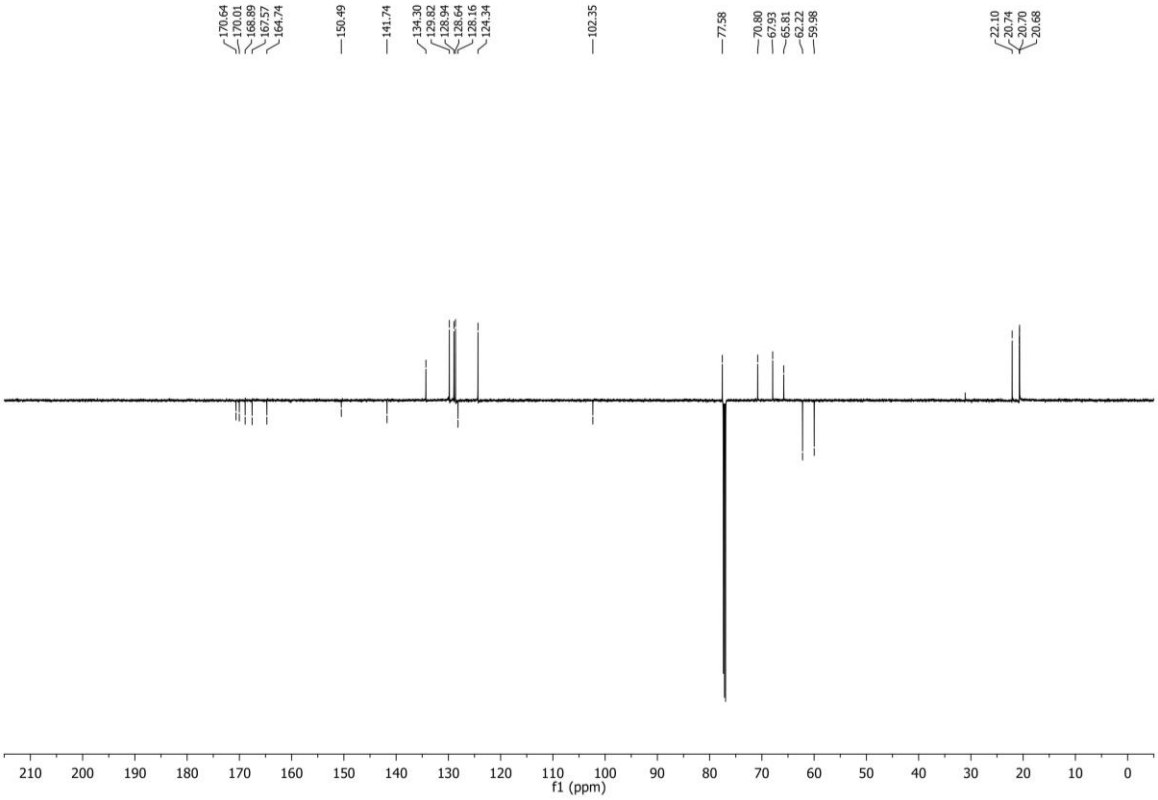


Figure 30: ^{13}C NMR (151 MHz, $CDCl_3$) of 1,2,3,7-tetra-*O*-acetyl-5-*O*-benzoyl-4-*O*-*para*-nitrobenzenesulfonyl-D-*glycero*-α-D-*lxyo*-hept-2-ulopyranose (**3.20b**).

6.2.4 1-Deoxy-1-fluoro-D-ribulose (1DFRu)

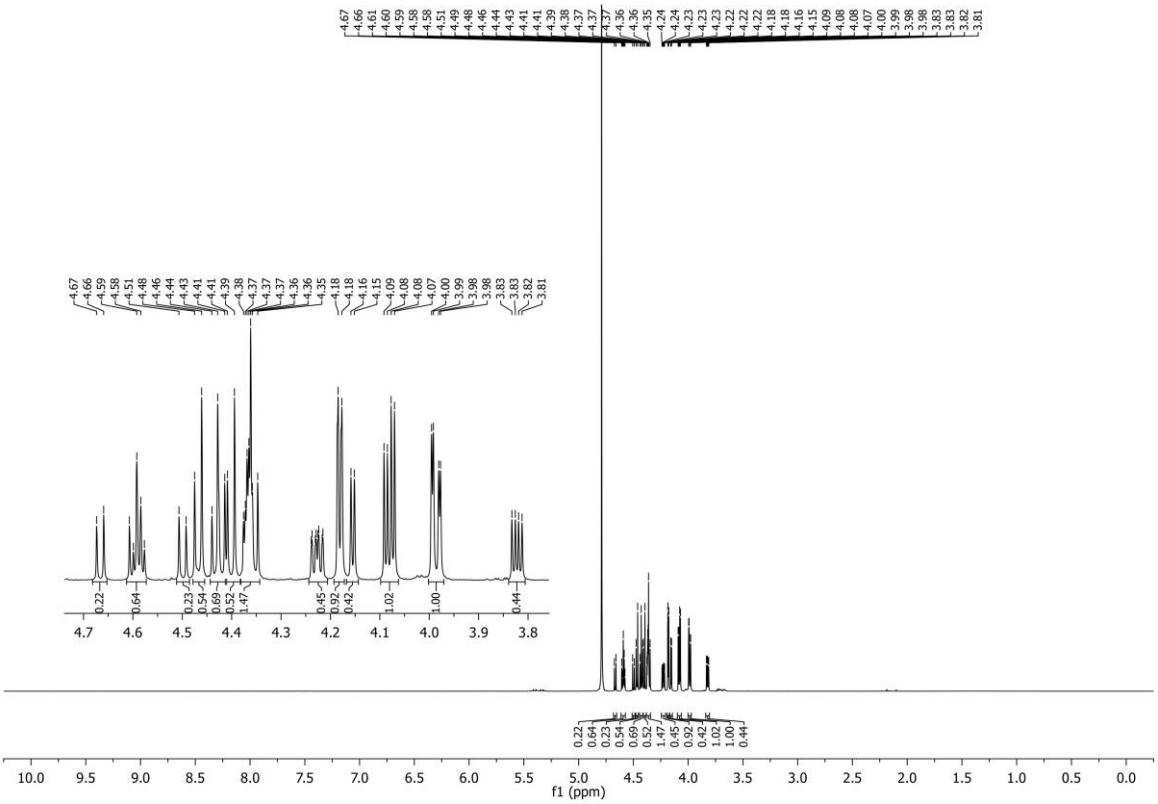


Figure 31: ^{1}H NMR (700 MHz, D_2O) of 1-deoxy-1-fluoro-D-ribulose (**1DFRu**).

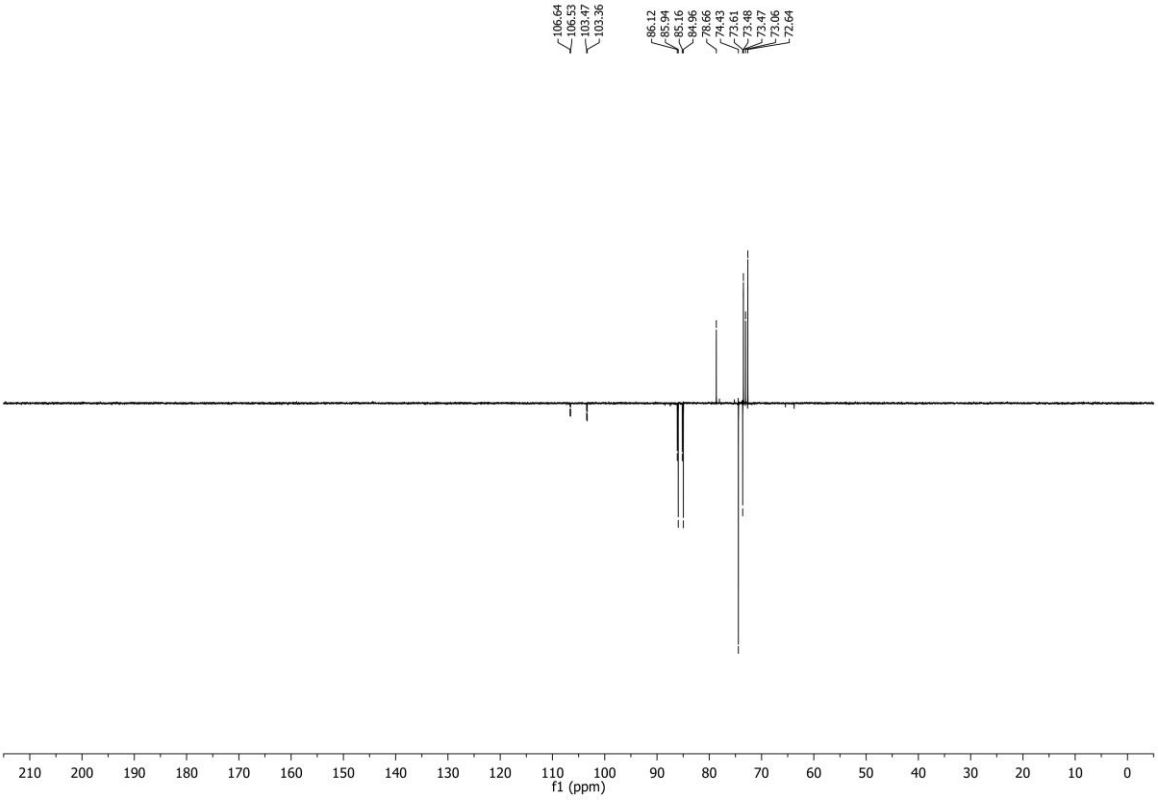


Figure 32: ^{13}C NMR (176 MHz, D_2O) of 1-deoxy-1-fluoro-D-ribulose (**1DFRu**).

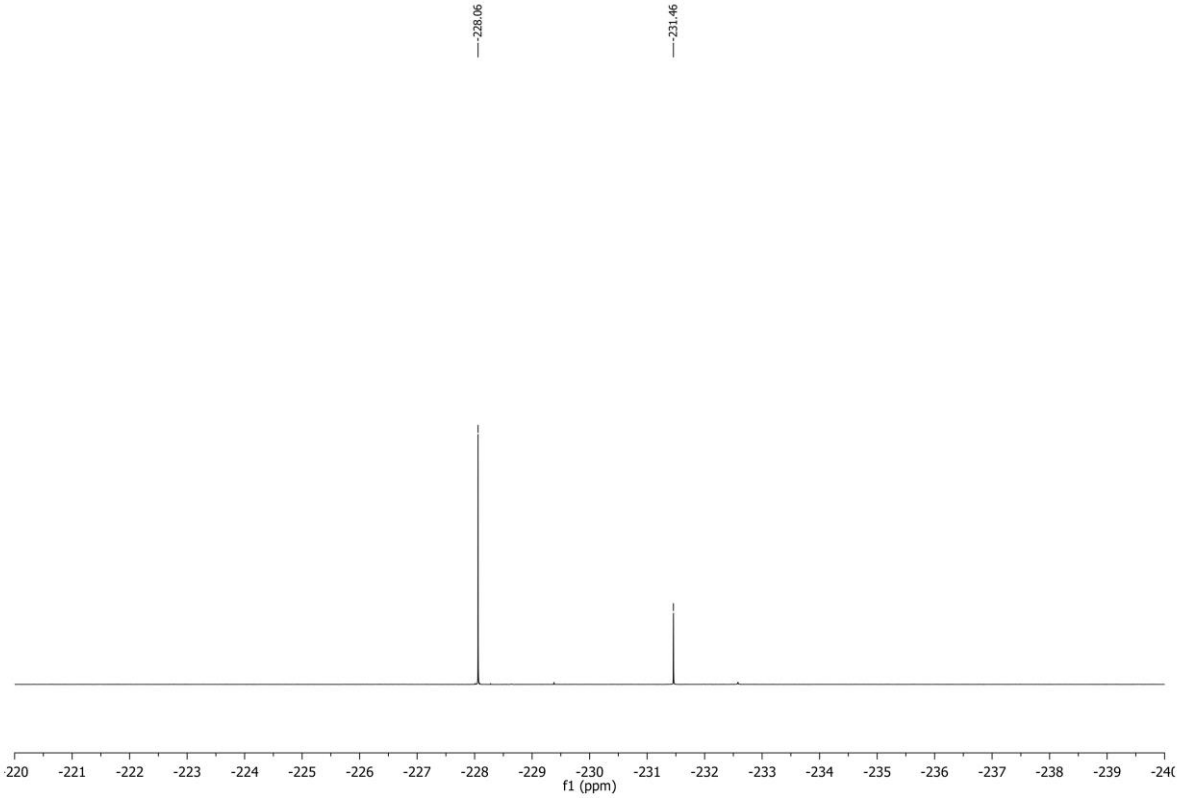


Figure 33: $^{19}F\{^{1}H\}$ NMR (659 MHz, D_2O) of 1-deoxy-1-fluoro-D-ribulose (**1DFRu**).

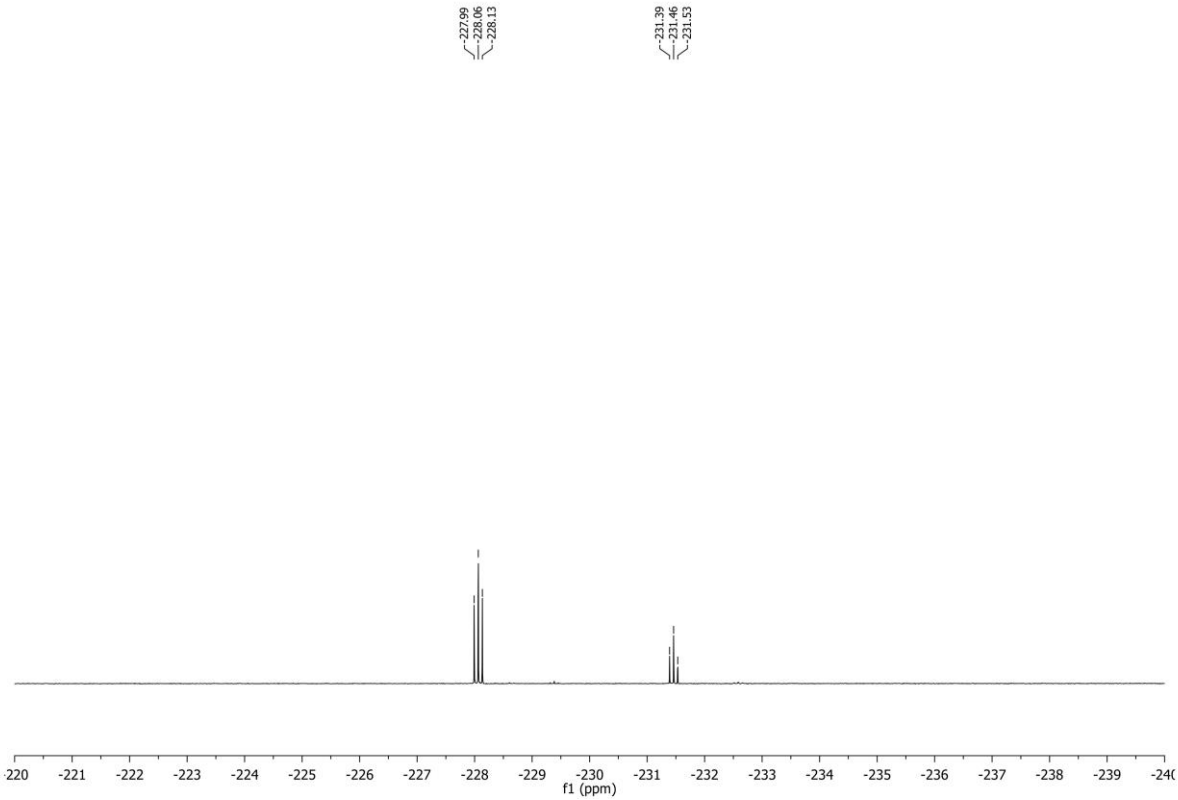


Figure 34: ^{19}F NMR (659 MHz, D_2O) of 1-deoxy-1-fluoro-D-ribulose (**1DFRu**).

6.2.5 Methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside (3.34)

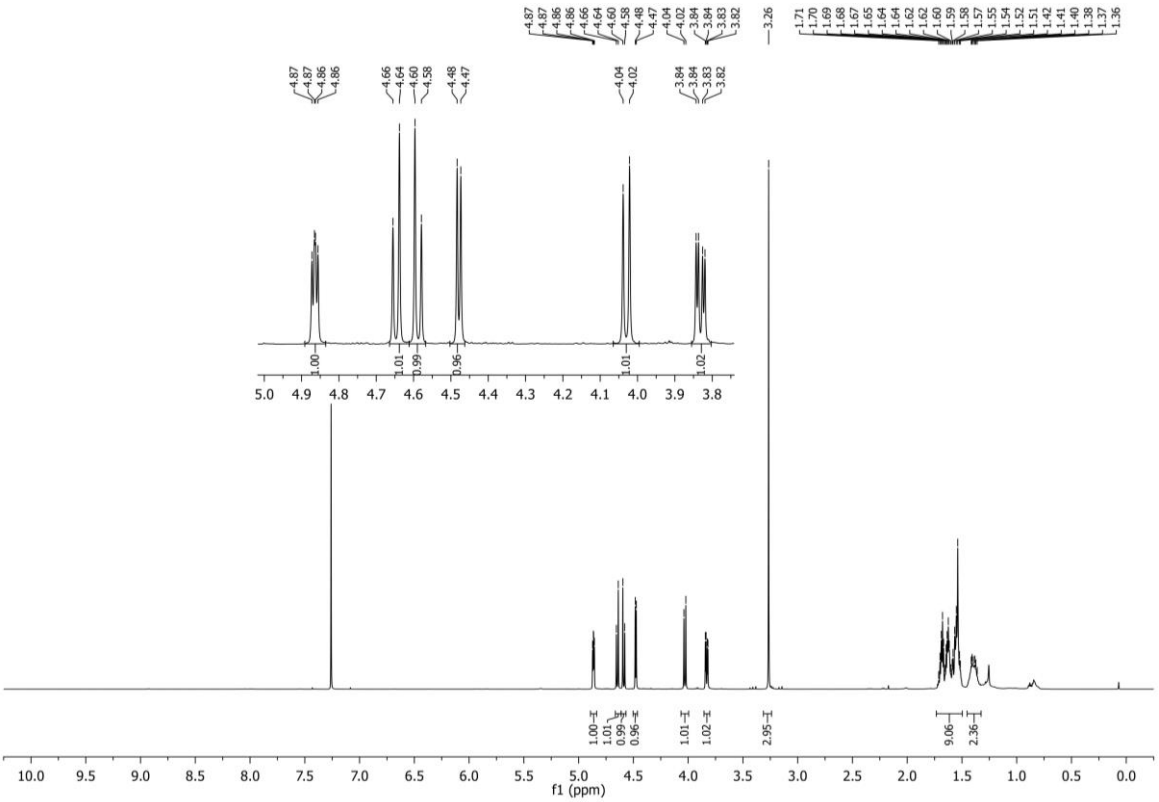


Figure 35: ^{1}H NMR (600 MHz, $CDCl_3$) of methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside (**3.34**).

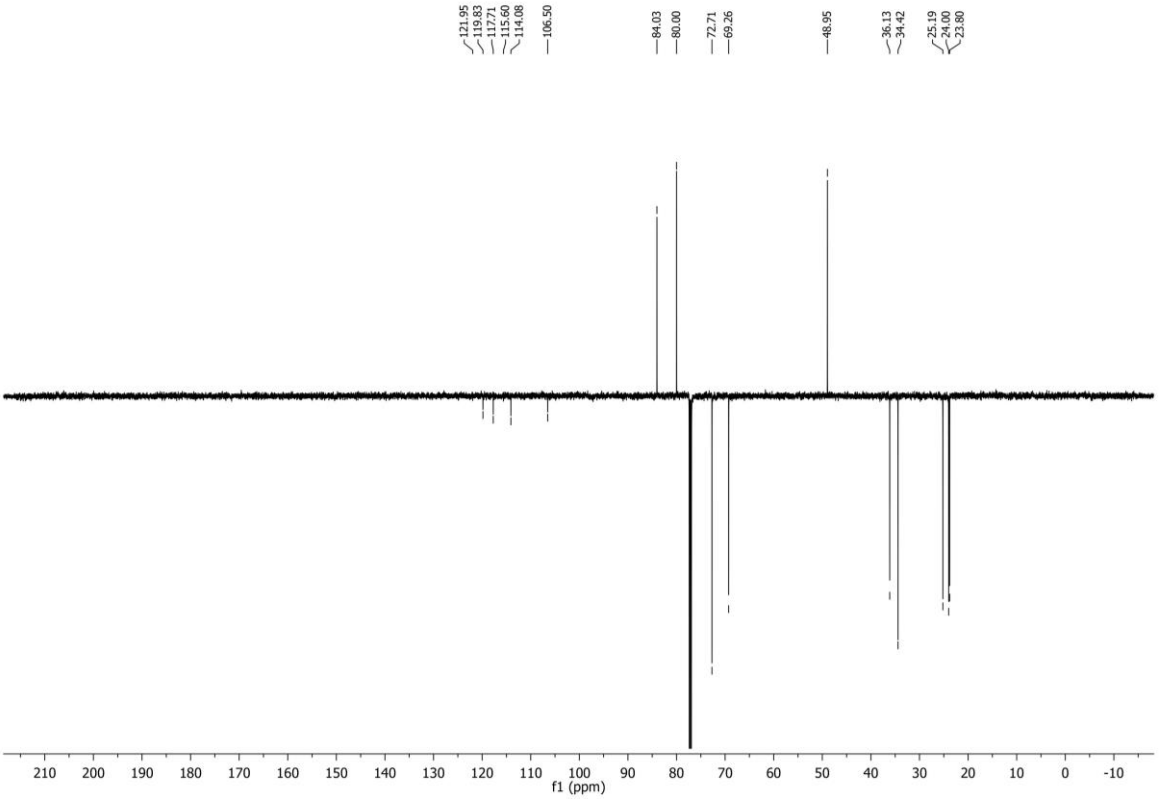


Figure 36: ^{13}C NMR (151 MHz, $CDCl_3$) of methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside (**3.34**).

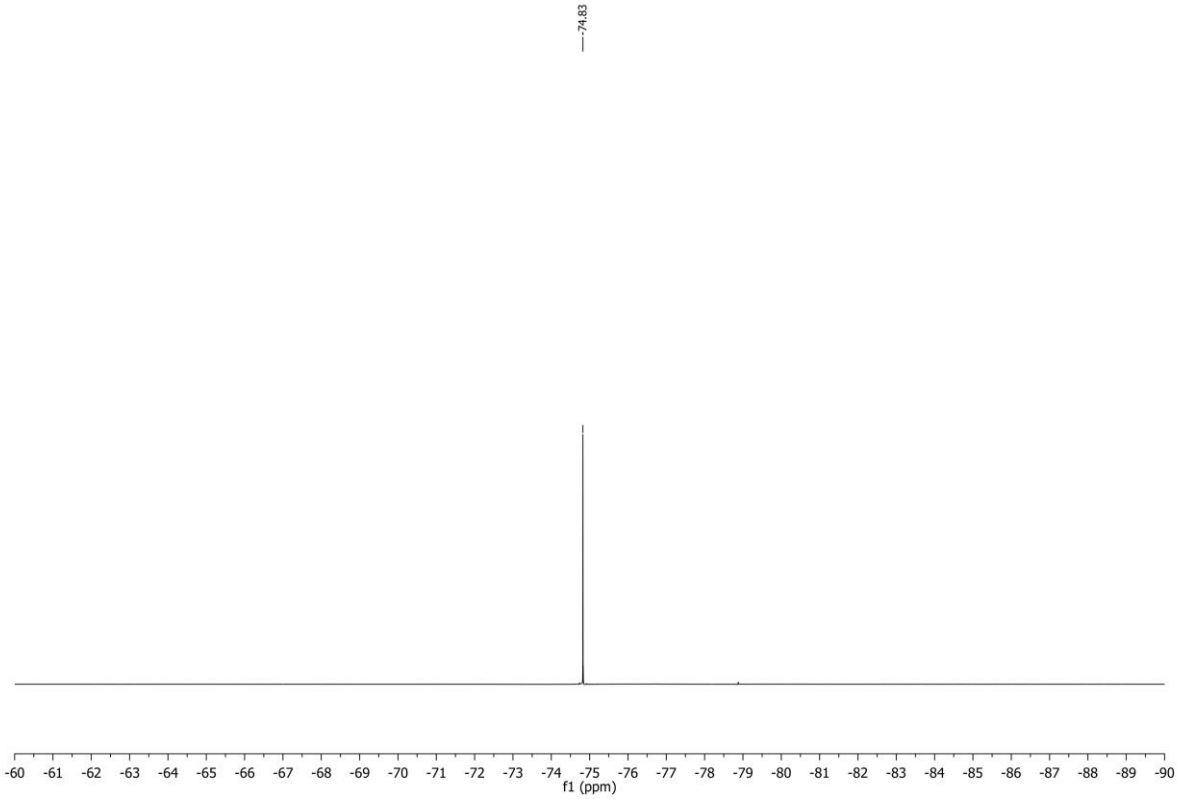


Figure 37: ^{19}F NMR (659 MHz, $CDCl_3$) of methyl 3,4-*O*-cyclohexylidene-1-*O*-trifluoromethanesulfonyl-β-D-*ribulo*-furanoside (**3.34**).

6.2.7 3-Deoxy-3-fluoro-D-ribulose (3DFRu)

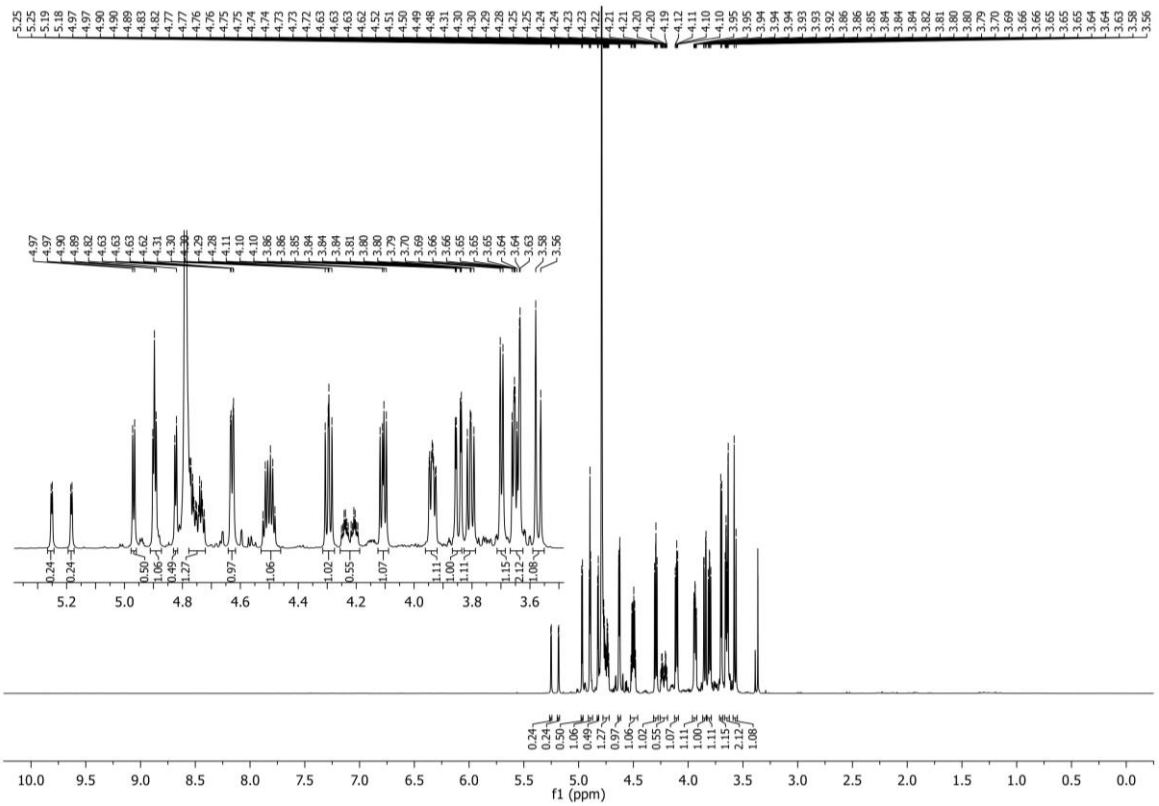


Figure 38: ^{1}H NMR (700 MHz, D_2O) of 3-deoxy-3-fluoro-D-ribulose (**3DFRu**).

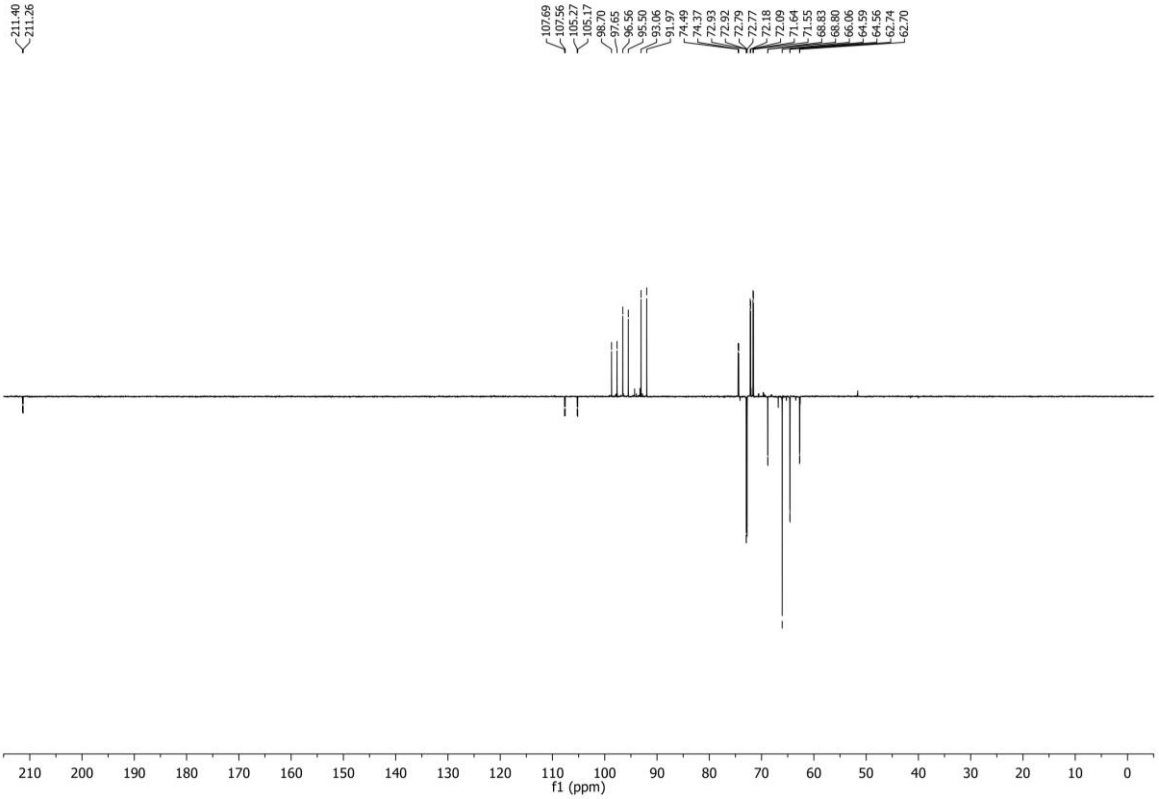


Figure 39: ^{13}C NMR (176 MHz, D_2O) of 3-deoxy-3-fluoro-D-ribulose (**3DFRu**).

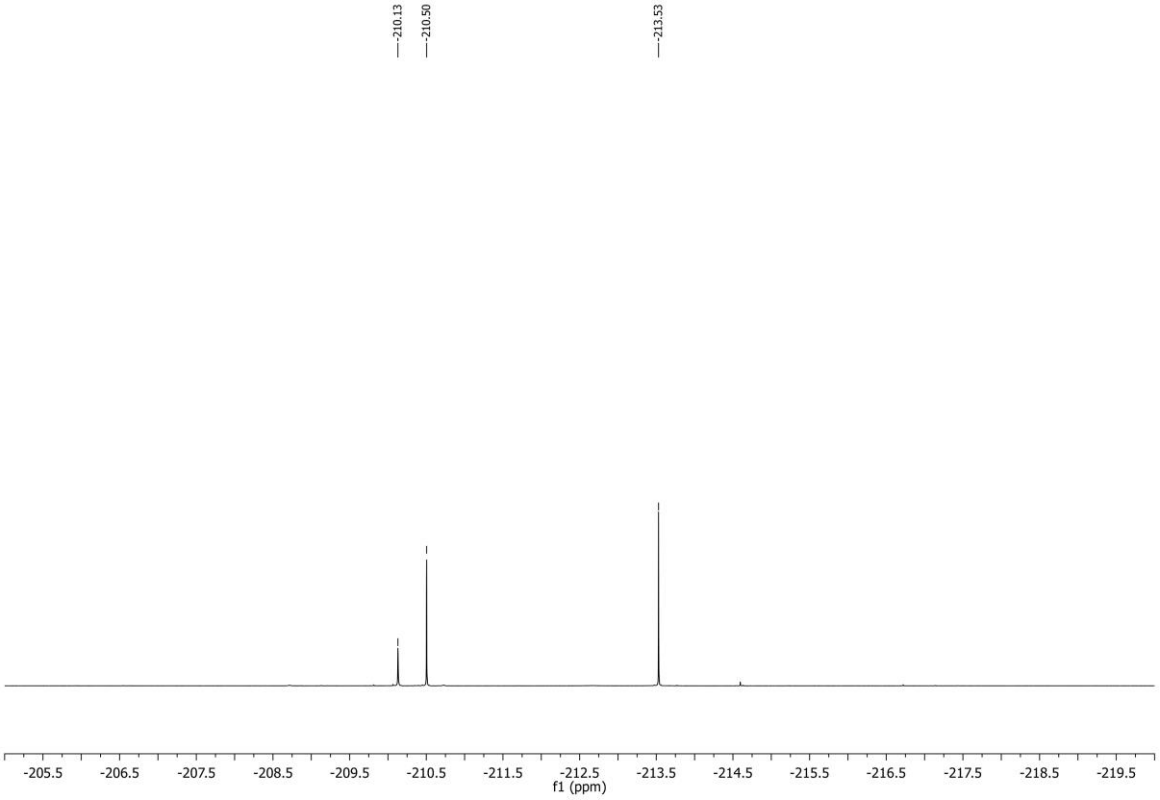


Figure 40: $^{19}F\{^{1}H\}$ NMR (659 MHz, D_2O) of 3-deoxy-3-fluoro-D-ribulose (**3DFRu**).

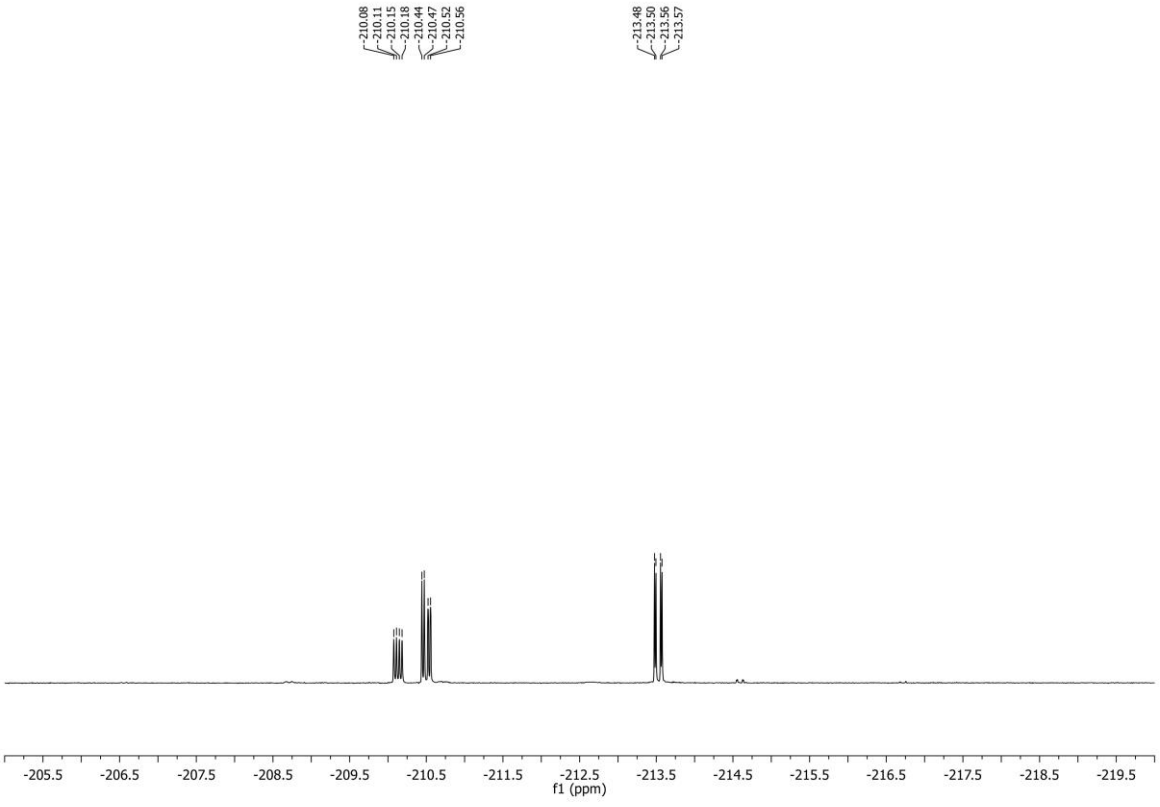


Figure 41: ^{19}F NMR (659 MHz, D_2O) of 3-deoxy-3-fluoro-D-ribulose (**3DFRu**).

6.2.8 2-Deoxy-2-fluoro-D-erythrose (2DFE)

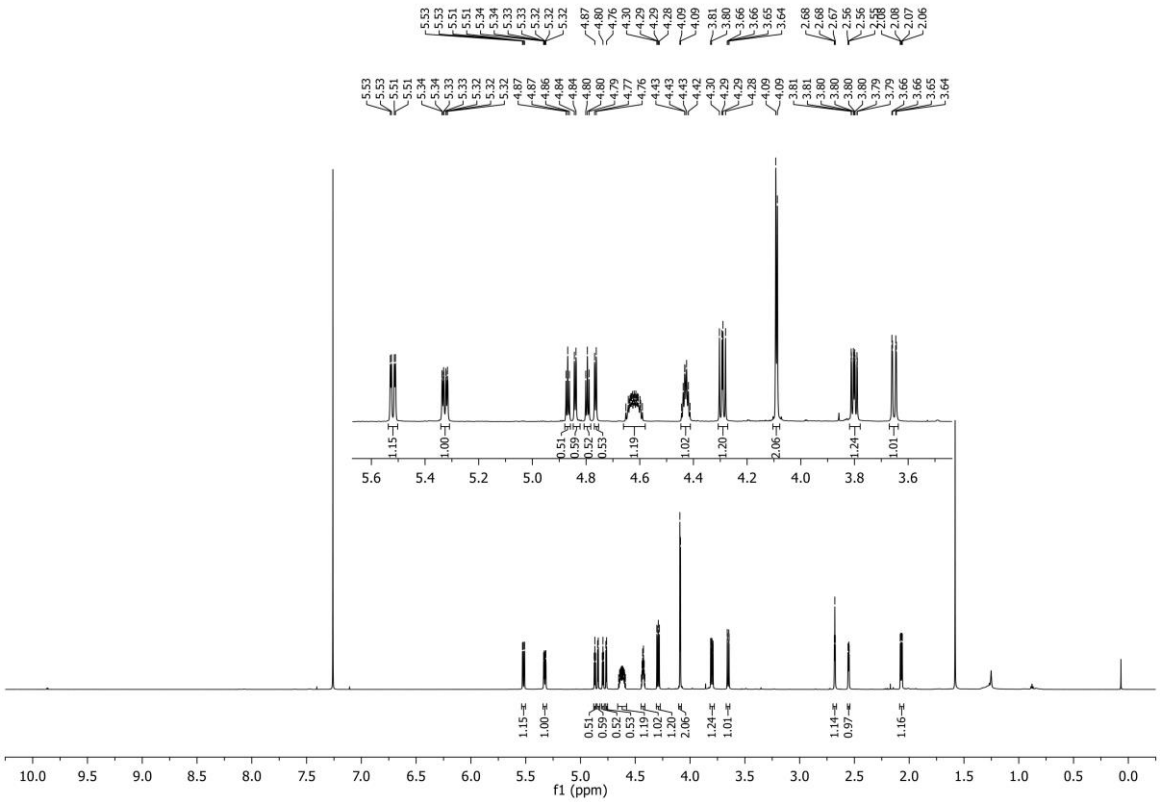


Figure 42: ^{1}H NMR (700 MHz, $CDCl_3$) of 2-deoxy-2-fluoro-D-erythrose (**2DFE**).

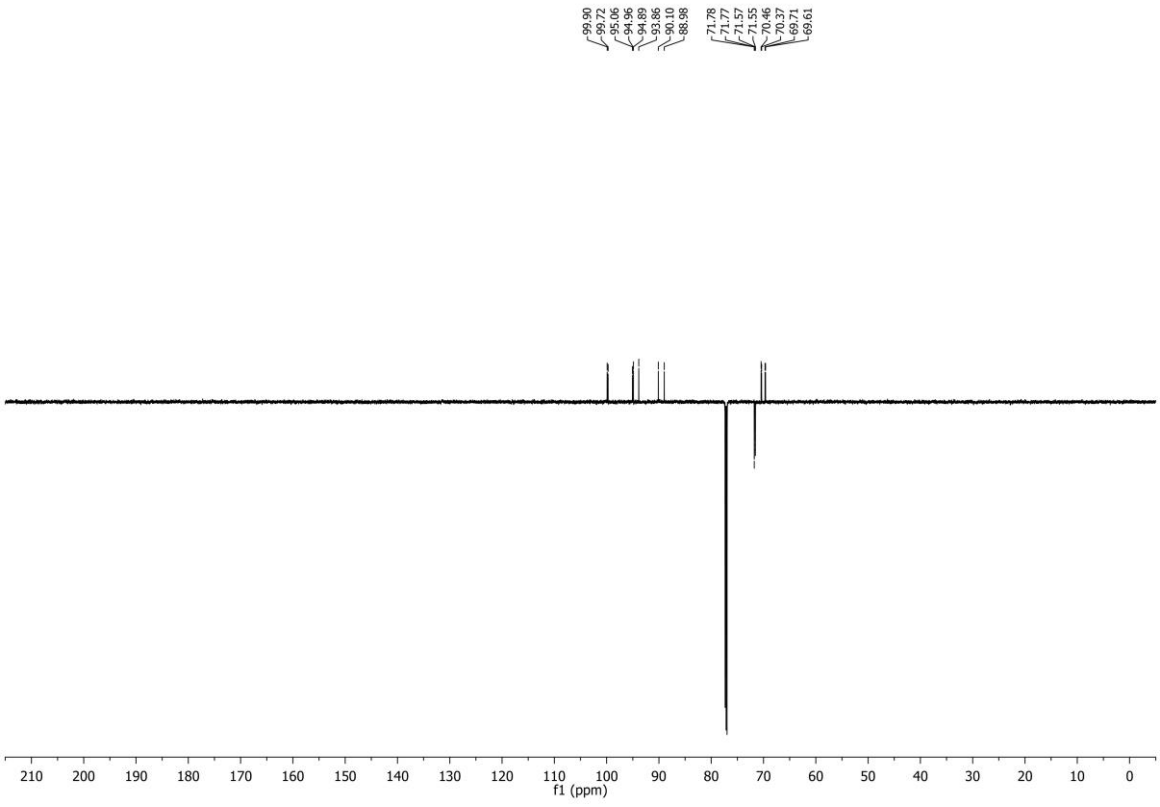


Figure 43: ^{13}C NMR (176 MHz, $CDCl_3$) of 2-deoxy-2-fluoro-D-erythrose (**2DFE**).

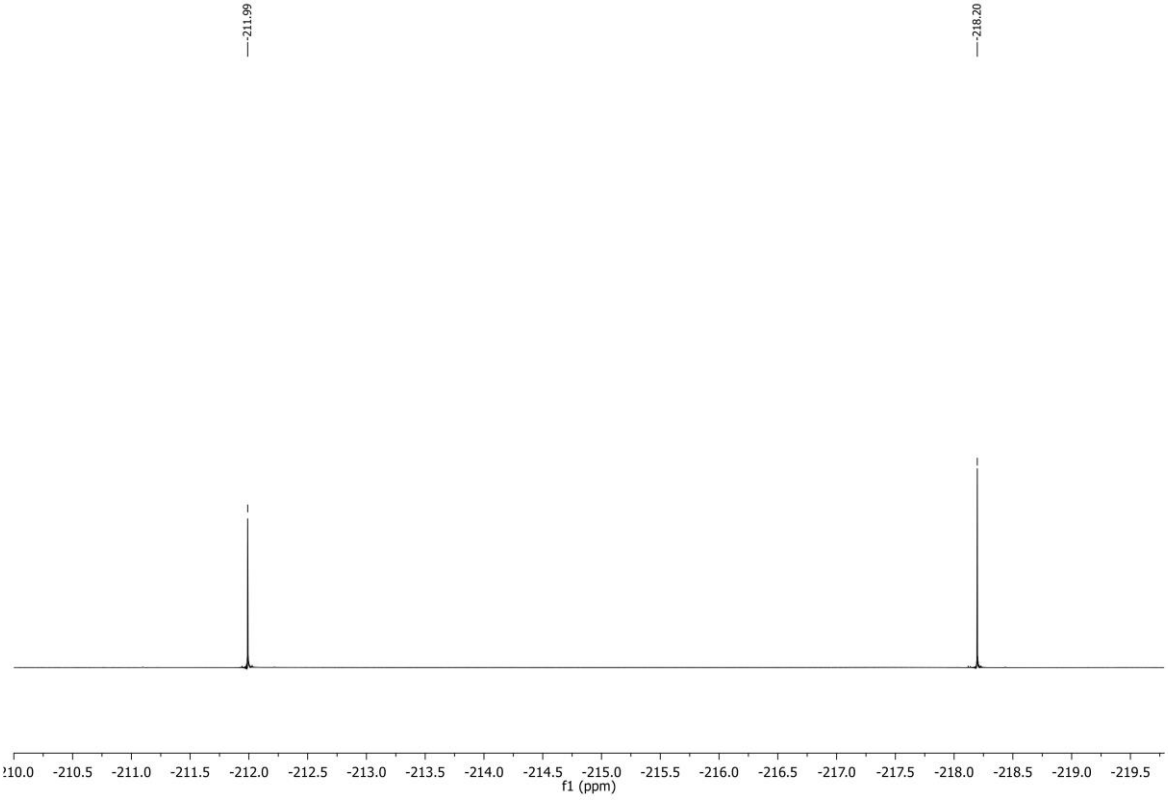


Figure 44: $^{19}F\{^{1}H\}$ NMR (659 MHz, $CDCl_3$) of 2-deoxy-2-fluoro-D-erythrose (**2DFE**).

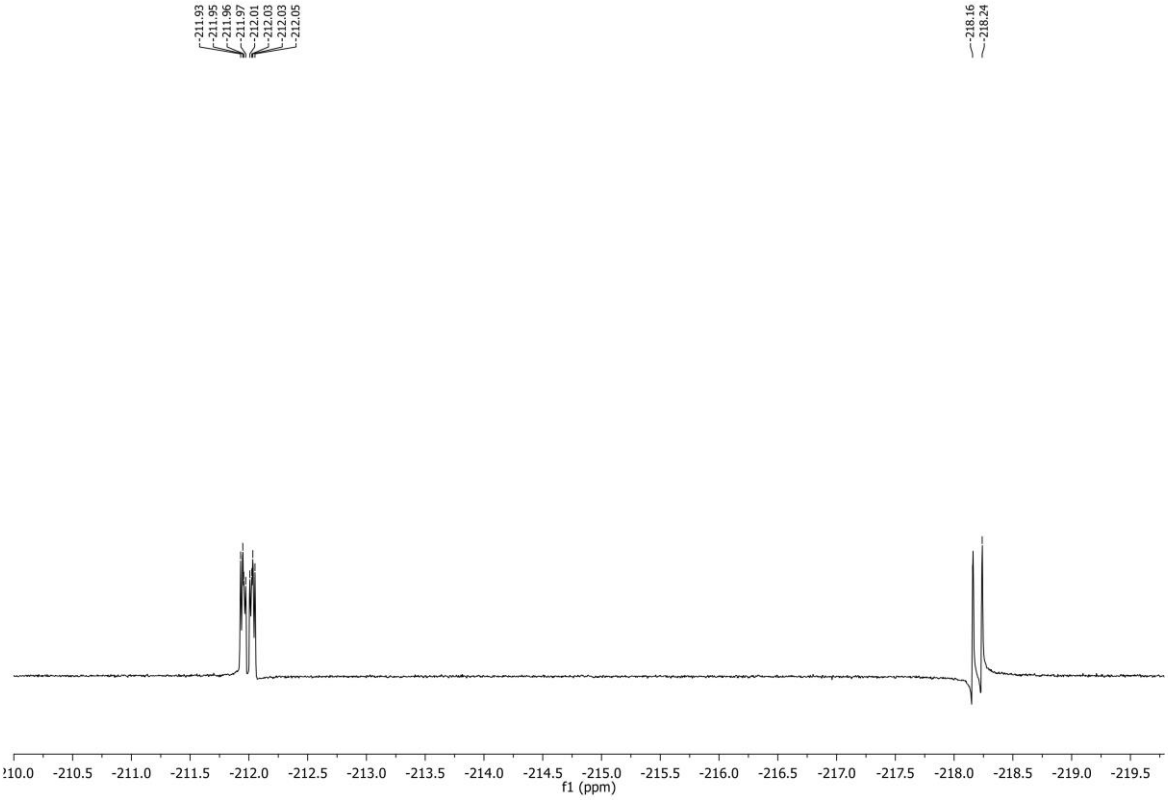


Figure 45: ^{19}F NMR (659 MHz, $CDCl_3$) of 2-deoxy-2-fluoro-D-erythrose (**2DFE**).

6.2.9 4-*O*-Benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (3.54)

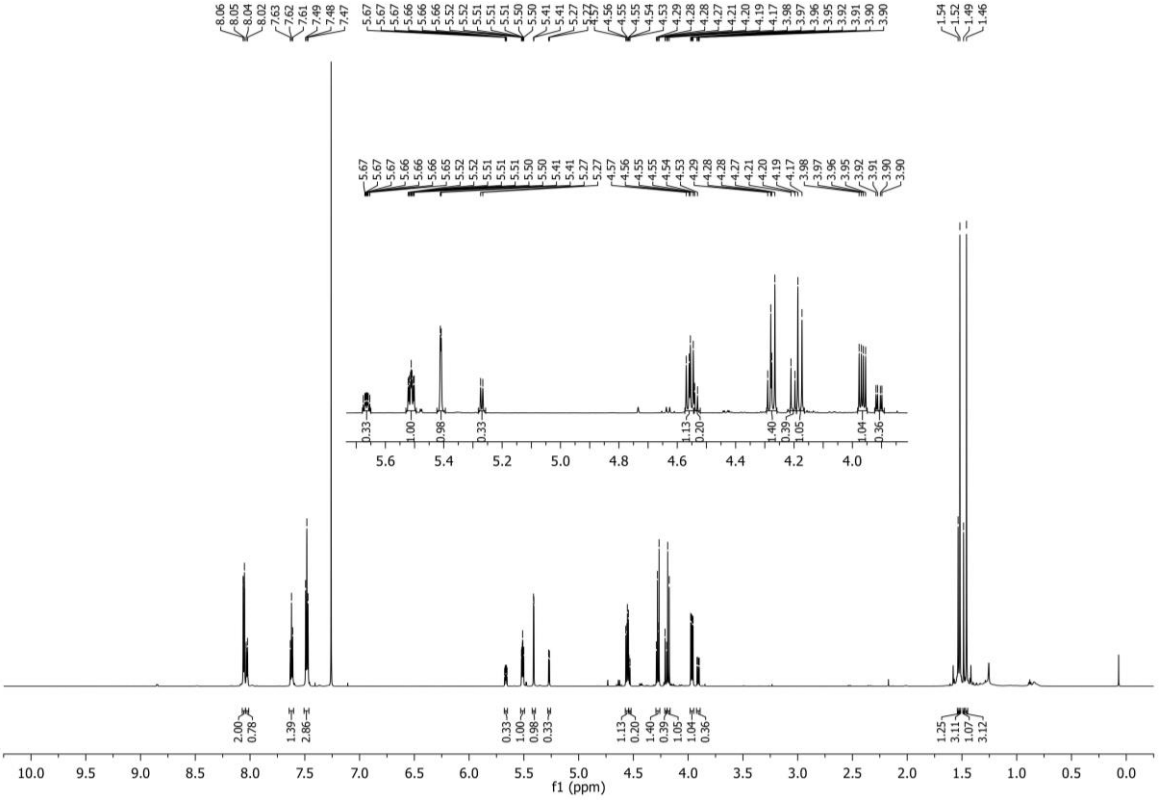


Figure 46: ^{1}H NMR (700 MHz, $CDCl_3$) of 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (**3.54**).

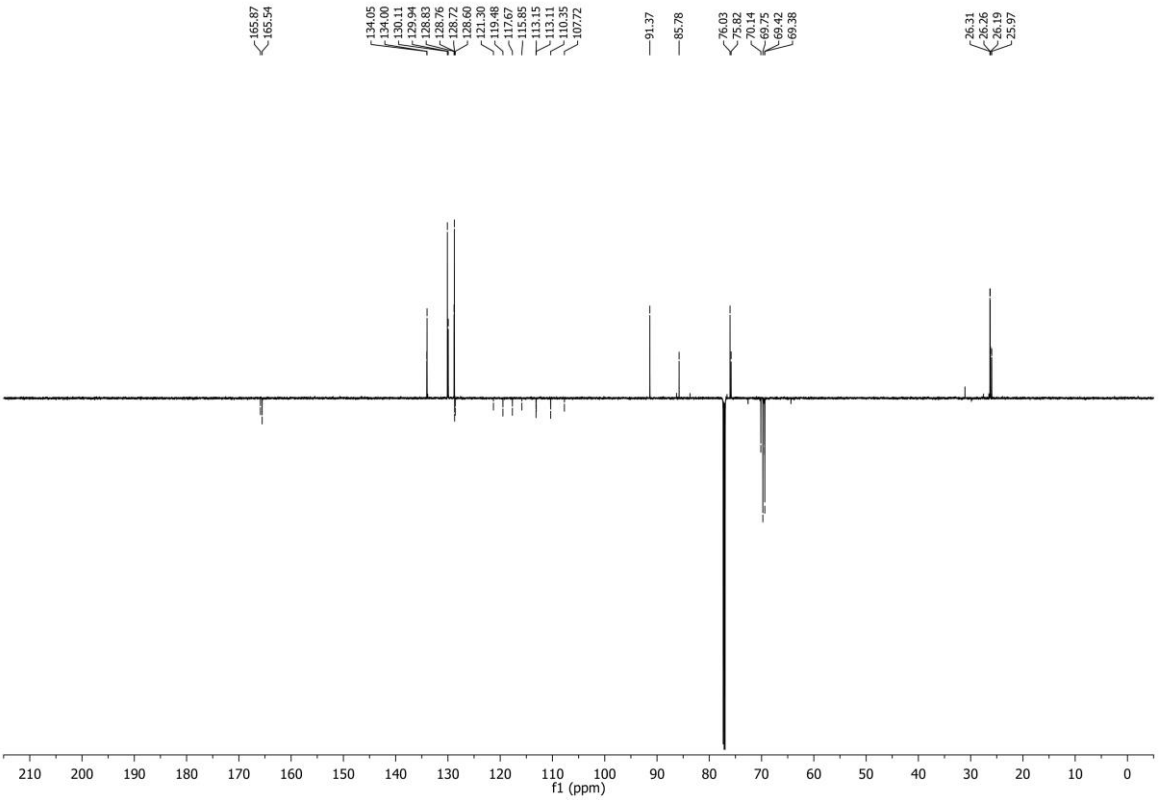


Figure 47: ^{13}C NMR (176 MHz, $CDCl_3$) of 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (**3.54**).

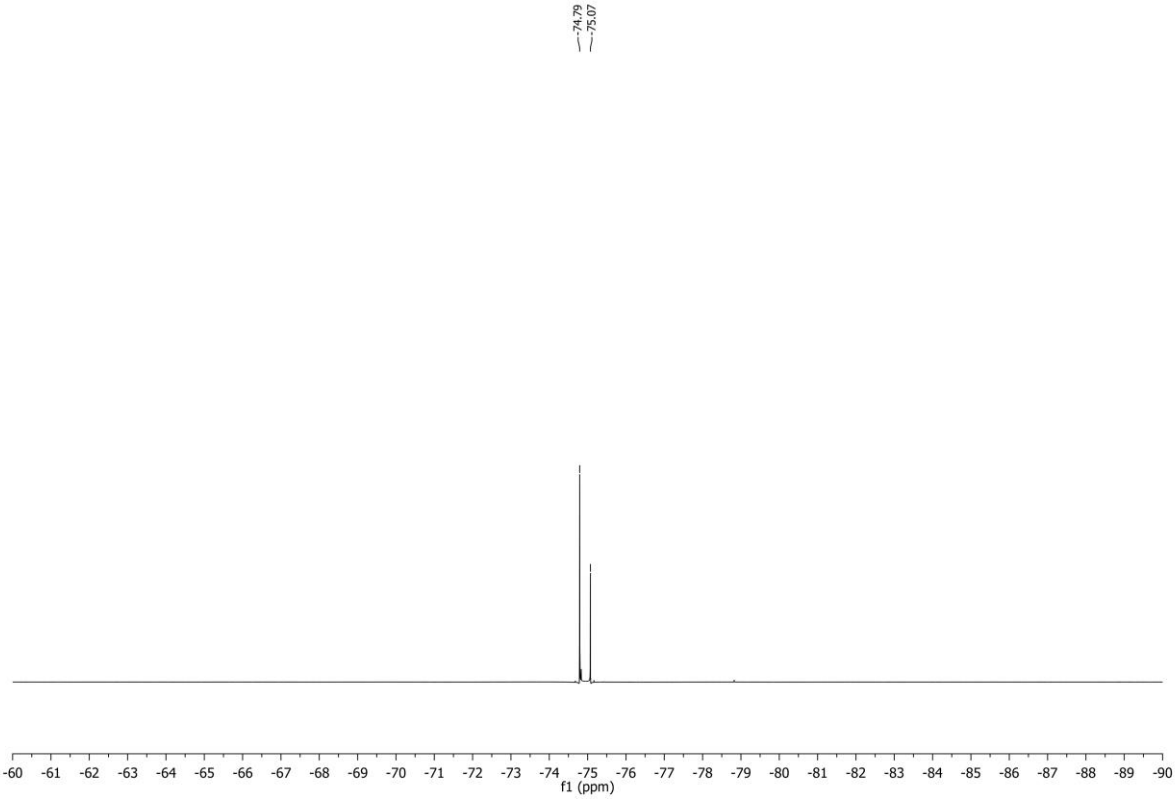


Figure 48: ^{19}F NMR (659 MHz, $CDCl_3$) of 4-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-D-xylulose (**3.54**).

7 References

1 J. McMurry and T. P. Begley, *The organic chemistry of biological pathways*, Roberts and Company Publishers, Greenwood Village, second edition, 2016.

2 J. M. Berg, J. L. Tymoczko, L. Stryer, B. Häcker and J. M. Berg, *Biochemie*, Spektrum Akademischer Verlag, Heidelberg, sechste Auflage, 2011.

3 T. K. Lindhorst and T. K. Lindhorst, *Essential of carbohydrate chemistry and biochemistry,* Wiley-VCH, Weinheim, third edition, 2008.

4 C. Riganti, E. Gazzano, M. Polimeni, E. Aldieri and D. Ghigo, The pentose phosphate pathway: An antioxidant defense and a crossroad in tumor cell fate, *Free Radic. Biol. Med.*, 2012, **53**, 421–436.

5 P. Jiang, W. Du and M. Wu, Regulation of the pentose phosphate pathway in cancer, *Protein Cell*, 2014, **5**, 592–602.

6 E. S. Cho, Y. H. Cha, H. S. Kim, N. H. Kim and J. I. Yook, The Pentose Phosphate Pathway as a Potential Target for Cancer Therapy, *Biomol. Ther.*, 2018, **26**, 29–38.

7 S. W. Kang, S. Lee and E. K. Lee, ROS and energy metabolism in cancer cells: alliance for fast growth, *Arch. Pharm. Res.*, 2015, **38**, 338–345.

8 O. Warburg, On the Origin of Cancer Cells, *Science*, 1956, **123**, 309–314.

9 V. L. Payen, P. E. Porporato, B. Baselet and P. Sonveaux, Metabolic changes associated with tumor metastasis, part 1: tumor pH, glycolysis and the pentose phosphate pathway, *Cell. Mol. Life Sci.*, 2016, **73**, 1333–1348.

10 Y. Cui, N. Nadiminty, C. Liu, W. Lou, C. T. Schwartz and A. C. Gao, Upregulation of glucose metabolism by NF-κB2/p52 mediates enzalutamide resistance in castration-resistant prostate cancer cells, *Endocr. Relat. Cancer*, 2014, **21**, 435–442.

11 P. Jiang, W. Du and X. Yang, A critical role of glucose-6-phosphate dehydrogenase in TAp73-mediated cell proliferation, *Cell Cycle*, 2013, **12**, 3720–3726.

12 Y. J. Cha, W. H. Jung and J. S. Koo, Differential Site-Based Expression of Pentose Phosphate Pathway-Related Proteins among Breast Cancer Metastases, *Dis. Markers*, 2017, **2017**, 1–10.

13 T. Ge, J. Yang, S. Zhou, Y. Wang, Y. Li and X. Tong, The Role of the Pentose Phosphate Pathway in Diabetes and Cancer, *Front. Endocrinol.*, 2020, **11**, 365.

14 H. Ying, A. C. Kimmelman, C. A. Lyssiotis, S. Hua, G. C. Chu, E. Fletcher-Sananikone, J. W. Locasale, J. Son, H. Zhang, J. L. Coloff, H. Yan, W. Wang, S. Chen, A. Viale, H. Zheng, J. Paik, C. Lim, A. R. Guimaraes, E. S. Martin, J. Chang, A. F. Hezel, S. R. Perry, J. Hu, B. Gan, Y. Xiao, J. M. Asara, R. Weissleder, Y. A. Wang, L. Chin, L. C. Cantley and R. A. DePinho, Oncogenic Kras Maintains Pancreatic Tumors through Regulation of Anabolic Glucose Metabolism, *Cell*, 2012, **149**, 656–670.

15 Y.-T. Chou, L.-Y. Chen, S.-L. Tsai, H.-C. Tu, J.-W. Lu, S.-C. Ciou, H.-D. Wang and C.-H. Yuh, Ribose-5-phosphate isomerase A overexpression promotes liver cancer development in transgenic zebrafish via activation of ERK and β-catenin pathways, *Carcinogenesis*, 2019, **40**, 461–473.

16 S. Ciou, Y. Chou, Y. Liu, Y. Nieh, J. Lu, S. Huang, Y. Chou, L. Cheng, J. Lo, M. Chen, M. Yang, C. Yuh and H. Wang, Ribose-5-phosphate isomerase A regulates hepatocarcinogenesis *via* PP2A and ERK signaling, *Int. J. Cancer*, 2015, **137**, 104–115.

17 C. Wang, K. Guo, D. Gao, X. Kang, K. Jiang, Y. Li, L. Sun, S. Zhang, C. Sun, X. Liu, W. Wu, P. Yang and Y. Liu, Identification of transaldolase as a novel serum biomarker for hepatocellular carcinoma metastasis using xenografted mouse model and clinic samples, *Cancer Lett.*, 2011, **313**, 154–166.

18 I. M.-J. Xu, R. K.-H. Lai, S.-H. Lin, A. P.-W. Tse, D. K.-C. Chiu, H.-Y. Koh, C.-T. Law, C.-M. Wong, Z. Cai, C. C.-L. Wong and I. O.-L. Ng, Transketolase counteracts oxidative stress to drive cancer development, *Proc. Natl. Acad. Sci.*, **113**, E725-E734.

19 A. Benito, I. H. Polat, V. Noé, C. J. Ciudad, S. Marin and M. Cascante, Glucose-6-phosphate dehydrogenase and transketolase modulate breast cancer cell metabolic reprogramming and correlate with poor patient outcome, *Oncotarget*, 2017, **8**, 106693–106706.

20 H. Liu, D. Huang, D. L. McArthur, L. G. Boros, N. Nissen and A. P. Heaney, Fructose Induces Transketolase Flux to Promote Pancreatic Cancer Growth, *Cancer Res.*, 2010, **70**, 6368–6376.

21 K. C. Patra and N. Hay, The pentose phosphate pathway and cancer, *Trends Biochem. Sci.*, 2014, **39**, 347–354.

22 C. Singh, E. Glaab and C. L. Linster, Molecular Identification of D-Ribulokinase in Budding Yeast and Mammals, *J. Biol. Chem.*, 2017, **292**, 1005–1028.

23 R. D. Bunker, E. M. M. Bulloch, J. M. J. Dickson, K. M. Loomes and E. N. Baker, Structure and Function of Human Xylulokinase, an Enzyme with Important Roles in Carbohydrate Metabolism, *J. Biol. Chem.*, 2013, **288**, 1643–1652.

24 A. Haschemi, P. Kosma, L. Gille, C. R. Evans, C. F. Burant, P. Starkl, B. Knapp, R. Haas, J. A. Schmid, C. Jandl, S. Amir, G. Lubec, J. Park, H. Esterbauer, M. Bilban, L. Brizuela, J. A. Pospisilik, L. E. Otterbein and O. Wagner, The Sedoheptulose Kinase CARKL Directs Macrophage Polarization through Control of Glucose Metabolism, *Cell Metab.*, 2012, **15**, 813–826.

25 S. M. Ametamey, M. Honer and P. A. Schubiger, Molecular Imaging with PET, *Chem. Rev.*, 2008, **108**, 1501–1516.

26 A. Dash and R. Chakravarty, Radionuclide generators: the prospect of availing PET radiotracers to meet current clinical needs and future research demands, *Am. J. Nucl. Med. Mol. Imaging*, 2019, **9**, 30–66.

27 K. Ahuja, H. Sotoudeh, S. J. Galgano, R. Singh, N. Gupta, S. Gaddamanugu and G. Choudhary, ^{18}F-Sodium Fluoride PET: History, Technical Feasibility, Mechanism of Action, Normal Biodistribution, and Diagnostic Performance in Bone Metastasis Detection Compared with Other Imaging Modalities, *J. Nucl. Med. Technol.*, 2020, **48**, 9–16.

28 A. Ahmadi, R. Klein, H. C. Lewin, R. S. B. Beanlands and R. A. deKemp, Rubidium-82 generator yield and efficiency for PET perfusion imaging: Comparison of two clinical systems, *J. Nucl. Cardiol.*, 2020, **27**, 1728–1738.

29 V. Pichler, N. Berroterán-Infante, C. Philippe, C. Vraka, E.-M. Klebermass, T. Balber, S. Pfaff, L. Nics, M. Mitterhauser and W. Wadsak, An Overview of PET Radiochemistry, Part 1: The Covalent Labels ^{18}F, ^{11}C, and ^{13}N, *J. Nucl. Med.*, 2018, **59**, 1350–1354.

30 M. Brandt, J. Cardinale, M. L. Aulsebrook, G. Gasser and T. L. Mindt, An Overview of PET Radiochemistry, Part 2: Radiometals, *J. Nucl. Med.*, 2018, **59**, 1500–1506.

31 www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases (retrieved August 16th, 2023).

32 J. J. Vaquero and P. Kinahan, Positron Emission Tomography: Current Challenges and Opportunities for Technological Advances in Clinical and Preclinical Imaging Systems, *Annu. Rev. Biomed. Eng.*, 2015, **17**, 385–414.

33 F. Ul-Hassan and G. J. Cook, PET/CT in oncology, *Clin. Med.*, 2012, **12**, 368–372.

34 C. C. Wagner and O. Langer, Approaches using molecular imaging technology – use of PET in clinical microdose studies, *Adv. Drug Deliv. Rev.*, 2011, **63**, 539–546.

35 A. Varrone, C. Bundgaard and B. Bang-Andersen, PET as a Translational Tool in Drug Development for Neuroscience Compounds, *Clin. Pharmacol. Ther.*, 2022, **111**, 774–785.

36 B. M. Gallagher, J. S. Fowler, N. I. Gutterson, R. R. MacGregor, C.-N. Wan and A. P. Wolf, Metabolic Trapping as a Principle of Radiopharmaceutical Design: Some Factors Responsible for the Biodistribution of [^{18}F]2-Deoxy-2-Fluoro-D-Glucose, *J. Nucl. Med.*, 1978, **19**, 1154–1161.

37 A. R. Sowa, I. M. Jackson, T. J. Desmond, J. Alicea, A. J. Mufarreh, J. M. Pham, J. Stauff, W. P. Winton, M. V. Fawaz, B. D. Henderson, B. G. Hockley, V. E. Rogers, R. A. Koeppe and P. J. H. Scott, Futureproofing [^{18}F]Fludeoxyglucose manufacture at an Academic Medical Center, *EJNMMI Radiopharm. Chem.*, 2018, **3**, 12.

38 E. Campbell, C. Jordan and R. Gilmour, Fluorinated carbohydrates for ^{18}F-positron emission tomography (PET), *Chem. Soc. Rev.*, 2023, **52**, 3599–3626.

39 Y. Kanazawa, Y. Momozono, M. Ishikawa, T. Yamada, H. Yamane, T. Haradahira, M. Maeda and M. Kojima, Metabolic pathway of 2-deoxy-2-fluoro-D-glucose studied by F-19 NMR, *Life Sci.*, 1986, **39**, 737–742.

40 T. M. O'Connell and R. E. London, Identification of 2-Fluoro-2-deoxy-D-glucose Metabolites by^{19}F{^{1}H} Hetero-RELAY, *J. Magn. Reson. B*, 1995, **109**, 264–269.

41 E.-M. Klebermass, M. Mahmudi, B. K. Geist, V. Pichler, C. Vraka, T. Balber, A. Miller, A. Haschemi, H. Viernstein, N. Rohr-Udilova, M. Hacker and M. Mitterhauser, If It Works, Don't Touch It? A Cell-Based Approach to Studying 2-[^{18}F]FDG Metabolism, *Pharmaceuticals*, 2021, **14**, 910.

42 V. Kepe, C. Scafoglio, J. Liu, W. H. Yong, M. Bergsneider, S.-C. Huang, J. R. Barrio and E. M. Wright, Positron emission tomography of sodium glucose cotransport activity in high grade astrocytomas, *J. Neurooncol.*, 2018, **138**, 557–569.

43 S. Furumoto, R. Shinbo, R. Iwata, Y. Ishikawa, K. Yanai, T. Yoshioka and H. Fukuda, In Vitro and In Vivo Characterization of 2-Deoxy-2- ^{18}F-Fluoro-D-Mannose as a Tumor-Imaging Agent for PET, *J. Nucl. Med.*, 2013, **54**, 1354–1361.

44 N. Tahara, J. Mukherjee, H. J. De Haas, A. D. Petrov, A. Tawakol, N. Haider, A. Tahara, C. C. Constantinescu, J. Zhou, H. H. Boersma, T. Imaizumi, M. Nakano, A. Finn, Z. Fayad, R. Virmani, V. Fuster, L. Bosca and J. Narula, 2-deoxy-2-[^{18}F]fluoro-D-mannose positron emission tomography imaging in atherosclerosis, *Nat. Med.*, 2014, **20**, 215–219.

45 M. E. Martínez, Y. Kiyono, S. Noriki, K. Inai, K. S. Mandap, M. Kobayashi, T. Mori, Y. Tokunaga, V. N. Tiwari, H. Okazawa, Y. Fujibayashi and T. Ido, New radiosynthesis of 2-deoxy-2-[^{18}F]fluoroacetamido-D-glucopyranose and its evaluation as a bacterial infections imaging agent, *Nucl. Med. Biol.*, 2011, **38**, 807–817.

46 K. Ishiwata, T. Takahashi, R. Iwata, M. Tomura, M. Tada, J. Itoh, M. Kameyama and T. Ido, Tumor diagnosis by pet: potential of seven tracers examined in five experimental tumors including an artificial metastasis model, *Int. J. Rad. Appl. Instrum. B*, 1992, **19**, 611–618.

47 K. Ishiwata, T. Ido, T. Nakajima, H. Ohrui, I. Kijima-Suda and M. Itoh, Tumor uptake study of ^{18}F-labeled N-acetylneuraminic acids, *Int. J. Rad. Appl. Instrum. B*, 1990, **17**, 363–367.

48 N. M. Evdokimov, P. M. Clark, G. Flores, T. Chai, K. F. Faull, M. E. Phelps, O. N. Witte and M. E. Jung, Development of 2-Deoxy-2-[^{18}F]fluororibose for Positron Emission Tomography Imaging Liver Function in Vivo, *J. Med. Chem.*, 2015, **58**, 5538–5547.

49 P. M. Clark, G. Flores, N. M. Evdokimov, M. N. McCracken, T. Chai, E. Nair-Gill, F. O'Mahony, S. W. Beaven, K. F. Faull, M. E. Phelps, M. E. Jung and O. N. Witte, Positron emission tomography probe demonstrates a striking concentration of ribose salvage in the liver, *Proc. Natl. Acad. Sci.*, 2014, **111**, E2866–E2874.

50 E. J. Postema, A. J. B. McEwan, T. A. Riauka, P. Kumar, D. A. Richmond, D. N. Abrams and L. I. Wiebe, Initial results of hypoxia imaging using 1-α-D-(5-deoxy-5-[^{18}F]-fluoroarabinofuranosyl)-2-nitroimidazole (^{18}F-FAZA), *Eur. J. Nucl. Med. Mol. Imaging*, 2009, **36**, 1565–1573.

51 F. C. Maier, M. Kneilling, G. Reischl, F. Cay, D. Bukala, A. Schmid, M. S. Judenhofer, M. Röcken, H.-J. Machulla and B. J. Pichler, Significant impact of different oxygen breathing conditions on noninvasive in vivo tumor-hypoxia imaging using [^{18}F]-fluoro-azomycinarabino-furanoside ([^{18}F]FAZA), *Radiat. Oncol.*, 2011, **6**, 165.

52 B. Alwadani, S. Dall'Angelo and I. N. Fleming, Clinical value of 3'-deoxy-3'-[^{18}F]fluorothymidine-positron emission tomography for diagnosis, staging and assessing therapy response in lung cancer, *Insights Imaging*, 2021, **12**, 90.

53 V. Gouverneur and K. Müller, *Fluorine in pharmaceutical and medicinal chemistry: from biophysical aspects to clinial applications*, Imperial College Press, London, 2012.

54 M. Inoue, Y. Sumii and N. Shibata, Contribution of Organofluorine Compounds to Pharmaceuticals, *ACS Omega*, 2020, **5**, 10633–10640.

55 D. W. Kim, Jeong, Hwan-Jeong, S. T. Lim, M.-H. Sohn, J. A. Katzenellenbogen and D. Y. Chi, Facile Nucleophilic Fluorination Reactions Using *tert*-Alcohols as a Reaction Medium: Significantly Enhanced Reactivity of Alkali Metal Fluorides and Improved Selectivity, *J. Org. Chem.*, 2008, **73**, 957–962.

56 K. Hamacher, H. H. Coenen and G. Stocklin, Efficient Stereospecific Synthesis of No-Carrier-Added 2-[^{18}F]-Fluoro-2-Deoxy-D-Glucose Using Aminopolyether Supported Nucleophilic Substitution, *J. Nucl. Med.*, 1986, **27**, 235–238.

57 P. J. Card and W. D. Hitz, Synthesis of 1'-deoxy-1'-fluorosucrose via sucrose synthetase mediated coupling of 1-deoxy-1-fluorofructose with uridine diphosphate glucose, *J. Am. Chem. Soc.*, 1984, **106**, 5348–5350.

58 A. S. Pilcher, H. L. Ammon and P. DeShong, Utilization of Tetrabutylammonium Triphenylsilyldifluoride as a Fluoride Source for Nucleophilic Fluorination, *J. Am. Chem. Soc.*, 1995, **117**, 5166–5167.

59 J. M. Percy, R. Roig and K. Singh, Fluorinated Analogues of Amicetose and Rhodinose - Novel Racemic and Asymmetric Routes, *Eur. J. Org. Chem.*, 2009, **2009**, 1058–1071.

60 N. Yan, Z.-W. Lei, J.-K. Su, W.-L. Liao and X.-G. Hu, Ring opening of sugar-derived epoxides by TBAF/KHF_2: An attractive alternative for the introduction of fluorine into the carbohydrate scaffold, *Chin. Chem. Lett.*, 2017, **28**, 467–470.

61 V. Denavit, D. Lainé, J. St-Gelais, P. A. Johnson and D. Giguère, A Chiron approach towards the stereoselective synthesis of polyfluorinated carbohydrates, *Nat. Commun.*, 2018, **9**, 4721.

62 G. A. Olah, M. Nojima and I. Kerekes, Synthetic Methods and Reactions II. Hydrofluorination of Alkenes, Cyclopropane and Alkynes with Poly-Hydrogen Fluoride/Pyridine (Trialkylamine)Reagents, *Synthesis*, 1973, **1973**, 779–780.

63 J. Jünnemann, I. Lundt, J. Thiem, C. B. Ivanov, R. Atanasova, A. Napoli, G. Sindona, D. W. Aksnes and G. W. Francis, Reaction of Epoxyaldonolactones with HF-Amine Complexes., *Acta Chem. Scand.*, 1994, **48**, 265–268.

64 W. J. Middleton, New fluorinating reagents. Dialkylaminosulfur fluorides, *J. Org. Chem.*, 1975, **40**, 574–578.

65 G. S. Lal, G. P. Pez, R. J. Pesaresi and F. M. Prozonic, Bis(2-methoxyethyl)aminosulfur trifluoride: a new broad-spectrum deoxofluorinating agent with enhanced thermal stability, *Chem. Commun.*, 1999, 215–216.

66 L. N. Markovskii, V. E. Pashinnik and E. P. Saenko, Dialkylaminodifluorosulfonium tetrafluoroborates, *Zh Org Khim*, 1977, **13**, 1116–1117.

67 F. Beaulieu, L.-P. Beauregard, G. Courchesne, M. Couturier, F. LaFlamme and A. L'Heureux, Aminodifluorosulfinium Tetrafluoroborate Salts as Stable and Crystalline Deoxofluorinating Reagents, *Org. Lett.*, 2009, **11**, 5050–5053.

68 T. Ido, C. N. Wan, J. S. Fowler and A. P. Wolf, Fluorination with molecular fluorine. A convenient synthesis of 2-deoxy-2-fluoro-D-glucose, *J. Org. Chem.*, 1977, **42**, 2341–2342.

69 T. Ido, C.-N. Wan, V. Casella, J. S. Fowler, A. P. Wolf, M. Reivich and D. E. Kuhl, Labeled 2-deoxy-D-glucose analogs. ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose and ^{14}C-2-deoxy-2-fluoro-D-glucose, *J. Label. Compd. Radiopharm.*, 1978, **14**, 175–183.

70 B. M. Gallagher, A. Ansari, H. Atkins, V. Casella, D. R. Christman, J. S. Fowler, T. Ido, R. R. MacGregor, P. Som, C. N. Wan, A. P. Wolf, D. E. Kuhl and M. Reivich, Radiopharmaceuticals XXVII. ^{18}F-labeled 2-deoxy-2-fluoro-D-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: tissue distribution and imaging studies in animals, *J. Nucl. Med. Off. Publ. Soc. Nucl. Med.*, 1977, **18**, 990–996.

71 R. E. Banks, Selectfluor^{TM} reagent F-TEDA-BF_4 in action: tamed fluorine at your service, *J. Fluor. Chem.*, 1998, **87**, 1–17.

72 E. Differding and H. Ofner, *N* -Fluorobenzenesulfonimide: A Practical Reagent For Electrophilic Fluorinations, *Synlett*, 1991, **1991**, 187–189.

73 T. Umemoto, Y. Yang and G. B. Hammond, Development of *N*-F fluorinating agents and their fluorinations: Historical perspective, *Beilstein J. Org. Chem.*, 2021, **17**, 1752–1813.

74 D. Waschke, Y. Leshch, J. Thimm, U. Himmelreich and J. Thiem, Synthesis of Fluorinated Ketoheptoses as Specific Diagnostic Agents, *Eur. J. Org. Chem.*, 2012, **2012**, 948–959.

75 G. Wittig and G. Geissler, Zur Reaktionsweise des Pentaphenyl-phosphors und einiger Derivate, *Justus Liebigs Ann. Chem.*, 1953, **580**, 44–57.

76 G. Wittig and U. Schöllkopf, Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien (I. Mitteil., *Chem. Ber.*, 1954, **87**, 1318–1330.

77 G. Wittig and U. Schöllkopf, Methylenecyclohexane, *Org. Synth.*, 1960, **40**, 66.

78 M. Julia and J.-M. Paris, Syntheses a l'aide de sulfones v$^{(+)}$- methode de synthese generale de doubles liaisons., *Tetrahedron Lett.*, 1973, **14**, 4833–4836.

79 J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, A direct synthesis of olefins by reaction of carbonyl compounds with lithio derivatives of 2-[alkyl- or (2′-alkenyl)- or benzyl-sulfonyl]-benzothiazoles, *Tetrahedron Lett.*, 1991, **32**, 1175–1178.

80 K. Takai, Y. Hotta, K. Oshima and H. Nozaki, Effective methods of carbonyl methylenation using CH_2I_2–Zn–Me_3Al and CH_2Br_2–Zn–$TiCl_4$ system, *Tetrahedron Lett.*, 1978, **19**, 2417–2420.

81 L. Lombardo, Methylenation of carbonyl compounds with Zn–CH_2Br_2–$TiCl_4$. Application to gibberellins, *Tetrahedron Lett.*, 1982, **23**, 4293–4296.

82 F. N. Tebbe, G. W. Parshall and G. S. Reddy, Olefin homologation with titanium methylene compounds, *J. Am. Chem. Soc.*, 1978, **100**, 3611–3613.

83 N. A. Petasis and E. I. Bzowej, Titanium-mediated carbonyl olefinations. 1. Methylenations of carbonyl compounds with dimethyltitanocene, *J. Am. Chem. Soc.*, 1990, **112**, 6392–6394.

84 R. C. Hartley, J. Li, C. A. Main and G. J. McKiernan, Titanium carbenoid reagents for converting carbonyl groups into alkenes, *Tetrahedron*, 2007, **63**, 4825–4864.

85 T. Kardon, V. Stroobant, M. Veiga-da-Cunha and E. V. Schaftingen, Characterization of mammalian sedoheptulokinase and mechanism of formation of erythritol in sedoheptulokinase deficiency, *FEBS Lett.*, 2008, **582**, 3330–3334.

86 L. Scheibelberger, T. Stankovic, M. Pühringer, H. Kählig, T. Balber, E.-M. Patronas, E. Rampler, M. Mitterhauser, A. Haschemi and K. Pallitsch, Synthesis of 4-Deoxy-4-fluoro-D-sedoheptulose: A Promising New Sugar to Apply the Principle of Metabolic Trapping, *Chem. – Eur. J.*, 2023, e202302277.

87 L. Scheibelberger, T. Stankovic, K. Liepert, A. Kienzle, E. Patronas, T. Balber, M. Mitterhauser, A. Haschemi and K. Pallitsch, Fluorinated Analogues to the Pentuloses of the Pentose Phosphate Pathway, *Eur. J. Org. Chem.*, 2023, e202300339.

88 M. B. Comba, M. I. Mangione, A. G. Suárez, A. M. Sarotti and R. A. Spanevello, A Domino Epoxide Ring-Opening Xanthate Migration Reaction: An Alternative Entry to Thiosugars: A Domino Epoxide Ring-Opening Xanthate Migration Reaction: An Alternative Entry to Thiosugars, *Eur. J. Org. Chem.*, 2018, **2018**, 6848–6856.

89 W. R. Dolbier Jr., *Guide to Fluorine NMR for Organic Chemists*, John Wiley & Sons Inc., Hoboken, 2008.

90 C.-R. Shie, Z.-H. Tzeng, S. S. Kulkarni, B.-J. Uang, C.-Y. Hsu and S.-C. Hung, $Cu(OTf)_2$ as an Efficient and Dual-Purpose Catalyst in the Regioselective Reductive Ring Opening of Benzylidene Acetals, *Angew. Chem. Int. Ed.*, 2005, **44**, 1665–1668.

91 M. Matwiejuk and J. Thiem, New Method for Regioselective Glycosylation Employing Saccharide Oxyanions, *Eur. J. Org. Chem.*, 2011, **2011**, 5860–5878.

92 Y.-H. Shi, Y.-F. Xie, Y.-Q. Liu, Q.-C. Wei, W.-R. Xu, L.-D. Tang and G.-L. Zhao, $SrCl_2$ as an efficient cocatalyst for acidic hydrolysis of methyl glycosides, *Chin. Chem. Lett.*, 2014, **25**, 561–566.

93 W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, Preparation and use of tetra-n-butylammonium per-ruthenate (TBAP reagent) and tetra-*N*-propylammonium per-ruthenate (TPAP reagent) as new catalytic oxidants for alcohols, *J. Chem. Soc. Chem. Commun.*, 1987, 1625.

94 J. D. Albright and L. Goldman, Dimethyl sulfoxide-acid anhydride mixtures for the oxidation of alcohols, *J. Am. Chem. Soc.*, 1967, **89**, 2416–2423.

95 D. B. Dess and J. C. Martin, Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, *J. Org. Chem.*, 1983, **48**, 4155–4156.

96 D. Waschke, J. Thimm and J. Thiem, Highly Efficient Synthesis of Ketoheptoses, *Org. Lett.*, 2011, **13**, 3628–3631.

97 V. VanRheenen, R. C. Kelly and D. Y. Cha, An improved catalytic OsO_4 oxidation of olefins to -1,2-glycols using tertiary amine oxides as the oxidant, *Tetrahedron Lett.*, 1976, **17**, 1973–1976.

98 K. M. Smith, F. L. Alkhateeb, K. Brennan, P. D. Rainville and T. H. Walter, Separation of Pentose Phosphate Pathway, Glycolysis, and Energy Metabolites Using an ACQUITY Premier System With an Atlantis Premier BEH Z-HILIC Column (Waters application note, 2021, www.waters.com/content/dam/waters/en/app-notes/2021/720007411/720007411-en.pdf, retrieved August 20th, 2023).

99 G. Schneider and Y. Lindqvist, Crystallography and mutagenesis of transketolase: mechanistic implications for enzymatic thiamin catalysis, *Biochim. Biophys. Acta BBA - Protein Struct. Mol. Enzymol.*, 1998, **1385**, 387–398.

100 N. Nemeria, S. Chakraborty, A. Baykal, L. G. Korotchkina, M. S. Patel and F. Jordan, The 1′,4′-iminopyrimidine tautomer of thiamin diphosphate is poised for catalysis in asymmetric active centers on enzymes, *Proc. Natl. Acad. Sci.*, 2007, **104**, 78–82.

101 S. Lüdtke, P. Neumann, K. M. Erixon, F. Leeper, R. Kluger, R. Ficner and K. Tittmann, Sub-ångström-resolution crystallography reveals physical distortions that enhance reactivity of a covalent enzymatic intermediate, *Nat. Chem.*, 2013, **5**, 762–767.

102 D. Kern, G. Kern, H. Neef, K. Tittmann, M. Killenberg-Jabs, C. Wikner, G. Schneider and G. Hübner, How Thiamine Diphosphate Is Activated in Enzymes, *Science*, 1997, **275**, 67–70.

103 M. Schwaiger, Isolation, Purification and Quantification of Sedoheptulose from *Sedum maximum* (master thesis, University of Natural Resources and Life Sciences, Vienna, 2014).

104 R. L. Whistler and M. L. Wolfrom, *Methods in carbohydrate chemistry. Volume 1, analysis and preparation of sugars*, Columbus Academic Press, New York, 1962.

105 W. T. Haskins, R. M. Hann and C. S. Hudson, Some Reactions and Derivatives of Sedoheptulosan, *J. Am. Chem. Soc.*, 1952, **74**, 2198–2200.

106 K. Heyns, W. Soldat and P. Köll, Darstellung von 2,7-Anhydro-β-D-*allo*-heptulopyranose-Derivaten durch stereoselektive Reduktion von 2,7-Anhydro-β-D-*ribo*-2,3-heptodiulopyranosen, *Chem. Ber.*, 1973, **106**, 1668–1677.

107 P. Köll and T. Schultek, Optisch aktive Carbonylverbindungen mit 6,8-Dioxabicyclo[3.2.1]octan-System, IV. Neue Derivate der 2,7-Anhydro-β-D-*altro*-heptulopyranose („Sedoheptulosan"), *Chem. Ber.*, 1977, **110**, 1994–2004.

108 K. Heyns, H. Neste and J. Thiem, Photolytische Decarbonylierung von Anhydrozucker-Ulosen zur Synthese von 1,5-Anhydro-β-D-lyxo- und -ribofuranosen sowie 2,6-Anhydro-β-D-psicofuranosen, *Chem. Ber.*, 1981, **114**, 891–908.

109 M. Adinolfi, G. Barone, L. Guariniello and A. Iadonisi, Facile cleavage of carbohydrate benzyl ethers and benzylidene acetals using the reagent under two-phase conditions, *Tetrahedron Lett.*, 1999, **40**, 8439–8441.

110 O. Mitsunobu and M. Yamada, Preparation of Esters of Carboxylic and Phosphoric Acid *via* Quaternary Phosphonium Salts, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 2380–2382.

111 M. Saïah, M. Bessodes and K. Antonakis, The use of chloroacetic acid in the mitsunobu reaction, *Tetrahedron Lett.*, 1992, **33**, 4317–4320.

112 F.-I. Auzanneau, M. Mialon, D. Promé, J.-C. Promé and J. Gelas, Synthesis of S-Linked Thiooligosaccharide Analogues of Nodulation Factors. 2.[1] Synthesis of an Intermediate Thiotrisaccharide, *J. Org. Chem.*, 1998, **63**, 6460–6465.

113 J. L. Luche, Lanthanides in organic chemistry. 1. Selective 1,2 reductions of conjugated ketones, *J. Am. Chem. Soc.*, 1978, **100**, 2226–2227.

114 S. J. Danishefsky, H. G. Selnick, R. E. Zelle and M. P. DeNinno, Total synthesis of zincophorin, *J. Am. Chem. Soc.*, 1988, **110**, 4368–4378.

115 R. Lattrell and G. Lohaus, Versuche zur Totalsynthese von Cephalosporinderivaten, II1) Substitutionsreaktionen an trans-3-Sulfonyloxy-2-azetidinonen. – Eine Synthese von cis-3-Acylamino-4-alkylthio-2-azetidinonen, *Justus Liebigs Ann. Chem.*, 1974, **1974**, 901–920.

116 R. Albert, K. Dax, R. W. Link and A. E. Stütz, Carbohydrate triflates: reaction with nitrite, leading directly to epi-hydroxy compounds, *Carbohydr. Res.*, 1983, **118**, C5–C6.

117 M. Zottola, B. V. Rao and B. Fraser-Reid, A mild procedure for cleavage of 1,6-anhydro sugars, *J. Chem. Soc. Chem. Commun.*, 1991, 969.

118 C. A. A. Van Boeckel and T. Beetz, Hydrazinedithiocarbonate (HDTC) as a new reagent for the improved removal of chloroacetyl and bromoacetyl protective groups, *Tetrahedron Lett.*, 1983, **24**, 3775–3778.

119 J. Cheng, Z. Fang, S. Li, B. Zheng and Y. Jiang, An efficient synthesis of D-mannoheptulose via oxidation of an olefinated sugar with potassium permanganate in aqueous acetone, *Carbohydr. Res.*, 2009, **344**, 2093–2095.

120 G. Zemplén and A. Kunz, Studien über Amygdalin, IV: Synthese des natürlichen L-Amygdalins, *Berichte Dtsch. Chem. Ges. B Ser.*, 1924, **57**, 1357–1359.

121 A. Chiotellis, F. Sladojevich, L. Mu, A. Müller Herde, I. E. Valverde, V. Tolmachev, R. Schibli, S. M. Ametamey and T. L. Mindt, Novel chemoselective ^{18}F-radiolabeling of thiol-containing biomolecules under mild aqueous conditions, *Chem. Commun.*, 2016, **52**, 6083–6086.

122 K. Liepert, Synthesis of monofluorinated rare sugars (master thesis, University of Vienna, 2022).

123 N. Cohen, B. L. Banner, A. J. Laurenzano and L. Carozza, 2,3-O-Isopropylidene-D-erythronolactone, *Org. Synth.*, 1985, **63**, 127.

124 T. Ueki and T. Kinoshita, Synthesis and stereochemistry of musacins isolated from Streptomyces griseoviridis (FH-S 1832), *Org. Biomol. Chem.*, 2005, **3**, 295.

125 R. Csuk and B. I. Glänzer, Methylenation of aldonolactones, *Tetrahedron*, 1991, **47**, 1655–1664.

126 D. Beer, R. Meuwly and A. Vasella, L-Erythruronic Acid Derivatives as Building Blocks for Nucleoside Analogs. Synthesis of 4'-C-Aryl-D-ribonucleosides, *Helv. Chim. Acta*, 1982, **65**, 2570–2582.

127 M. A. Ciufolini, M. V. Deaton, S. Zhu and M. Chen, A remarkable ene-like reaction: Development and synthetic applications, *Tetrahedron*, 1997, **53**, 16299–16312.

128 R. Criegee, Eine oxydative Spaltung von Glykolen (II. Mitteil. über Oxydationen mit Blei(IV)-salzen), *Berichte Dtsch. Chem. Ges. B Ser.*, 1931, **64**, 260–266.

129 A. B. Smith, G. A. Sulikowski, M. M. Sulikowski and K. Fujimoto, Applications of an asymmetric [2+2]-photocycloaddition. Total synthesis of (-)-echinosporin. Construction of an advanced 11-deoxyprostaglandin intermediate, *J. Am. Chem. Soc.*, 1992, **114**, 2567–2576.

130 J. Jarý, M. Masojídková, I. Kozák, M. Marek and J. Staněk, The preparation of 3-amino-3-deoxy-1,2-*O*-isopropylidene-α-L-erythrofuranose, 3-amino-3-deoxy-1,2-*O*-isopropylidene-β-D-threofuranose and their derivatives, *Collect. Czechoslov. Chem. Commun.*, 1980, **45**, 3378–3390.

131 R. G. Soengas, M. Begoña Pampín, J. C. Estévez and R. J. Estévez, Stereocontrolled transformation of nitrohexofuranoses into cyclopentylamines via 2-oxabicyclo[2.2.1]heptanes. Part 2: Synthesis of (1S,2R,3S,4S,5R)-3,4,5-trihydroxy-2-aminocyclopentanecarboxylic acid, *Tetrahedron Asymmetry*, 2005, **16**, 205–211.

132 S. van der Vorm, T. Hansen, E. R. van Rijssel, R. Dekkers, J. M. Madern, H. S. Overkleeft, D. V. Filippov, G. A. van der Marel and J. D. C. Codée, Furanosyl Oxocarbenium Ion Conformational Energy Landscape Maps as a Tool to Study the Glycosylation Stereoselectivity of 2-Azidofuranoses, 2-Fluorofuranoses and Methyl Furanosyl Uronates, *Chem. – Eur. J.*, 2019, **25**, 7149–7157.

133 G. Wang, J. Wan, Y. Hu, X. Wu, M. Prhavc, N. Dyatkina, V. K. Rajwanshi, D. B. Smith, A. Jekle, A. Kinkade, J. A. Symons, Z. Jin, J. Deval, Q. Zhang, Y. Tam, S. Chanda, L. Blatt and L. Beigelman, Synthesis and Anti-Influenza Activity of Pyridine, Pyridazine, and Pyrimidine *C* -Nucleosides as Favipiravir (T-705) Analogues, *J. Med. Chem.*, 2016, **59**, 4611–4624.

134 O.-M. Soueidan, B. J. Trayner, T. N. Grant, J. R. Henderson, F. Wuest, F. G. West and C. I. Cheeseman, New fluorinated fructose analogs as selective probes of the hexose transporter protein GLUT5, *Org. Biomol. Chem.*, 2015, **13**, 6511–6521.

135 A. Steimmig, B. Oxidation unter C–C–Spaltung *in* Oxidation II: Metallische und organische Oxidationsmittel, elektrochemische Oxidation, Oxidationshemmung, Georg Thieme Verlag, Stuttgart, 1975.

136 R. Csuk, M. Kühn and D. Ströhl, Easy access to C-glycosides from aldonolactones by a Claisen-type chain-extension reaction, *Tetrahedron*, 1997, **53**, 1311–1322.

137 T. Wu, M. Froeyen, V. Kempeneers, C. Pannecouque, J. Wang, R. Busson, E. De Clercq and P. Herdewijn, Deoxythreosyl Phosphonate Nucleosides as Selective Anti-HIV Agents, *J. Am. Chem. Soc.*, 2005, **127**, 5056–5065.

138 T. Bach and F. Höfer, Photochemical Deconjugation of Chiral 3-Methyl-2-butenoates Derived from Carbohydrate-Based Alcohols: The Influence of the Sugar Backbone on the Facial Diastereoselectivity, *J. Org. Chem.*, 2001, **66**, 3427–3434.

139 W. G. Earley, J. E. Jacobsen, A. Madin, G. P. Meier, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, Aza-Cope Rearrangement−Mannich Cyclizations for the Formation of Complex Tricyclic Amines: Stereocontrolled Total Synthesis of (±)-Gelsemine, *J. Am. Chem. Soc.*, 2005, **127**, 18046–18053.

140 Z. P. Cannone and M. W. Peczuh, A method for preparing N-alkylated kanosamines from diacetone d-glucose, *Tetrahedron Lett.*, 2019, **60**, 1830–1833.

141 A. Horn and U. Kazmaier, Purified *m* CPBA, a Useful Reagent for the Oxidation of Aldehydes: Purified *m*CPBA, a Useful Reagent for the Oxidation of Aldehydes, *Eur. J. Org. Chem.*, 2018, **2018**, 2531–2536.