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Stereoselective Microwave-assisted Synthesis of 2-Deoxy-2-fluoro-α-glycosides

Bachelor's Thesis

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Degree in Chemistry

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Donar les gràcies a tota la gent amb qui vaig compartir laboratori durant aquesta etapa: Arnau, Irene, Macarena i Carla. Us desitjo el millor en les vostres recerques.

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Abbreviations and acronyms

Ac	Acetyl group
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Bn	Benzyl group
d	Doublet
dd	Double doublet
ddd	Double doublet of doublet
EtOAc	Ethyl acetate
FCC	Flash column chromatography
Hz	Hertz
J	Coupling constant
m	Multiplet
MeOH	Methanol
MS	Molecular sieves
NMR	Nuclear Magnetic Resonance
ppm	Parts per million
Py	Pyridine
R_f	Factor of retention
SelectFluor™	1-chloromethyl-4-fluoro-1,4 diazoniabicyclo [2.2.2] octane bis(tetrafluoroborate)
TLC	Thin layer chromatography

1. Introduction

1.1. Fluorine in chemistry

Molecules containing carbon-fluorine bonds do not usually occur in nature apart from a few exceptions., even though, inorganic fluorine compounds are widely present in the nature as minerals (fluorite, CaF_2 and fluorapatite, $CaF_2 \cdot 3Ca_3(PO_4)_2$). Inorganic fluorine compounds are used in a wide range of applications, such as metallurgy, aluminum manufacture, ceramics etc.[1]

On the other hand, fluorine-containing polymers are an important group of organofluorine compounds, highly valued for their many remarkable properties. The most well-known example is polytetrafluoroethylene (PTFE), a thermoplastic polymer highly inert due to the aggregate effect of carbon-fluorine bonds. Organofluorine compounds are also used for biomedical applications and have application in the pharmaceutical and agrochemical industries. It is estimated that 20 % of modern pharmaceuticals,[2] and 30–40 % of agrochemicals, contain fluorine. Many drugs are fluorinated to increase metabolic stability, moreover, C-F bond in very stable and the fluorine atom acts as a bioisostere of hydrogen.

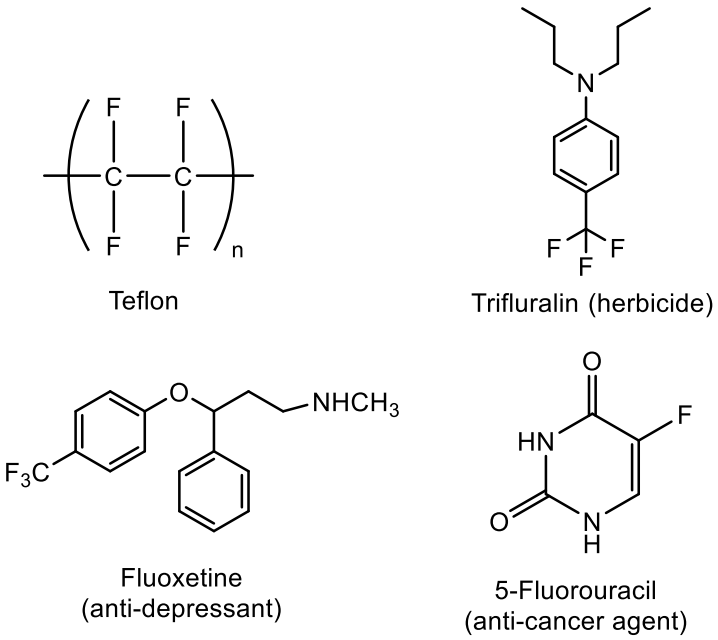


Figure 1. Examples of commercial fluorinated products.

[1] Thomas, Emmanuelle Maitrise de Chimie. *Electrophilic fluorination methodology*. Diss. Durham University, **2002**.

[2] Thayer, A. M. Fabulous fluorine. *Chem. Eng. News*. **2006**, *84* (23), 15-24.

1.1.1. Physical properties of fluorine[3]

Most of the effects induced by the presence of fluorine atoms in a molecule come from the structure and atomic properties of the fluorine atom.

Table 1. Atomic parameters of fluorine and other elements.

Atom	Ionization Potential (kcal/mol)	Electron Affinity (kcal/mol)	Atom Polarizability (Å^3)	Van der Waals Radii (Å)	Pauling's Electronegativity
H	313.6	17.7	0.667	1.20	2.20
F	**401.8**	**79.5**	**0.557**	**1.47**	**3.98**
Cl	299.0	83.3	2.18	1.75	3.16
Br	272.4	72.6	3.05	1.85	2.96
I	241.2	70.6	4.7	1.98	2.66
C	240.5	29.0	1.76	1.70	2.55
N	335.1	- 6.2	1.10	1.55	3.04
O	314.0	33.8	0.82	1.52	3.44

The high electronegativity of fluorine, its small size and the excellent overlap of the 2s or 2p orbitals with the orbitals of carbon determine the inertness of C-F bond.

C-F bonds are strongly polarized from the sp^3 carbon (δ^+) to the fluorine atom (δ^-) due to the high electronegativity of fluorine. This implies that C-F bond has a relatively important ionic character and a stronger energy than other carbon-halogen bonds.

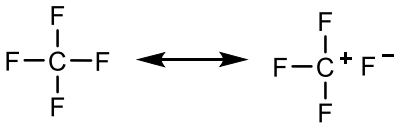


Figure 2. Resonance stabilization in tetrafluoromethane.

The stability of the carbon-fluorine bond increases in accordance with the number of fluorine atoms, CH_3F being the least stable (C–F bond length 1.384 Å) and CF_4 the most stable (C–F bond length 1.335 Å).

1.1.2. ^{19}F NMR

^{19}F has a nuclear spin of ½, a 100 % natural abundance and a high gyromagnetic ratio, which means that this isotope is highly responsive to NMR measurements.[4] ^{19}F NMR signals are sharp and its spectral window is very wide: ^{19}F chemical shift can range from

[3] Bégué, Jean-Pierre, and Danièle Bonnet-Delpon. *Bioorganic and medicinal chemistry of fluorine*. John Wiley & Sons, **2008**.

[4] Tóth, G. Basic one-and two-dimensional NMR spectroscopy. *Magnetic Resonance in Chemistry*. **2001**, *39*(10), 656-656.

550 to -250 ppm. Therefore, ^{19}F NMR spectroscopy is a valuable tool for monitoring interactions between fluorinated motifs and targets. For example, ^{19}F NMR was a useful tool in the determination of the molecular mechanism of glycosidases and glycosyltransferases by trapping any glycosyl-enzyme intermediate.[5] In the case of 2-fluoro-2-deoxysugars, decoupled ^{19}F NMR displays two peaks corresponding to α and β anomers. Coupled spectrum shows two overlapping multiplets. α-anomer usually shows as a ddd, has a higher chemical shift and a characteristic $J_{F2, H2} \approx 49$ Hz and $J_{C1, H1} > 175$ Hz. On the other hand, β-anomer often appears as a dd and shows slightly downfield with a characteristic $J_{F2, H2} \approx 51$ Hz and $J_{C1, H1} < 168$ Hz.

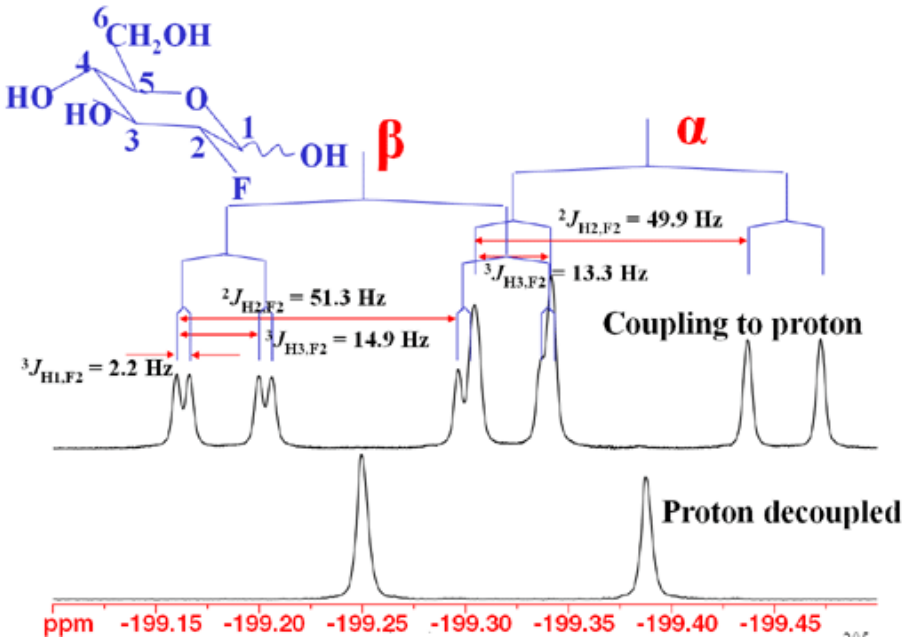


Figure 3. ^{19}F NMR spectrum of 2-fluoro-2-deoxyglucose.

1.2. Fluorosugars

Chemical synthesis is problematic due to the absence of participating groups at the position 2 and a mixture of α and β anomers is usually obtained.[6] 2-Deoxy-2-fluoroglycosides are compounds of increasing importance in biochemistry and medicinal research, especially as antiviral agents, cancer diagnosis probes, etc. Several methods have been developed[7] for introducing fluorine into organic compounds. The most efficient is the reaction between 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octane bis(tetrafluoroborate), usually named SelectFluor™, with glycals. This was the fluorination method followed in this project.

[5] Tai, V. W. F., & Imperiali, B. Substrate specificity of the glycosyl donor for oligosaccharyl transferase. *The Journal of organic chemistry*. **2001**, *66* (19), 6217-6228.

[6] Veyrieres, A., Ernst, B., Hart, G. W., & Sinaý, P. Special Problems in Glycosylation Reactions: 2-Deoxy Sugars. *Carbohydrates in chemistry and biology*. **2000**, 367-405.

[7] Dax, K., Albert, M., Ortner, J., & Paul, B. J. Synthesis of deoxyfluoro sugars from carbohydrate precursors. *Carbohydrate research*. **2000**, *327* (1), 47-86.

1.2.1 General glycosylation mechanism[8]

A glycosylation reaction involves nucleophilic substitution at the anomeric carbon (position 1). In this reaction, a glycosyl donor, which is the nucleophile, and a glycosyl acceptor, which is the electrophile, react via S_N1 mechanism where the intermediate is an oxocarbenium ion. In most cases, an activator (promoter or catalyst) is required to assist the departure of the anomeric leaving group. The nucleophilic attack can occur from either bottom/axial (α anomer) or top/equatorial face (β anomer) of the pyranose. Nevertheless, α anomer is thermodynamically favored because of the anomeric effect.

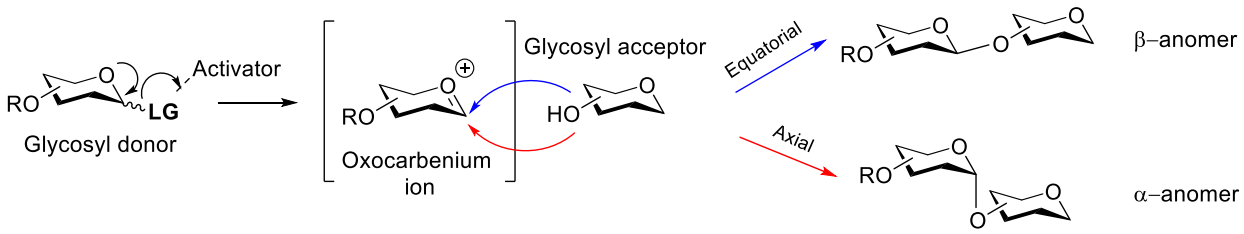


Figure 4. General glycosylation mechanism.

The stereochemistry and reactivity of glycosylation reaction may be affected by:

- Anomeric effect
- Neighboring group participation
- Protecting groups

1.2.2. Anomeric effect[9]

The anomeric effect is defined as the tendency of electronegative substituent of the glycosyl donor to be axially oriented, favoring the formation of α anomers. In a comparative cyclohexane system, the most favored position for a substituent attached to the ring is an equatorial position as this would be expected under normal thermodynamic considerations. Currently, two theories are accepted to explain this fact. The most common explanation is the occurrence of hyperconjugative stabilization between the non-bonding electron pair in oxygen orbital (n) with the anti-bonding orbital (σ*) of the anomeric C-O bond. Therefore, the molecule must align the lone pair of electrons antiperiplanar (180º) to the σ* orbital, which implies an axial conformation.

The other explanation for the anomeric effect is the dipole minimization. In the equatorial configuration, there is an electrostatic repulsion between the aligned dipoles. This alignment disfavors the β-configuration. However, axial configuration has opposite dipoles, representing a more stable configuration.

[8] Demchenko, Alexei V., ed. Handbook of chemical glycosylation: advances in stereoselectivity and therapeutic relevance. John Wiley & Sons, **2008**.
[9] Juaristi, E., & Cuevas, G. Recent studies of the anomeric effect. *Tetrahedron*. **1992**, *48* (24), 5019-5087.

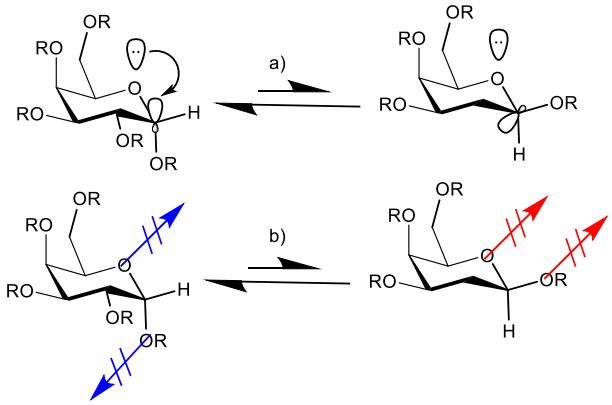


Figure 5. Anomeric effect. a) Hyperconjugation stabilization. b) Dipole minimization.

1.2.3. Neighboring group participation

One strategy employed to control the diastereoselectivity of glycosylation is the participation of a neighboring group. It is generally accepted that the positioning of an ester group (e.g. acetyl or benzoyl) in the C2 produces an orthoester intermediate after leaving group activation. Such intermediate displays a blocked axial face, only allowing a S_N2-like reaction to proceed affording a β-glycosidic bond.

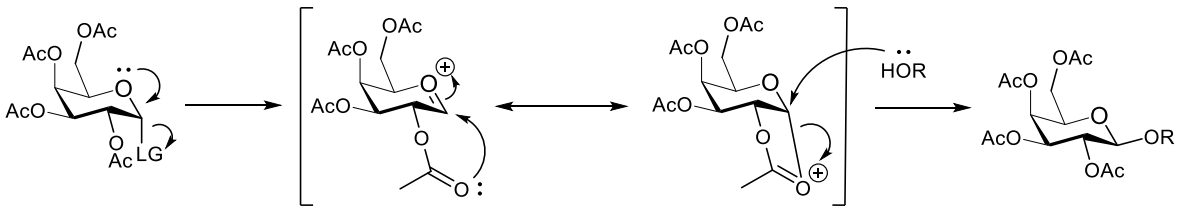


Figure 6. Neighboring group participation. Favoring the formation of a β-anomer.

The absence of a participating group at the position 2 implies that nucleophilic attack may take place at either axial or equatorial face. Formation of α anomer is favored due to the anomeric effect.

1.2.4. Protecting groups

Another factor affecting glycoside bond formation is the nature of the protecting groups. Usually, electron-withdrawing groups such as acetyl or benzoyl, decrease the reactivity of the donor/acceptor. They are called disarming groups. Electron-donating groups, such as benzyl groups, increase the reactivity of the donor/acceptor and they are called arming groups. This fact can be disseminated into two types of effect: electronic and torsional.

Electronic effect

The selectivity of the reaction can be also controlled due to the nature of the protecting groups. The glycosylation between an armed and disarmed sugar is more favorable than the glycosylation between two disarmed sugars. Stronger electron withdrawing substituent in disarmed sugars lead to a greater destabilization of the oxocarbenium ion and allows disaccharide formation to occur with the armed sugar.

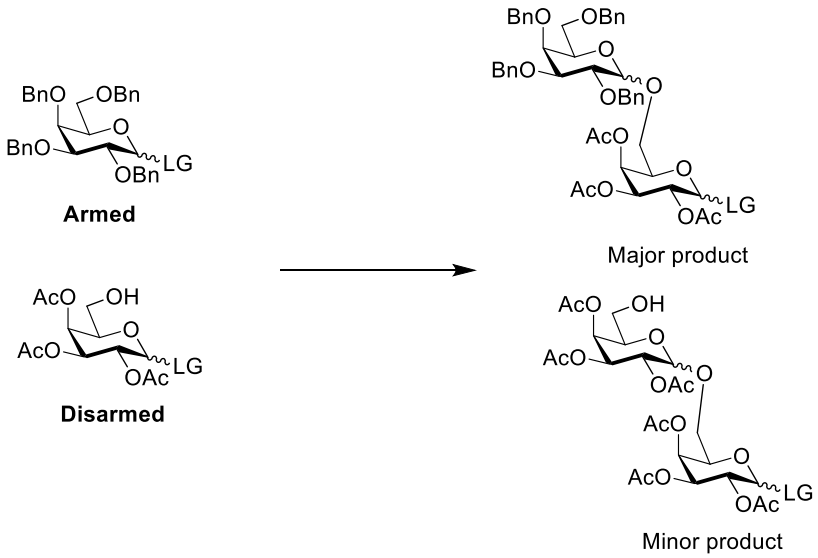
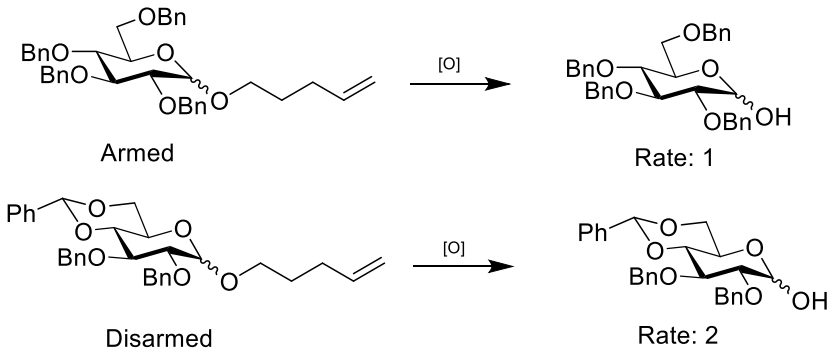


Figure 7. Electronic effect in armed-disarmed sugars.

Torsional effect

Disarming sugars can be accomplished by torsional strain.[10] During the formation of the oxocarbenium ion, the carbohydrate adopts a half chair conformation. It is possible to increase the energy of this conformation through cyclic protecting groups, such as 1,3-dioxanes or 1,3-dioxolanes. The loss of electron density at the endocyclic oxygen results in a destabilization of the oxocarbenium ion, slowing its formation and disarming the carbohydrate.



[10] Fraser-Reid, B., Wu, Z., Andrews, C. W., Skowronski, E., & Bowen, J. P. Torsional effects in glycoside reactivity: saccharide couplings mediated by acetal protecting groups. *Journal of the American Chemical Society*. **1991**, *113* (4), 1434-1435.

Figure 8. Hydrolysis rate in torsional effect.

1.3. Microwave-assisted organic synthesis

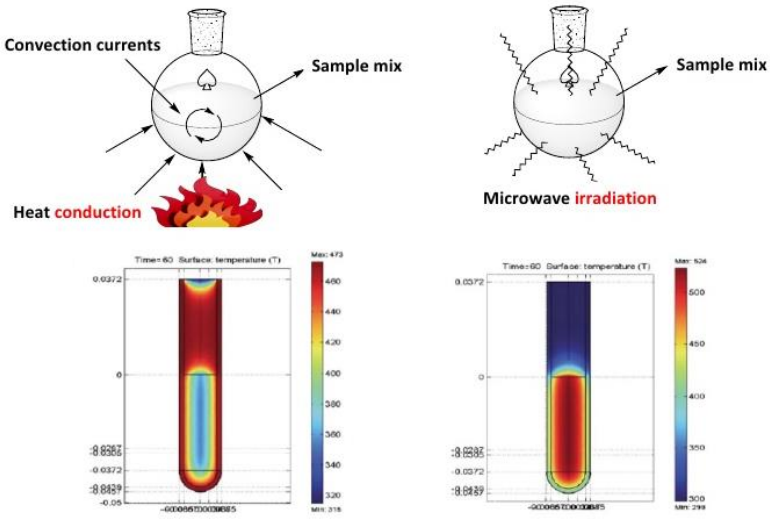
Microwave irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. During recent years, microwaves have been extensively used for carrying out chemical reactions and have become a useful non-conventional energy source for performing organic synthesis.

Microwave is a form of electromagnetic energy that falls at the lower frequency of the electromagnetic spectrum. Within this region of electromagnetic energy, only molecular rotation is affected, not the molecular structure.[11]

Nowadays, organic reactions usually take place by two ways of heating:[12]

- **Conventional heating**: Reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel to reach the solvent and the reactants. This is a slow and inefficient method for transferring energy into the reacting system.

- **Microwave heating**: Microwaves incise directly with the molecules of the entire reaction mixture, leading to a rapid rise in the temperature. Since the process is not limited by the thermal conductivity of the vessel, the result is an instantaneous localized superheating of any substance that will respond to either dipole rotation or ionic conductivity. Only the reaction vessel contents are heated and not the vessel itself. Better homogeneity and selective heating of polar molecules might be achieved.



[11] Brittany L. Hayes Ph.D., Recent Advance in Microwave Assisted Synthesis, 2002, pp. 1-6.
[12] Surati, M. A., Jauhari, S., & Desai, K. R. A brief review: Microwave assisted organic reaction. *Archives of Applied Science Research*. **2012**, *4* (1), 645-661.

Figure 9. Microwave vs conventional heating. In conventional heating, the walls of vessel are more heated than the sample mixture.

For microwave heating, the substance must possess a dipole moment. The dipole is sensitive to external electric field, which continuously change, and tries to align itself with the field by rotation. Therefore, only polar molecules interact with microwave energy. Less polar substances, such as aromatic hydrocarbons or compounds with no net dipole moment (e.g. CO_2) are poorly absorbing. Thus, polar molecules in a non-polar solvent absorb energy, but no the solvent or the reaction vessel. This fact let a selective absorption for the polar compounds which means a larger reaction rate.

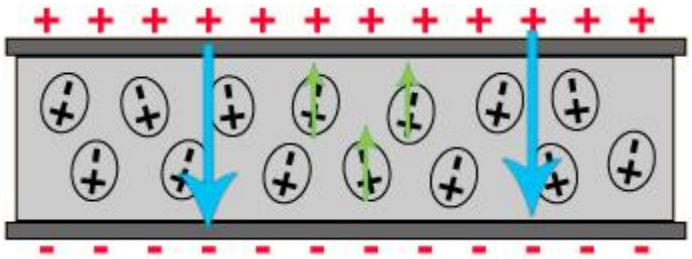


Figure 10. Dipolar polarization. Molecules with a dipolar moment ≠ 0.

In brief, the advantages of microwave-assisted organic synthesis are:

- Homogeneity of heating.
- Speed of heating.
- Clean, reproducible and easily automated.
- Less side-products and improved yields.
- Higher energy efficiency.
- Wider usable range of temperature

But there are some disadvantages, such as heat force control is difficult (that often implies evaporation of the solvent) and closed reaction vessel or containers are dangerous because they could burst.

2. Objectives

The main objectives of the present project are:

a) To prepare several glycosyl donors.

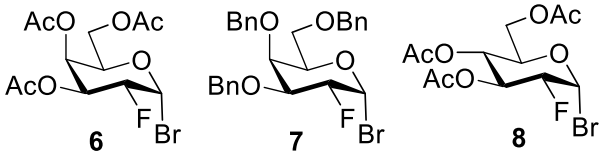


Figure 11. Synthetized glycosyl donors.

b) To optimize the glycosylation reaction assisted by microwave to obtain mainly α-anomer.

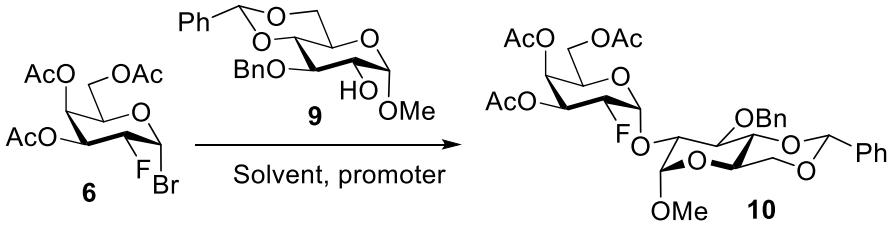


Figure 12. Optimization step.

c) To explore the scope of this procedure to find out its utility.

d) To characterize glycosylation products by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy.

3. Results and discussion

3.1. Synthesis of glycosyl donors

Before the glycosylation reaction between glycosyl donor and glycosyl acceptor, various glycosyl donors were synthetized.

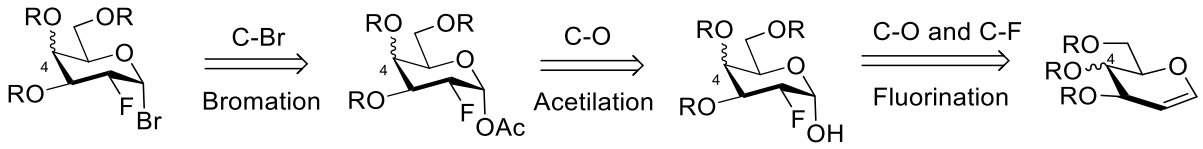


Figure 13. General retrosynthetic scheme. R = Ac, Bn; Position 4 configuration = *Gluco*, *Galacto.*

The first step of the synthesis was the fluorination[13] at the position 2. The starting material was glycal **1** (3,4,6-tri-*O*-acetyl-D-galactal) and the selective fluorination was carried out by SelectFluor™, a commercial electrophilic fluorinating agent.

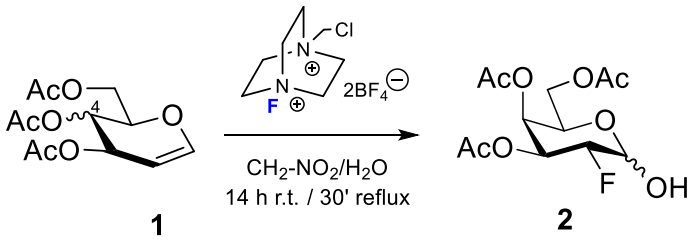


Figure 14. Synthetic method of electrophilic fluorination.

The reaction mechanism is an electrophile addition to the double bond. Sugar **1** acts as nucleophile and SelectFluor™ is the electrophile agent able to convert glycals to 2-deoxy-2-fluorosugars, reaching good to excellent yields. SelectFluor™ is soluble in only a few polar solvents, such as CH_3NO_2/ water. The use of nitromethane may be helpful since does not glycosylate. Other solvents, such as acetonitrile, are more coordinating and may glycosylate. Detailed ^{19}F NMR spectroscopic studies[14] demonstrated that SelectFluor™ adds to the glycal in a *syn* fashion, which then slowly anomerizes to more thermodynamically stable intermediate. Fluorine addition depends on protecting groups and configuration of the sugar. If steric bulk increase, alpha selectivity is favored.[15]

[13] Albert, M., Paul, B. J., & Dax, K. Synthesis of (2-Deoxy-2-Fluoro-Glycosyl) Amino-Acids. *Synlett*. **1999**, *199 9*(09), 1483-1485.

[14] Vincent, S. P., Burkart, M. D., Tsai, C. Y., Zhang, Z., & Wong, C. H. Electrophilic Fluorination− Nucleophilic Addition Reaction Mediated by Selectfluor: Mechanistic Studies and New Applications. *The Journal of Organic Chemistry*. **1999**, *64* (14), 5264-5279.

[15] Nyffeler, P. T., Durón, S. G., Burkart, M. D., Vincent, S. P., & Wong, C. H. Selectfluor: mechanistic insight and applications. *Angewandte Chemie International Edition*. **2005**, *44* (2), 192-212.

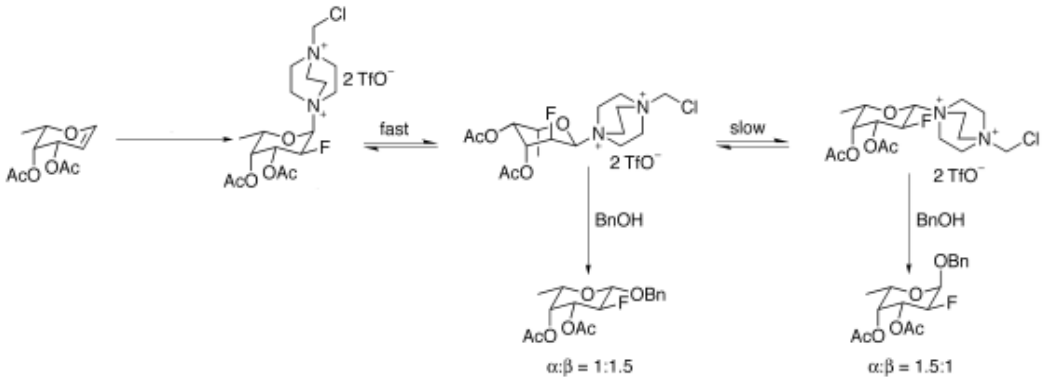


Figure 15. Electrophilic fluorination mechanism.

This reaction was carried out twice. The first time, after 60 minutes of reflux, TLC monitoring showed up two spots. One of the spot was product **2** and the other was a substantial unknown by-product.

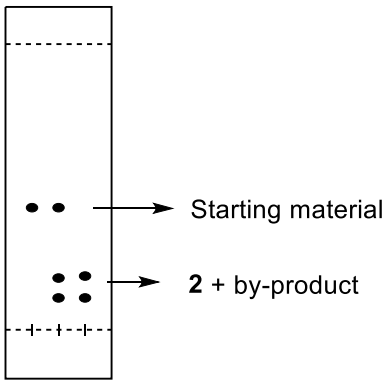


Figure 16. TLC- Fluorination reaction.

^{19}F and ^{1}H NMR experiments were performed to find out the nature of the by-product. ^{1}H NMR spectrum showed up a characteristic aldehyde peak at 9.7 ppm (see Annex). It was found in the literature that SelectFluor™ is also an oxidative agent, which means that may oxidize hydroxyl groups to aldehydes. With this outcome, it was decided to control the heating time to avoid the oxidation of hydroxyls. It was decided to reduce the refluxing time to 30 minutes, thus avoiding the formation of aldehyde. Thus, reflux time is an important parameter to control in this reaction due to the oxidative effect of SelectFluor™. The absence of double bound signals was found in ^{1}H NMR spectrum. The mixture of α and β anomers was used in the next step without further purification.

The next step was the acetylation of the fluorinated mixture. The aim was to protect hydroxyl group of sugar **2** as an acetyl group. This is a very well-known classical reaction.[16]

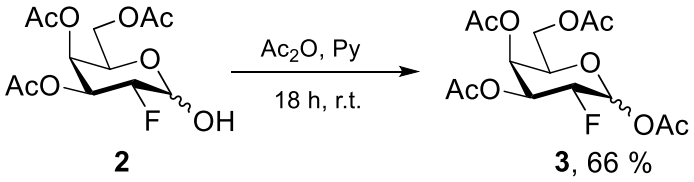


Figure 17. Synthetic method of acetylation reaction.

Lone pair of the oxygen attacks one of the carbonyl group of acetic anhydride, causing a nucleophilic acyl substitution. Pyridine acts as base using its free electron pair to neutralize the acid formed (acetic acid) during the reaction.

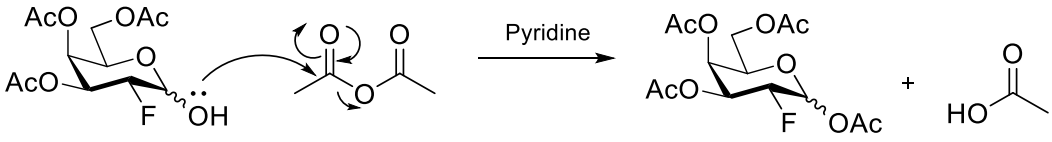


Figure 18. Nucleophilic acyl substitution mechanism.

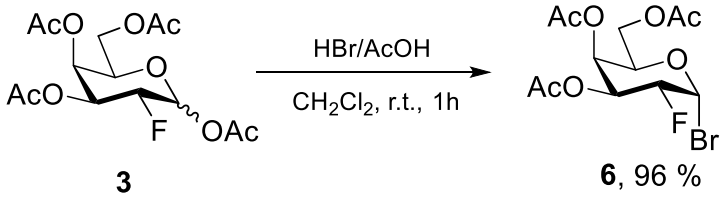
Reaction control by TLC helped to figure out the end of the reaction. Carbohydrate **3** is less polar than **2**, therefore its spot is higher on the TLC sheet. ^{19}F NMR allowed a quick and easy first analysis of the mixture. ^{19}F NMR spectrum of the reaction outcome showed α and β anomeric signals, already described in the literature[17]. After flash column chromatography afforded a mixture of α/β (2:1) anomers determined by ^{19}F NMR in a 66 % of yield. The configuration and conformation of the products were confirmed by ^{1}H, ^{13}C, COSY and HSQC. In the ^{19}F NMR spectrum, peaks at -209.1 (ddd, $J_{F,2}$ = 51.2 Hz, $J_{F,3}$ = 12.1 Hz, $J_{F,4}$ = 4.5 Hz, F-2, α-anomer) and -208.2 ppm (ddd, $J_{F,2}$ = 51.5 Hz, $J_{F,3}$ = 12.6 Hz, $J_{F,4}$ = 2.8 Hz, F-2, β-anomer) were found. Acetylation of sugar **2** was also confirmed in ^{13}C and ^{1}H NMR spectra, which displayed new signals corresponding to the Ac group.

After acetylation, the next step was the placement of a leaving group at the anomeric carbon obtaining this way the glycosyl donor. The chosen leaving group was bromide.

[16] Durantie, E., Bucher, C., & Gilmour, R. Fluorine-Directed β-Galactosylation: Chemical Glycosylation Development by Molecular Editing. *Chemistry-A European Journal*, **2012**, *18* (26), 8208-8215.

[17] Adam, M. J., Pate, B. D., Nesser, J. R., & Hall, L. D. A rapid, stereoselective synthesis of fluorinated carbohydrates: Addition of acetyl hypofluorite to vinyl ether derivatives of sugars. *Carbohydrate research*, **1983**, *124* (2), 215-224.

Therefore, a bromination[18] reaction was performed. Product **3** was treated with HBr/AcOH solution in dry CH_2Cl_2.

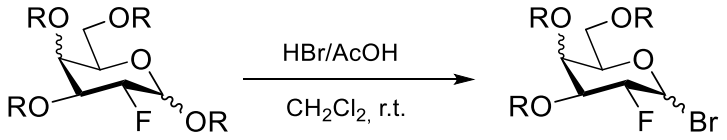


3 **6**, 96 %

Figure 19. Synthetic method of bromination reaction.

Reaction was completed within 60 minutes (TLC monitoring). Immediately, acid neutralization was carried with aqueous $NaHCO_3$. ^{19}F NMR spectrum indicated that the major product was the α anomer, displaying a peak at –195.0 (ddd, $J_{F,2}$ = 50.1 Hz, $J_{F,3}$ = 9.9 Hz, $J_{F,4}$ = 3.0 Hz, F-2). This outcome was expected considering the anomeric effect. The loss of one Ac group by sugar **3** was confirmed by ^1H and ^{13}C NMR. Spectroscopic data was identical to that previously reported. [18] The same reaction was carried out with different sugars, changing either the configuration (*galacto* and *gluco*) or the protecting groups employed. All of them were used in the next step without further purification.

Table 2. Bromination step summary.



3-5 **6-8**

Entry	Donor	R	α/β[b]	% Yield
1	**3**	$Ac^{Galacto}$	Only α	96 (**6**)
2	**4**	$Bn^{Galacto}$	Only α	92 (**7**)
3	**5**	Ac^{Gluco}	95:5	80 (**8**)

[a]See experimental section for detailed reaction condition; [b]Determinated by ^{19}F NMR.

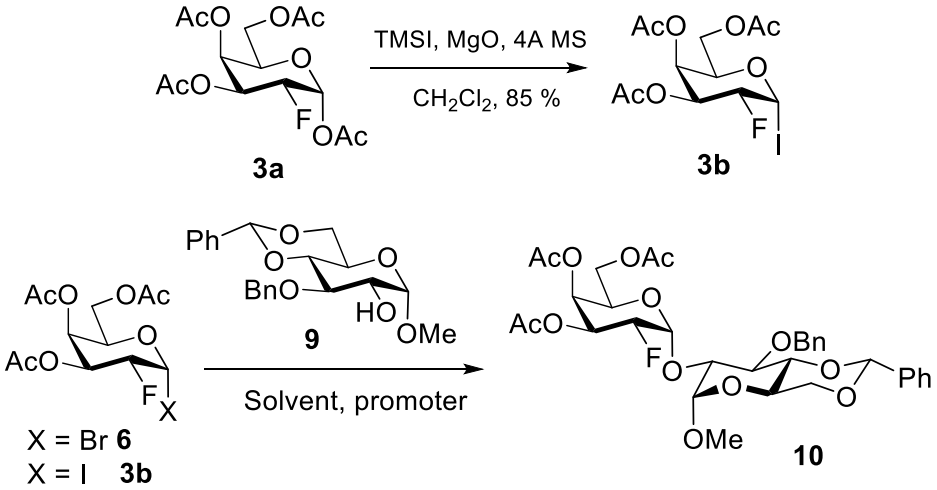
The structure of glycosyl donors **6**, **7** and **8** were fully confirmed by ^1H, ^{13}C, COSY and HSQC spectra. In all cases, α-anomer is the major product and the presence of by-products is minimum assuring excellent yields (up to 96 %).

[18] Albert, M., Dax, K., & Ortner, J. A novel direct route to 2-deoxy-2-fluoro-aldoses and their corresponding derivatives. *Tetrahedron*. **1998**, *54* (19), 4839-4848.

3.2. Glycosylation optimization step

Once glycosyl donors were synthesized, the next step was the reaction optimization. Dr. Boutureira Martín has performed a previous examination of various leaving groups and reaction conditions in glycosylation of 2-deoxy-2-fluoro-galactoside. (**Table 3, entry 1-9**)

Table 3. Examination of various leaving groups and reaction conditions in glycosylation of 2-deoxy-2-fluoro-galactoside.

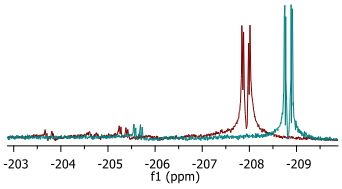


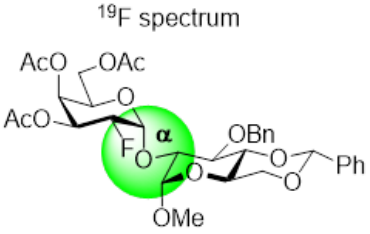
Entry	X	Reaction conditions (equiv)	Yield [%]
1[c]	**3a**	1) TMSI (1), CH_2Cl_2, 0 ºC to RT, 38 h 2) TBAI (2), DIPEA (2), PhH, reflux, 16 h	12[d]
2[c]	**3a**	1) TMSI (1), CH_2Cl_2, 0 ºC to RT, 38 h 2) TBAI (2), DIPEA (2), PhH, reflux, 21 h	18[d]
3	**3b**	2) TBAI (2), 4Å MS, PhMe, reflux, 7 h	27[d] (35)
4	**3b**	AgOTf (1), Ag_2CO_3 (2.2), Drierite^R, 12:1 dioxane/Et_2O, RT, 22 h	12[d]
5	**3b**	$AgClO_4$ (1), Ag_2CO_3 (2.2), Drierite^R, 12:1 dioxane/Et_2O, RT, 17 h	31[d]
6	**3b**	$AgNO_3$ (1), Ag_2CO_3 (2.2), Drierite^R, 12:1 dioxane/Et_2O, RT, 24 h	[e]
7	**3b**	Ag_2O (0.6), quinoline, 65 ºC, 0.5 h	[d,e]
8	**3b**	I_2 (1.5), 4Å MS, 1:3 PhMe/dioxane, RT, 3 d	63
9[f]	**3b**	1) $Bu_3SnAllyl$ (1.3), TfOH (0.3), PhMe, RT, 2 h 2) Reflux, 20 h	51
10	**6**	CH_3-Ph, 4Å MS	0
11	**6**	CH_3-Ph, 4Å MS, $Bu_3SnAllyl$	0
12	**6**	CH_3-Ph, 4Å MS, TfOH	0
13	**6**	CH_3-Ph, 4Å MS, $Bu_3SnAllyl$, TfOH	[g]
14	**6**	CH_3-Ph, 4Å MS, $Bu_3SnAllyl$, TfOH (*in situ*)	[g]

[a] General conditions: donor (1 equiv), acceptor 6 (2 equiv) unless otherwise indicated; [b] Isolated yield. In parenthesis yield based on recovered starting material. [c] Consecutive procedure (α-galactosyl iodide 2 was used in the next step without further purification). [d] 20–60% of the corresponding 2-fluorogalactal

was also obtained. [e] 30–57% of the corresponding 2-deoxy-2-fluorogalactose was also obtained. [f] In situ tributylstannyl alkoxyde preparation from 6 prior to glycosylation reaction. TBA=tetrabutylammonium. DIPEA=N-ethyldiisopropylamine. PhH=benzene, PhMe=toluene. [g]not determinated.

This project is focused on the reaction performed in the Table 3, entry 9. Control experiments were performed to find out the optimal glycosylation conditions. (**Table 3, entry 10-14**) Bromide glycosyl donors were used instead of iodine since they are easier to prepare and more stable. Reagents used in the glycosylation reaction were: Triflic acid (TfOH), tributylallyltin ($Bu_3SnAllyl$), 4Å molecular sieves (MS) and dry toluene as solvent. Mixtures were transferred to quartz reaction tubes and heated in microwave instrument. After 45 minutes of reaction, the TLC showed no conversion, only starting material was observed (**Table 3, entry 10**). The ^{19}F NMR showed only the starting material peak. Therefore, a promoter is required. Addition of $Bu_3SnAllyl$ in the absence of TfOH showed no conversion as determined by TLC and ^{19}F NMR analysis. (**Table 3, entry 11**) Addition of TfOH to the mixture in absence of $Bu_3SnAllyl$ showed no formation of glycosylated product. (**Table 3, entry 12**) Glycosyl acceptor **9**, tributylallyltin and TfOH in dry toluene were mixed during at least 2 hours at room. Next, glycosyl donor **6** was added. The crude was analyzed by TLC and ^{19}F NMR. Formation of glycosylated product was found. (**Table 3, entry 13**) The same reaction was performed but then all reagents were mixed at the same time. *In situ* glycosylation crude was analyzed by ^{19}F RMN and glycosylated product was obtained. (**Table 3, entry 14**) Therefore, the glycosylation only works if $Bu_3SnAllyl$ and TfOH are together: the formation of the tributylstannyl alkoxide is needed. The following figure shows the overlap of both ^{19}F NMR spectra (**Table 3, entry 13 and 14**) of the reaction crudes. A comparison between *in situ* (green line) and pre-generated (red line) stannylene glycosylation was done. Both spectra offered similar results, but *in situ* glycosylation offered less by-products.





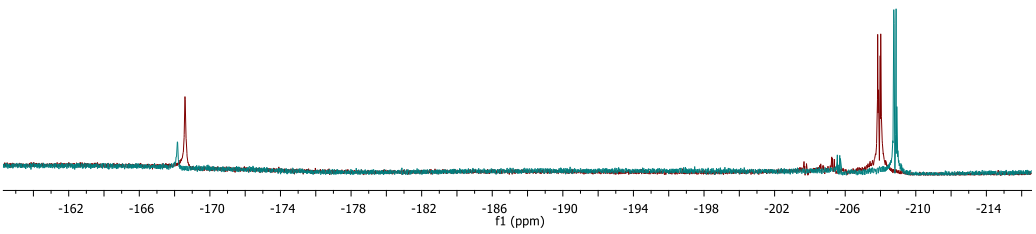


Figure 20. ^{19}F NMR spectra overlap.

With this outcome, *in situ* glycosylation was the chosen method. It is less time-consuming than wait 2 hours at least for the tributylstannyl alkoxide preparation. The next step was the purification by flash column chromatography of disaccharide **10**, which was then analyzed by spectroscopic techniques. In the ^{19}F NMR spectrum only α anomer was identified. In ^{1}H NMR spectrum, peaks corresponding to acceptor **9** were identified since the R_f values of the product and acceptor were similar. Precipitation/crystallization techniques also failed to purify the product. Alternatively, using the acceptor as the limiting reagent would be optimal to purify the product. Nevertheless, the isolation of a pure fraction of **10** enabled complete characterization by ^{1}H, ^{13}C, ^{19}F, COSY, HSQC and NOESY. In the ^{19}F NMR spectrum was found a major signal at -208.3 ppm (ddd, $J_{F,2}$ = 50.0 Hz, $J_{F,3}$ = 10.8 Hz, $J_{F,1}$ = 2.8 Hz, F-2). This signal indicates an α-anomer. In NOESY spectrum, H_3 and H_5 were coupled, which means that they are in contact, at the same face. H_1 and H_{2*} were coupled as well. A value of $J_{C1, H1}$ = 174.5 Hz was observed in coupled HSQC. Values over 170 Hz corresponds to an α-anomer.

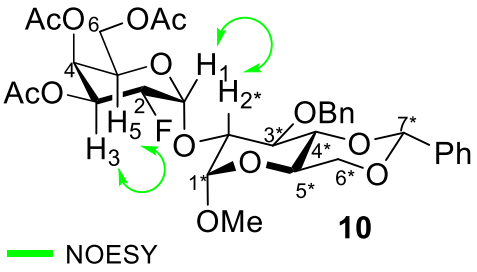


Figure 21. NOESY coupling.

3.3. Reaction scope

With the optimal conditions in hands, the scope of this reaction was evaluated with a series of glycosyl donors bearing different protecting groups (Bn, Ac) and multiple configurations (D-*gluco* and D-*galacto*), and with a series of glycosyl acceptors. ^{19}F NMR spectra analysis was performed in the reaction crudes to determine the conversions and α/β ratios. All spectra can be found in the annex section.

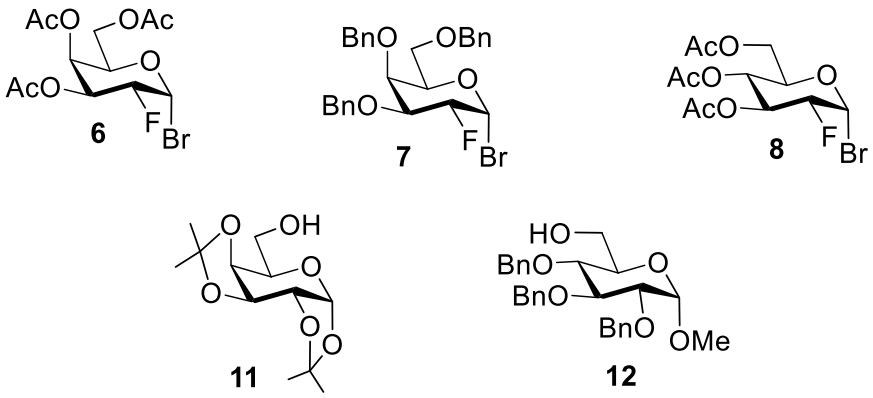
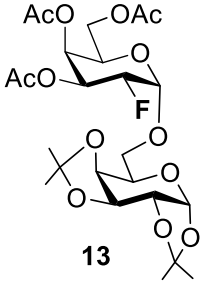
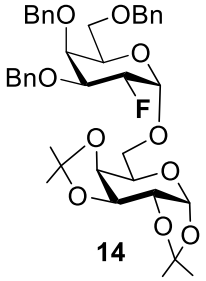
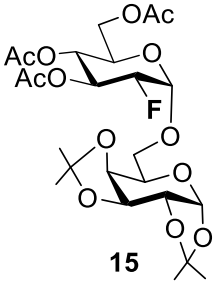
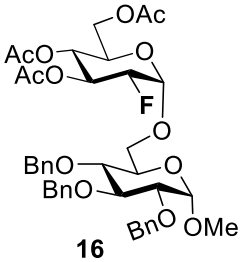


Figure 22. Glycosyls donors (**6**, **7** and **8**) and glycosyls acceptors (**11** and **12**) used in the reaction scope.

Table 4. Summary of scope study.

Entry	Glycosyl donor	Glycosyl acceptor	Disaccharide	α/β ratio[b]	Yield [%]
1	**6**	**11**	 **13**	8.4:1.4	[c]
2	**7**	**11**	 **14**	1:2.75	24
3	**8**	**11**	 **15**	-	[a]
4	**8**	**12**	 **16**	-	[a]

[a]Glycosylated product was not obtained. [b]Determinated by ^{19}F NMR. [c]Not determinated.

^{19}F NMR spectrum of disaccharide **13** (Table 4, entry 1) demonstrated that glycosylated product had been formed and no starting material remained. Peaks at -206.5 ppm (dd) and -208.2 ppm (ddd, major signal) were observed. According to others glycosylation reactions, ddd peak between -207 and -210 ppm at ^{19}F NMR is characteristic of a α-anomer. On the other hand, slightly downfield of α-anomer is characteristic of a β-anomer. Glycosylated product in disaccharide **14** (Table 4, entry 2) was found in ^{19}F NMR spectrum. Signals at -204.9 ppm (ddd, β-anomer major signal) and -208.0 ppm (ddd, α-anomer) were observed. That was an interesting outcome, β-anomer was major than α-anomer. The structural difference between **13** and **14** are the protecting groups. R. Gilmour [16] and his research group concluded that glycosylation reaction under kinetic conditions in *galacto* sugars bearing Bn protecting groups yields to high β-selectivity (up to β/α 300:1). A simple substitution of Bn by Ac erodes selectivity (β/α 1:1). The same glycosylation reaction was performed in this project (Table 4, entry 2) under thermodynamic conditions and the result coincides with Gilmour ones, β-anomer was the major anomer. Changing Bn for Ac group, β-selectivity decreased and the major product was α-anomer. (Table 4, entry 1) Glycosylated product was not found by ^{19}F NMR spectrum. (Table 4, entry 3) However, ^{19}F NMR spectrum showed two signas at -201.8 ppm (dd, major signal) and -199.8 ppm (dd). These signs may correspond to product of elimination. A side reaction that competes with substitution (glycosylation) is the elimination. H2 is antiperiplanar respect of the leaving group. Such configuration favors elimination to produce glycal **18**. In the case of *galacto* series, the C4 substituent impedes a base approach by steric effect which is absent in the *gluco* configuration.

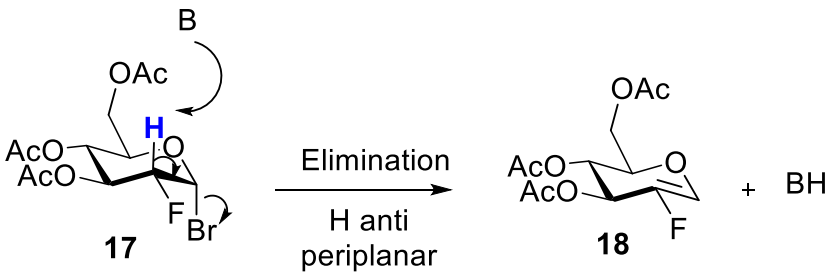


Figure 23. Elimination reaction mechanism.

Glycosylated product was not observed by ^{19}F NMR spectrum. (Table 4, entry 4) Signals at -201.1 ppm (dd, major sign) and -199.1 ppm (dd) were found as well. As explained before, *gluco* configuration favors the elimination reaction.

4. Conclusions

A microwave-assisted glycosylation method was carried out in this project.

- One of the first goals were the regioselective preparation of glycosyl donors, and it was achieved. Glycosyls donors **6**, **7** and **8** were synthetized achieving good yields (up to 96 %). α-anomer was the main product in all experiments.

- Optimization step: The main objective was to perform a microwave-assisted glycosylation to obtain mainly α anomer. Control experiments proved that *in situ* reaction was successful, thus avoiding previous preparation of tributylstannyl alkoxide, and reducing the overall time. Purification by flash column chromatography was difficult and excess of acceptor remained. Better purification success is expected using donor in excess.

- Experiments carried out with *gluco* glycosyl donors afforded no disaccharides but elimination by-products were obtained instead.

- β-selectivity was observed in *galactal* sugars bearing Bn protecting groups. That outcome was not expected since glycosylation reactions were performed under thermodynamic conditions which favors the anomer more stable.

- Synthetized products and its conformations were confirmed by ^{1}H, ^{13}C, ^{19}F, COSY, HSQC, HMBC and NOE RMN spectroscopic techniques.

5. Experimental section

5.1. General remarks

All reagents were purchased from Sigma Aldrich, Alfa Aesar and Fluka companies. Dichloromethane (CH_2Cl_2) and toluene (CH_3Ph) were dried using standard methods. Glycosylation reactions were carried out by a CEM Discover microwave reactor. ^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or on a Varian® NMR System 400 (400 MHz and 100.6 MHz respectively) spectrometer. NMR Spectra were fully assigned using COSY, HSQC and HMBC. Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, bt = broad triplet, bq = broad quadruplet and app = apparent. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck® aluminum backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λmax = 254 nm) and/or by heating plates that were dipped in a H_2SO_4/ethanol (1:15). Flash chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230–400 mesh).

5.2. Synthetic procedures and characterization

General microwave-assisted reaction process

The following procedure was followed for the glycosylation reactions.

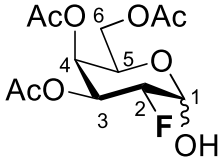
Glycosylation mixtures were transferred to a reaction vessel for microwave. Then, the vessel was inserted in the microwave instrument and parameters were set up.

Table 5. Microwave parameters used during the glycosylation reactions.

Parameters of the instrument	
Power	300 W
Temperature	120 ºC
Hold time	5 minutes
Reaction time	60 minutes
Pressure	250 psi
Stirred	High
Cooling	On

5.2.1. Synthesis and glycosylation of 2-Deoxy-2-fluoroglycosides

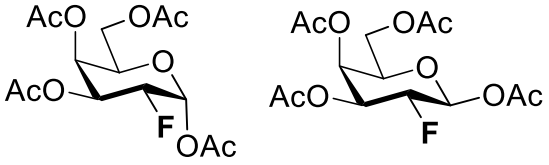
3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-D-galactopyranose (2)



To a solution of 3,4,6-tri-O-acetyl-D-galactal (0.99 g, 3.6 mmol, 1.0 eq.), nitromethane (10 mL, 2.8 mL/mmol), H_2O (2 mL, 0.6 mL/mmol) and Selectfluor® (1.55 g, 4.4 mmol, 1.2 eq.) were added. The mixture was stirred at room temperature for 14 h and then warm up to 98°C and stirred for 30 minutes. The crude was then evaporated to dryness, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure to afford a colorless syrup. The product was used in the next step without further purification.

R_f 0.31 (hexane/EtOAc 1:1).

1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-D-galactopyranose (3)

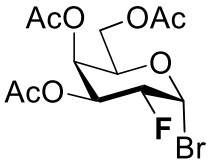


Ac_2O (0.86 mL, 9.1 mmol, 2.5 eq.) was added to a solution of **2** (0.99 g, 3.6 mmol, 1.0 eq.) in pyridine (3.60 mL, 1 mL/mmol). The mixture was stirred at room temperature for 18 h. The crude was then evaporated to dryness, diluted with EtOAc and washed twice with 10 mL of saturated aqueous solution of $CuSO_4$, NH_4Cl and NaCl. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The product was purified by flash column chromatography (SiO_2, hexane/EtOAc 7:3) to afford **3** as a white solid (0.65 g, 66 %, α: β 2:1).

R_f 0.24 (hexane/EtOAc 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.44 (d, $J_{1,2}$ = 4.0 Hz, 1H, H1α), 5.77 (dd, $J_{1,2}$ = 8.0 Hz, $J_{F,1}$ = 4.1 Hz, 0.4H, H1β), 5.49 (td, $J_{F,4}$ = 1.3 Hz, $J_{3,4}$ = $J_{4,5}$ = 3.4 Hz, 1H, H4α), 5.43 (appt, $J_{3,4}$ = 3.0 Hz, 0.4H, H4β), 5.42 – 5.35 (m, 1H, H3α), 5.16 (ddd, $J_{F,3}$ = 13.2 Hz, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 3.6 Hz, 0.4H, H3β), 4.87 (ddd, $J_{F,2}$ = 49.2 Hz, $J_{2,3}$ = 10.2 Hz, $J_{1,2}$ = 4.0 Hz, 1H, H2α), 4.62 (ddd, $J_{F,2}$ = 51.6 Hz, $J_{2,3}$ = 9.9 Hz, $J_{1,2}$ = 8.0 Hz, 0.4H, H2β), 4.29 (td, $J_{6a,b}$ = $J_{6b,a}$ = 6.7 Hz, $J_{4,5}$ = 1.3 Hz, 1H, H5α), 4.16 – 4.02 (m, 5H, 2 x H6α, 2 x H6β, H-5β), 2.17, 2.16, 2.04, 2.04, 2.02, 2.01 (s, 18H, 6CH_3, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 169.8, 169.7, 169.7, 138.6, 168.6 (6C=O, Ac), 169.7, 169.7, 169.7, 169.5, 169.6, 168.5 (6C=O, Ac), 91.2 (d, $J_{F,1}$ = 24.6 Hz, C1β), 88.7 (d, $J_{F,1}$ = 22.5 Hz, C1α), 86.7 (d, $J_{F,2}$ = 187.7 Hz, C2β), 84.0 (d, $J_{F,2}$ = 190.6 Hz, C2α), 71.4 (C5β), 70.6 (d, $J_{F,3}$ = 18.7 Hz, C3β), 68.3 (C4β), 67.9 (d, $J_{F,3}$ = 18.9 Hz, C3α), 67.7 (C4α), 67.6 (C5α), 60.7 (C6α), 60.7 (C6β), 20.5,

20.5, 20.3, 20.3, 20.2, 20.2 (6CH_3, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –208.2 (ddd, $J_{F,2}$ = 51.5 Hz, $J_{F,3}$ = 12.6 Hz, $J_{F,4}$ = 2.8 Hz, F-2, β-anomer), -209.1 (ddd, $J_{F,2}$ = 51.2 Hz, $J_{F,3}$ = 12.1 Hz, $J_{F,4}$ = 4.5 Hz, F-2, α-anomer).

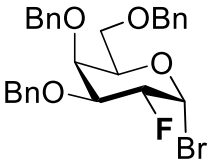
3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl bromide (6)



To a solution of **3** (401.6 mg, 1.15 mmol, 1.0 eq.) in dry CH_2Cl_2 (8.1 mL, 7.15 mL/mmol) was added 33% HBr in AcOH (4.01 mL, 3.5 mL/mmol). Temperature must be controlled during the HBr addition due it is an exothermic reaction. The mixture was stirred at room temperature for 4 h. The mixture reaction was then diluted with CH_2Cl_2 and washed with sat. aq. solution of $NaHCO_3$. The organic combined phases were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **6** (383.3 mg, 96 %) as a yellowish solid. Used in the next step without further purification.

R_f 0.43 (hexane/EtOAc 6:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.61 (d, $J_{1,2}$ = 4.2 Hz, 1H, H-1), 5.53 (td, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 5.47 (td, $J_{F,3}$ = $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.4 Hz, 1H, H-3), 4.76 (ddd, $J_{F,2}$ = 50.2 Hz, $J_{2,3}$ = 10.0 Hz, $J_{1,2}$ = 4.2 Hz, 1H, H-2), 4.51 (appt, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, $J_{4,5}$ = 1.2 Hz, 1H, H-5), 4.17 (dd, $J_{6a,b}$ = 11.5 Hz, $J_{5,6a}$ = 6.4 Hz, 1H, H-6a), 4.11 (dd, $J_{6a,b}$ = 11.5 Hz, $J_{5,6b}$ = 6.4 Hz, 1H, H-6b), 2.14, 2.06, 2.05 (s, 9H, 3CH_3, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.4, 169.8, 169.8 (3C=O, Ac), 87.0 (d, $J_{F,1}$ = 25.6 Hz, C–1), 84.2 (d, $J_{F,2}$ = 194.9 Hz, C-2), 71.3 (C-5), 69.0 (d, $J_{F,3}$ = 18.0 Hz, C-3), 67.5 (d, $J_{4\text{-}F}$ = 7.53 Hz, C-4), 60.7 (C-6), 20.7, 20.7, 20.6 (3CH_3, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –195.0 (ddd, $J_{F,2}$ = 50.1 Hz, $J_{F,3}$ = 9.9 Hz, $J_{F,4}$ = 3.0 Hz, F-2).

3,4,6-Tri-O-benzyl-2-deoxy-2-fluoro-D-galactopyranosyl bromide (7)

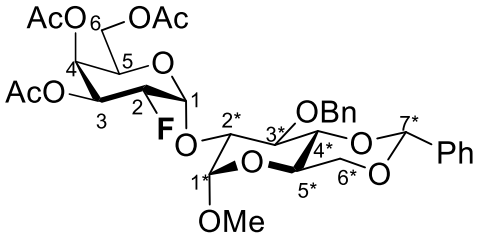


To a solution of 1-acetyl-3,4,6-Tri-O-benzyl-2-deoxy-2-fluoro-D-galactopyranose (199.9 mg, 0.40 mmol, 1.0 eq.) in dry CH_2Cl_2 (11.74 mL, 29.35 mL/mmol) was added 33% HBr in AcOH (0.70 mL, 1.74 mL/mmol). Temperature must be controlled during the HBr addition due is an exothermic reaction. The mixture was stirred at room temperature for 30 minutes. The mixture reaction was then diluted with CH_2Cl_2 and washed with sat. aq. solution of $NaHCO_3$. The organic combined phases were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **7** (183.3 mg, 92 %) as a brownish syrup. The product was used in the next step without further purification.

R_f 0.20 (hexane/EtOAc 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40 – 7.25 (m, 15H, ArH), 6.62 (d, $J_{1,2}$ = 4.1 Hz, 1H, H-1), 4.99 – 4.83 (appm, $J_{F,2}$ = 50.6 Hz, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 4.2 Hz, 1H, H-2), 4.94 (d, $J_{a,b}$ = 11.2 Hz, 1H, CHPh), 4.84 (d, $J_{a,b}$ = 11.9 Hz, 1H, CHPh), 4.70

(d, $J_{a,b}$ = 11.8 Hz, 1H, CHPh), 4.55 (d, $J_{a,b}$ = 11.2 Hz, 1H, CHPh), 4.50 (d, $J_{a,b}$ = 11.8 Hz, 1H, CHPh), 4.43 (d, $J_{a,b}$ = 11.8 Hz, 1H, CHPh), 4.22 (appt, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H-5), 4.08 (td, $J_{F,3}$ = $J_{2,3}$ = 9.4 Hz, $J_{3,4}$ = 2.9 Hz, 1H, H-3), 4.03 (appt, $J_{3,4}$ = 3.0 Hz, 1H, H-4), 3.62 (dd, $J_{6a,b}$ = 9.4 Hz, $J_{5,6a}$ = 7.3 Hz, 1H, H-6a), 3.57 (dd, $J_{6a,b}$ = 9.4 Hz, $J_{5,6b}$ = 5.9 Hz, 1H, H-6b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1, 138.0, 137.7 (C, Ar), 128.7, 128.7 128.5, 128.4, 128.1, 128.0, 127.8 (CH, Ar), 90.0 (d, $J_{F,1}$ = 26.0 Hz, C-1), 88.3 (d, $J_{F,2}$ = 192.6 Hz, C-2), 77.8 (d, $J_{F,3}$ = 15.3 Hz, C-3), 75.4, 74.8 (2 x CH_2Ph), 74.7 (C4), 74.4 (C5), 73.7, 73.4 73.4 (3 x CH_2Ph), 67.6 (C6); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –194.1 (ddd, $J_{F,2}$ = 50.5 Hz, $J_{F,3}$ = 9.2 Hz, $J_{F,4}$ = 4.1 Hz, F-2).

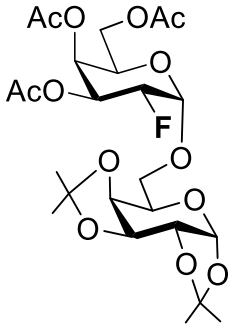
Glycosylation of 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl bromide (6) with acceptor (9)



A solution of **6** (25.5 mg, 0.07 mmol, 1.0 eq) and acceptor **9** (31.5 mg, 0.08 mmol, 1.25 eq.) in dry toluene (1.38 mL, 20 mL/mmol) under an atmosphere of Ar was added 4 Å sieves molecules, allyl tributyltin (34 µL, 0.11 mmol, 1.3 eq.), TfOH (1 drop, 0.02 mmol, 30% molar) and carried out for 60 minutes under general microwave-assisted reaction. The crude was then diluted with EtOAc and washed with sat. aq. solution of $NaHCO_3$ and NaF. The organic combined layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.55 – 7.23 (m, 10H, ArH), 5.60 (s, 1H, H-7*), 5.50 (apptd, ^3J= 10.5 Hz, $J_{3,4}$ = 3.5 Hz, 1H, H-3), 5.29 (apptd, $J_{3,4}$= 3.3 Hz, ^3J = 1.2 Hz, 1H, H-4), 5.23 (d, $J_{F,1}$= 3.7 Hz, 1H, H-1), 4.96 (d, $J_{a,b}$ = 10.6 Hz, 1H, CHPh), 4.88 (d, $J_{F,1}$ = 3.6 Hz, 1H, H-1*), 4.79 (appm, $J_{F,2}$ = 53.3 Hz, $J_{2,3}$ = 10.3 Hz, $J_{1,2}$ = 3.6 Hz, 1H, H-2) 4.70 (d, $J_{a,b}$ = 10.6 Hz, 1H, CHPh), 4.45 (appt, ^3J = 6.5 Hz, 1H, H-5), 4.32 (dd, , ^3J = 10.1 Hz, , ^3J = 4.7 Hz, 1H, H-6a), 4.09 (appt, , $J_{2*,3*}$ = $J_{3*,4*}$ = 9.3 Hz, 1H, H-3*), 3.83 (appdd, $J_{2,3}$ = 9.5 Hz, $J_{2,1}$ = 3.6 Hz, 1H, H-2*), 3.77 (dd, , J = 10.8 Hz, , ^3J = 4.8 Hz, 1H, H-6b), 3.93 – 3.73 (m, 3H, H-5*, H-6*a, H-6b*), 3.65 (appt, $J_{3*,4*}$ = $J_{4*,5*}$ = 9.3 Hz, 1H, H4*), 3.46 (s, 3H, OMe), 2.10, 2.05,1.90 (s, 9H, $3CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.4, 170.1, 169.9 (3C=O, Ac), 138.2, 137.4 (C, Ar), 129.1, 128.7, 128.4, 128.1, 125.1 (CH, Ar), 101.5 (C7*), 97.6 (C1*), 94.6 (d, $J_{F,1}$ = 21.0 Hz, C-1), 85.4 (d, $J_{F,2}$ = 191.1 Hz, C-2), 83.0 (C4*), 77.4 (C3*), 75.9 (CH_2Ph), 75.7 (C2*), 69.1 (C6), 68.6 (C4), 68.0 (C3), 6 6.7 (C5), 62.4 (C5*), 61.3 (C6*), 55.7 (CH_3, OMe), 20.8, 20.7, 20.6 ($3CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –208.83 (ddd, $J_{F,2}$ = 50.0 Hz, $J_{F,3}$ = 10.8 Hz, $J_{F,1}$ = 2.8 Hz, F-2).

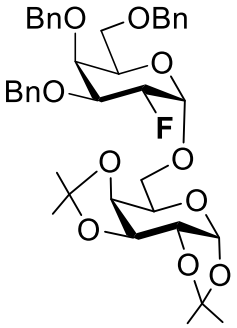
Glycosylation of 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl bromide (6) with acceptor (11)



A solution of **6** (25.0 mg, 0.07 mmol, 1.0 eq) and acceptor **11** (24.8 mg, 0.09 mmol, 1.25 eq.) in dry toluene (1.35 mL, 20 mL/mmol) under an atmosphere of Ar was added 4 Å sieves molecules, allyl tributyltin (38.4 µL, 0.12 mmol, 1.3 eq.), TfOH (1 drop, 0.02 mmol, 30% molar) and carried out for 60 minutes under µW conditions. The crude was then diluted with EtOAc and washed with sat. aq. solution of $NaHCO_3$ and NaF. The organic combined layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –208.2 (ddd, $J_{F,2}$ = 50.5 Hz, ^3J = 11.1 Hz, ^3J = 3.8 Hz, F-2), -206.5 (dd, $J_{F,2}$ = 52.43 Hz, ^3J = 14.1 Hz, F-2).

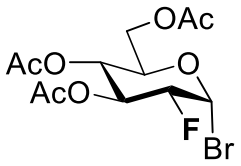
Glycosylation of 3,4,6-Tri-O-benzyl-2-deoxy-2-fluoro-D-galactopyranosyl bromide (7) with acceptor (11)



A solution of **7** (75.8 mg, 0.15 mmol, 1.0 eq) and acceptor **11** (77.2 mg, 0.21 mmol, 1.25 eq.) in dry toluene (3.1 mL, 20 mL/mmol) under an atmosphere of Ar was added 4 Å sieves molecules, allyl tributyltin (81.5 µL, 0.26 mmol, 1.3 eq.), TfOH (1 drop, 0.02 mmol, 30% molar) and carried out for 60 minutes under µW conditions. The crude was then diluted with EtOAc and washed with sat. aq. solution of $NaHCO_3$ and NaF. The organic combined layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –208.0 (ddd, $J_{F,2}$ = 50.0 Hz, ^3J = 9.5 Hz, ^3J = 4.4 Hz, F-2), -204.9 (ddd, $J_{F,2}$ = 51.5 Hz, ^3J = 9.5 Hz, ^3J = 6.3 Hz F-2).

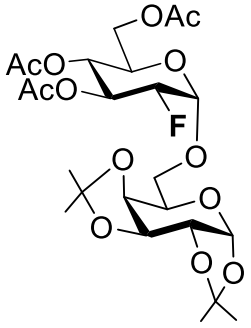
3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (8)



To a solution of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-α/β-D-glucopyranose (498.2 mg, 1.42 mmol, 1.0 eq.) in dry CH_2Cl_2 (10.10 mL, 7.1 mL/mmol) was added 33% HBr in AcOH (4.97 mL, 3.5 mL/mmol). Temperature must be controlled during the HBr addition due it is an exothermic reaction. The mixture was stirred at room temperature for 4 h. The mixture reaction was then diluted with CH_2Cl_2 and washed with sat. aq. solution of $NaHCO_3$. The organic combined phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **8** (397.8 mg, 80 %) as brownish oil. The product was used in the next step without further purification.

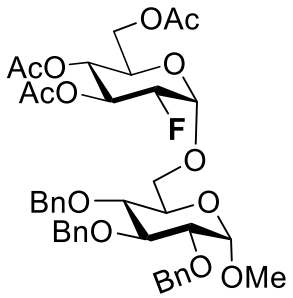
R_f 0.44 (hexane/EtOAc 6:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.50 (dd, $J_{1,2}$ = 4.3 Hz, $J_{F,1}$ = 1.3 Hz, 1H, H-1), 5.57 (appdt, $J_{F,3}$ = 11.3 Hz, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, 1H, H-3), 5.07 (appt, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, 1H, H-4), 4.50 (ddd, $J_{F,2}$ = 49.4 Hz, $J_{2,3}$ = 9.4 Hz, $J_{1,2}$ = 4.3 Hz, 1H, H-2), 4.31- 4.24 (m, 2H, H-5, H-6a), 4.07 (apptd, $J_{6a,b}$ = 3.3 Hz, $J_{5,6b}$ = 1.8 Hz, 1H, H-6b), 2.04, 2.04, 2. 01 (s, 9H, $3CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.4, 169.8, 169.5 (3C=O, Ac), 86.3 (d, $J_{F,2}$ = 199.3 Hz, C-2), 85.6 (d, $J_{F,1}$ = 25.0 Hz, C–1), 72.2 (C-5), 71.1 (d, $J_{F,3}$ = 18.7 Hz, C-3), 66.6 (d, $J_{F,4}$ = 7.4 Hz, C-4), 60.9 (C-6), 20.7, 20.7, 20.6 ($3CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –188.5 (dd, $J_{F,2}$ = 49.3 Hz, $J_{F,3}$ = 11.3 Hz, F-2).

Glycosylation of 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (8) with acceptor (11)



A solution of **8** (59.5 mg, 0.16 mmol, 1.0 eq) and acceptor **11** (74.8 mg, 0.20 mmol, 1.25 eq.) in dry toluene (3.2 mL, 20 mL/mmol) under an atmosphere of Ar was added 4 Å sieves molecules, allyl tributyltin (81.7 µL, 0.26 mmol, 1.3 eq.), TfOH (1 drop, 0.02 mmol, 30% molar) and carried out for 60 minutes under µW conditions. The crude was then diluted with EtOAc and washed with sat. aq. solution of $NaHCO_3$ and NaF. The organic combined layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

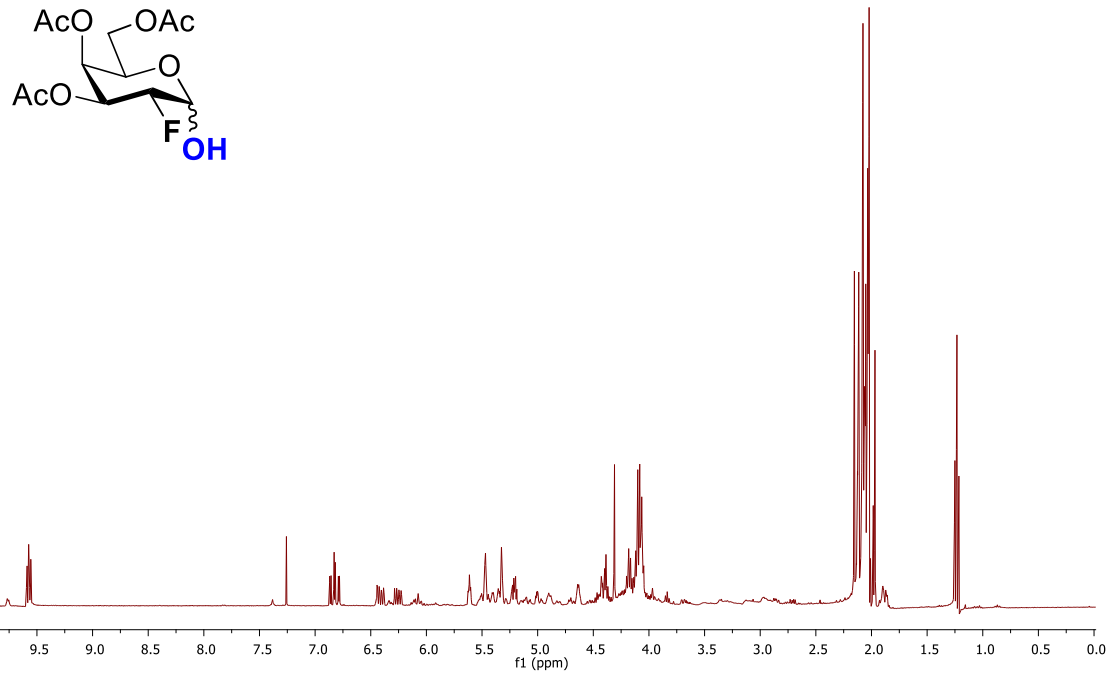
Glycosylation of 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (8) with acceptor (12)



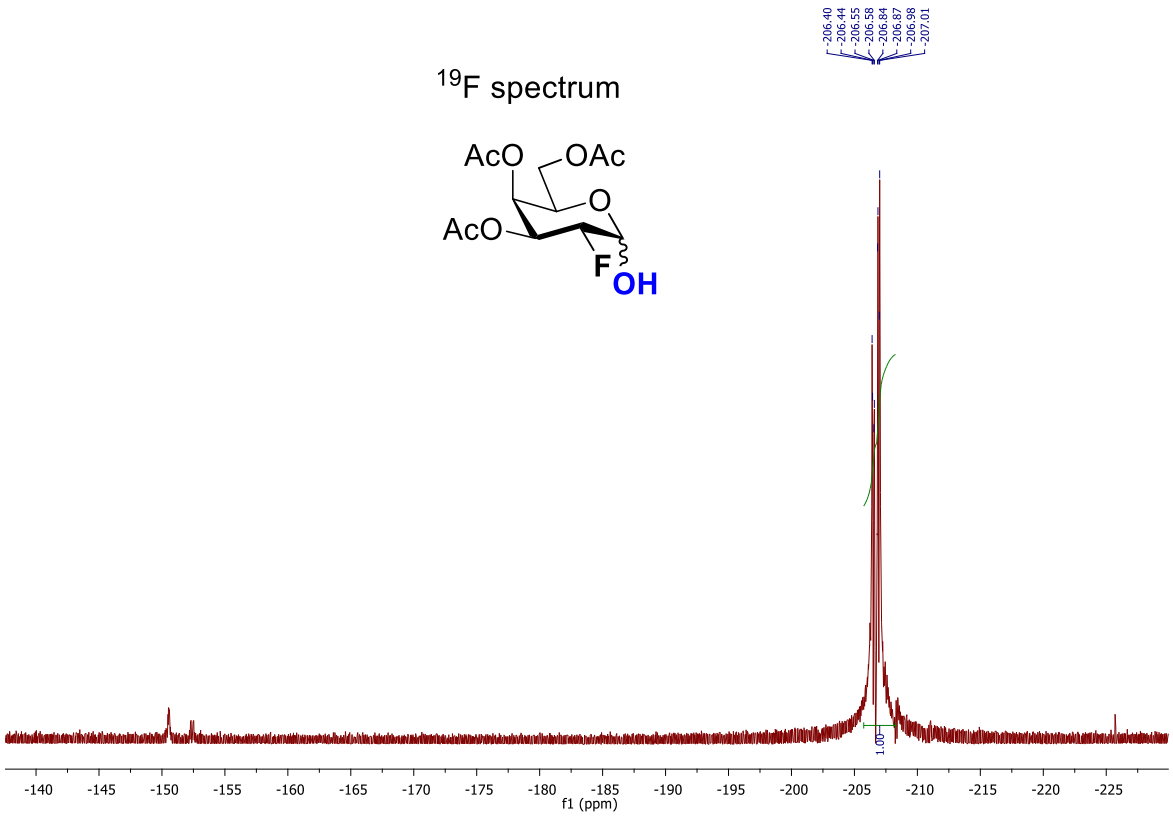
A solution of **8** (60.0 mg, 0.16 mmol, 1.0 eq) and acceptor **12** (98 mg, 0.21 mmol, 1.25 eq.) in dry toluene (3.2 mL, 20 mL/mmol) under an atmosphere of Ar was added 4 Å sieves molecules, allyl tributyltin (84.6 µL, 0.27 mmol, 1.3 eq.), TfOH (5.5 µL, 0.06 mmol, 30% molar) and carried out for 60 minutes under µW conditions. The crude was then diluted with EtOAc and washed with sat. aq. solution of $NaHCO_3$ and NaF. The organic combined layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

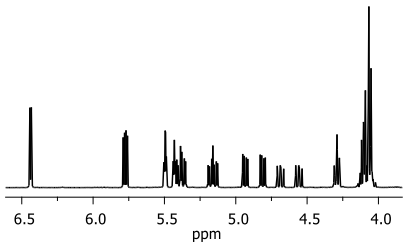
6. Annex

^{1}H spectrum

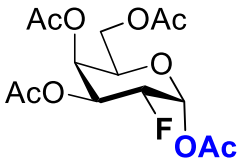


^{19}F spectrum

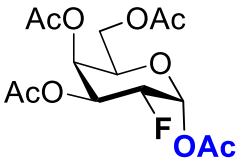


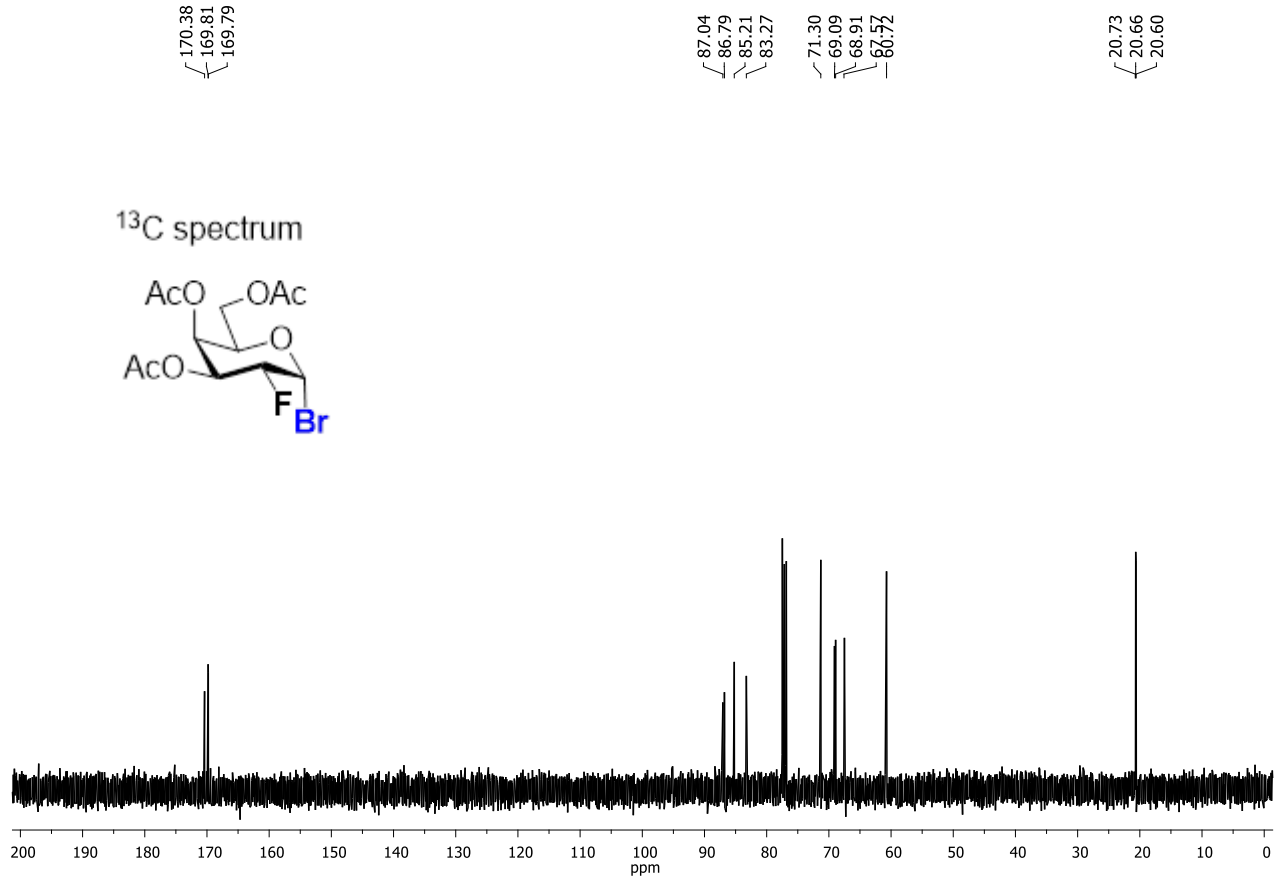


^{1}H spectrum



^{13}C spectrum

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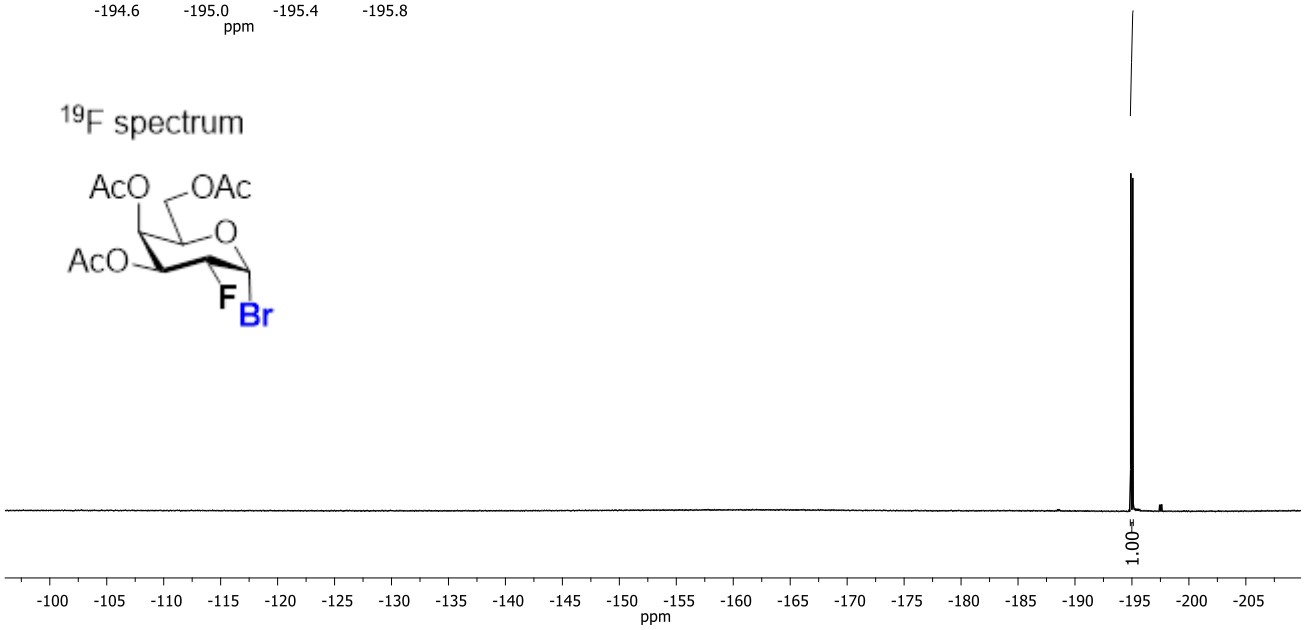
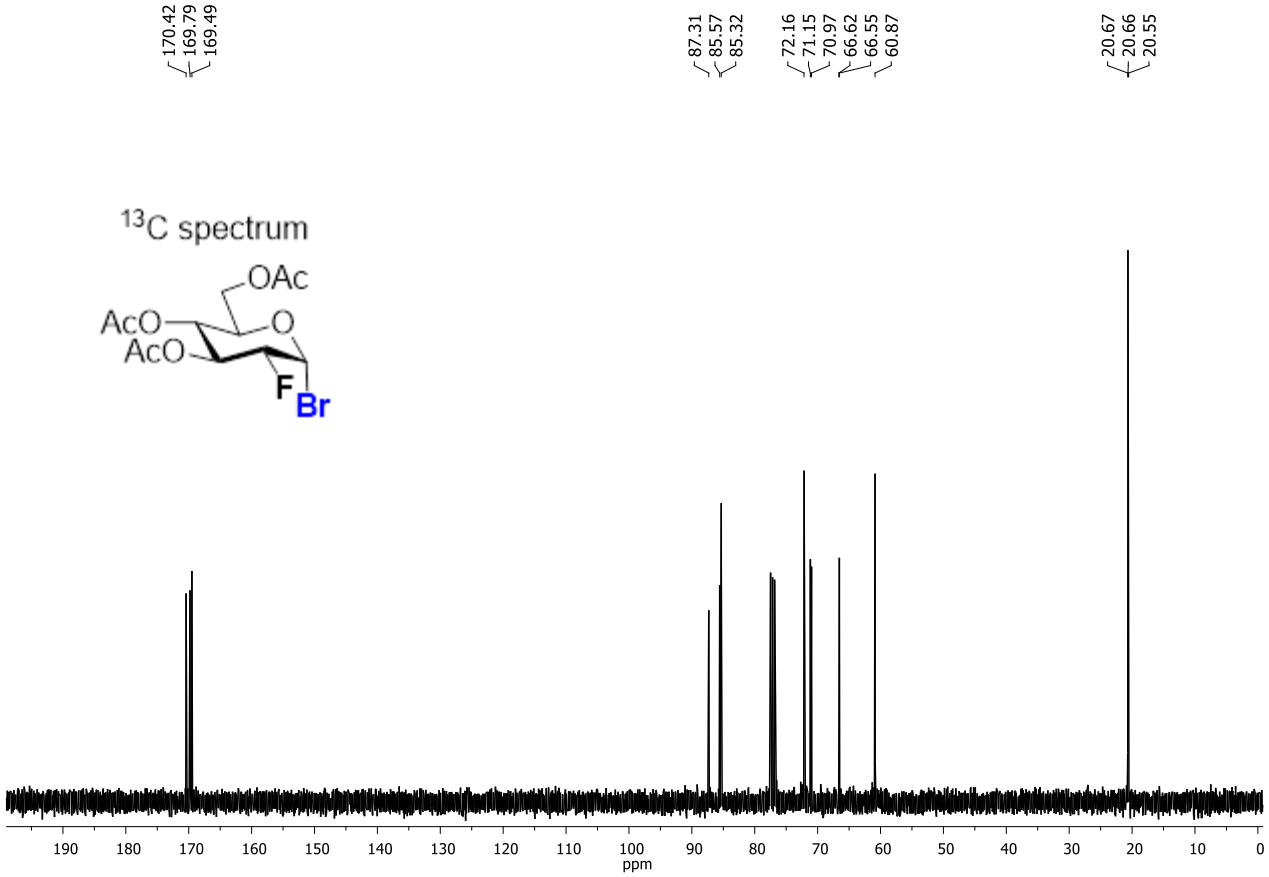
169.79
87.04
86.79
85.21
83.27
71.30
69.09
68.91
67.52
60.52
20.73
20.66
20.60
13C spectrum
AcO
OAc
O
AcO
F
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


-194.90
-194.91
-194.92
-194.93
-195.03
-195.04
-195.06
-195.07
1.00
-194.6
-195.0
-195.4
-195.8
ppm


19F spectrum
AcO
OAc
O
AcO
F
Br
1.00
-100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205
ppm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85.32
72.16
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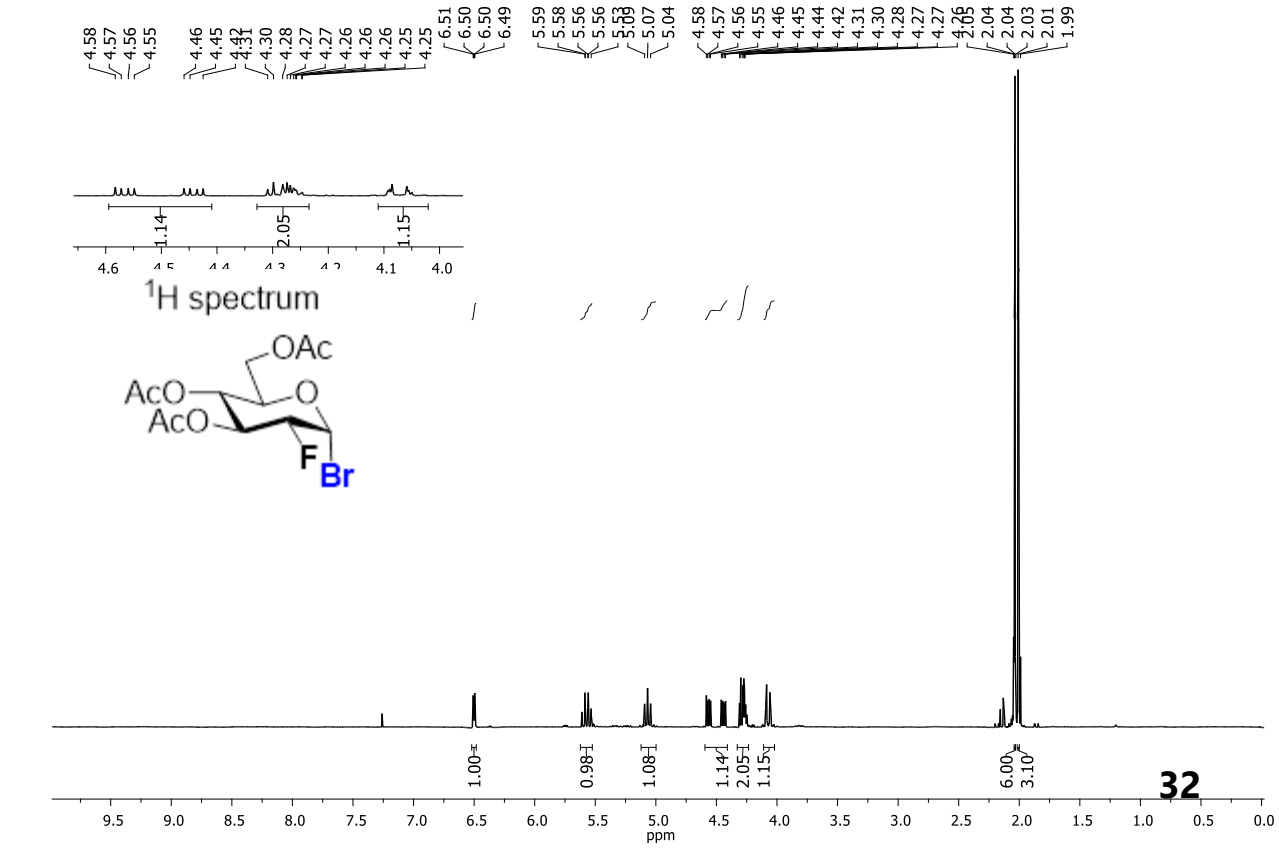
66.62
66.55
60.87
20.67
20.66
20.55
13C spectrum
OAc
AcO
AcO
O
F
Br
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm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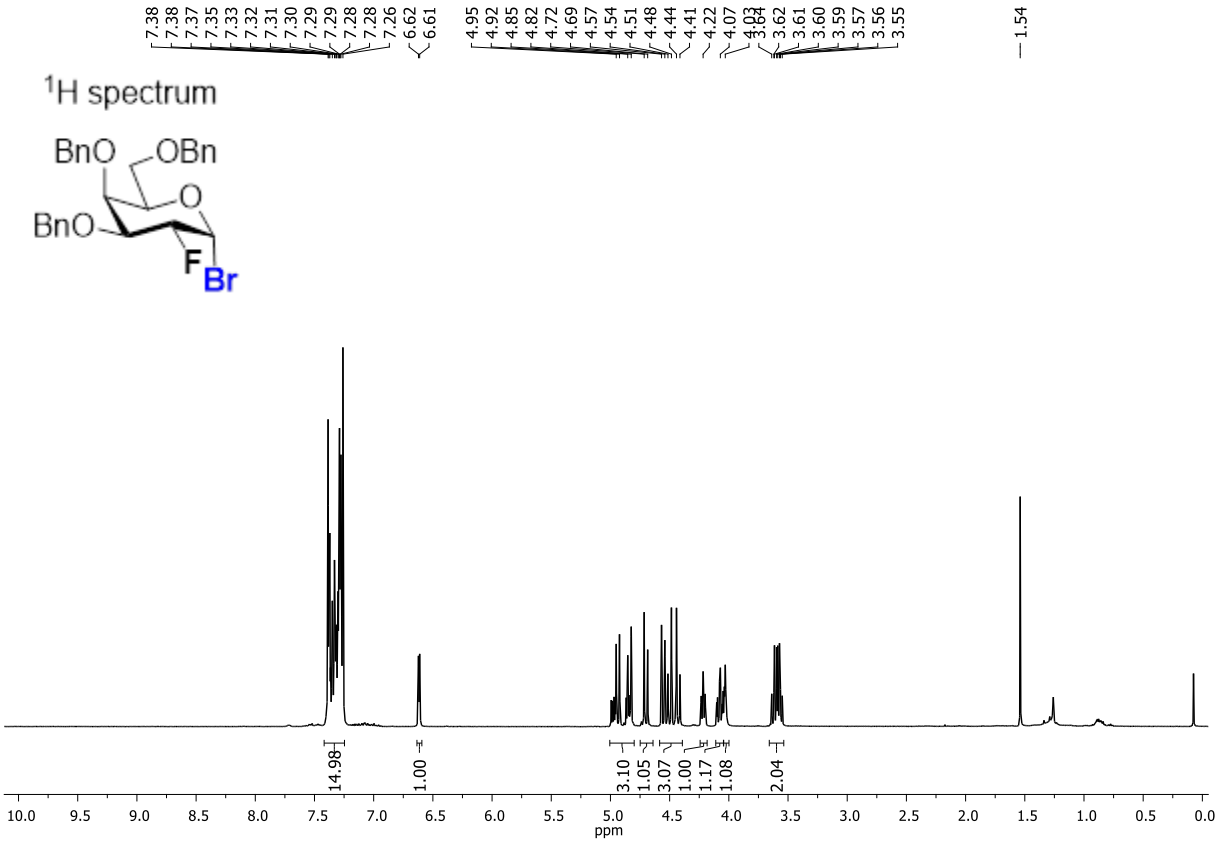
5.56
5.07
5.04
2.04
2.03
2.01
1.99
1.14
2.05
1.15
4.6
4.1
4.0
1H spectrum
OAc
AcO
AcO
O
F
Br
1.00
0.98
1.08
1.14
2.05
1.15
6.00
3.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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4.22
4.07
4.03
3.84
3.62
3.61
3.60
3.59
3.57
3.56
3.55
1.54
1H spectrum
BnO
OBn
O
BnO
F
Br
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1.00
3.10
1.05
3.07
1.00
1.17
1.08
2.04
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6.5
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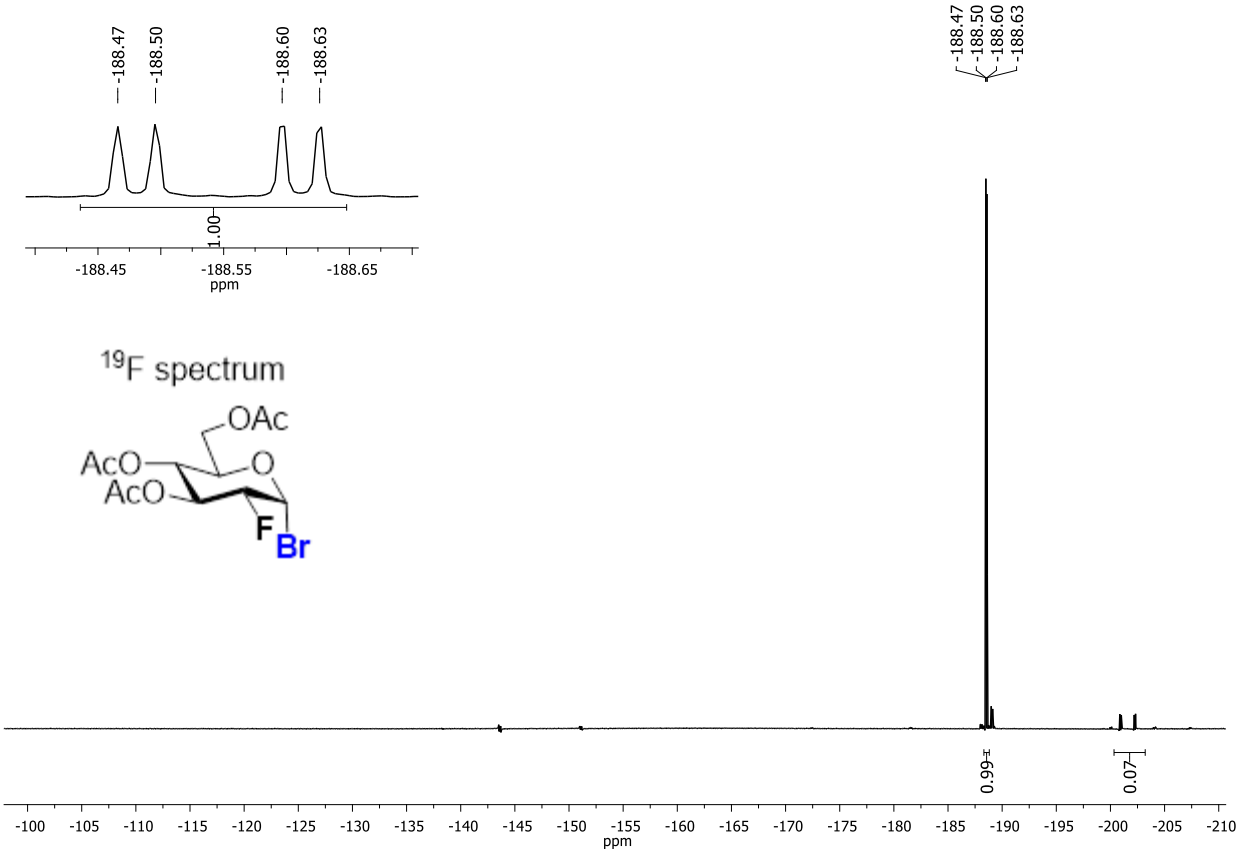
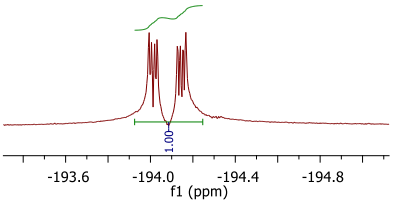
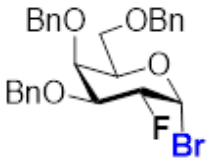
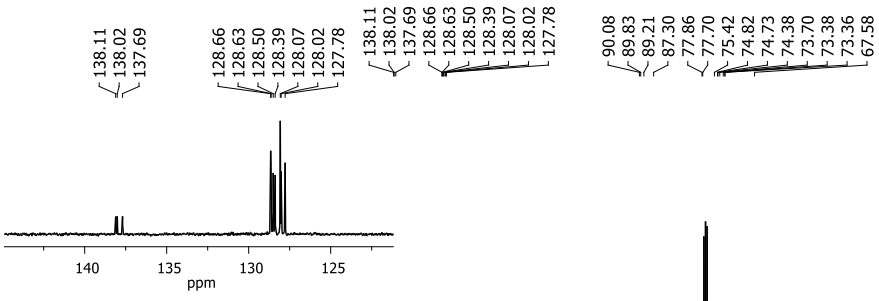
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


-188.47
-188.50
-188.60
-188.63
1.00
-188.45
-188.55
-188.65
ppm
19F spectrum
OAc
AcO
O
AcO
F
Br
0.99
0.07
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
ppm

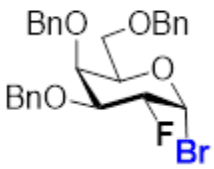


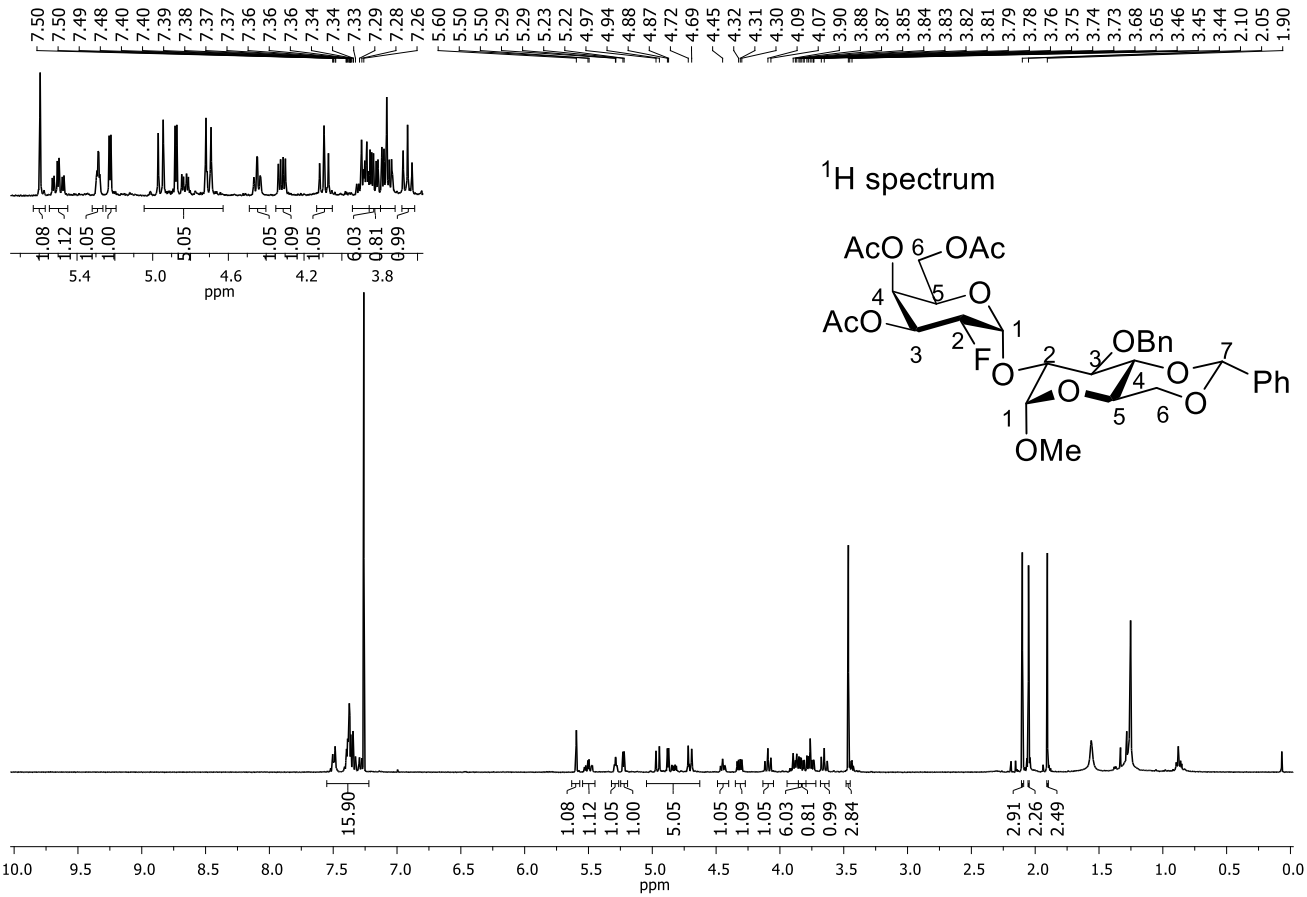
^{19}F spectrum

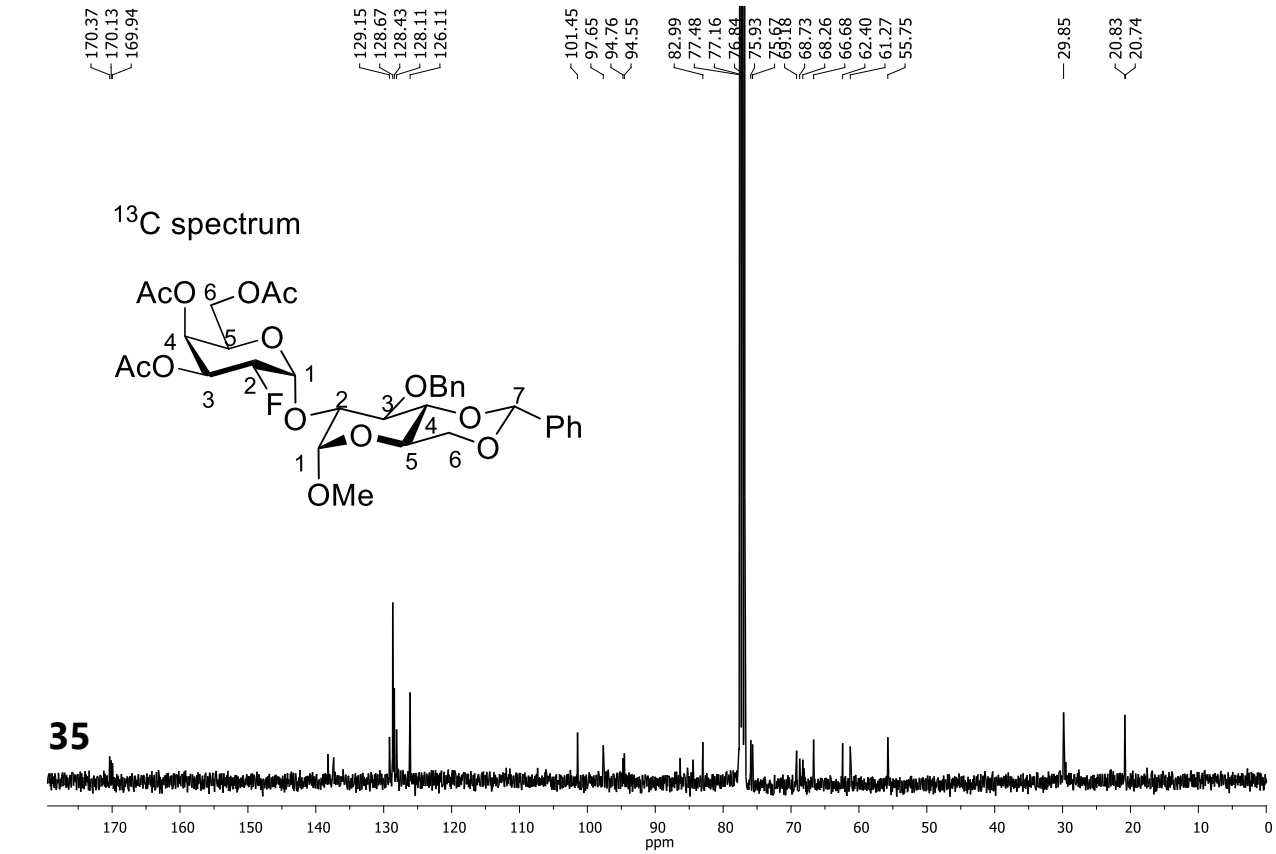


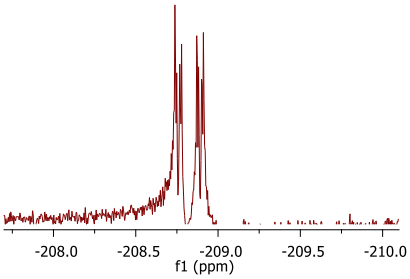


^{13}C spectrum

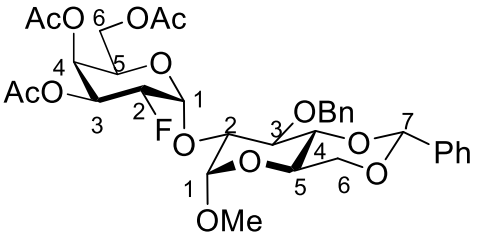


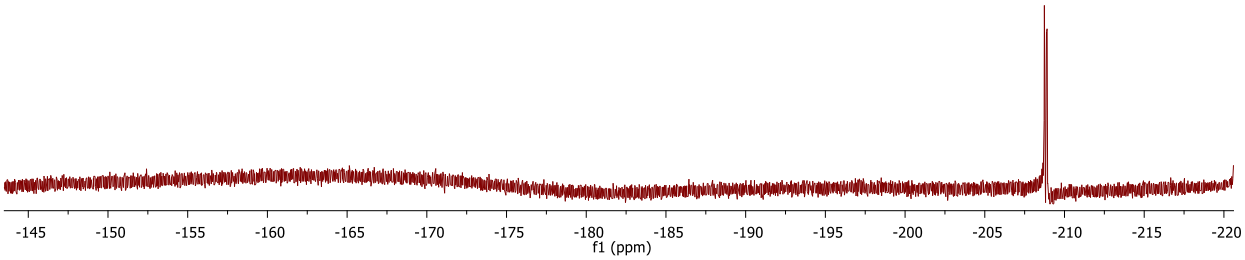

^{1}H spectrum
AcO
OAc
AcO
F
OBn
Ph
OMe
ppm

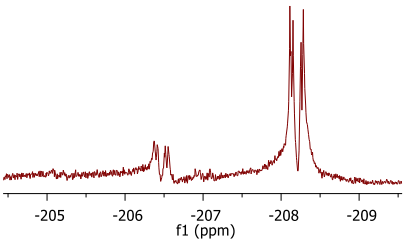

^{13}C spectrum
AcO
OAc
AcO
F
OBn
Ph
OMe
ppm



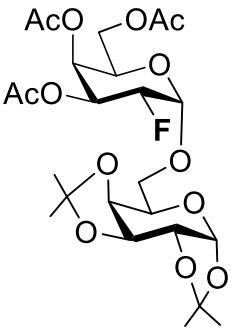
^{19}F spectrum

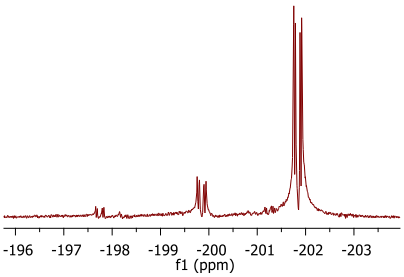




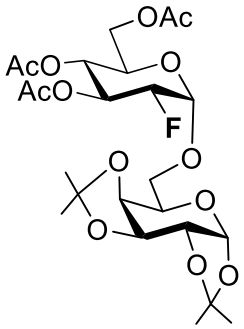


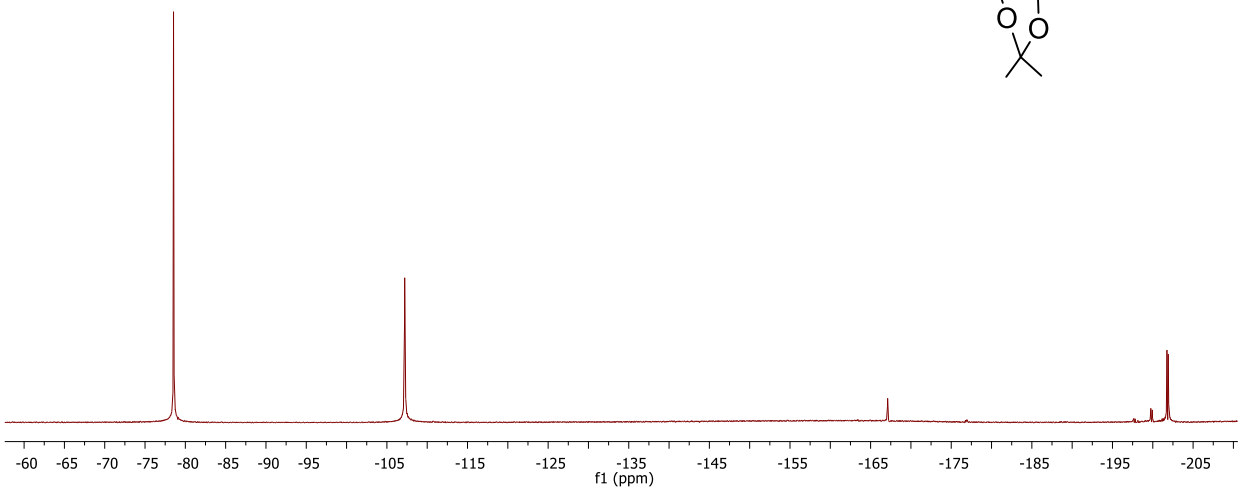
^{19}F spectrum

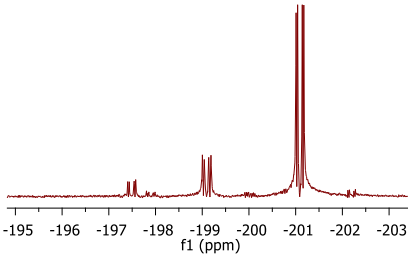




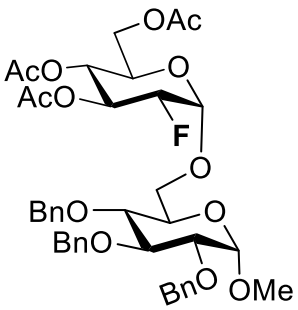
^{19}F spectrum







^{19}F spectrum



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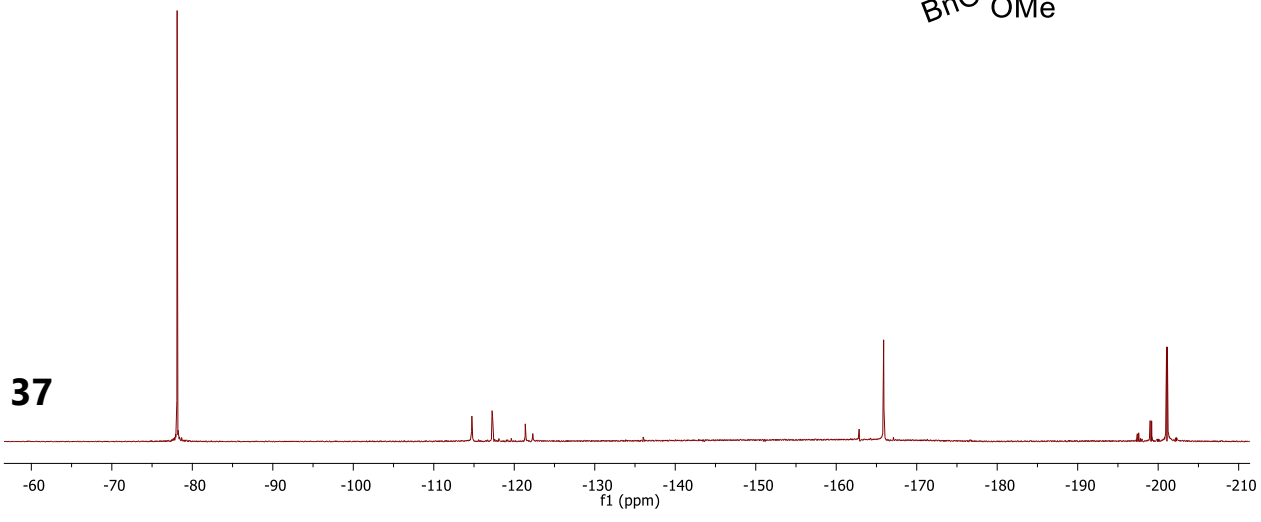

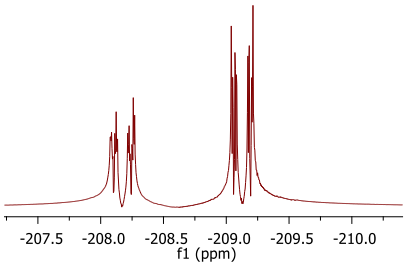

^{19}F spectrum