Fluorine-Containing Glycomimetics

Subjects: Chemistry, Medicinal

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Glycomimetics, which are synthetic molecules designed to mimic the structures and functions of natural carbohydrates, have been developed to overcome the limitations associated with natural carbohydrates. The fluorination of carbohydrates has emerged as a promising solution to dramatically enhance the metabolic stability, bioavailability, and protein-binding affinity of natural carbohydrates.

glycomimetics fluorination synthesis

1. Introduction

Carbohydrates play major structural, physical, and biological roles in organisms. They often form complex and diverse glycans on the cell surface by interacting with protein and lipid scaffolds. The glycan molecules bind to proteins and actively participate in various biological processes, such as embryogenesis, adhesion, immunity, inflammation, cancer metastasis, and host–pathogen interactions [1][2][3]. The composition of glycans changes during cell differentiation and tissue development. Disease states and the degree of inflammation also influence the compositional changes. These changes can be attributed to the altered degree of the expression of glycosidase and/or glycosyltransferase (GT) in cells. The generation of this dynamic expression is an integral part of the cell-to-cell communication process, and it can potentially provide new targets for disease treatment. Carbohydrate–protein binding is achieved by exploiting low-energy interactions (such as hydrogen bonding, salt bridges, and metal chelation), which cannot compensate for the high enthalpy cost of the desolvation of polar substrates and shallow protein-binding sites. The high polar surface area of natural carbohydrates hinders the passive penetration of the molecules into the intestinal membrane, making them non-bioavailable orally. It has also been observed that natural carbohydrates exhibit inherently poor pharmacokinetic properties, limiting their therapeutic potential [4][5].

Natural carbohydrates can be modified to improve their drug-like properties, and “carbohydrate-like compounds” can be designed to mimic the structure and function of natural carbohydrates to improve their affinity, pharmacokinetic properties, and bioavailability [6][7]. Fluorine, which exhibits unique properties, has been widely used in drug design and development. Its high electronegativity makes it a powerful tool for modulating the pKa and electron density of the groups present in its proximity, and it can serve as a considerable element to control molecular conformation [8][9][10]. Pharmaceuticals containing fluorine exhibit the property of tunable lipophilicity and increased metabolic stability. It is noteworthy that the oxidative metabolism of these molecules can be prevented. The strategy of the fluorination of carbohydrates has long been used to investigate protein-carbohydrate and carbohydrate-carbohydrate interactions. This method has been used to investigate the contributions of individual sugar alcohol groups [11][12][13] or design mechanism-based inhibitors [14][15]. The excellent NMR (nuclear magnetic

resonance) properties of the ^{19}F nucleus have been analyzed to study protein-carbohydrate binding at the molecular level [16][17][18][19][20][21][22][23][24]. The method of fluoridation is also used in drug discovery programs and to develop synthetic carbohydrate vaccines [25][26][27][28][29][30]. Fluorination could optimize the physicochemical properties, absorption ability, and distribution properties of natural sugars, and the introduction of fluorine can also help improve the binding affinity and pharmacokinetic properties of natural sugars [31][32].

2. Synthesis of Fluorine-Containing Glycomimetics

In essence, the fluorine-based carbohydrate modification method is followed to substitute various atoms on the molecular skeleton with fluorine atoms or fluorine-containing groups such as polyfluorene. The fluorinating reagents used for fluorination include deoxyfluorination agents: DAST (diethylaminosulfur trifluoride, **1**) [33][34]; nucleophilic fluorination agents: TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate, **2**) [35]; TBAF (tertbutylammonium fluoride, **3**) [36]; MF_n (Metal fluorides, **4**) [37]; KHF_2 (**5**) [38]; anhydrous hydrogen fluoride system (**6**) [39]; electrophilic fluorination agents: SelectFluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), also abbreviated as F-TEDA-BF_4, **7**) [40]; NFSI (N-fluorobenzenesulfonimide, **8**) [41]; etc. (**Figure 1**). With the use of these fluorinating reagents above, the reactions for fluorination of sugars could be divided into nucleophilic reactions, electrophilic addition reactions, radical reactions, metal-catalyzed reactions, and de novo synthesis with fluorine-containing blocks.

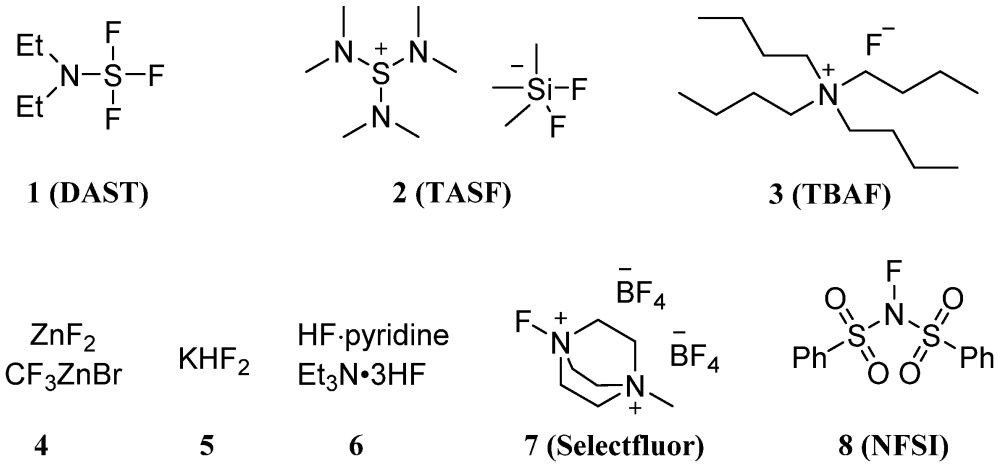

Figure 1. Typical fluorinating reagents: **1**, DAST (diethylaminosulfur trifluoride); **2**, TASF ((tris(dimethylamino)sulfonium difluorotrimethylsilicate), **3**, TBAF (tertbutylammonium fluoride); **4,** Metal fluorides; **5**, KHF_2; **6**, anhydrous hydrogen fluoride system; **7**, SelectFluor, (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) and **8**, NFSI (N-fluorobenzenesulfonimide).

2.1. Fluorination of Carbohydrates via Nucleophilic Fluorination

A large number of fluorine-containing carbohydrates are synthesized via nucleophilic reactions with fluoride ions. Depending on the reaction condition, fluoride ions can act as good nucleophilic reagents in polar non-protonic solvents [42]. Currently, fluorinated reagents such as DAST (diethylaminosulfur trifluoride), TASF

(tris(dimethylamino)sulfonium difluorotrimethylsilicate), KHF_2, etc., are mainly used to provide nucleophilic fluorine atoms, which subsequently replace the hydroxyl or sulfonate groups on the sugar ring to obtain fluorinated sugars. These are the most popular methods for the preparation of fluorinated carbohydrates [43][44][45][46] (**Figure 2**a–c). The fluorination of the equatorial hydroxyl group obtained **10** with fluorine nucleophilic substituted in the axial position, which undergoes an S_N2 reaction mechanism. The stereo-configuration of the fluorination product is generally flipped from the starting material.

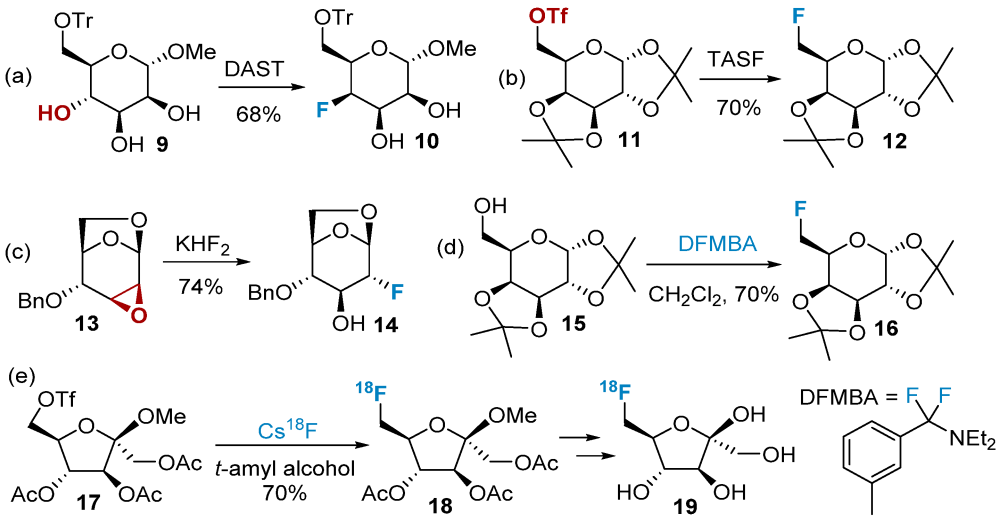

Figure 2. Nucleophilic fluorination of carbohydrates using different fluorinating reagents: (**a**) DAST as fluorinated reagents, (**b**) TASF as fluorinated reagents, (**c**) KHF_2 as fluorinated reagents, (**d**) DFMBA as fluorinated reagents, (**e**) $Cs^{18}F$ as fluorinated reagents.

While reagents like DAST and TASF have been traditionally used in fluorination reactions, researchers have encountered certain drawbacks associated with their use. For example, protecting group migration can be a significant issue in some fluorination reactions, leading to reduced yields or even the absence of the desired target product [47]. DFMBA is considered milder compared to reagents like DAST and exhibits improved compatibility with various protecting groups [48][49], such as acetyl, methyl, silyl, benzyl, etc. (**Figure 2**d). In addition to the above-mentioned organic fluorinating agents, other inorganic fluorine-containing compounds, such as hydrogen fluoride, TBAF, CsF, AgF, iodine–fluorine compounds, etc., can also provide nucleophilic fluoride ions [45]. Cheeseman's group successfully synthesized fluorinated furanose **18** using CsF as the fluorinating agent. This method allowed for the introduction of fluorine-18 into the substrate. After deprotection, the resulting product **19** was found to be suitable as a contrast agent for breast cancer (**Figure 2**e).

Polyfluorinated carbohydrates have gained attention due to their unique properties and potential applications in medicinal chemistry. The positional combinations for deoxy polyfluorination of pentoses and hexoses have been extensively studied in the context of nucleophilic fluorination reactions. Epoxide opening with fluoride sources is a versatile method for introducing fluorine in a regioselective manner. Thus, 2,3,4-trideoxy-2,3,4-trifluoro-D-glucopyranose (**24**) can be synthesized selectively, utilizing the regioselective opening of the epoxide, displacement of the triflate intermediate using $Et_3N{\cdot}3HF$, and subsequent nucleophilic fluorination with DAST

(**Figure 3**). The synthesis of polyfluorinated carbohydrates, including ketosugars (such as sialic acids), aminosugars, and nucleosides, with controlled fluorine introduction at specific positions has garnered significant attention in recent years. This area of research has been recently reviewed [50].

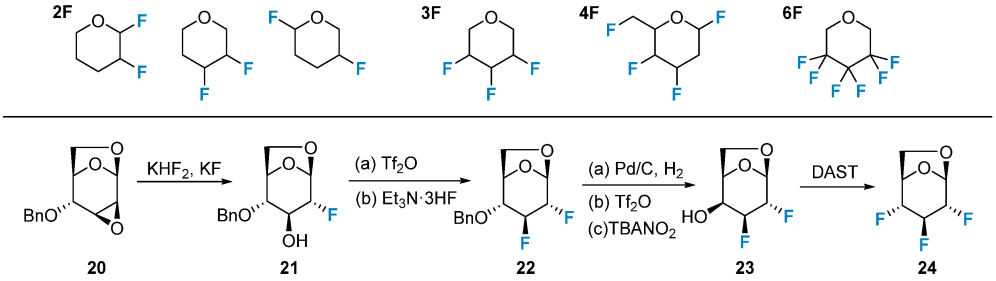

Figure 3. Polyfluorination of carbohydrates via iterative nucleophilic reactions and the synthesis of 2,3,4-trifluoro-glucopyranose.

The nucleophilic reaction of carbonyl-containing glycans with difluoroalkylation reagents produces difluorinated modification of glycans. This type of reaction was first reported by Bobek et al. in 1977 [51]. They utilized a DAST reagent to modify furanose **25** by introducing a difluoromethyl group, resulting in the formation of product **26** (**Figure 4**a). However, the yield of this reaction was low, and its applicability was limited, particularly for pyranose. In 2009, Jiménez-Barbero et al. [52] successfully synthesized difluorine-modified carboglycosides **28** using the Deoxo-Fluor reagent (**Figure 4**b). CBr_2F_2 is another commonly used reagent for difluorination, often in conjunction with additional phosphorus-containing small molecules to generate the active intermediate carbene. Slawin's group [53] employed this method to successfully synthesize compound **30** (**Figure 4**c), which, upon reduction, produced the extracyclic difluoromethyl glycosides **31**.

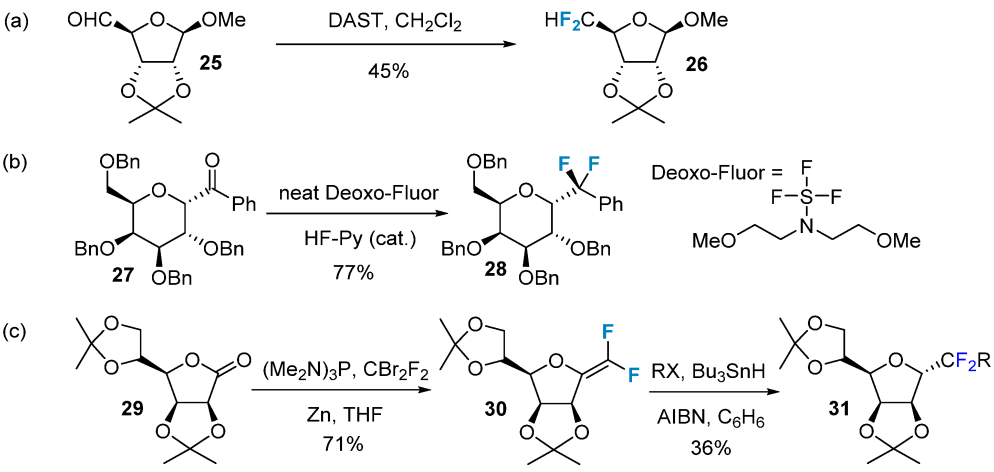

Figure 4. Difluorination of carbohydrates via nucleophilic reactions. (**a**) nucleophilic difluoroalkylation via DAST, (**b**) nucleophilic difluoroalkylation via Deoxo-Fluor, (**c**) nucleophilic difluoroalkylation via CBr_2F_2.

In recent years, newly developed difluoroalkylation reagents have emerged as effective tools for the difluorinated substitution modification of sugars. One commonly used and cost-effective difluoroalkylation reagent is $BrCF_2CO_2Et$ [54]. Quirion's group [55] utilized the Reformatsky reaction to efficiently and smoothly introduce the

CF_2CO_2Et moiety into lactone **32**, yielding the exocyclic difluorocarboside **33** (**Figure 5**a). This reaction exhibits high stereoselectivity and directly forms the β-mannose carboglycoside bond. Another reagent frequently employed for introducing 2-(ethoxycarbonyl)difluoromethyl is difluoroenol silyl ether. Quirion's group [56], in 2009, employed this reagent in conjunction with boron trifluoride ether as a catalyst to couple with compound **34**, resulting in the formation of exocyclic difluorocarboside **35** (**Figure 5**b).

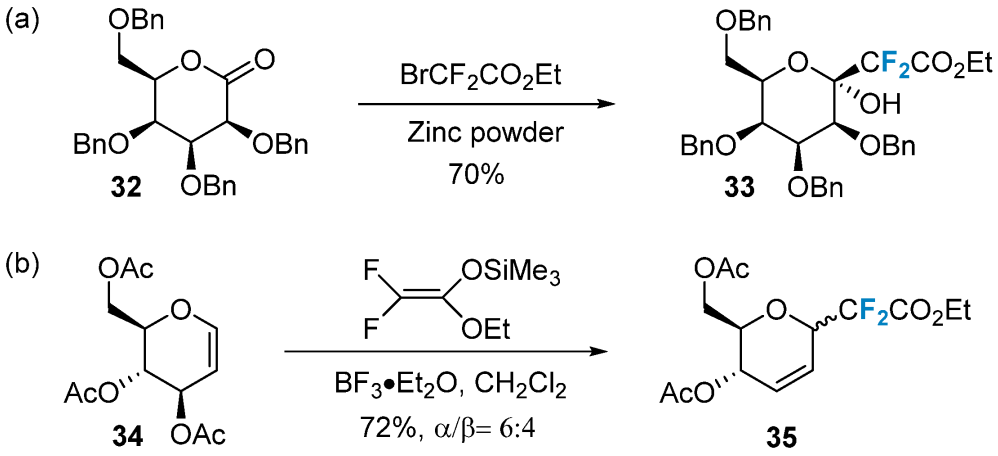

Figure 5. Difluoroalkylation of sugars via nucleophilic reactions. (**a**), difluoroalkylation via $BrCF_2CO_2Et$, (**b**) difluoroalkylation via CF_2CO_2Et.

The trifluoromethylation of carbohydrates can be achieved via the nucleophilic addition of trifluoromethyl groups to aldehydes or ketones. A commonly employed nucleophilic trifluoromethyl reagent is $TMSCF_3$. This reagent enables the direct introduction of trifluoromethyl to the carbonyl carbon in the sugar structure. For instance, $TMSCF_3$ was used to treat lactone **36**, leading to the formation of compound **37** (**Figure 6**a) [57]. Moreover, $TMSCF_3$ can also react with other carbonyl-containing sugars and subsequently undergo the Barton–McCombie dehydroxylation reaction to produce the corresponding trifluoromethyl-modified carbohydrates (**Figure 6**b,c) [58].

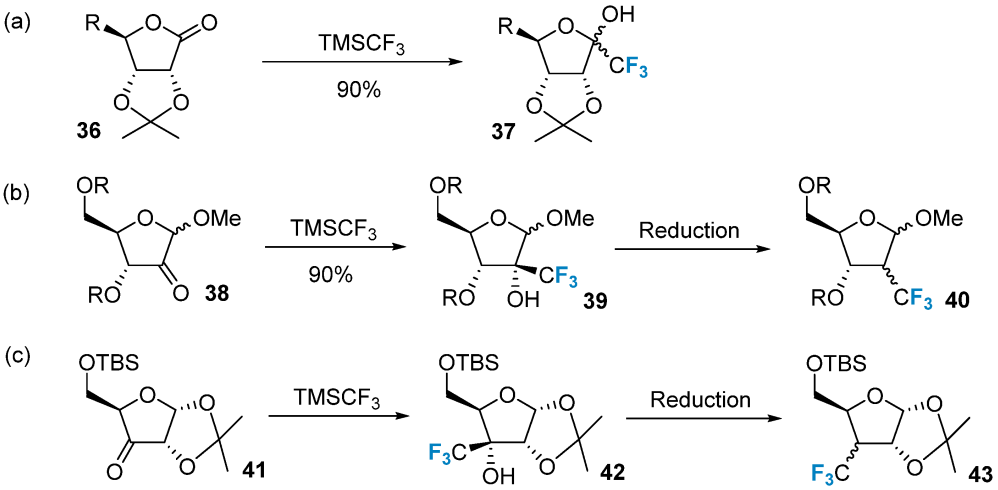

Figure 6. Trifluoromethylation of sugars via nucleophilic reactions. (**a**) trifluoromethylation via the nucleophilic addition of $TMSCF_3$ to ketone on C-1, (**b**) trifluoromethylation of ketone on C-2, (**c**) trifluoromethylation of ketone on

C-3.

2.2. Fluorination of Carbohydrates via Electrophilic Addition Reactions

In contrast to nucleophilic reactions, electrophilic addition reactions predominantly involve glycals. The commonly utilized reagents for these reactions are N-F reagents and F-O reagents. N-F reagents are well established, commercially available, and have proven their usefulness in numerous important reactions [59]. Established and readily available N-F reagents have demonstrated their utility in a variety of important reactions [59]. For instance, the Selectfluor reagent has proven to be a highly efficient and mild reagent for fluorination, surpassing the effectiveness of the DAST reagent. In 1997, Wong's group [60] discovered that the Selectfluor reagent could be used for the one-pot synthesis of 2-fluoroglycosides (**Figure 7**a). The resulting product, 2-fluoro-2-deoxyglycoside **46**, was utilized as a probe to investigate the catalytic mechanisms of glycosidases and glycosyltransferases. In that same year, Dax's group [61] successfully achieved electrophilic addition to glycals using another N-F reagent known as N-fluorobenzenesulfonamide (**Figure 7**b).

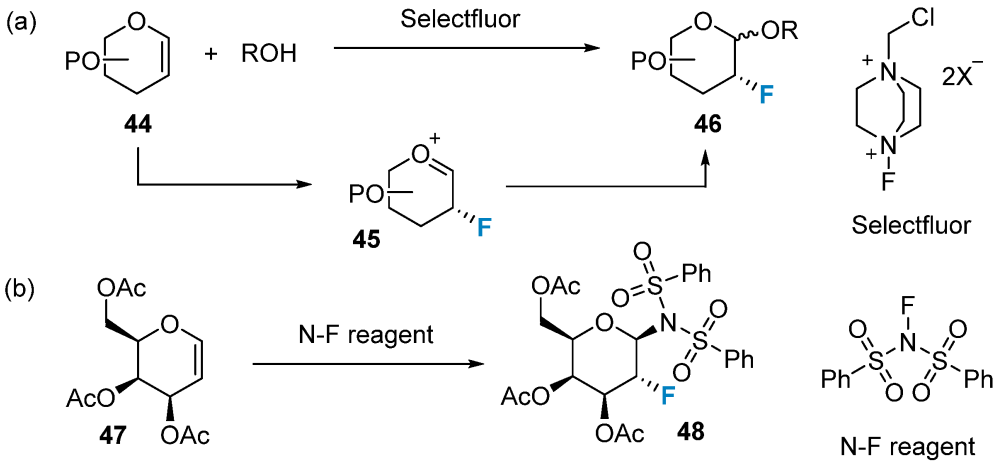

Figure 7. Monofluorination of glycals using N-F reagents. (**a**) monofluorination via Selectfluor, (**b**) monofluorination via N-fluorobenzenesulfonamide.

In addition to N-F-type fluorination reagents, certain O-F-type reagents can also be employed in the electrophilic addition reactions of glycals. In 1970, Adamson's group [62] first synthesized 2-Fluoro-2-deoxy-D-glucose **49** using CF_3OF (**Figure 8**). Since then, efforts have been made to improve this method. In 2006, Schrobilgen's group [63] achieved the introduction of a fluorine atom into C-2 of glucal **34** using $AcO^{18}F$ (**Figure 8**). Interestingly, contrary to their expectations, they discovered that the resulting product was not 2-fluoro-2-deoxy-D-glucose but rather 2-fluoro-2-deoxy-D-allose. The researchers proposed that the acetyl groups at positions C-3 and C-4 were involved in the reaction, giving rise to an intermediate that caused a configuration change in the hydroxyl group at position C-3. Leveraging this method, they successfully synthesized 2-fluoro[^{18}F]-2-deoxy-D-allose **50**.

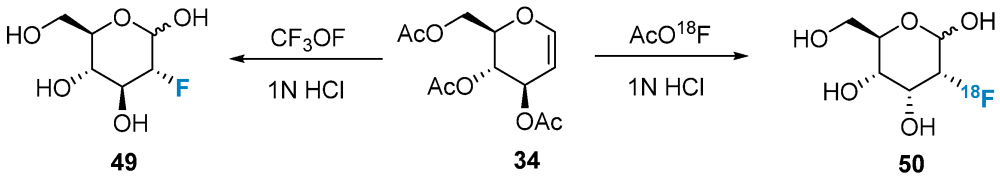

Figure 8. Monofluorination of glycals using O-F reagents.

2.3. Fluorination of Carbohydrates via Radical Reactions

In addition to nucleophilic and electrophilic reactions, radical reactions have also been employed in the fluorination of sugars. In 2020, Li's group [64] successfully introduced a fluorine atom at the C-5 position of compound **56** using an Ag(II)-initiated radical reaction (**Figure 9**). The authors observed that the carbon atom at the C-6 position underwent an elimination reaction. They proposed a potential reaction mechanism as follows: Ag(II) initiates a radical reaction, leading to the transformation of the C-6 hydroxyl group of the sugar into the oxygen radical intermediate **57**. Subsequently, intermediate **58** is formed via β-scission, followed by the fluorination of intermediate **58** to yield the final product **59**. By utilizing this strategy, the group successfully synthesized a range of rare sugars and accomplished the total synthesis of *Clostridium jejuni* tetrasaccharides [65].

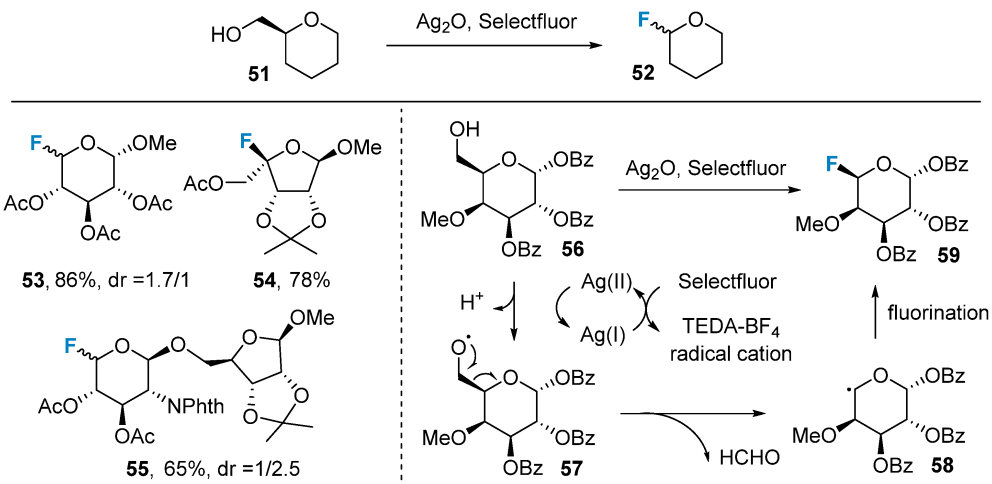

Figure 9. Dehydroxymethylative fluorination of sugars via Ag(II)-initiated radical reaction.

Based on the previous work, Li's group further advanced the method for decarboxylative fluorination of uronic acids, employing a silver radical pathway [66] (**Figure 10**a). This reaction demonstrates superior substrate scope and compatibility with functional groups compared to dehydroxymethylative fluorination. Notably, it successfully transforms sugars containing benzyl groups and a hexp-(1-4)-hexp moiety. In a recent development, Li's group established a protocol for the organophotocatalytic synthesis of glycosyl fluorides without the addition of silver species. This method relies on 9-mesityl-10-methyl-acridinium (Mes-Acr$^+$)-mediated oxidative decarboxylative fluorination of uronic acids [67] (**Figure 10**b). The potential of this method is promising in the synthesis of fluorinated nucleosides.

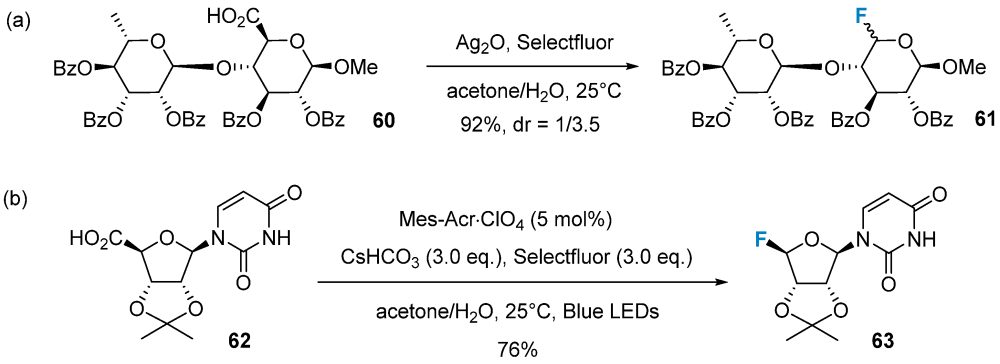

Figure 10. Decarboxylative fluorination of uronic acids via radical reaction. (**a**) decarboxylative fluorination via silver radical pathway, (**b**) Mes-Acr$^+$-mediated oxidative decarboxylative fluorination.

Difluorinated sugars can also be synthesized via the radical addition to glycals. Commonly employed radical initiation conditions include BEt_3 and metal catalysis, and others. Quirion's group [68] achieved the successful introduction of 2-(ethoxycarbonyl)difluoromethyl into glycal **64** using BEt_3 as a radical initiator, resulting in the formation of CF_2-glycoside **65** (**Figure 11**).

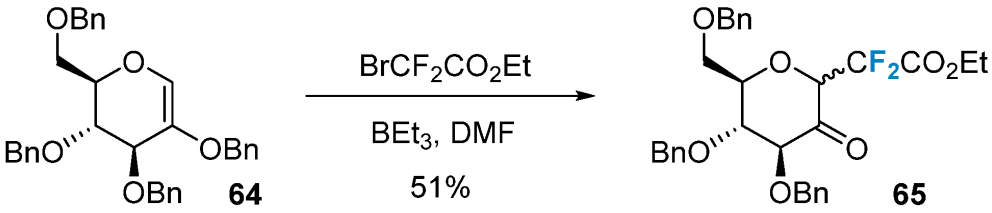

Figure 11. Difluoromethylation of glycals via radical reaction.

Radical addition reactions can also be employed in the preparation of trifluoromethyl-modified sugars. In 2015, Ye's group [69] developed a photocatalytic C-H trifluoromethylation method using glycal **66** as substrates and Umemoto reagent as a trifluoromethyl source. This method exhibits mild reaction conditions, excellent compatibility with various protecting groups (such as acetyl, benzyl, and p-methoxybenzyl), and applicability to glycals featuring different types of sugars (such as glucose, galactose, rhamnose, arabinose, and lactose) (**Figure 12**).

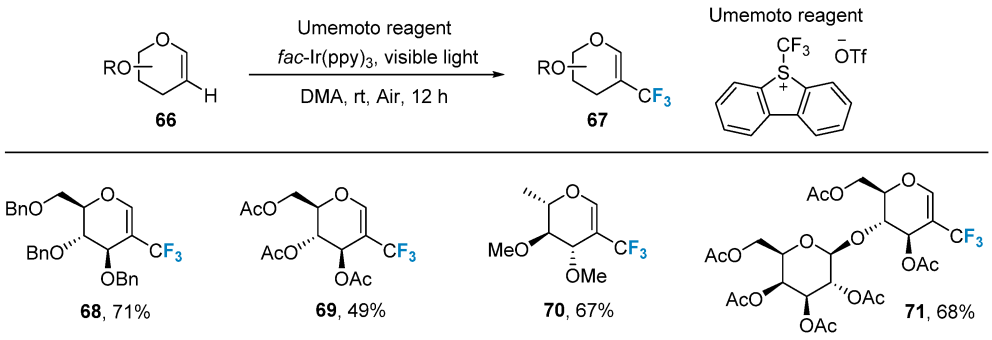

Figure 12. Trifluoromethylation of glycals using Umemoto reagent.

In 2018, Vincent's group [70] successfully accomplished the C-H trifluoromethylation of exo-glycal **72** using photoredox and copper catalysis methods. Two different trifluoromethyl sources, A and B, were employed under distinct reaction conditions. The method displayed excellent selectivity in producing Z-configured trifluoromethylation product **73** (**Figure 13**) while maintaining good compatibility with various protecting groups, such as benzyl, silyl, and acetyl.

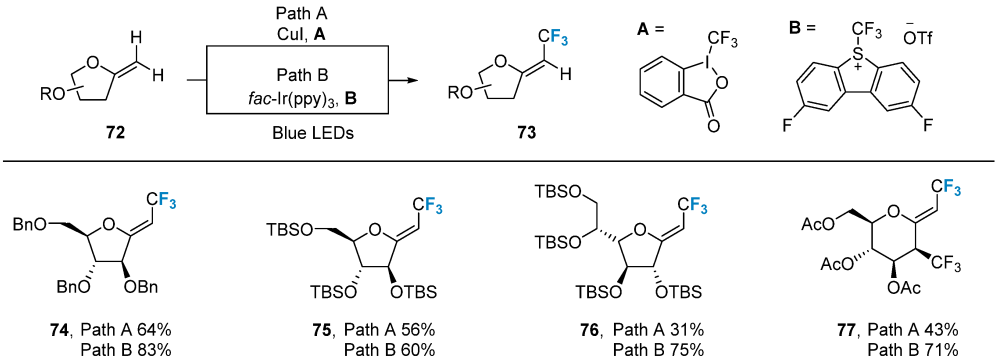

Figure 13. Trifluoromethylation of glycals via photoredox and copper catalysis.

In 2021, Ye's group [71] used electrochemical methods for the first time in the trifluoromethyl modification of glycoconjugates. The authors used glycal **66** as the substrate, a cheap and readily available sodium trifluoromethanesulfonate reagent as the trifluoromethyl source, and added $MnBr_2$ as the redox medium, and the reaction was carried out in acetonitrile solution. The method is mild and suitable for a wide range of glycoconjugate substrates protected by different protecting groups (**Figure 14**).

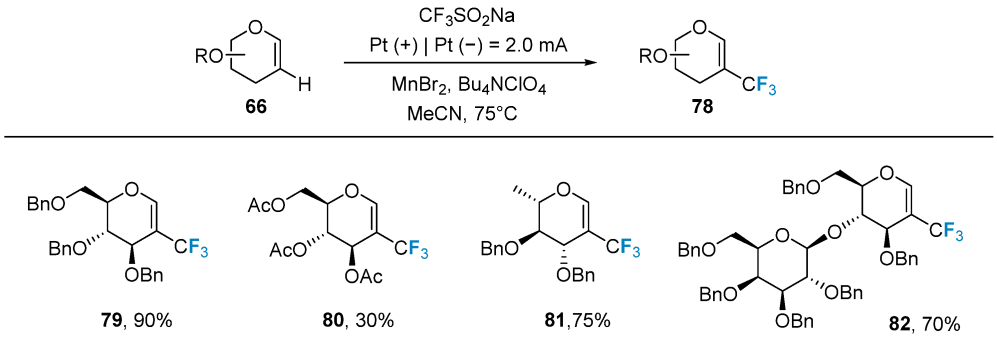

Figure 14. Trifluoromethylation of glycals via electrochemical method.

In 2020, Postigo's group [72] utilized glycal **83** as a substrate, combined with iodinated perfluoroalkanes as a fluorine source, and employed $Ir[dF(CF_3)PPy]_2(dtbPy)PF_6$ as a photocatalyst to achieve the synthesis of perfluoroalkyl-modified glycal **84** under blue light conditions (**Figure 15**).

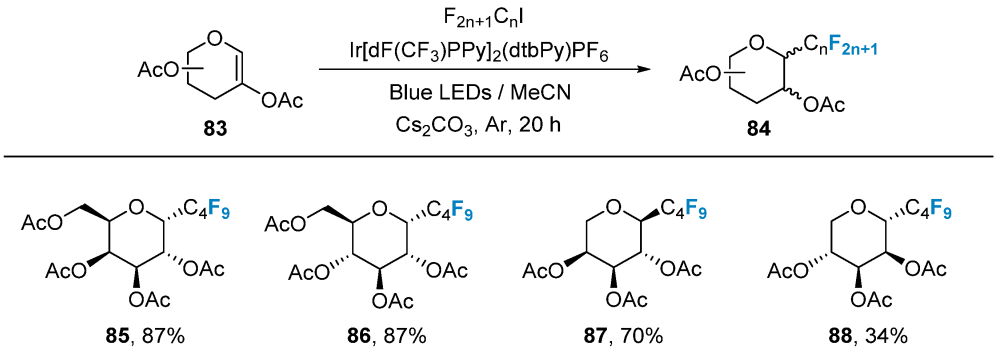

Figure 15. Photocatalyzed reductive fluoroalkylation of 2-acetoxyglycals.

2.4. Fluorination of Carbohydrates via Metal-Catalyzed Coupling Reactions

Pannecoucke's group [73][74] developed a copper-catalyzed method for the synthesis of difluoroalkylated glycals. The researchers synthesized a series of difluoroalkylation-modified glycals using $Cu(PF_6)(MeCN)_4$ as the catalyst, $BrCF_2CO_2Et$ as the difluoroalkylation reagent, and 1,10-phenanthroline as the ligand (**Figure 16**). This method exhibited good compatibility with various protecting groups (benzyl, acetyl, methyl, etc.) and could be applied to different types of sugars (glucose, galactose, rhamnose, arabinose, etc.). The proposed reaction mechanism suggests that, initially, copper(I) $Cu(PF_6)(MeCN)_4$ undergoes oxidative addition with $BrCF_2CO_2Et$ to form compound **93**, resulting in the trivalent copper species. Compound **93** then undergoes an addition reaction with glycal **66**, selectively adding to the electron-rich C-2 position, generating the oxonium intermediate **94**. Subsequently, the base removes a proton to form compound **95**, which is, ultimately, reduced and eliminated to yield the desired product **89**.

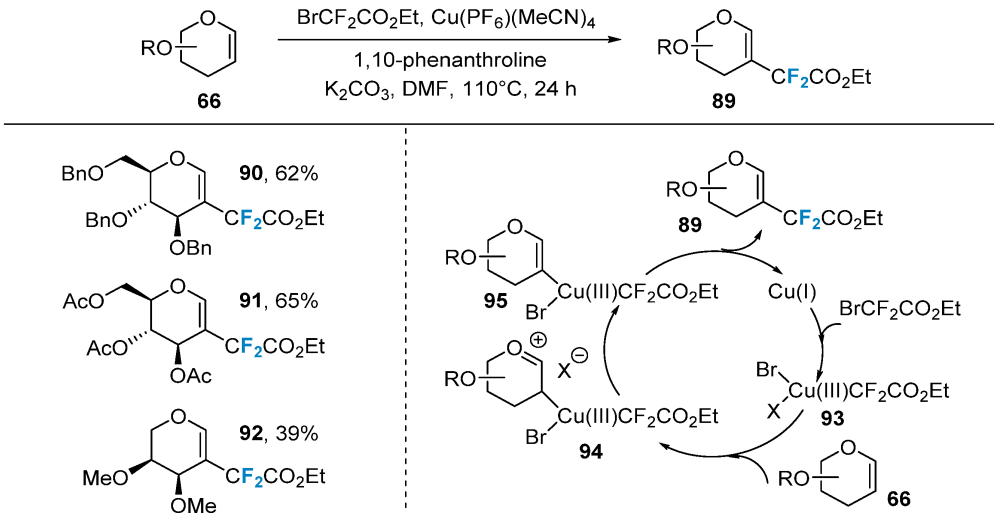

Figure 16. Copper-catalyzed β-difluoroacetylation of glycals via direct C–H functionalization.

The introduction of trifluoromethyl to the glycal was also achieved via metal-catalyzed coupling reactions. Boutureira's group [75] utilized a 2-iodoglycal **96** as the substrate and $CuCF_3$ as the trifluoromethyl source to successfully obtain the trifluoromethyl-modified glycal **97** in a satisfactory yield upon heating at 50 °C (**Figure 17**).

However, this method required the pre-preparation of 2-iodoglycal, making it somewhat tedious and limited in scope. Alternatively, metal-catalyzed coupling reactions were employed to introduce perfluoroalkyl groups into glycal. Boutureira's group [76] utilized 2-iodoglycal **96** as the substrate and CuC_2F_5 as the perfluoroalkyl source, achieving the synthesis of perfluoroalkyl-modified glycal **98** with higher yields under heating at 50 °C.

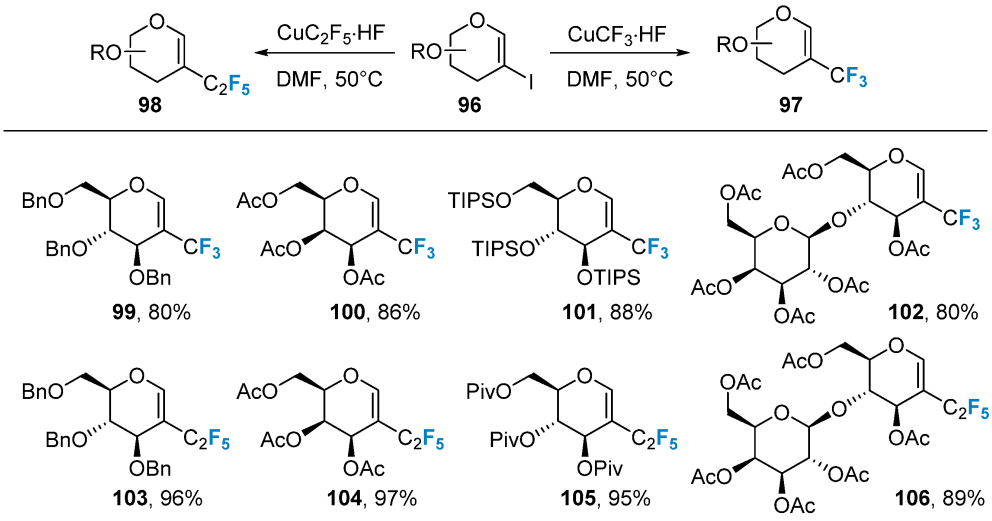

Figure 17. Copper-catalyzed trifluoromethylation of 2-iodoglycals.

2.5. Fluorination of Carbohydrates via Building Block Strategy

Fluorine-modified sugars can be synthesized using a fluorine-containing building block strategy. In 2007, Mootoo's group [77] successfully synthesized monofluorinated glycosides using compounds **107** as the initial materials in a four-step tandem reaction, as shown in **Figure 18**: esterification, Takai reaction, cyclization reaction, and borohydride oxidation reaction. Through variation in the R group, a wide range of fluorinated carbohydrates with different substituents can be obtained.

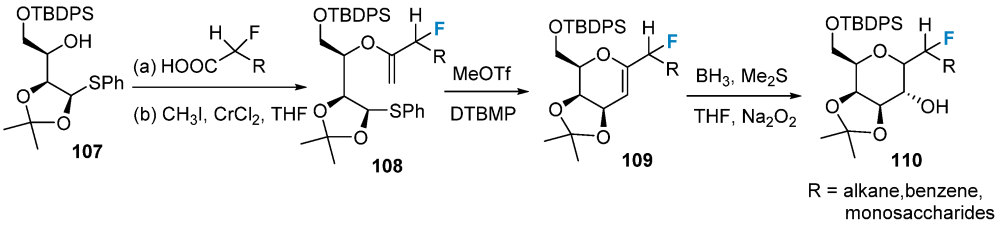

Figure 18. Monofluorination of sugars via building block strategy.

In addition to the methods mentioned above, fluorocarbohydrates can be obtained by modifying the backbone of the raw material using fluorinated reagents. **Figure 19**a shows the introduction of difluoroalkyl into the precursor **111** via the Reformatsky reaction, followed by ring closure to achieve difluoro-C-glycosides **113** [78]. Alternatively, the difluoroalkylated product **116** can be obtained by initially introducing two fluorine atoms at the C-2 position of the sugar ring, followed by a one-step ring closure (**Figure 19**b) [79].

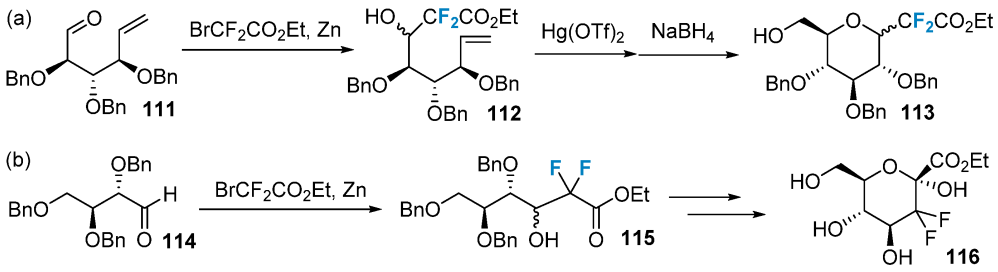

Figure 19. Difluorination of sugars via building block strategy: (**a**) synthesis of difluoro-C-glycosides **113** via building block strategy, (**b**) synthesis of difluoroalkylated product **116** via building block strategy.

The synthesis of saccharides modified with trifluoromethyl groups using non-sugar compounds as starting materials was initially achieved by the Kobayashi group [80]. They employed the trifluoromethyl-containing compound **117** as the starting material and generated the intermediate product **118** via a Lewis acid-catalyzed aldol condensation reaction. The carbonyl group in **118** was subsequently reduced, yielding the reduced compound. Furthermore, the double bond in the product was oxidized using a dilute potassium permanganate solution to produce the dihydroxy compound **120** (**Figure 20**a). In a related study, Burger's group [81] utilized methyl trifluoropyruvate **122** as a source of trifluoromethyl groups. This compound was catalytically coupled with compound **121** using titanium trichloride, leading to the formation of compound **123**. Subsequently, compound **123** underwent a ring-closing reaction under acidic conditions, resulting in the formation of compound **124**. Finally, compound **125** was synthesized in a single vessel via a reductive reaction (**Figure 20**b).

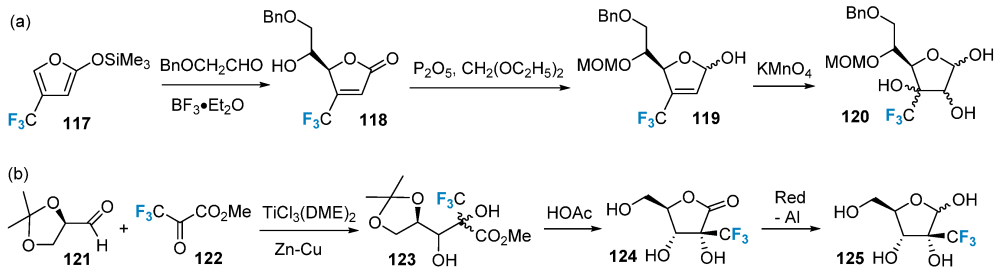

Figure 20. Trifluoromethylation of sugars via building block strategy: (**a**) synthesis of trifluoromethylated product **120** via building block strategy, (**b**) synthesis of trifluoromethylated product **125** via building block strategy.

The synthesis of sugars modified with polyfluorinated groups was achieved using non-sugar compounds that contained polyfluorinated modifications. In 2013, Vincent's group [82] utilized compound **126**, which featured a CF_2CF_2 structure, as the starting material. Through a ring-closing reaction, they successfully obtained the final product **128** (**Figure 21**).

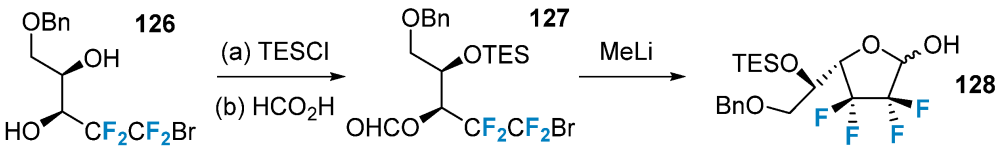

Figure 21. Polyfluorination of sugars via building block strategy.

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