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Review

C-Difluoromethylene-containing, *C*-trifluoromethyl and *C*-perfluoroalkyl carbohydrates. Synthesis by carbohydrate transformation or building block methods

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Abstract

The synthetic methods for preparing carbohydrates bearing a C-branched substituent of the type CF_2–Y, with Y = F, Y = C_nF_{2n+1} or Y = a carbon-attached or heteroatom-attached nonfluorinated residues, are reviewed. Both direct introduction of C-branched fluorinated substituents (direct trifluoromethylation, perfluoroalkylation or difluoromethylenation) and building block methods from fluorinated synthons are considered. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *C*-Difluoromethylene carbohydrates; *C*-Trifluoromethyl carbohydrates; *C*-Perfluoroalkyl carbohydrates; Fluorinated synthons

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1. Introduction and scope

Fluorine-substituted carbohydrates have been a topic of interest for many years [1], with applications mainly directed towards bioorganic chemistry. Sugar-derived compounds linked to a long perfluoroalkyl (*F*-alkyl) chain via a hydrocarbon spacer or via an ether or an ester function have also been widely studied for their surfactant and mesogenic properties [2]. The interest in fluorinated carbohydrates where fluorine is attached to a C-branched alkyl substituent has appeared much more recently, and in contrast to the two above-mentioned families, no review has been dedicated to this topic so far. Our purpose is to fill this gap.

To simplify the writing and the scope of this review, we will use *C*-*F*-alkyl carbohydrates or sugars for structures including a *C*-branched CF_2–Y substituent as well as for actual long R^F chain C-branched compounds. Hence, the scope of this review is extended to carbohydrates bearing a C-branched CF_2–Y substituent, where Y can be a fluorine atom (*C*-trifluoromethyl = *C*-CF_3), a C_nF_{2n+1} group (*C*-*F*-alkyl), or a nonfluorinated residue (H atom, an alkyl group, a heteroatom-linked group). Although 1-*C*–*F*-alkyl carbohydrates could be considered as fluorinated uloses rather than actual *C*–*F*-alkyl derivatives, they are included in this review, as are the compounds bearing the *F*-alkyl substituent linked to the terminal carbon. Thus, the structures covered by this review are summarized in Scheme 1.

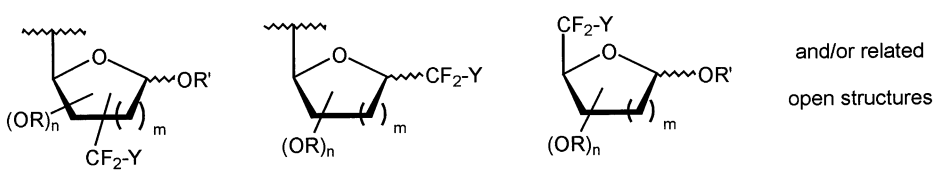
The usual discrimination between moderately and highly fluorinated compounds may be applied to *C*–*F*-alkyl carbohydrates as it is to other organofluorine compounds: when the syntheses were performed for targeted applications, *C*-CF_2Y derivatives with $Y \neq C_nF_{2n+1}$ were studied as bioactive compounds, and long-chain *C*-C_nF_{2n+1} derivatives were considered for their amphiphilic character. As the biological [3] as well as amphiphilic [4] aspects are reviewed in specific chapters of this special issue, this review is devoted essentially to the various synthetic methods available to prepare the *C*-*F*-alkyl carbohydrates whose structures have been defined above (Scheme 1).

For each family, we will consider the methods of direct introduction of the CF_2–Y moiety into the carbohydrate, as well as the building block methods where the final compounds are derived from non-carbohydrate fluorinated synthons. Although grafting of CF_3 or C_nF_{2n+1} often uses similar reactions (nucleophilic or radical addition) on similar sugar substrates, the fluorinated reagents are generally significantly different. Hence, we choose to present this review according to the families of compounds synthesized rather than by the methods used.

This descriptive review covers the literature until early 1999.

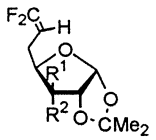
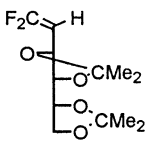
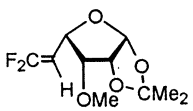
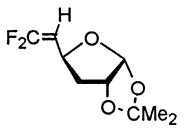
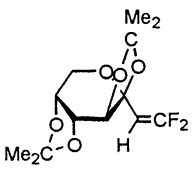
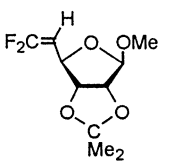
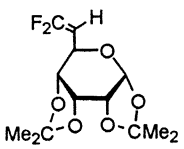
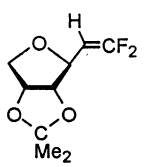
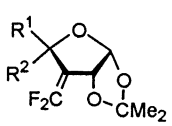
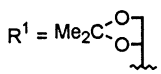
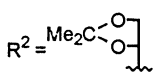
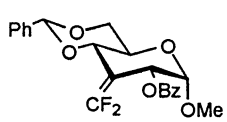
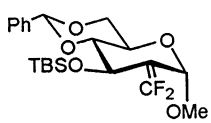
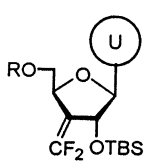
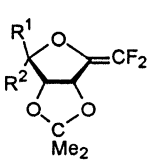
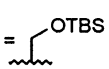
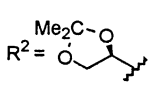
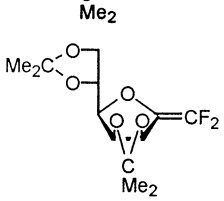
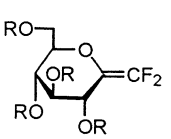
2. *C*-CF_2–Y carbohydrates with $Y \neq F$, C_nF_{2n+1}

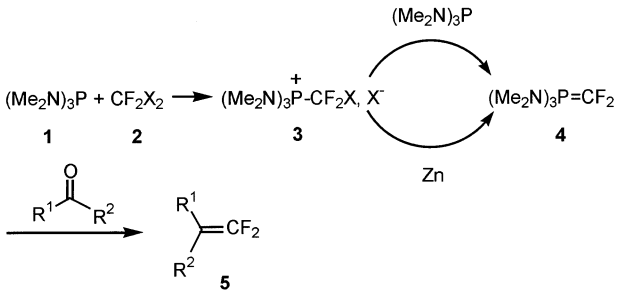
The synthesis of difluoromethylene containing compounds is a topic of wide interest [5]. The difluoromethylene group is considered as isopolar and bioisosteric to oxygen; hence, many reports have appeared concerning sugars



Scheme 1.

Table 1
Formation of *C*-difluoromethylene carbohydrates from the corresponding carbonylated precursors

		Yield	Ref.		Yield	Ref.
Conditions: CF_2Br_2–$(Me_2N)_3P$–DME–20 °C						
	R^1 = OMe, R^2 = H R^1 = OBn, R^2 = H R^1 = H, R^2 = OMe	60–72 % 56–74 % 60–67 %	[9, 10] [9, 10] [9, 10]		62%	[10]
		64 %	[10]		71%	[9]
		58–74 %	[9, 10]		69%	[9]
		60%	[10]		61%	[9]
Conditions: CF_2Cl_2–KF–PPh_3–DME–20 °C						
	R^1 =  R^2 = H R^1 = H R^2 = 				65% 28%	[11] [11]
Conditions: CF_2Br_2–$(Me_2N)_3P$–THF–r.t.						
			[12]		71%	[13]
Conditions: CF_2Br_2–$(Me_2N)_3P$–Zn–THF–Δ						
	U = Uracil R = DMTr R = TBS				69–74%	[14]
	R^1 =  R^2 = H R^1 = H R^2 = 				68% 71%	[15, 16] [15, 16]
		71%	[15, 16]		R = TMS R = Bn	69% 63%	[15, 16] [15, 16]



Scheme 2.

or nucleosides bearing this structural fragment. Two main methods were used: transformation of an unsaturated difluoromethylene intermediate, which can lead to almost every kind of CF_2–Y bond and introduction of the CF_2–Y moiety, for example, by reaction with a lithio derivative, $LiCF_2Y$. A few building block-based syntheses have also been reported.

2.1 Synthesis of C-*difluoromethylene carbohydrates.*

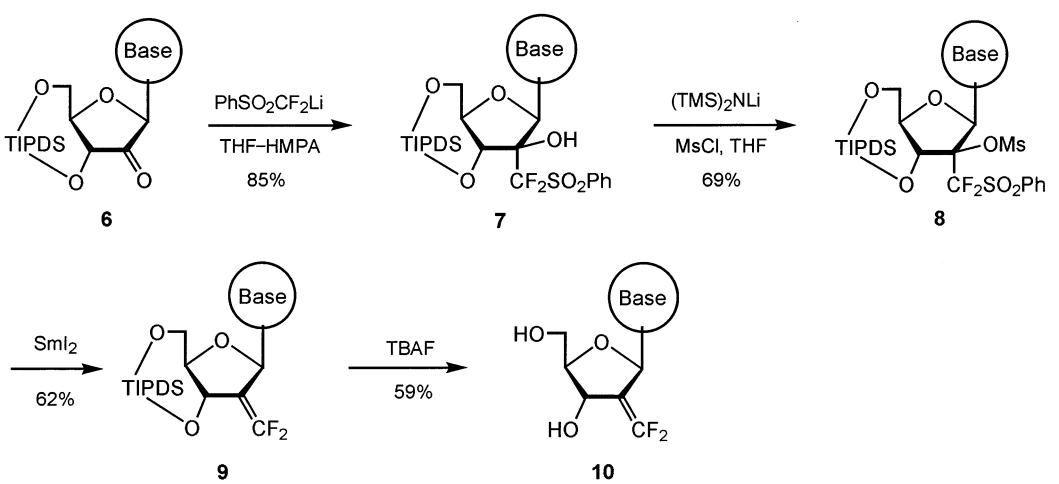
Most *C*-difluoromethylene carbohydrates **5** have been prepared by a Wittig type olefination reaction using the difluoromethylene ylides **4** developed by Burton's group and derived from hexamethylphosphorous triamide **1** and a dihalodifluoromethane **2** [6,7]. Other phosphines such as triphenylphosphine have been used uniquely in the sugar series. Two procedures were used to generate the ylide: addition of an excess of phosphine [6], or addition of a metal, generally zinc (Scheme 2) [7]. The chemistry of difluoromethylene ylides was recently reviewed in detail [8].

We summarize in Table 1 the various derivatives prepared thus far [9–16]. The precursor carbonyl group may be of a ketone type, of an aldehyde type (terminal position) and even of a lactone type (anomeric position). Yields are generally good, sometimes because of a suitable adaptation of the experimental conditions. A general feature of these reactions is the large excess of phosphonium salt used.

Another method was developed to convert a 2-oxonucleoside into the corresponding difluoromethylene derivatives. Whereas the above-mentioned Wittig type reaction failed, the authors found that a modified Julia olefination applied to a suitably protected nucleoside **6** allowed the $C{=}O \rightarrow C{=}CF_2$ conversion for such a highly functionalized compound (Scheme 3) [17]. To be successful in obtaining the cytidine derivative **10**, the deprotection of the base moiety must be carried out just after the addition step.

2.2 C-*Difluoromethyl carbohydrates*

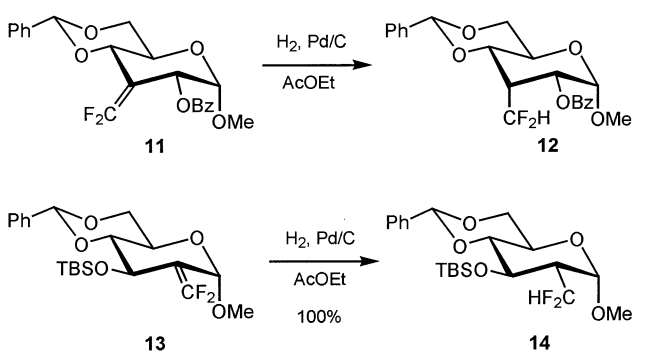
C-Difluoromethylene carbohydrates have sometimes been easily converted into the corresponding *C*-difluoromethyl deoxy derivative by a simple catalytic hydrogenation. Generally the hydrogenation is stereospecific, taking place on the less hindered face and controlled



Scheme 3.

by the vicinal asymmetric carbon atoms. This hydrogenation leads to a sugar derivative in which the OH group has been substituted for CF_2H. Only a few deoxy-*C*-difluoromethyl compounds have been described in comparison with the numerous difluoromethylene precursors. Yamazaki and co-workers reported the synthesis of a 3-deoxy-3-*C*-difluoromethyl-D-allose derivative **12** [12] and a 2-deoxy-2-*C*-difluoromethyl-D-glucose derivative **14** [13], whose difluoromethylene precursors **11** and **13** are both derived from a methyl α-D-glucopyranoside derivative. It should be noticed that, in both cases, as the anomeric methoxy groups are in the α configuration, hydrogenation took place specifically from the β-face. Consequently, the difluoromethylenation–hydrogenation gave an inversion of configuration at C-3 and retention of the configuration at C-2 (Scheme 4).

Motherwell's group reported a range of carbohydrate mimics **15**–**18** with a difluoromethyl group in place of the anomeric hydroxyl [15,16]. Here too, the hydrogenation step is most often stereospecific, leading to stereodefined carbohydrate mimics whose pseudo anomeric carbon configuration is controlled by C-2 (Scheme 5).



Scheme 4.

2.3 C-CF_2Y carbohydrates with Y = carbon-attached substituent

2.3.1 By radical addition.

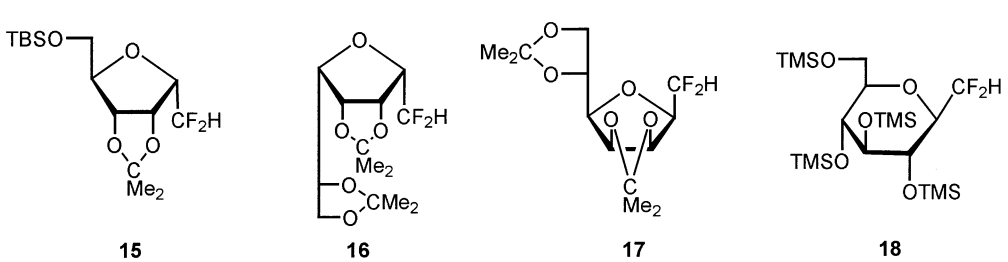
This methodology was mainly studied by Motherwell's group. Two strategies were considered: addition of a carbon-centered radical to the difluoromethylene derivatives described formations were essentially carried out at the anomeric position, leading to difluoro-*C*-glycosides.

Addition of simple nucleophilic alkyl radicals to a 1-*C*-difluoromethylene glucose derivative **19** gave poor yields of the corresponding difluoro-*C*-glycosides **20** (Scheme 6) [18,19].

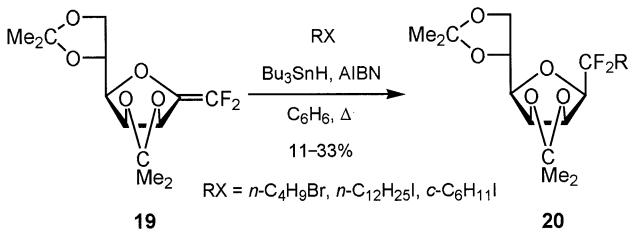
The hydrogen transfer takes place with essentially total selectivity via the less hindered face of the intermediate radical adduct. Thus, the configuration of the anomeric center is controlled by C-2. Several difluoro-*C*-disaccharides **22** were prepared using the same conditions with protected 6-halo (Br or I) D-gluco- or D-galactopyranosides as radical precursors [19]. As observed for simple primary alkyl radicals, the yields are generally low (Scheme 7).

Electrophilic radicals such as those derived from ethyl bromoacetate **24** add more efficiently to these difluoroenolethers (Scheme 8). An interesting extension was found in the addition cyclization of diethyl allyliodomalonate **29** using the iodine atom transfer methodology, which led, after the reduction of the carbon–iodine bond, to the spirofused difluoro compound **30** (Scheme 8) [19].

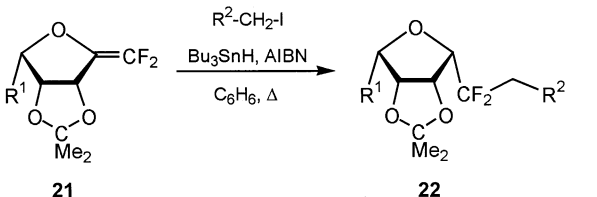
An efficient alternative consisted in adding the difluoromethylenic radical to an unsaturated substrate. The radical precursor **31** or **33** was derived from *C*-difluoromethylene compounds **19** or **26** by radical addition of thio-

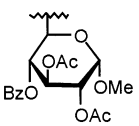
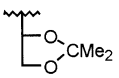
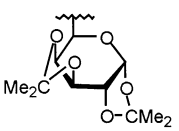
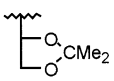
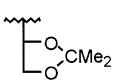
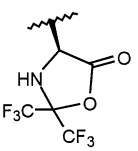


Scheme 5.



Scheme 6.

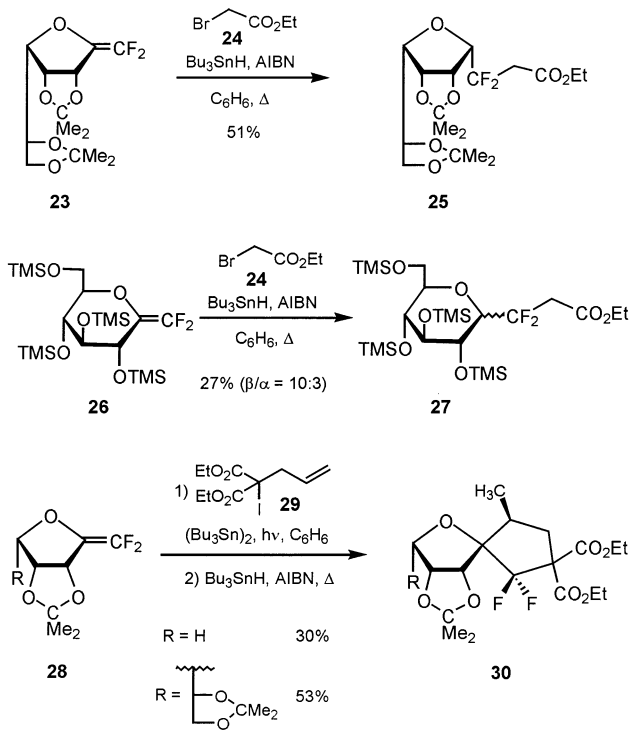


R^1	R^2	Yield
H		23%
	id.	40%
H		14%
	id.	20%
		30%

Scheme 7.

phenol [18]. Efficient syntheses of C-CF_2 allyl derivatives **32** or **34** were performed by this methodology (Scheme 9).

The two symmetrical strategies were applied by the same group to difluoromethylene glycopeptide analogues (Scheme 10) [20]. Addition of the CF_2-centered radical to a radicophilic amino acid precursor **40** gave better results, but stereoselectivity was not complete. As illustrated in one example, it is a valuable method to prepare, in one further and easy step, a CF_2 analogue of a glycodipeptide **41**.

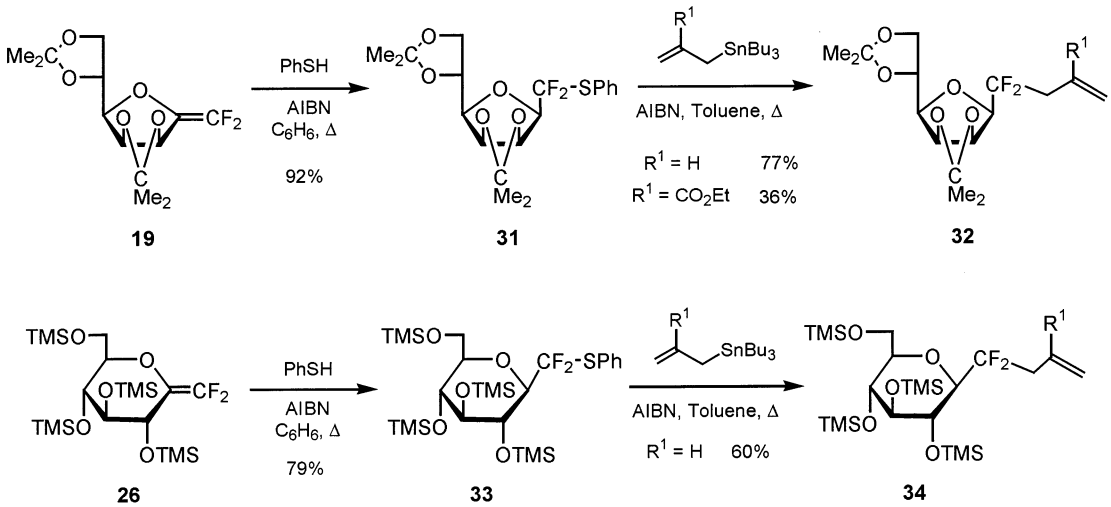


Scheme 8.

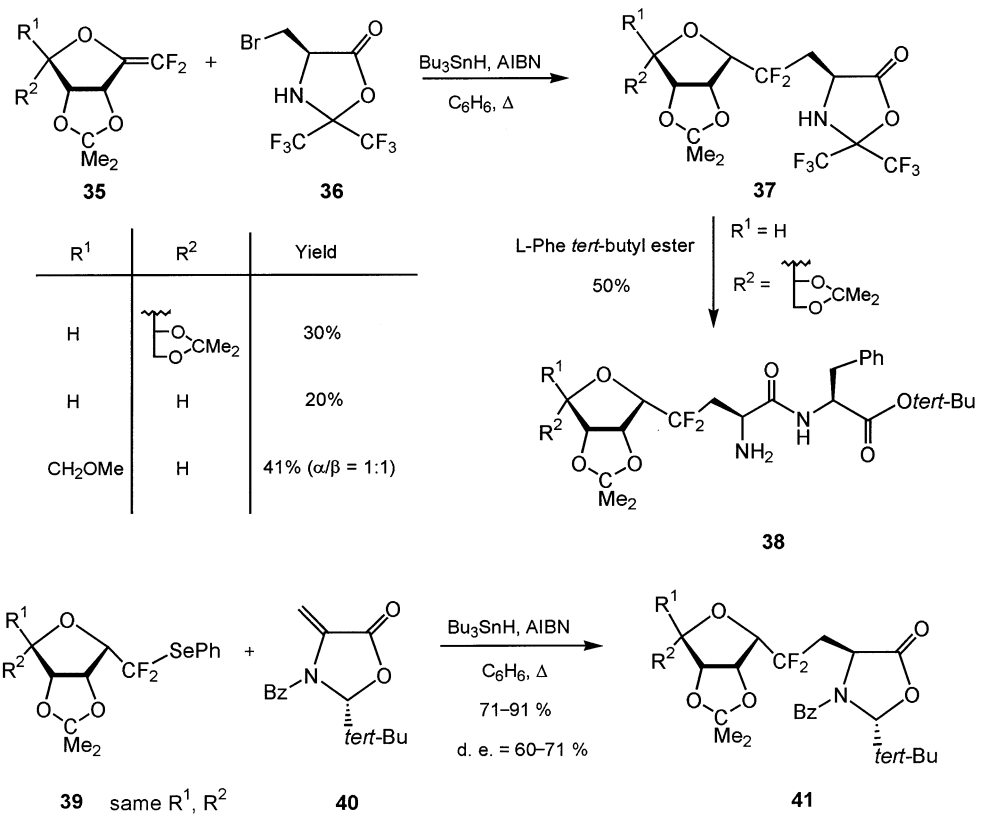
2.3.2 By electrophilic glycosylation of a difluoromethylene acceptor.

C-Glycosyl compounds bearing a difluoromethylene group in place of the anomeric oxygen were prepared in our group by a completely different approach, using difluoroenoxysilanes as the glycosyl acceptor [21]. The difluoroenoxysilanes **44**, **46** are prepared in situ by reaction of trifluoromethyltrimethylsilane with an acylsilane [22]. This methodology was applied to tri-*O*-acetyl-D-glucal **42**, activated with boron trifluoride etherate (Scheme 11). The preparation of a difluoro-*C*-disaccharide **47** was achieved using a D-xylose-derived acylsilane as a starting material [21].

This methodology was not compatible with a glycosyl donor bearing a participating ester group at C-2. As outlined in Scheme 12, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose (**48a**) was converted to a product derived from a reaction with the benzylic carbon atom **49**, comparable with the orthoester byproduct in some glycosylation reactions, whereas the corresponding 2-deoxy derivative **48b** gave a good yield of the expected C-CF_2 glycoside **50**. It is noteworthy that a single stereoisomer was formed [23].



Scheme 9.

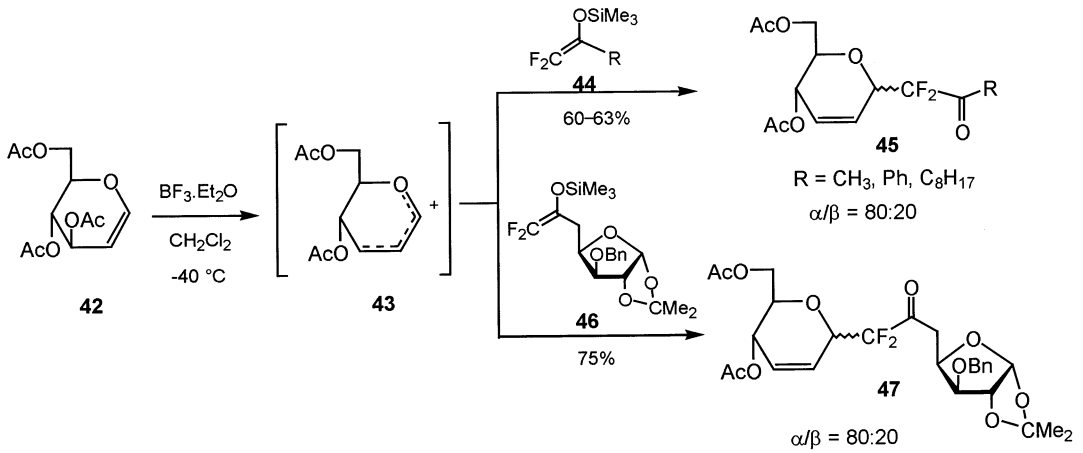


R^1	R^2	Yield
H		30%
H	H	20%
CH_2OMe	H	41% (α/β = 1:1)

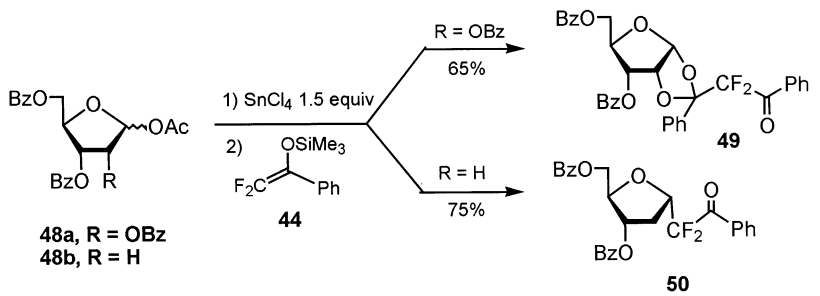
Scheme 10.

2.4 C-CF_2–P(Z)(OR)$_2$ (Z = O, S).

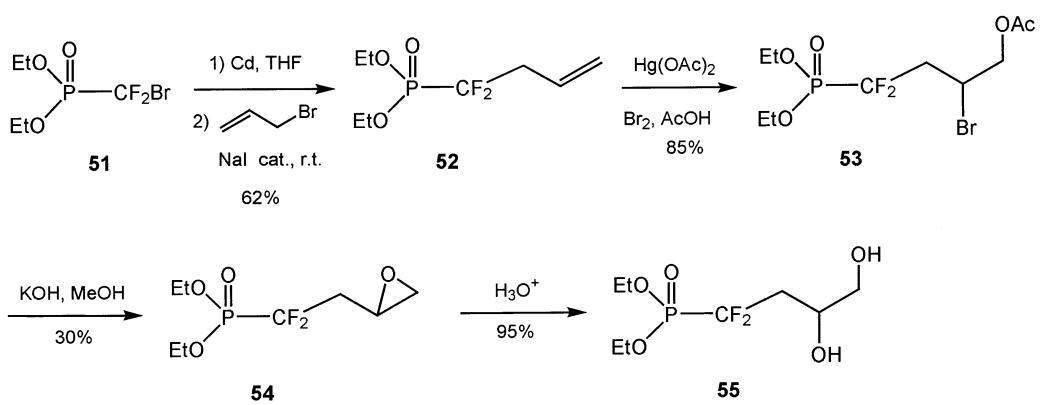
The difluoromethylenephosphonate (CF_2 phosphonate) is one of the first fluorinated substituents considered to be isopolar and bioisosteric to the phosphate group [24]. Moreover, CF_2 phosphonate derivatives are stable to hydrolysis. Hence, many studies have appeared in the literature over the last 10 years, and several methodologies are available. Both organometallic and radical approaches were investigated for the synthesis of *C*-CF_2 phosphonate carbohydrates. Not surprisingly, the researchers were mainly interested in 5′-deoxy-5′-difluorophosphonyl derivatives as 5′-phosphate mimics.



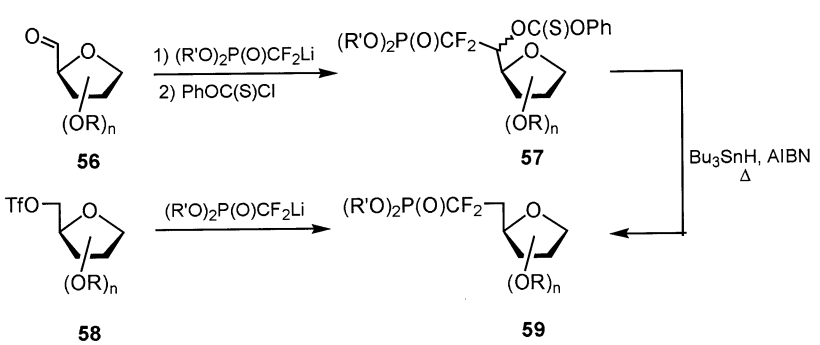
Scheme 11.



Scheme 12.

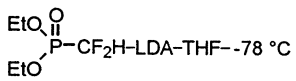
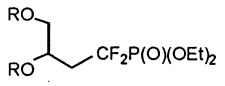
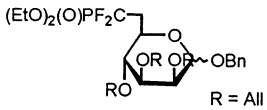
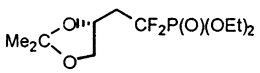
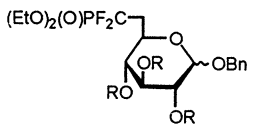
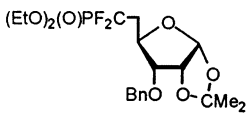
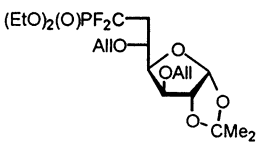
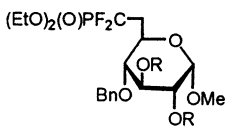
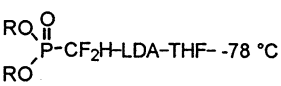
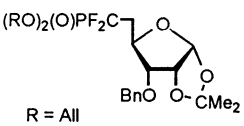
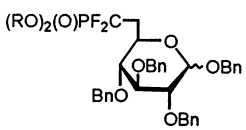


Scheme 13.



Scheme 14.

Table 2
Formation of *C*-difluoromethylene phosphonate by a triflate group displacement according to Scheme 14

	Yield	Ref		Yield	Ref
Conditions: 					
 R = *n*-hexyl	88%	[27]	 R = All	74%	[29]
	63%	[28]		78–82%	[29]
	83%	[29, 30]			
	65%	[29]		59–81%	[29]
Conditions : 					
 R = All	50–64 %	[31]		56–62 %	[31]

2.4.1 Organometallic approach.

The lithium salt of diethyl difluoromethylphosphonate [8,25] is a widely used reagent to synthesize phosphate mimics by nucleophilic addition or displacement. A cadmium reagent has also been used in the synthesis of a difluoro analogue of glycerol phosphate **55** (Scheme 13) [26].

With regard to phosphate mimics, two methods were applied, which are summarized in Scheme 14.

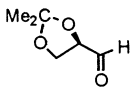
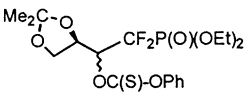
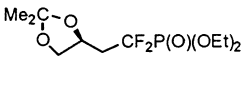
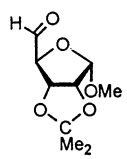
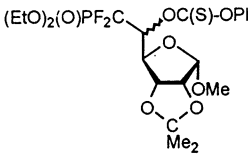
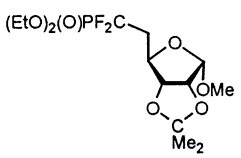
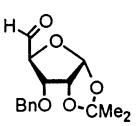
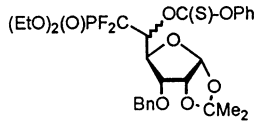
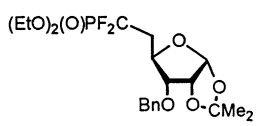
The CF_2 phosphonate **59** may be prepared directly by displacement of a triflate group **58** [27–31]. Neither halides nor secondary triflates are satisfactory substrates for these reactions (Table 2).

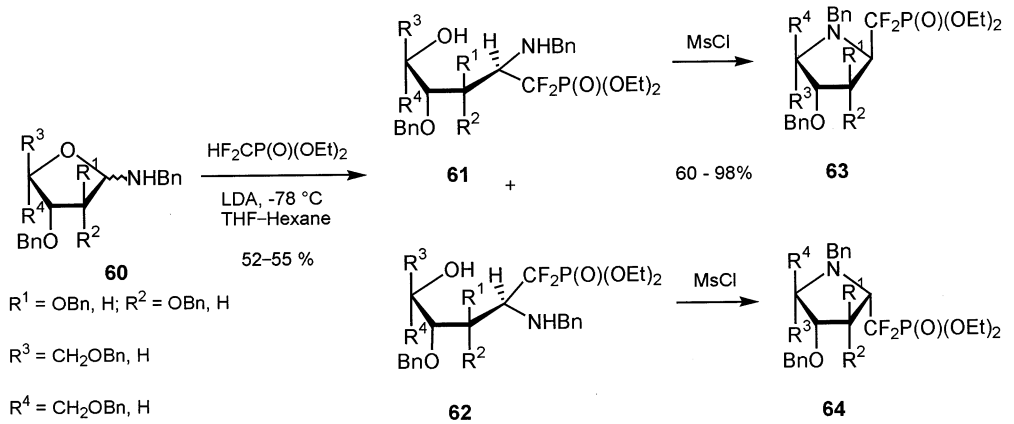
Alternatively, addition on an *aldehydo*-sugar **56** gave the corresponding β-hydroxy CF_2 phosphonate derivative. In the sugar series, the alkoxide intermediate was generally converted in situ into a phenyl thionocarbonate **57** for further deoxygenation [32,33] (Table 3).

An anomeric type CF_2 phosphonate **63**, **64** has been prepared in the aza sugar series by addition of the lithio CF_2 phosphonate to furanosylamines **60** (Scheme 15) [34].

These compounds, prepared as intermediates toward glycosyl transferase inhibitors, seem to be the only examples of addition of Li–CF_2 phosphonate to an imine function.

Table 3
Formation of *C*-difluoromethylene phosphonate by a nucleophilic addition-deoxygenation sequence according to Scheme 14

Conditions : 1) $(EtO)_2P(O)CF_2H$–LDA–THF– -78 °C 2) PhO-C(S)Cl 3) Bu_3SnH–AIBN–Δ			Ref
	 83%	 80%	[32]
	 87%	 89%	[32]
	 68%	 71%	[33]

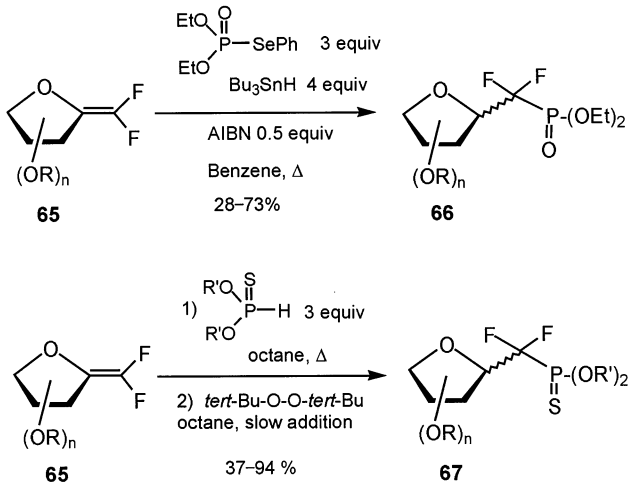


Scheme 15.

2.4.2 Radical approach.

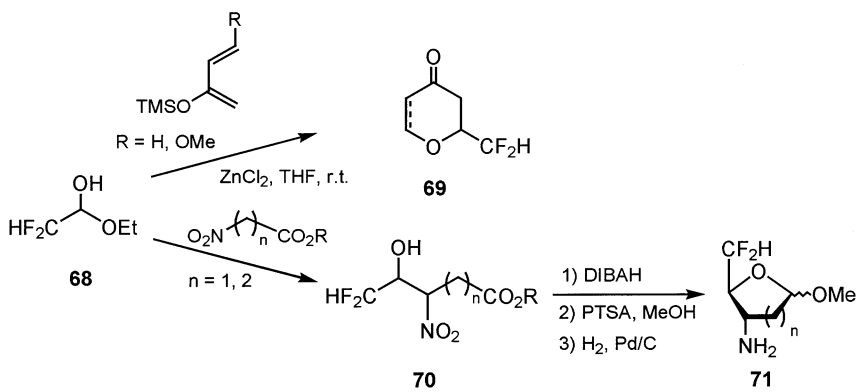
In the above section, mainly concerned with CF_2 phosphonates as mimics of the 5′-phosphate moiety of biologically interesting compounds, the radical synthesis developed by Motherwell's group gave access to anomeric CF_2 phosphonate **66** [35,36] and anomeric CF_2 phosphonothioates **67** [36]. Addition of a dialkylphosphite to the anomeric difluoromethylene compounds **65** (vide supra), initiated by di-*tert*-butyl peroxide, gave poor yields of the expected CF_2 phosphonate. Better results were obtained using AIBN, a (phenylselenyl) phosphonate and tributyltin hydride to improve hydrogen and chain transfers. In contrast, di-*tert*-butyl peroxide-initiated addition of diethylthiophosphite worked effectively, probably because of a weaker P–H bond (Scheme 16).

The stereochemical outcome of this addition is different from the ones observed for sulfur- or carbon-centered radicals, and oppo-

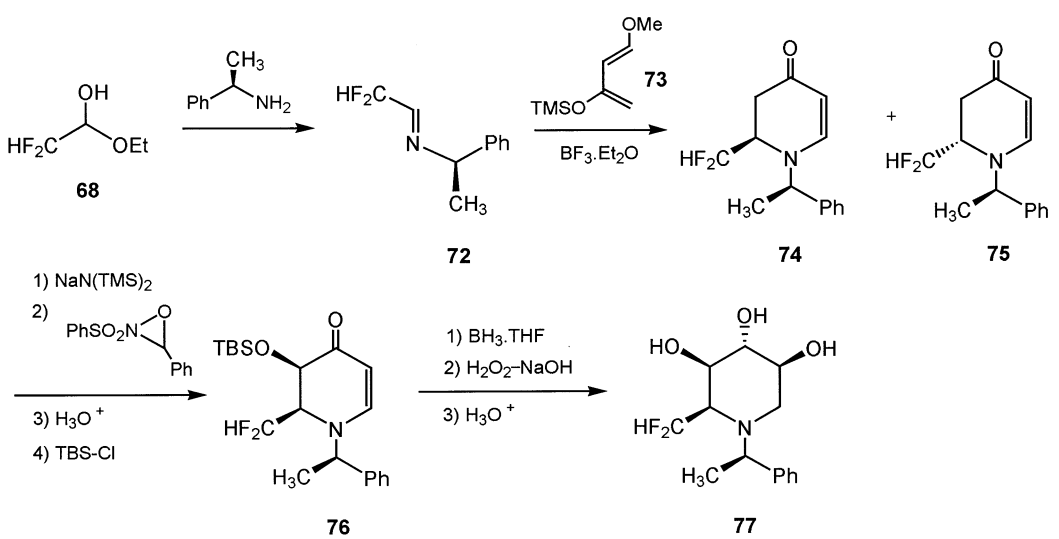


Scheme 16.

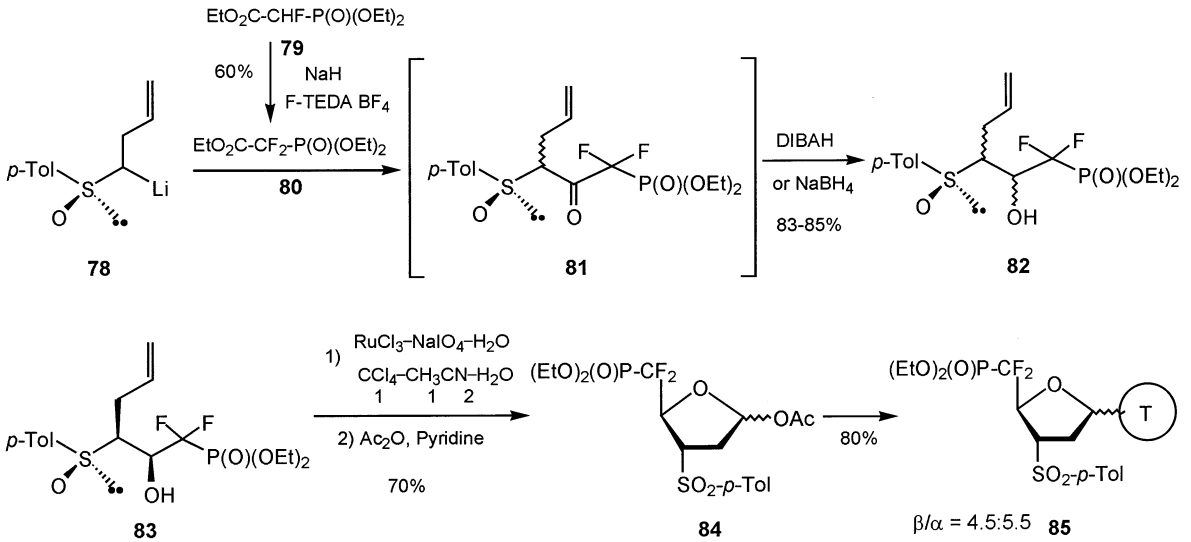
site to the one expected for such furanose derivatives. For example, all derivatives bearing a 2,3-*O*-isopropylidene moiety at the α-face were preferentially converted into the β-anomeric CF_2 phosphonate or phosphonothioate, indicating a hydrogen transfer from the more hindered face. The authors explained this behavior by a hyperconjugative interaction forcing the singly occupied orbital and the CF_2–P bond into an eclipsed conformation, and by steric hindrance of the phosphonyl group.



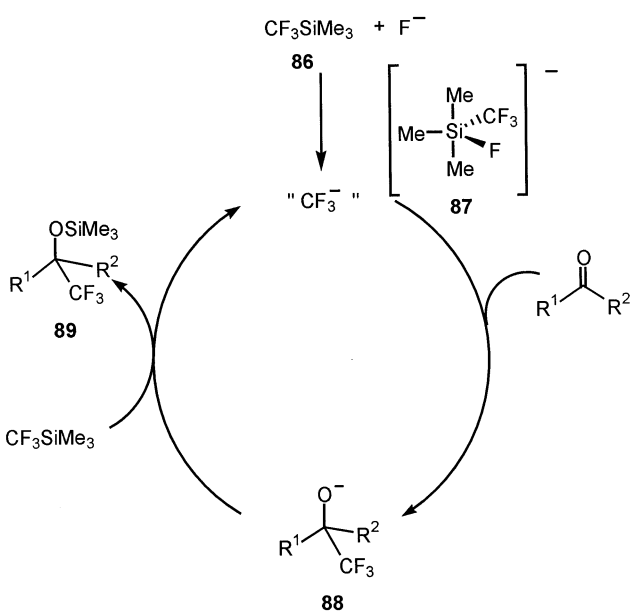
Scheme 17.



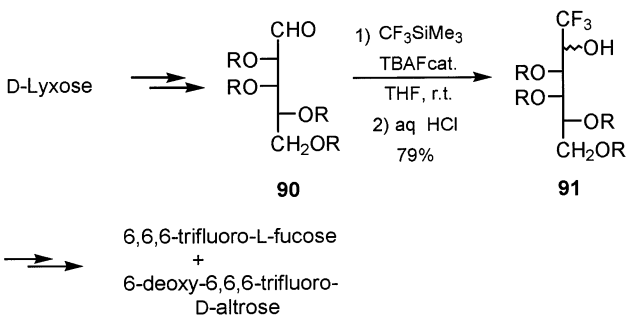
Scheme 18.



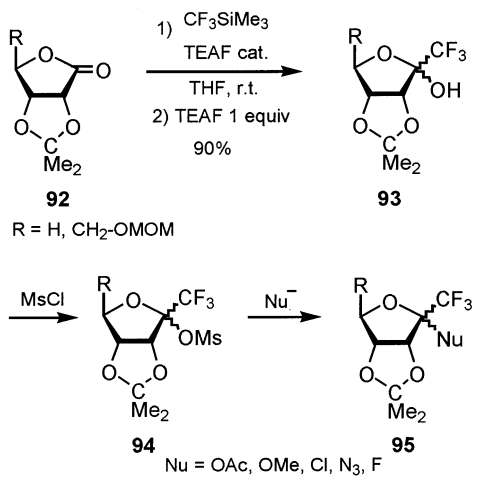
Scheme 19.



Scheme 20.



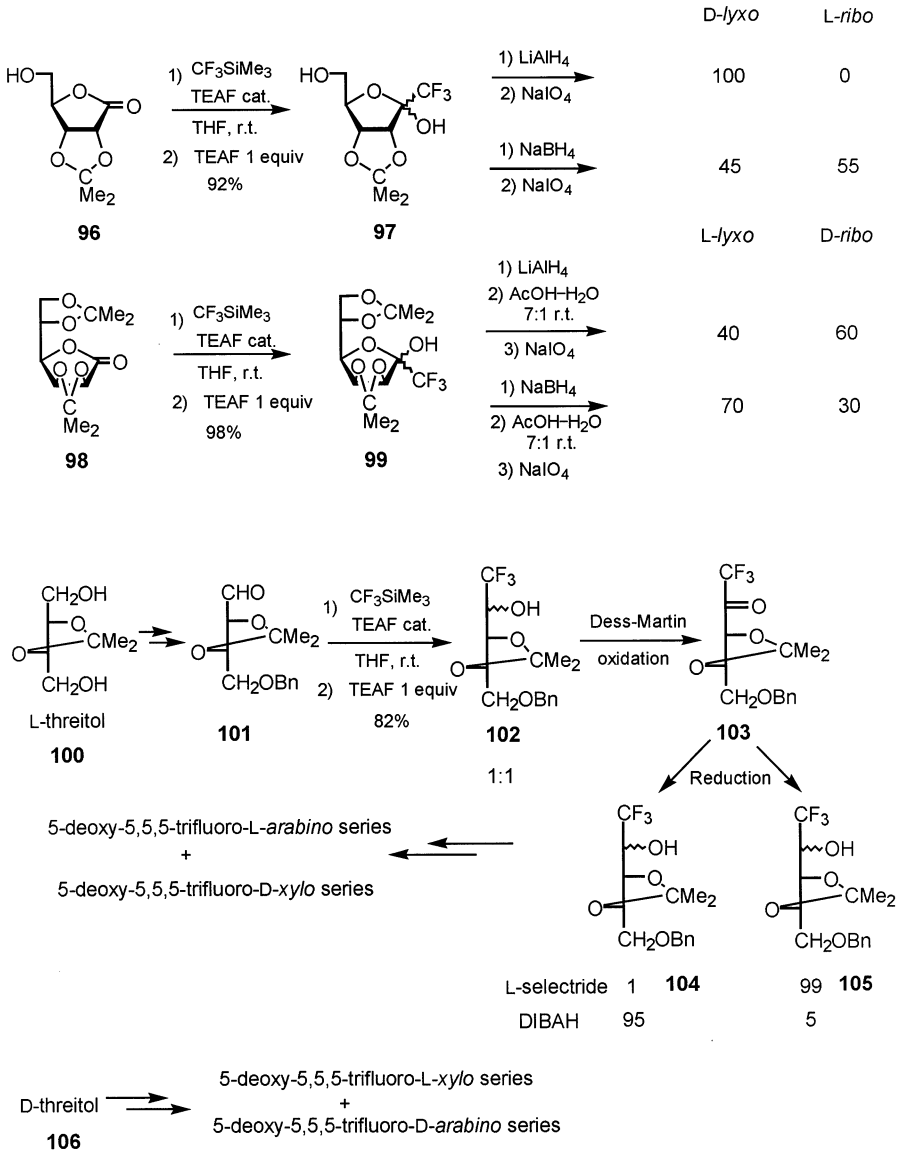
Scheme 21.



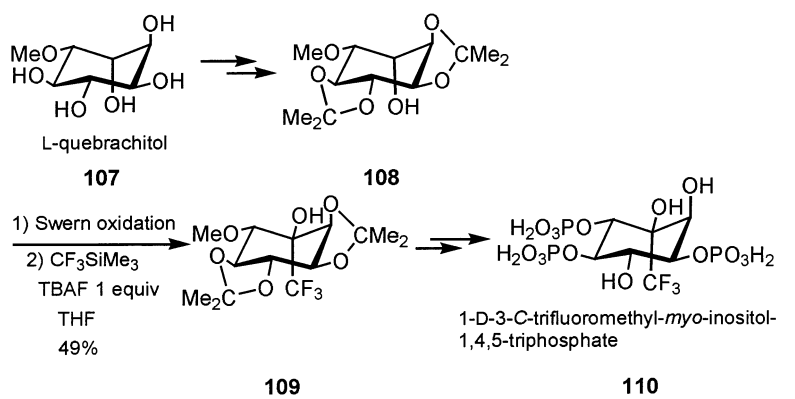
Scheme 22.

2.5 Building block based synthesis of C-CF_2Y carbohydrates.

Difluoroethanal ethylhemiacetal **68** was demonstrated to be an interesting starting building block giving access to difluoromethylsugar derivatives [37]. For example, Lewis acid activated cycloaddition with dienoxysilanes gave 2-difluoromethylpyran-4-one derivatives **69**, which can be considered as sugar precursors (Scheme 17). The same difluorosynthon was used in nitroaldol reactions



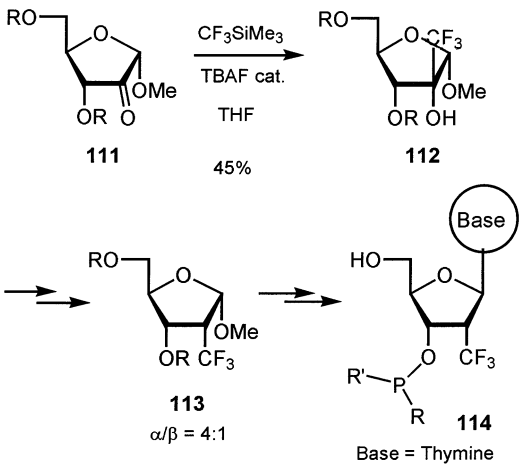
Scheme 23.



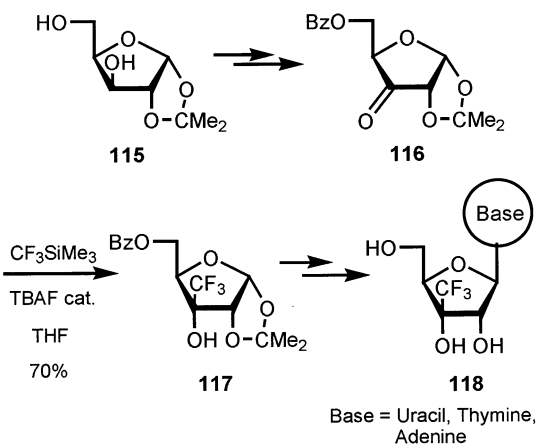
Scheme 24.

to give intermediates that are transformed into deoxydifluoromethyl amino sugars **71**.

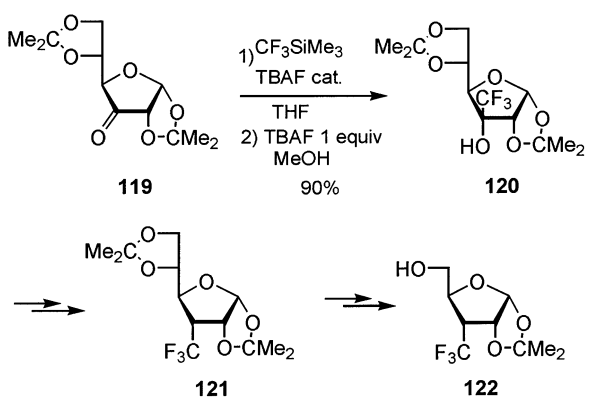
An interesting synthesis of 6,6-difluoroazasugar derivatives has been proposed also starting from difluoroethanal [38,39]. The key step of the synthesis was an aza-Diels–Alder reaction between a chiral, enantiopure imine of



Scheme 25.



Scheme 26.



Scheme 27.

difluoroethanol **72** and Danishefsky's diene **73**, to give 6-difluoromethyl-5,6-dihydropyridin-4-one **74**, **75**. The other important features of this synthesis, which is described in Scheme 18, are the stereoselective enolate hydroxylation (using an oxaziridine) and the hydroboration. Only one difluoroazasugar **77** is described in Scheme 18. Two other epimers were reported, either from the diastereomer formed in the cycloaddition step, or from an epimerization of the product of the first hydroxylation.

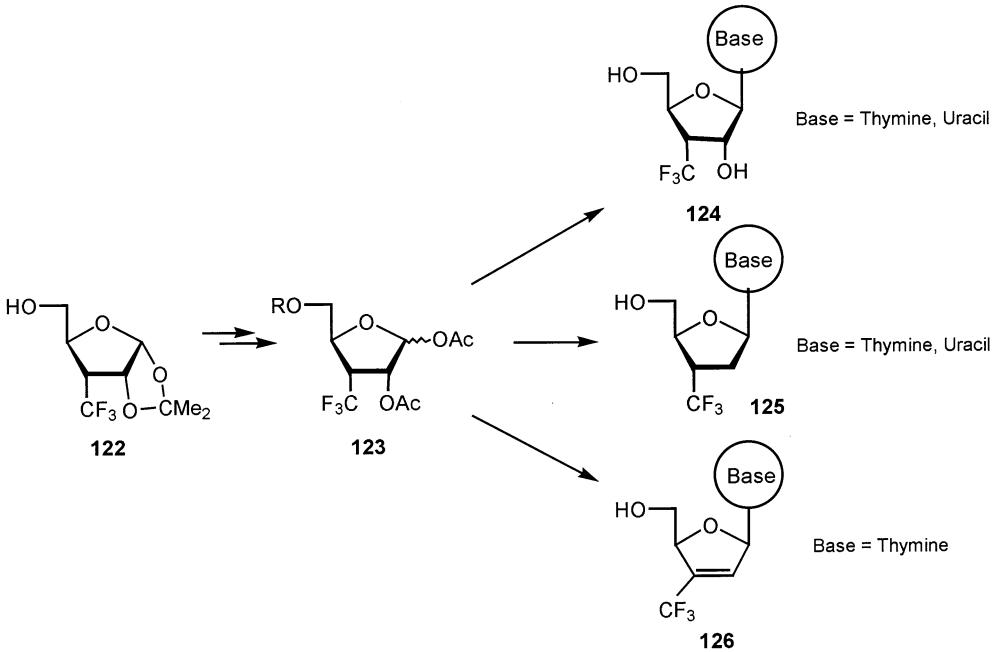
Difluorophosphonate analogues of thymidine were synthesized according to Scheme 19 [40]. The starting difluoro synthon was ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate (**80**), obtained from the commercially available 2-fluoroprecursor **79**. The key step was the α-acylation of 4-(*p*-tolylsulfinyl)but-1-ene (**78**). Subsequent reduction of the carbonyl group, separation of diastereomers, oxidative cleavage of the terminal double bond and Vorbrüggen type coupling with thymine gave the epimeric nucleoside analogues **85**.

3. *C*-Trifluoromethyl carbohydrates

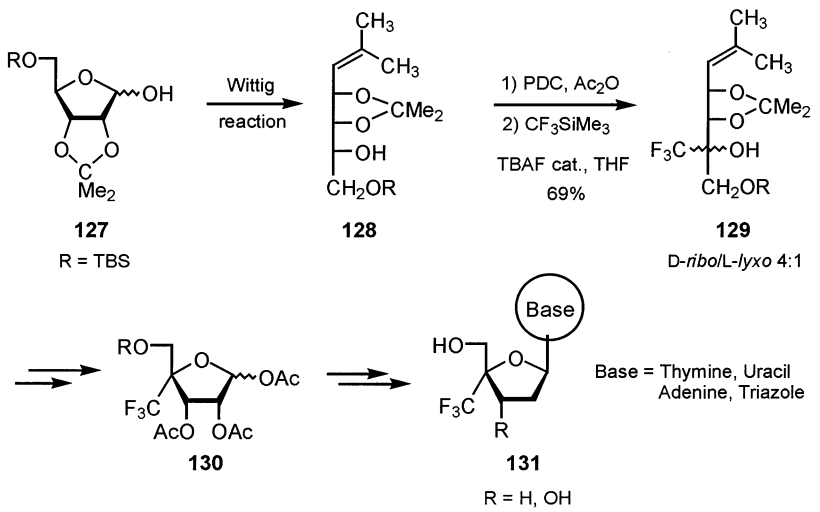
This is certainly the richest family of *C*-*F*-alkyl sugars. The literature affords many papers describing the synthesis of sugars bearing a trifluoromethyl group on any of the carbon atoms. Most syntheses were performed by nucleophilic trifluoromethylation of a carbonylated substrate. Some others used radical trifluoromethylation of an unsaturated carbohydrate or fluoride addition to a difluoromethylene derivative. Lastly, some syntheses from trifluoromethylated synthons will be described.

3.1 Nucleophilic trifluoromethylation.

The most useful method of grafting a CF_3 group on a carbohydrate is the nucleophilic addition of a trifluoromethyl organometallic reagent to a carbonylated sugar. The most convenient reagent for such a purpose is trifluoromethyltrimethylsilane **86** (TFMTMS, Ruppert's reagent) [41]. The properties and methods of preparation of this reagent as a convenient source of nucleophilic CF_3 were



Scheme 28.



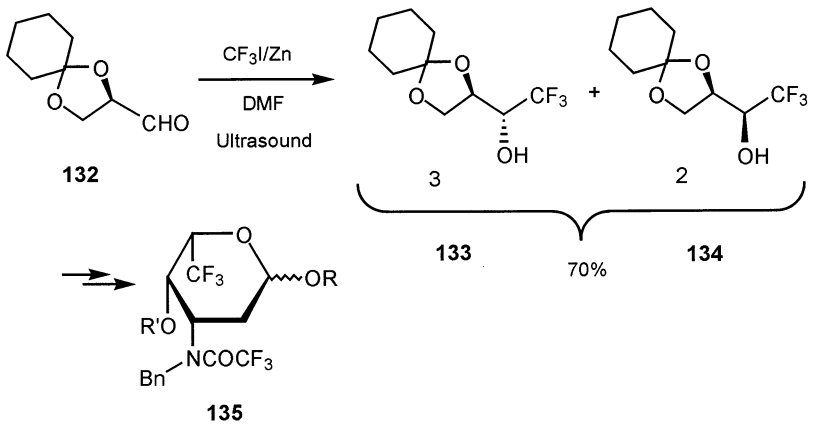
Scheme 29.

recently reviewed by Prakash and co-workers [42]. Activation of TFMTMS is generally initiated by fluoride ions to give the nucleophilic CF_3 species stabilized within a pentavalent silicon adduct **87** able to smoothly deliver a CF_3 carbanion to the carbonyl group. The resulting alcoxide intermediate **88** can itself activate TFMTMS (Scheme 20) so that only a catalytic amount of fluoride is sufficient. Subsequent hydrolysis or treatment with one equivalent of TBAF gives the corresponding trifluoromethylated alcohols.

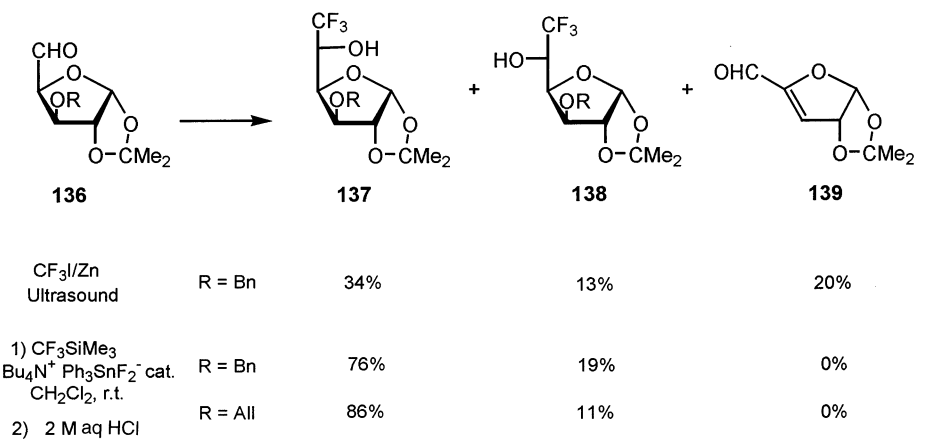
For carbohydrates, the first use of TFMTMS was reported by Toyokuni and coworkers [43]. To obtain new chemotherapeutic agents, they substituted the methyl group in the L-fucose residue by the more hydrophobic CF_3 group. Addition of TFMTMS to the D-*lyxo* derivative **90**, followed by selective oxidation with the Collins reagent, gave the 6,6,6-trifluoro-L-fucose. Unfortunately, the nucleophilic addition was not stereoselective and led to a 1:1 mixture of 6-deoxy-L-*galacto* and 6-deoxy derivatives. It is worth noting

that the replacement of the methyl group with a CF_3 group increases the furanose proportion at equilibrium (Scheme 21).

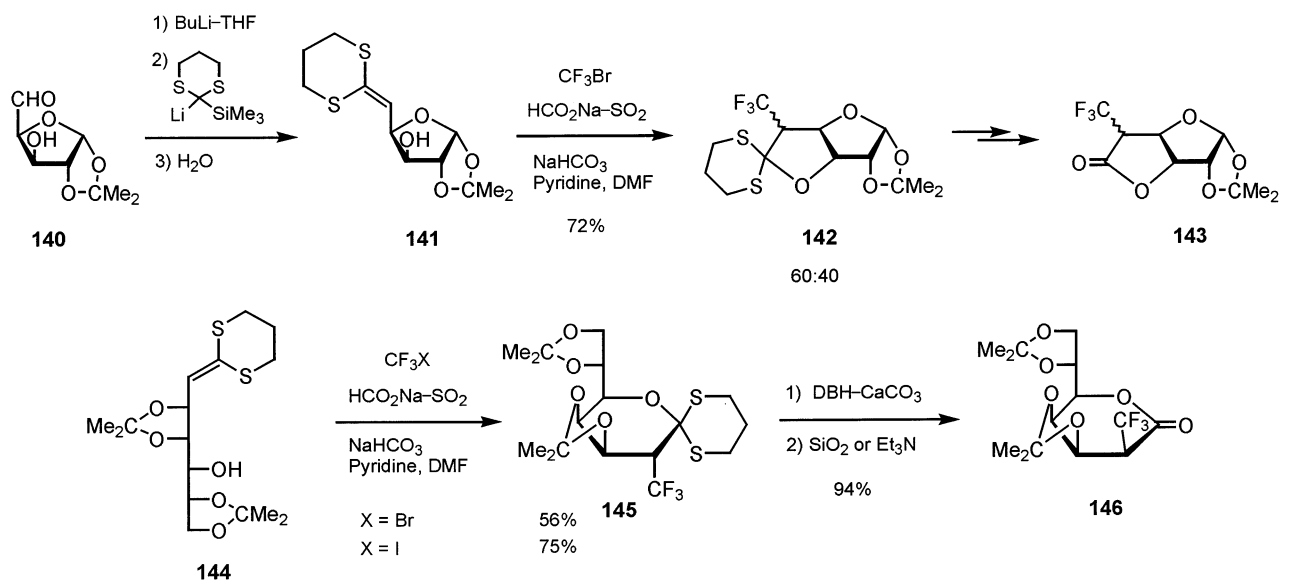
More recently, a French group was interested in trifluoromethylation of different sugar lactones. They first synthesized a new class of



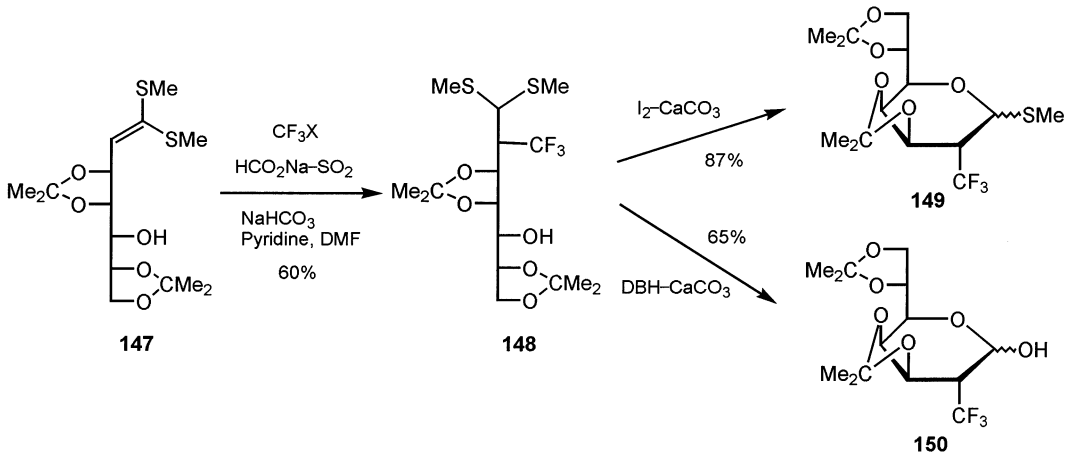
Scheme 30.



Scheme 31.



Scheme 32.



Scheme 33.

carbohydrates with a stabilized glycosidic bond: 1-deoxy-1,1,1-trifluoropent(hex)-2-uloses (**95**), by replacement of the anomeric hydrogen by a CF_3 group (Scheme 22). After mesylation of the anomeric hydroxyl group, substitution with different nucleophiles was realized and the anomeric configuration was studied [44].

The different epimers of 5-deoxy-5,5,5-trifluoropentoses have been synthesized, from sugar lactones **96** and **98** for D- and L-ribose [45,46] and -lyxose derivatives, and from L- or D-threitol **100** and **106** for D- and L-arabinose and -xylose derivatives [44]. The key step of the synthetic sequence is the selective reduction of the hemiacetal or carbonyl group. This reduction strongly depends on the nature of the carbohydrate substrate, the nature of the reducing reagent, and the presence of the CF_3 group [47] (Scheme 23).

The syntheses of 3-*C*-trifluoromethyl derivatives of 1-D-*myo*-inositol-1,4,5-triphosphate (**110**) and 1-L-*chiro*-inositol-1,2,3,5-tetrakisphosphate have been carried out using TFMTMS and commercially available L-quebrachitol **107** [48] (Scheme 24).

The need for new antiviral agents has recently generated considerable interest in the synthesis of nucleoside analogs bearing a CF_3 group on the carbohydrate residue. The CF_3 group was generally introduced on the sugar before its conversion into a nucleoside.

Schmit reported the introduction of a CF_3 group at the 2-position of a D-ribose derivative as the first step towards 2′-deoxy-2′-*C*-trifluoromethyl ribonucleosides (Scheme 25) [49]. The nucleophilic trifluoromethylation led to a unique stereoisomer resulting from the attack of the CF_3 group on the β-face of the sugar ring. Radical deoxygenation gave the sugar derivative with the CF_3 group in the 2′α position as the major isomer ($\alpha/\beta = 4{:}1$) due to the congestion around the α-face.

In the same way, Johnson et al. [50] introduced a CF_3 group at C-3 of a sugar residue and synthesized 3′-*C*-trifluoromethyl ribonucleosides **118** (Scheme 26).

We performed the synthesis of a 3-deoxy-3-*C*-trifluoromethyl-D-ribose **122** from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**119**) by a reaction sequence where the key steps of trifluoromethylation and radical deoxygenation are highly stereoselective [51] (Scheme 27).

Their transformation into 3′-deoxy-3′-*C*-trifluoromethyl-D-*ribo*- and 2′,3′-dideoxy-3′-*C*-trifluoromethyl-D-*erythro*-pentofuranosylnucleosides (**124**, **125**) and antiviral evaluation of these molecules, as well as a 3′-*C*-trifluoromethyl analogue of d_4T **126**, have been recently described [52] (Scheme 28).

Johnson's group has developed a method for introduction of the CF_3 group at the 4-position of D-ribose. The 4-*C*-trifluoromethyl-D-ribose (**130**) was coupled with various bases according to the Vorbrüggen protocol to give some new trifluoromethylated nucleoside analogues **131** (Scheme 29) [53].

In addition to TFMTMS, trifluoromethylation of *aldehydo*-sugars was carried out with

CF_3ZnI under ultrasonic irradiation. Addition to a protected D-glyceraldehyde **132** led to trifluoromethyl alcohols **133**, **134** which were further converted into 6,6,6-trifluoro-L-daunosamine (**135**) (Scheme 30) [54].

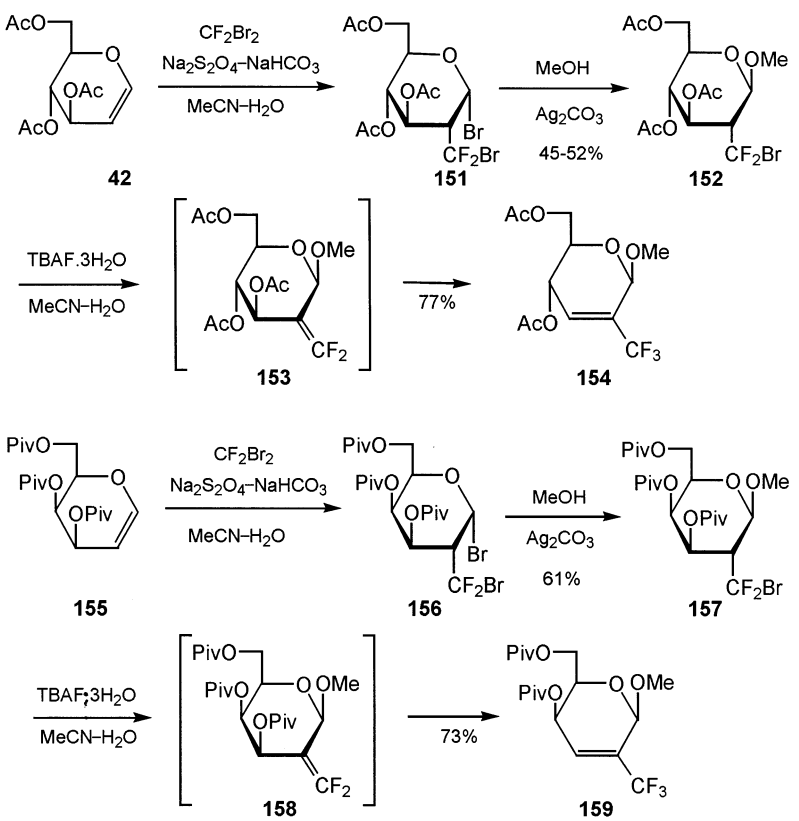
The same procedure was applied to a protected pentodialdo-D-xylofuranose **136**, giving a diastereomeric mixture of 6-deoxy-6,6,6-trifluoro-L-idose **137** (major) and -D-glucose **138** derivatives. The yield of adducts was limited by the formation of an elimination byproduct **139** (Scheme 31) [54]. The use of TFMTMS in the above described conditions allowed us to prepare the same compounds in quantitative yields, with a better L-*ido* selectivity, even though a chelating zinc effect was not involved (Scheme 31) [55].

3.2 Radical trifluoromethylation and related methods.

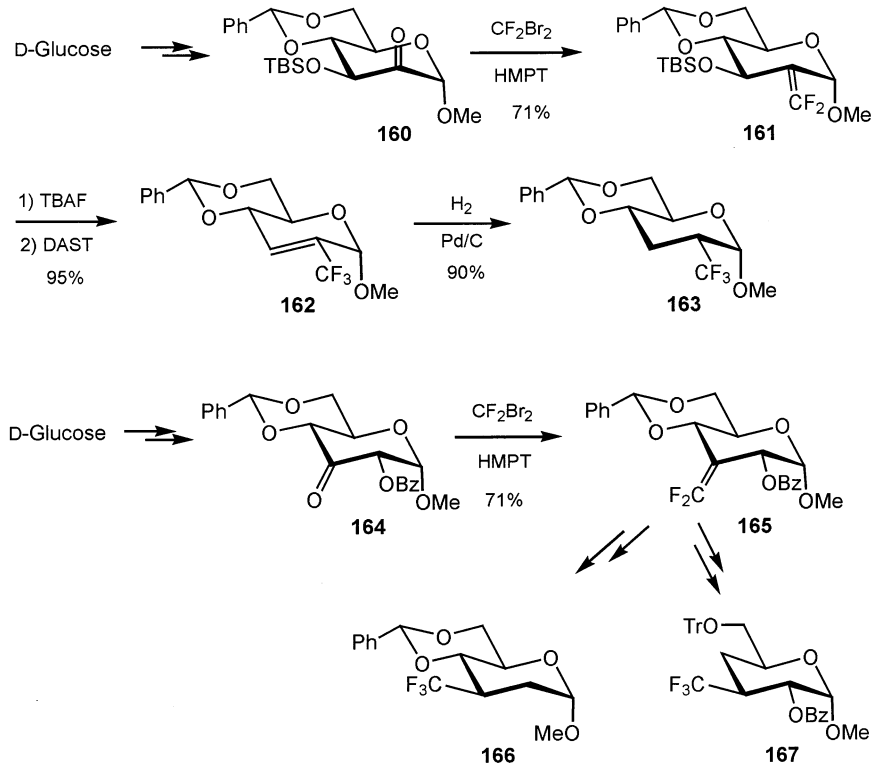
C-trifluoromethyl hexose and heptose derivatives have recently been synthesized by our group from sugar-derived ketene dithioacetals **141**, **144**, using a radical trifluoromethylation–nucleophilic cyclization sequence. The substrates were prepared by a Peterson olefination of a pentodialdo-D-xylofuranose derivative **140** [56] or 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose [57]. The overall transformation is featured by (i) a sequential radical addition–intramolecular nucleophilic displacement by a free hydroxyl group on the carbohydrate; (ii) a concomitant one carbon homologation of the sugar. The radical trifluoromethylation was induced by single-electron transfer from the HCO_2Na/SO_2 system [58]. Application of this method to the ketene dithioacetal derived from the pentodialdo D-xylofuranose derivative **141** led, after oxidative dethioketalization, to the two epimeric 5-deoxy-5-*C*-trifluoromethyl alduronolactones **143** [56] (Scheme 32).

On the other hand, a ketene dithioacetal built on C-1 led to 2-deoxy-2-*C*-CF_3 derivatives **149**, **150**, as illustrated with the substrate derived from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**147**) (Scheme 33).

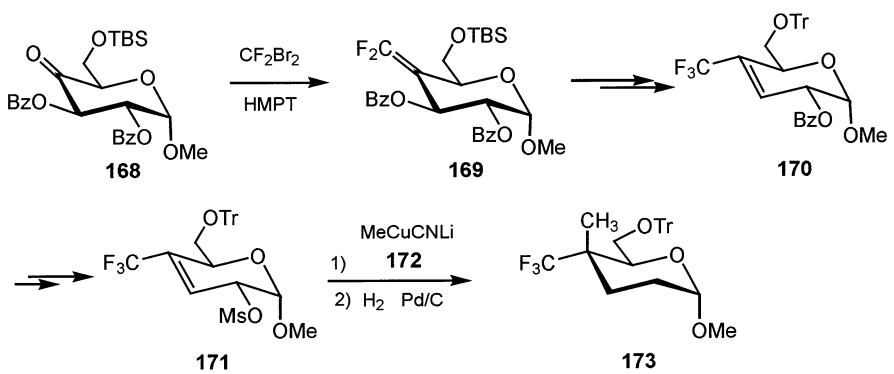
The latter was converted in two steps into either 2-deoxy-2-*C*-trifluoromethyl-D-*glycero*-



Scheme 34.



Scheme 35.



Scheme 36.

D-*galacto*-heptopyranose (**150**), or the corresponding methyl thioglycoside **149**, or to the 2-deoxy-2-*C*-trifluoromethyl-D-*glycero*-D-*talo*-heptonolactone (**146**) [57]. The versatility in this series comes from the selective halotrifluoromethylation–cyclization or hydrotrifluoromethylation depending on the sulfur substituents, and an easy and quantitative epimerization at C-2 upon conversion to the lactone and its purification over silica gel. Moreover, the radical addition in the D-mannose series proved to be highly stereoselective.

Miethchen and co-workers reported the radical bromodifluoromethylation of protected D-glucal **42** and D-galactal **155** with dibromodifluoromethane initiated by sodium dithionite [59] according to a procedure previously applied to F-alkylation of D-glucal (vide infra). Methanolysis of the bromo 2-*C*-bromodifluoromethyl glycoside (**151**, **156**) was followed by a treatment with *n*-tetrabutylam monium fluoride which acts as a base (HBr elimination), then as a nucleophile (S'_N2) to give the corresponding methyl 2,3-dideoxy-2,3-didehydro-2-*C*-trifluoromethyl-D-glucoside (**154**) and -D-galactoside (**159**) (Scheme 34).

3.3 Via a C-difluoromethylene carbohydrate.

Kitazume and co-workers. described the introduction of a trifluoromethyl group at C-2 [13] or C-3 [12] from a D-glucose derivative. Difluoromethylenation (vide supra), selective deprotection of the vicinal hydroxyl group and treatment with DAST gave, via an S'_N2 reaction [60], an unsaturated trifluoromethyl compound, which is stereoselectively hydrogenated into the corresponding derivatives of 2,3-dideoxy-2- or -3-*C*-trifluoromethyl-D-glucose (**163** or **166**) or into 3,4-dideoxy-3-*C*-trifluoromethyl-D-glucose (**167**) (Scheme 35) [61].

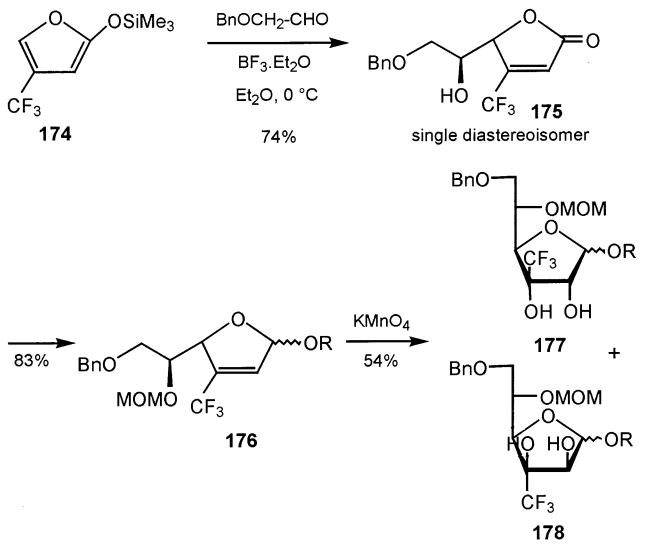
The synthesis of a 4-*C*-methyl-4-*C*-trifluoromethyl-D-glucose derivative **173** has been carried out from protected 4-*C*-difluoromethylene-D-glucose (**169**) by a reaction sequence involving the installation of the methyl group by an S'_N2 displacement of an allylic mesylate with a methyl cyanocuprate **172** [62] (Scheme 36).

3.4 The building block approach.

Other methods to design the construction of trifluoromethylated sugars use trifluoromethylated building blocks as starting materials, which are transformed in several steps into *C*-trifluoromethyl carbohydrate analogues.

The first example was reported by Kobayashi and co-workers, describing the synthesis of 3-*C*-trifluoromethyl-DL-hexoses from 4 - trifluoromethyl - 2 - trimethylsilyloxyfurane (**174**) [63]. A diastereoselective Lewis acid catalyzed aldol reaction, followed by dihydroxylation of the resulting butenolide, led to 3-*C*-trifluoromethyl-*gulo*- and -*talo*-furanoside analogues **177** and **178** (Scheme 37).

Kitazume, Yamazaki and co-workers reported the synthesis of 6-deoxy-6,6,6-trifluoro hexoses via an efficient enzymatic resolution from optically active butenolides bearing a CF_3 group. The key step of these syntheses is the 1,2-shift of a *tert*-butyldimethylsilyl group from a trifluoromethylcarbinol function to a nonactivated hydroxyl group. Owing to the modification of the butenolide double bond (hydrogenation, mono- or dihydroxylation), a wide series of more or less deoxygenated 6-deoxy-6,6,6-trifluoro hexopyranoses (**182**, **185**, **188**, **191**, **194**, **196**) were synthesized [64]



Scheme 37.

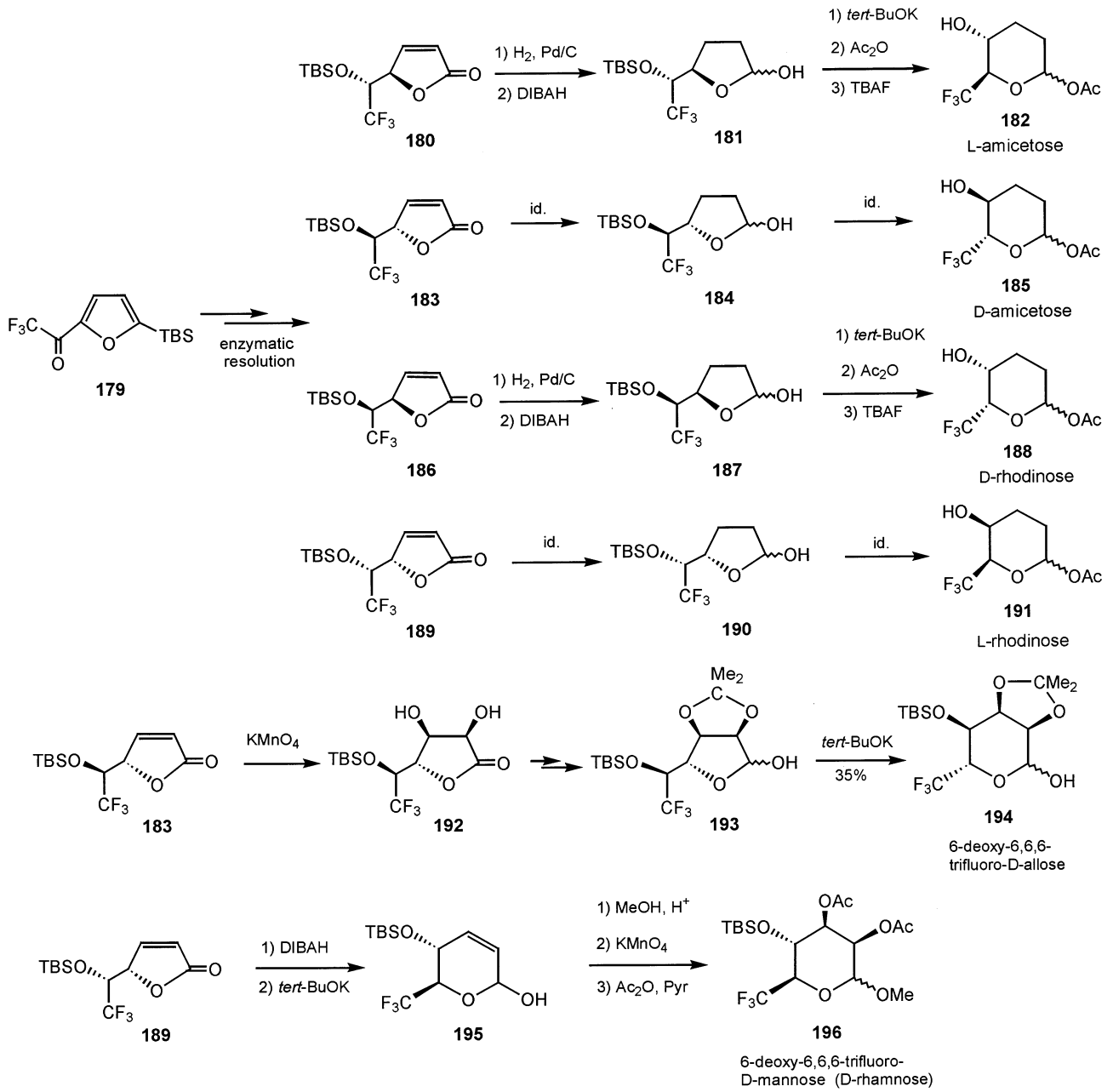
(Scheme 38). The 2,3-dideoxy derivatives thus obtained were used as chiral dopants for ferroelectric liquid crystals [65].

The same authors described the synthesis of 2,6-dideoxy-6,6,6-trifluorosugars **201**–**204** from triols, obtained by a two-step transformation of a trifluoromethyl propargylic alcohol **198**, itself resolved enzymatically [66] (Scheme 39).

A Japanese patent reported the synthesis of 2′,3′-dideoxy-3′-*C*-trifluoromethyl ribonucleosides **209** from 1,1,1-trifluorobutane-2,3-diol (**205**) [67] (Scheme 40). The drawback of this strategy, compared with the sugar trifluoromethylation procedure (vide supra 2.1) is the number of steps and the nonstereoselective coupling with the base due to the 2-deoxygenated position.

Burger's group reported the synthesis of 3-deoxy-2-*C*-trifluoromethyl pentoses **214**, **215** [68] and 2-*C*-trifluoromethyl pentoses **218** [69] successively using trifluoromethylpyruvates **210** as the starting material. The multistep sequence led to 2-*C*-trifluoromethyl DL-ribose and -arabinose and the corresponding 3-deoxy analogues, which exhibited enhanced anomeric and furanose stability (Scheme 41).

(Trifluoroacetylvinyl)methyl ether **219** was the building block chosen by chemists from Ciba-Geigy to prepare a 6-deoxy-6,6,6-trifluoro glycal (**221**) which was included in a disaccharide for the synthesis of avermectine analogues. The first key step of this multistep synthesis is a Lewis acid catalyzed [4 + 2] cy-



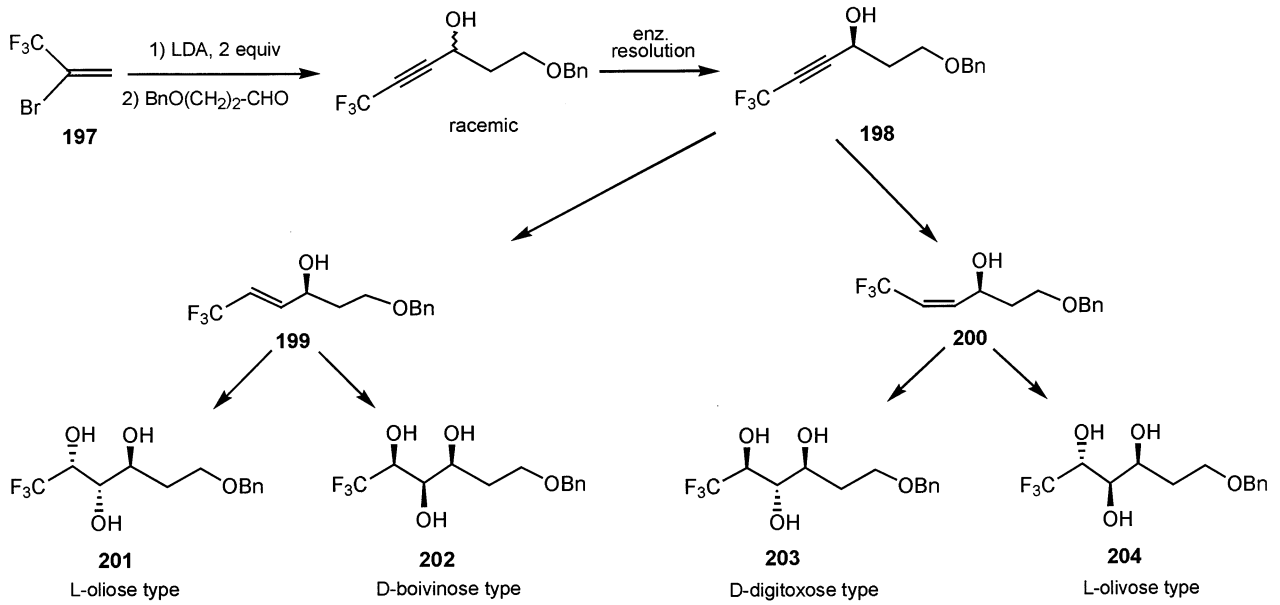
Scheme 38.

cloaddition reaction with ethyl vinyl ether **220** (Scheme 42) [70].

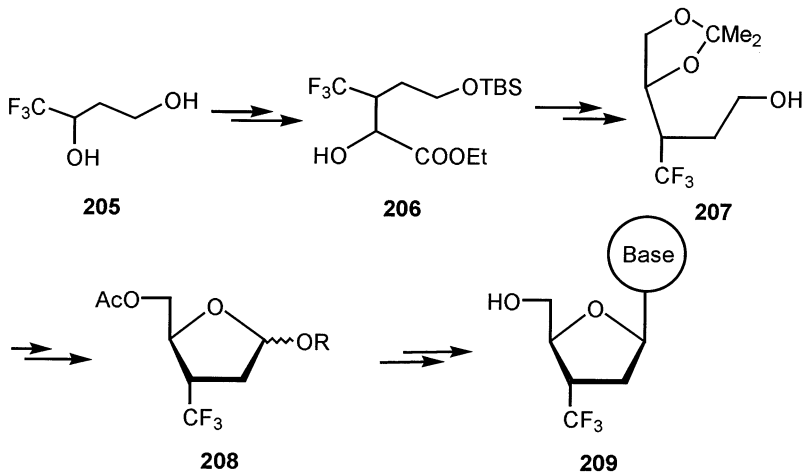
By a similar methodology, an Australian group recently reported the synthesis of 2,6-dideoxy - 6,6,6 - trifluoro - DL - *arabino* - hexose (**227**, **228**). The key step in the synthesis involved the Lewis acid catalyzed hetero-Diels–Alder reaction of (*E*)-4-benzyloxy-1,1,1-trifluorobut-3-en-2-one (**223**) and benzyl vinyl ether **224**. Hydroboration–oxidation of the resulting cycloadduct and debenzylation gave the desired compounds in a 59% overall yield. These products were further used for *C*-glycosylation with aromatic alcohols (Scheme 43) [71].

4. *C*-Perfluoroalkyl carbohydrates

Perfluoroalkyl monosaccharides bearing a strongly hydrophobic and lipophobic perfluoroalkyl chain and a biocompatible polar



Scheme 39.

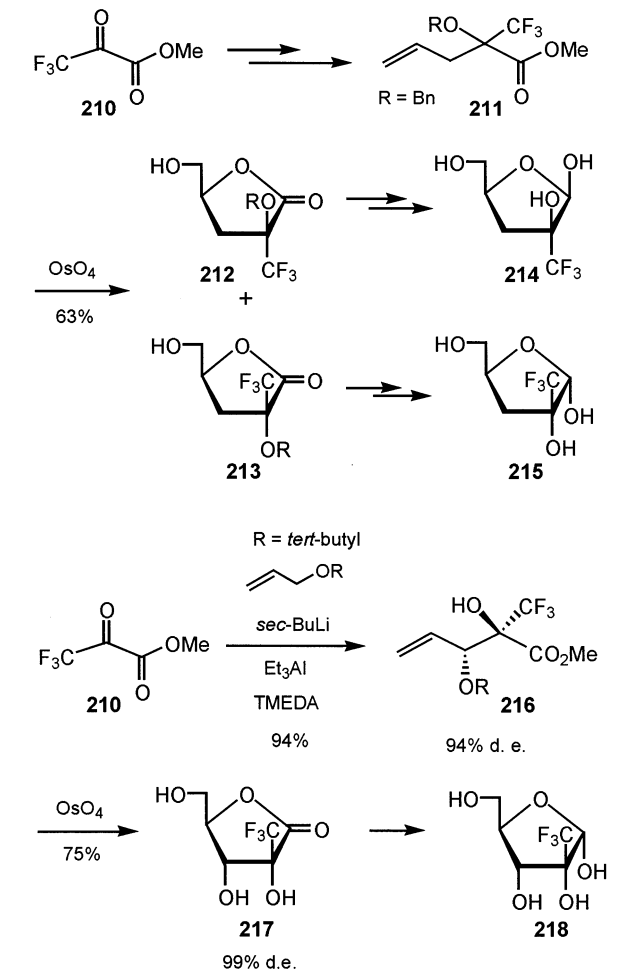


Scheme 40.

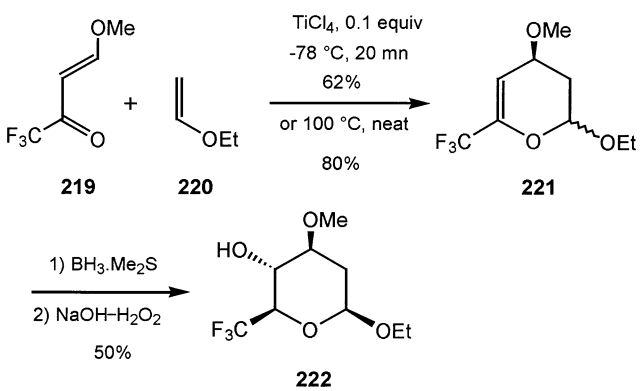
head have been principally studied as surfactants and emulsifiers for biomedical applica tions, and some of them have exhibited interesting liquid-crystalline properties [2,4]. Most of the reported perfluoroalkyl carbohydrates contain a hydrocarbon or a functional group spacer between the hydrophilic sugar moiety and the *F*-alkyl chain. Only those bearing the *F*-alkyl chain grafted onto the sugar backbone by a stable C–C bond are reviewed here. As the fluorinated moiety is the costly part of the molecule, the economical value of the process imposes its introduction at the end of the syntheses. Hence, not surprisingly, the building block approach is uninteresting, and the syntheses reported so far have involved direct nucleophilic or radical introduction of the *F*-alkyl group, the reagents of choice for this purpose being *F*-alkyl iodides.

4.1 Nucleophilic addition.

Owing to their limited stability, main group *F*-organometallic reagents [72] are often generated in situ by a halogen–metal exchange reaction. Some Barbier-type additions have also been reported, as well as additions from long *F*-alkyltrimethylsilanes.



Scheme 41.



Scheme 42.

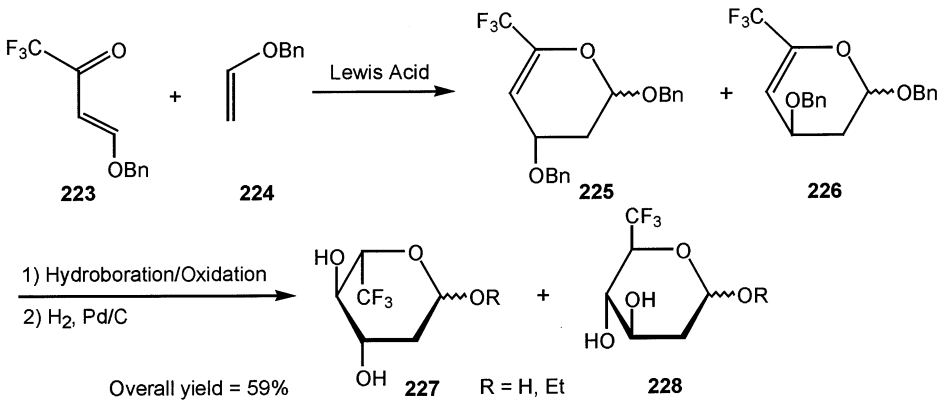
We performed several syntheses of 1-*C*-, 3-*C*- and 6-*C*–*F*-alkylsugars by addition of *F*-alkylmagnesium bromide to the corresponding carbonylated substrate. In some cases, *F*-alkyltrimethylsilanes were also investigated in order to assess the influence of the metal on the stereochemical course of the addition and, in addition, to compare the results with those reported above and obtained with TFMTMS [55].

Addition of *F*-organomagnesium reagents on protected D-glucono-1,5-lactone (**229**) proved to be a very effective reaction (Scheme 44). The optimization of the reactants and reaction conditions (protection–deprotection) allowed us to synthesize 1-*C*-*F*-alkyl-D-glucose (**231**, **232**) with an overall yield of 92% in three steps [73]. Owing to the protection method used, total deprotection may be carried out in one step or a selectively protected product may be prepared.

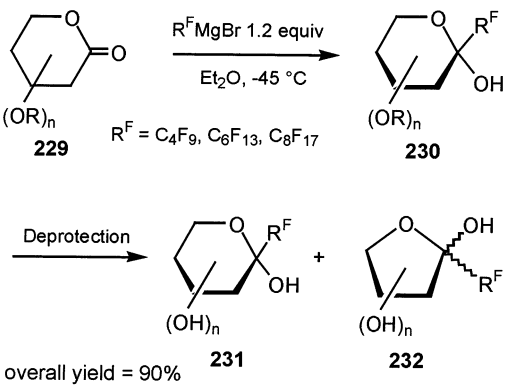
Similar *F*-alkylation in the pentodialdo-D-xylofuranose series **136** gave the results depicted in Scheme 45. The stereoselectivity depends strongly on the metal. A complete L-*ido* selectivity was observed with *F*-alkylmagnesium bromide, whereas the corresponding trimethylsilyl reagent gave, as with TFMTMS, excellent yields but a fair L-*ido* selectivity. The chelation effect by magnesium is obvious. Nevertheless, a stereoelectronic effect (electronic repulsion of the *F*-alkyl chain and the oxygen rich endo region of the substrate) must be considered to explain a much better stereoselectivity than in usual nonfluorinated organomagnesium reagents [55].

Miethchen and co-workers recently reported the nucleophilic F-alkylation of the same aldehyde using a sonochemically assisted Barbier-type reaction with R^FI and Zn (Scheme 45) [74]. They demonstrated the dramatic sonication effect. Despite the convenient reaction conditions, the yields and stereoselectivity with zinc reagents are poorer than with the magnesium ones prepared by iodine–magnesium exchange. The mesogenic properties of the deprotected adducts have been described [75].

The addition of *F*-alkylmagnesium bromide or the corresponding trimethylsilane to 1,2:5,-6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose-3-ulose (**119**) gave the corresponding 3-*C*-*F*-alkyl products **235**, **236** with a metal-dependent epimeric distribution with some different features not found in non-fluorinated series. The results are however less impressive than above and more difficult to be rationalized (Scheme 46) [55].



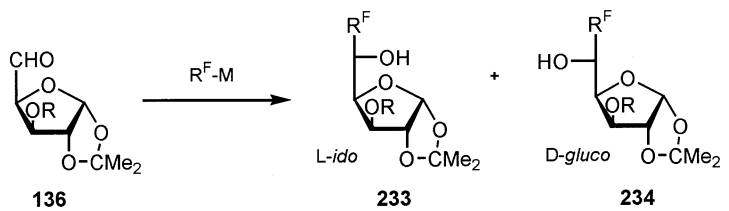
Scheme 43.



Scheme 44.

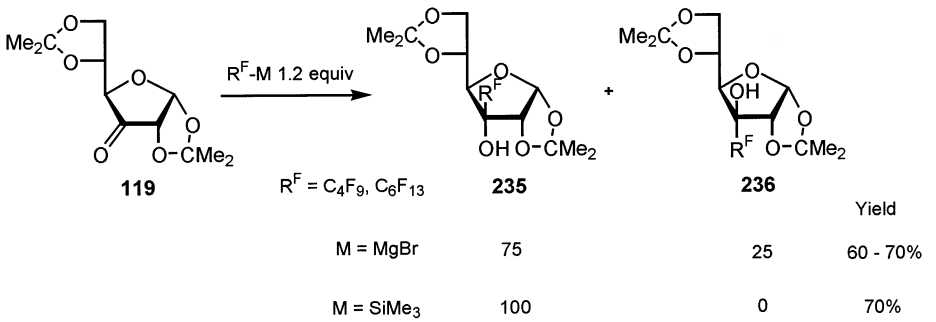
4.2 Radical perfluoroalkylation.

The radical addition of R^FI to unsaturated compounds is a convenient method for F-alkylation [76]. Such reactions are usually initiated by heat, light, radical initiators or single-electron transfer. The first direct grafting of the perfluoroalkyl chain on a carbohydrate framework was described by Huang and co-workers, who have added an *F*-alkyl iodide to a protected D-glucal **42**. The reaction was initiated by sodium dithionite (electron trans-

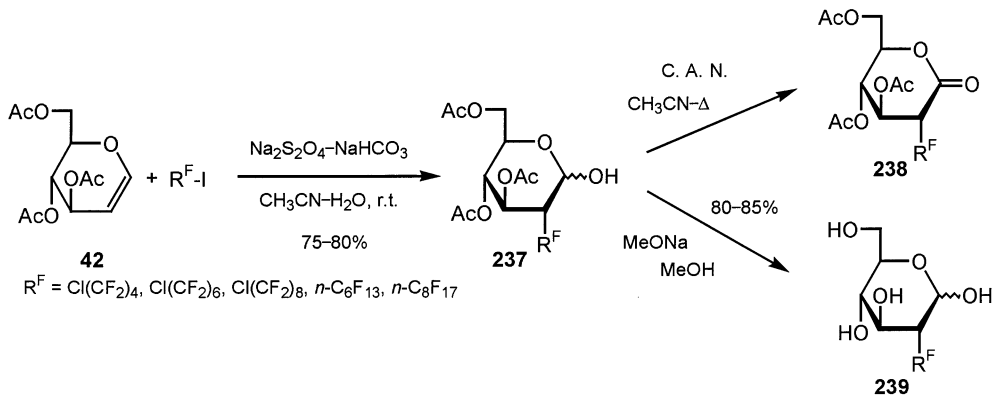


Conditions	R	R_F	Yield (%)		Ref
R^F-I / Zn / DMF sonication, r.t., 1.5 - 8 h	Bn	C_4F_9	36	17	[74]
		C_6F_{13}	38	12	
		C_8F_{17}	27	12	
1) R^F-$SiMe_3$ (1.1 equiv) F^- cat., CH_2Cl_2, r.t. 2) H_3O^+ or TBAF	Bn	C_4F_9	55	10	[55]
1) R^F-MgBr (1.2 equiv) Et_2O, -45 °C 2) H_3O^+	Bn	C_4F_9	64	0	
		C_6F_{13}	57	0	
	All	C_4F_9	68	0	
		C_6F_{13}	60	0	

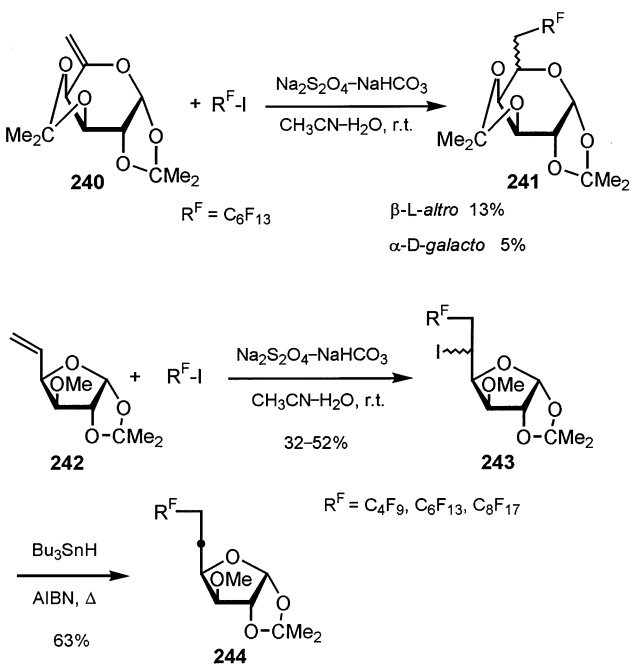
Scheme 45.



Scheme 46.



Scheme 47.

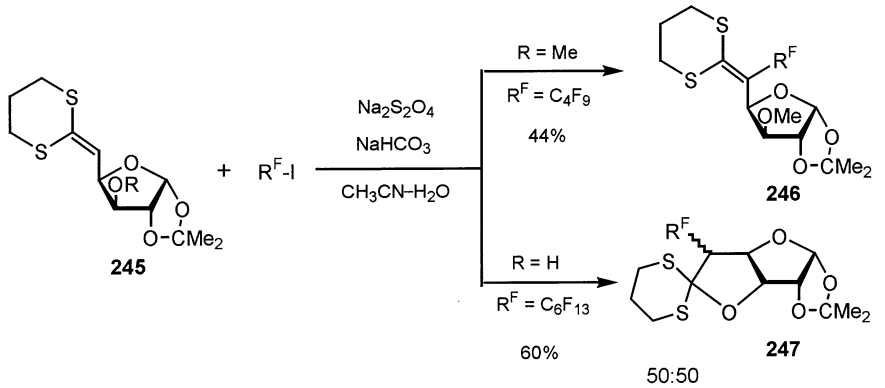


Scheme 48.

fer) in an aqueous–organic medium allowing the direct formation of the hydrolyzed hemiacetalic sugar **237** (Scheme 47) [77].

Miethchen and co-workers developed a similar method of radical perfluoroalkylation of unsaturated monosaccharides with an exocyclic double bond at the 5-position **240**, **242** [78]. The F-alkylation took place selectively at the terminal position but the yields of the desired perfluoroalkylated compounds are moderate owing to the formation of some byproducts (Scheme 48).

We investigated the radical perfluoroalkylation of ketene dithioacetals derived from 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**245**) and 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**144**) (vide supra). In the former case, the reaction was not stereoselective and was more effective when an intramolecular trapping of the adduct is allowed by a free OH group at C-3, even if the yields are at best fair (Scheme 49) [79]. In the D-mannose series, the 2-*F*-alkyl heptose deriva-



Scheme 49.

tive was obtained with a high α-stereoselectivity [80].

5. Conclusions

This review emphasizes the large interest for *C*-*F*-alkyl carbohydrates, whatever the degree of fluorination. Besides some elegant building block strategies developed in a small number of groups and encountered for difluoro or trifluoro derivatives, methods based on organometallic and radical addition may be considered as the most frequently used, even if the reagents, the substrates and the reaction conditions are diverse. Some grafting methods were exemplified on a very few carbohydrate derivatives, simply showing their feasibility in the synthesis of more or less elaborated structures. A large field still remains open, by variation of the sugar substrate structures, to achieve original *C*-*F*-alkyl sugars for various applications.

As far as applications are concerned, as stated in the introduction, compounds such as *C*-difluorophosphonates, *C*-trifluoromethyl, and related ones were synthesized and studied for bioassay purposes (antiviral nucleosides, enzyme inhibitors). Long-chain *C*-*F*-alkyl carbohydrates remain scarce compared with compounds containing a spacer. They have not yet been considered for a possible biomedical use (i.e., fluorocarbon emulsion), but they have been claimed as interesting compounds for fire extinguishers and cosmetic formulations, and liquid crystal properties have been observed. It would be interesting to further study these types of amphiphiles and to assess their properties, with an extension to the disaccharide series for better solubility.

There is no doubt that this very wide spectrum of actual or potential applications, from bioactive to mesogenic compounds, will bring about numerous works in the future and we hope this review will help any development in the field.

Acknowledgements

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