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Carbohydrate- and related polyol-derived fluorosurfactants: an update

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Abstract

A short review of recent literature is presented on the synthesis, biological properties, colloid and surface chemistry, and applications of carbohydrate- and related polyol-derived amphiphiles with perfluoroalkyl hydrophobes. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Perfluoroalkyl(ated) carbohydrates; Perfluoroalkyl(ated) amphiphiles; (Per)fluorosurfactants; Fluorocarbons; Fluorinated colloids; Self-aggregation; Biological properties

Contents

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1. Introduction and scope

The primary purpose of this mini review is to update the chapter on perfluoroalkylated sugar-derived surfactants that appeared in 'Carbohydrates as Organic Raw Materials', the monograph edited by Gérard Descotes in the wake of a Symposium held on this topic in Lyon in 1992 [1].

The principal reasons for synthesizing fluorinated surfactants (fluorosurfactants, i.e., surfactants with one or more perfluoroalkylated hydrophobic chain(s), C_nF_{2n+1}), and in particular derivatives of carbohydrates and other polyhydroxylated compounds were: (i) to provide or facilitate the access to novel colloidal systems, including various types of emulsions with a dispersed or continuous fluorocarbon phase, fluorinated vesicles (liposomes), and other highly fluorinated self-assemblies, susceptible of applications in the oxygen and drug delivery area, and (ii) to allow determination of the impact of perfluoroalkyl (*F*-alkyl) tail chains (hydrophobes) on the formation, nature, stability, structure and properties of such colloids. This knowledge was in turn expected to help control the properties of these systems [2–4]. Carbohydrate-derived polar headgroups are attractive for particle targeting purposes. Specific recognition of carbohydrates by membrane lectins is indeed known to be involved in numerous biological events (see, for example [5–8]). Some carbohydrate-derived amphiphiles have shown adjuvant activity [9], anti-tumor activity [10] or anti-HIV activity [11]. Such amphiphiles are also being used as emulsifiers [12] and for membrane protein extraction [13,14]. These compounds tend to self-assemble into diverse supramolecular structures [15–17].

Colloidal systems with highly fluorinated components have significant potential in the biomedical field [4,18,19]. Several fluorocarbon-based products are in advanced stages of clinical evaluation for use as an injectable oxygen carrier (blood substitute) during surgery [20,21], for liquid ventilation [22,23], or as a contrast agent for diagnosis by ultrasound imaging [24–26]. One such agent has recently been approved in the United States [27]. A fluorinated surfactant plays a key role in another of these products by allowing the preparation and stabilization of an injectable emulsion of perfluoropentane [25]. The approval of this product should help to remove the reluctance that has so far hindered the use of fluorosurfactants in pharmaceuticals, in spite of their outstanding surfactant properties.

This paper will review the recent literature (until mid 1999) on carbohydrate-derived fluorosurfactants. Telomeric amphiphiles with multiple tris(hydroxymethyl) residues will be included because of their closely related polyhydroxylated headgroups and because they were synthesized for similar purposes. Fluorosurfactants with *F*-alkyl chains linked to a sugar molecule through a C–C bond will not be discussed as they are the topic of another paper in this issue (see also, for example [28,29]). Similarly, amphiphiles with mesogenic properties (see for example [30,31]) will not be discussed. CF_3 derivatives will be mentioned only when they are part of a series of compounds including longer *F*-alkyl chains. Several recent reviews are available on fluorinated amphiphiles [32–34].

2. Synthesis and characterization

A modular molecular design has often been adopted, which combines, using diverse types of junction units between the hydrophilic head and hydrophobic tail, one or more (identical or different) *F*-alkyl chains, hydrocarbon chains and hydrocarbon spacers of variable length, with a variety of polar heads [34–36].

Most of the reactions utilized for synthesizing *F*-alkylated derivatives of carbohydrates and related polyols are classical and were simply adapted to the particular substrate selected. In some instances, however, the *F*-alkyl chain was found to change the outcome of the procedure, as, for example, with the Kœnigs–Knorr reaction [37,38] when the *F*-alkyl chain is close to the reaction site. The fluorinated chain usually confers high surface activity on the products and decreases their solubility in both water and lipophilic solvents, which can considerably complicate separation and purification procedures.

2.1 Glycosides

2.1.1 O-Glycosides.

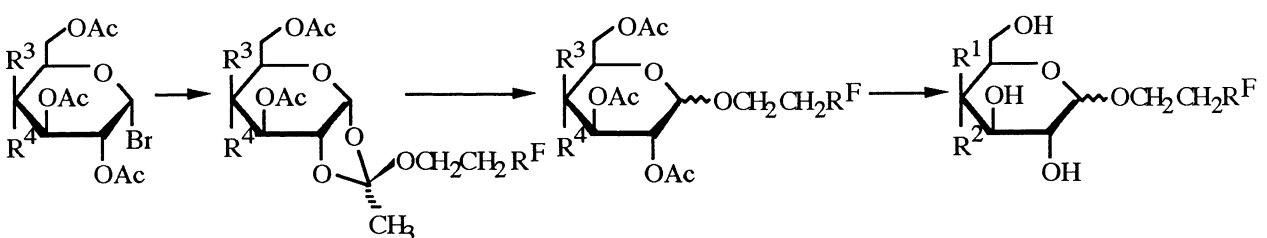
Two strategies were employed for the preparation of (*F*-alkyl)alkyl glycosides: (i) a convergent block synthesis involving the preparation of aglycones containing the *F*-alkyl chain, followed by glycosylation, and (ii) a linear synthesis strategy involving the preparation of glycosides with a hydrocarbon chain containing a double bond on which the *F*-alkyl segment is eventually grafted. The latter approach has the advantage of introducing the most expensive reagent during the last steps of the synthesis.

Convergent block synthesis. The convergent block strategy is by far the best documented [37–48]. Some studies confirm the unusual behavior of *F*-alkylated alcohols that have a short hydrocarbon 'screen' or spacer, such as CH_2 or CH_2CH_2 groups, between the hydroxyl function and the *F*-alkyl segment [37,47].

Some trifluoromethyl glycopyranosides were synthesized through the reaction of tris-(dimethylamino)sulfonium trifluoromethoxide with electrophilic carbohydrate species, but these compounds were unstable [40]. Thus, trifluoromethyl 2,3,4,6-tetra-*O*-methyl-β-D-glucoside undergoes a slow, non-catalyzed solvolysis in ethanol, and trifluoromethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside could not be deacetylated without decomposition [40]. Similarly, 1,1,2-trifluoro-2-chloroethyl D-glucopyranoside [41] decomposes slowly in water with a half-life of 680 h at 25 °C. In order to be stable, *F*-alkyl glycosides require that a hydrocarbon spacer be present between the sugar head and the *F*-alkyl chain.

The Kœnigs–Knorr reaction and orthoester approaches. Condensation of 2-(*F*-hexyl)ethanol with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the usual Kœnigs–Knorr reaction conditions [49] did not yield the expected glycoside but, predominantly, the 1,2-orthoester (**2a** in Scheme 1, 64%) [37,38,42]. Several authors have reported the formation of the 1,2-orthoester as a by-product, but usually only in small amounts, and the glycoside always remains the primary reaction product [49–51]. A likely reason for this abnormal result of the Kœnigs–Knorr reaction may be the inductive effect of the *F*-alkyl group, which lowers the nucleophilicity of the hydroxyl function. Indeed, the reaction became normal again when the hydrocarbon screen inserted between the *F*-alkyl chain and the hydroxyl group was longer [37,38,48,52]. Thus, for example, 11-(*F*-alkyl)-10-undecenol or 5-(*F*-alkyl)-4-pentenol reacted normally with per-*O*-acetyl-maltosyl bromide, which resulted in a high yield of the β-maltoside [38].

Sugar 1,2-orthoesters actually offer an interesting alternative route to trans-1,2-glycosides [49]. The yields of orthoesters **2a–c** were first improved by specific alternative synthesis; the orthoesters were then converted into glycosides **3a–c** (Scheme 1) in 66–79%



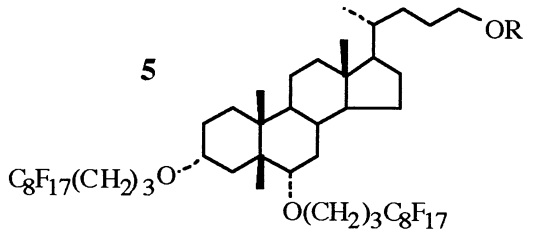
$R^F = C_6F_{13}, C_8F_{17}$

a for glucose: $R^3 = H$, $R^4 = OAc$ or $R^1 = H$, $R^2 = OH$

b for galactose: $R^3 = OAc$, $R^4 = H$ or $R^1 = OH$, $R^2 = H$

c for maltose: $R^3 = H$, $R^4 = \alpha$-D-$(AcO)_4$ glucopyranosyl or $R^1 = H$, $R^2 = \alpha$-D-glucopyranosyl

Scheme 1. Synthesis of 2-(*F*-alkyl)ethyl glycosides by the orthoester method.

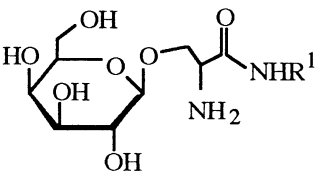


Glucose: R = β-D-glucopyranosyl

Cellobiose: R = β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl

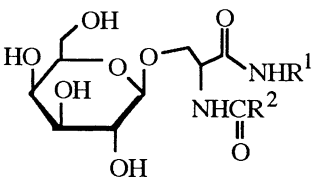
Maltose: R = α-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl

Scheme 2. *F*-Alkyl-containing steroidal glycosides.



$R^1 = (CH_2)_{11}(CF_2)_5CF_3$

6a



$R^1 = (CH_2)_{13}CH_3$ $R^2 = (CH_2)_{10}(CF_2)_3CF_3$

$R^1 = (CH_2)_{15}CH_3$ $R^2 = (CH_2)_{10}(CF_2)_5CF_3$

$R^1 = (CH_2)_{11}C_4F_9$ $R^2 = (CH_2)_{10}(CF_2)_5CF_3$

6b

Scheme 3. β-Galactolipid amphiphiles derived from serine.

yields by refluxing in nitromethane with a catalytic amount of mercury(II) bromide [37,38]. With very few exceptions [53–55] this conventional orthoester glycosylation proceeds with high stereospecificity to yield the 1,2-trans-glycoside [49]. This was not the case here: a mixture of the two anomeric glycosides was obtained in 60–80% yield from **2a**–**c**. The β:α ratio of purified glycosides **3a**–**c** was in the 3:2–7:3 range [37]. The steric outcome of the procedure has been shown to depend on the basicity of the alcohol involved [53]. After purification, the two *F*-alkylated anomers were deacetylated to compounds **4a**–**c**. On a 250-g scale preparation, the maltoside **4c** with the *F*-hexyl group was obtained as its anomeric mixture in 40% yield from **1c**.

The Kœnigs–Knorr reaction was also used to produce the steroidal glycosides **5** (glucose, cellobiose or maltose) with two *F*-alkyl chains (Scheme 2), in view of investigating their monolayers with cellulase at the air–water interface (vide infra) [48,52].

The glycosylimidate and peracetate route. Using Schmidt's methodology [56], the coupling of galactosyl trichloroacetamidate with suitable *F*-alkylated alcohols stereospecifically afforded β-galactose derivatives [44,45,57]. The single- and double-tailed galactolipids, **6a** and **6b**, obtained after deacetylation (Scheme 3) are mimics of the galactosylceramide, which has been proposed as an alternative HIV receptor on CD4(−) cells [44,45,58].

Compounds **7** (Scheme 4) were obtained in about 10% yield by condensation of 1,3-di-*F*-(10′ - chloro - 1′*H*,1′*H*,2′*H*,2′*H* - decylthio) - 2-propanol on per-*O*-acetyl-glucose, -maltose and -maltotriose in the presence of trimethylsilyl triflate, followed by conventional deacetylation. The glycosides were in the α anomeric form for the glucose derivative and in the β form for the two other sugar derivatives [46]. Similarly, condensation of suitable *F*-alkylated alcohols with β-peracetylated laminari-oligosaccharides using stannic tetrachloride as the Lewis acid catalyst produced the expected glycosides in 21–34% yield, which, after quantitative deprotection and sulfation with the sulfur–pyridine complex, afforded compounds **8**, which were tested for anti-HIV activity [11] (Scheme 4).

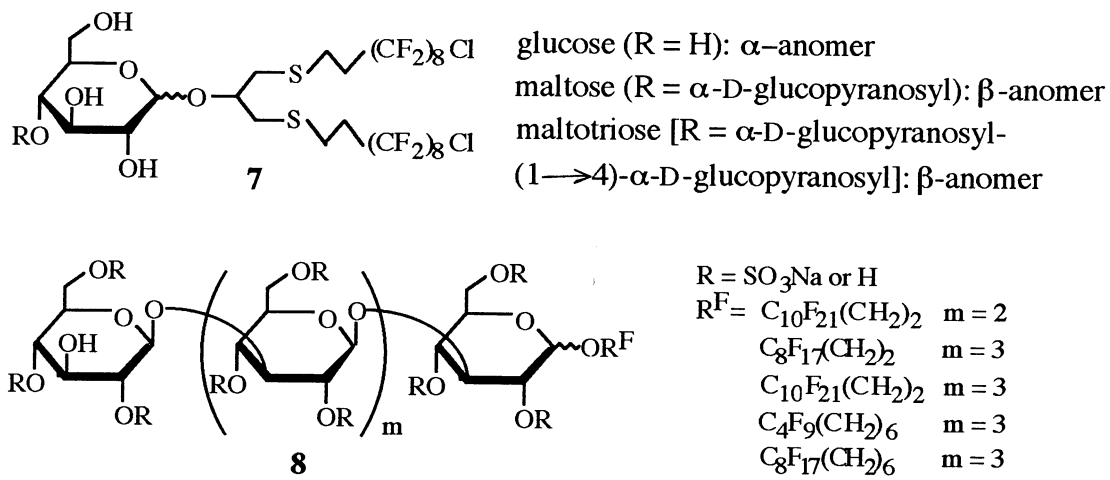
Preparation through glycosylidene carbenes. Some *F*-alkylated glucopyranosides **10** were prepared from 1-azi-2,3,4,6-tetra-*O*-benzyl-1-deoxy-D-glucopyranose (**9**) (Scheme 5), and the corresponding alcohols were synthesized via a thermally generated glycosylidene carbene [43]. The yields and diastereoselectivity depended upon the pK_a values of the alcohol, the solvent and the reaction temperature. The strongly acidic (*F*-alkyl)methanols and 2-(*F*-alkyl)ethanols gave higher diastereoselectivi-

ties than their hydrocarbon counterparts. The best results were obtained at 25 °C in dioxane with a β:α ratio of about 3:1. Higher yields (85%) but lower diastereoselectivity (β:α = 57:43) were obtained in dichloromethane. The compounds were not debenzylated, since the aim of the authors was to develop new glycosidation procedures and not to synthesize new surfactants.

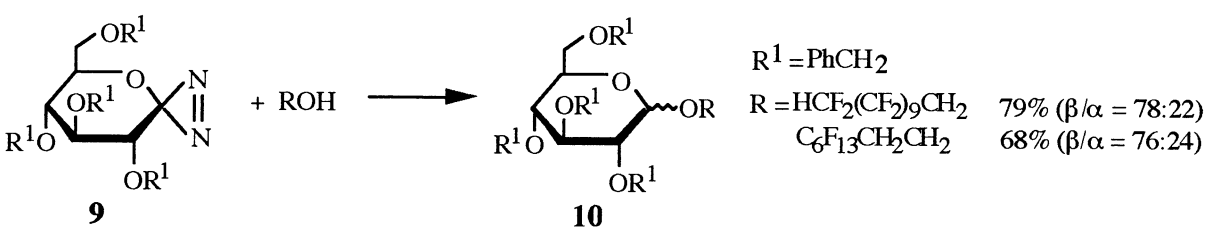
The Mitsunobu route. Due to their low pK_a value, (*F*-alkyl)methanols are well suited to the Mitsunobu reaction conditions [59], as has been shown in the synthesis of fluoroethers [60,61]. The glycoside was obtained in a 40–87% yield when these conditions were applied to various fluorinated alcohols and sugars with a free anomeric hydroxyl group; the α:β ratio varied from 1:4 to 3:2, depending on the alcohol [47]. One drawback of this method is that it requires a large excess (2–8 equivalents) of expensive fluorinated material. The last two studies confirm the unusual behavior of *F*-alkylated alcohols with a short hydrocarbon screen between the hydroxyl function and the *F*-alkyl segment.

Linear synthesis strategy. Diverse mono-, di-, and trisaccharide precursors with an allyl or 9-undecenyl group in the anomeric position were prepared [38,62,63], to which *F*-alkyl iodides were subsequently added in ≥ 70% yields using various well-established radical reaction processes (Scheme 6) [64,65]. Intermediate iodides **12a** and **12c** gave (*F*-alkyl)alkenyl (**13a**,**c**) or (*F*-alkyl)alkyl (**15a**) glycosides after dehydroiodination [38] or hydrogenolysis [62], respectively, followed by deacetylation. One team showed that the product obtained by addition of an *F*-alkyl iodide on allyl glycosides provides an attractive anomeric protection. The anomeric 2-iodo-3-(*F*-alkyl)propyl anchor was efficiently eliminated in the presence of zinc powder and ammonium chloride in ethanol to give sugar derivatives with a free anomeric hydroxyl group [63].

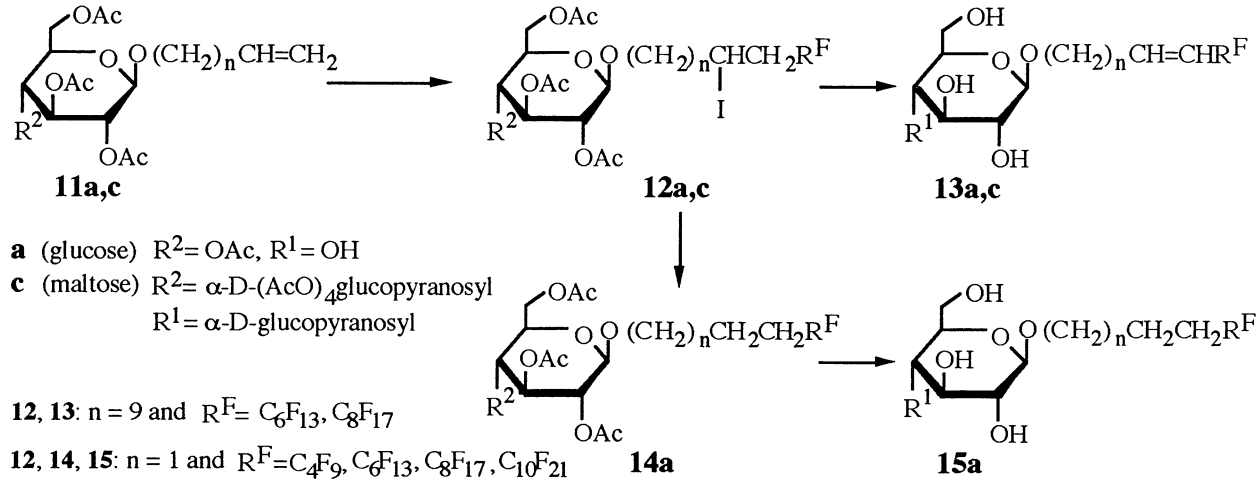
Using this strategy, a series of fluoro-containing muramyl dipeptide analogs **16**, with potential immune activity, was synthesized in five steps with about 40% overall yields [66,67]. The perfluorinated tails were located



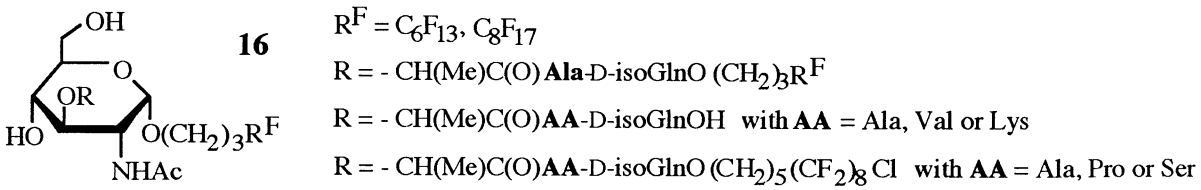
Scheme 4. Amphiphiles **7** and **8** were studied for their recognition interaction with concanavalin A (see below) and anti-HIV activity, respectively.



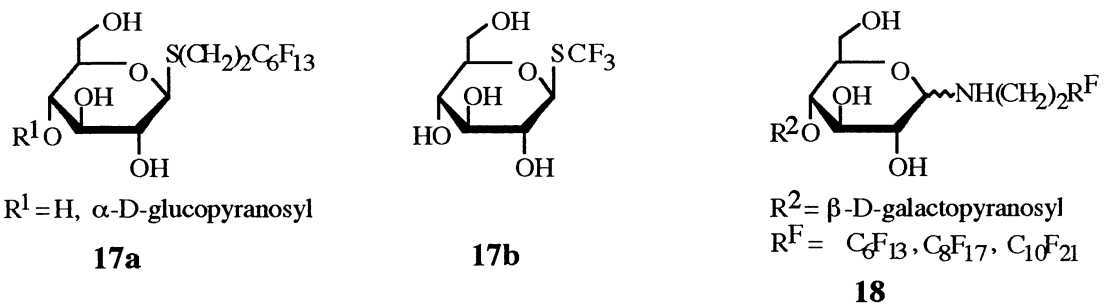
Scheme 5. Glycosidation of *F*-alkylated alcohols using glucosylidene-derived diazirine.



Scheme 6. Linear synthesis of (*F*-alkyl)alkyl glycosides.



Scheme 7. Fluorinated muramyl dipeptide analogs.



Scheme 8. *F*-alkylated *S*- and *N*-glycosides.

on the anomeric position or the C-terminus of the peptide chain (Scheme 7).

2.1.2 S-Glycosides and glycosylamines.

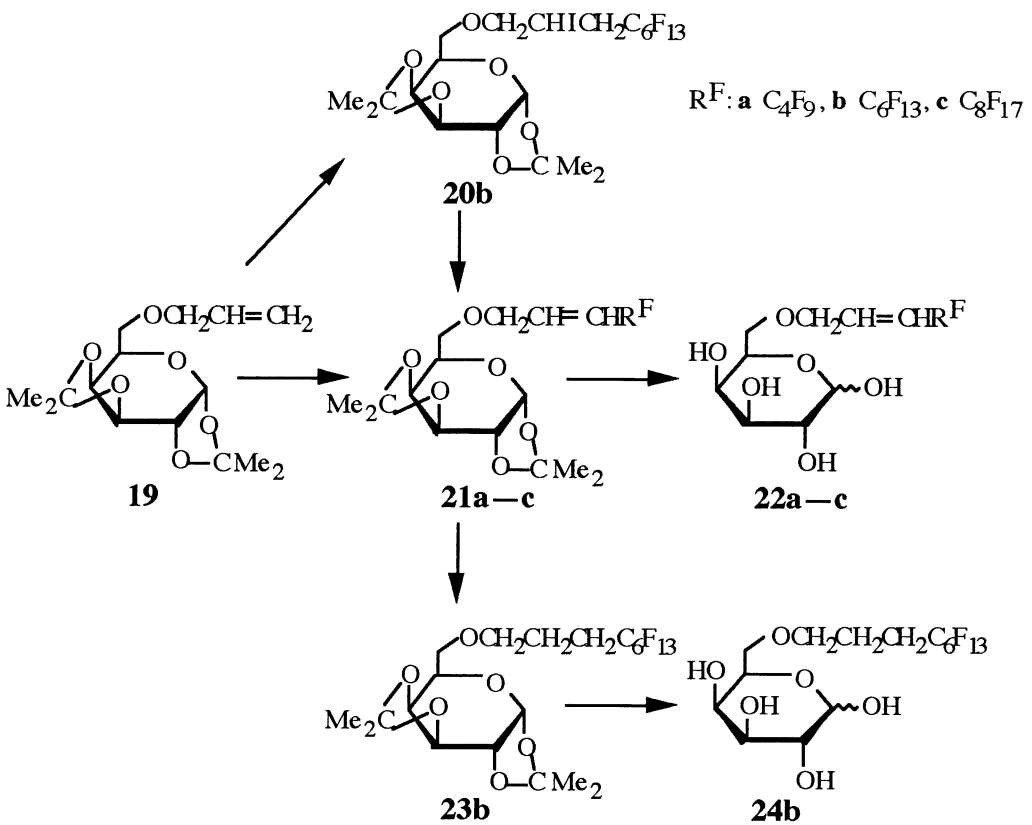
Only two syntheses of *F*-alkylated *S*-glycosides and one of glycosylamines have been reported. Concerning the *S*-glycosides, the first report described the synthesis of **17a** using a standard process: condensation of 2-(*F*-hexyl)ethanethiol onto per-*O*-acetyl-D-glucose or maltose, with boron trifluoridediethyl etherate catalysis, followed by deacetylation (Scheme 8). However, few details, and no yields, were given [68]. The second report, more original, involves only CF_3 compounds. The introduction of the *F*-methyl group was achieved by treatment of a protected sugar thiocyanate with trifluoromethyltrimethylsilane and tetra-*n*-butylammonium fluoride as a catalyst. The *S*-trifluoromethyl 1-thio-β-D-glucopyranoside (**17b**), which was shown to be a weak competitive inhibitor of the almond β-glucosidase, was obtained after deprotection in 60% overall yield [68b]. The report concerning *N*-glycosides describes the synthesis of *N*-[2-(*F*-alkyl)ethyl]lactosamine (**18**) [69,70] by the reaction of a 2-(*F*-alkyl)ethyl azide, via an iminophosphorane intermediate, with lactose (Scheme 8). No protection was required, and the yields were in the 50–55% range.

2.2 Ethers and esters.

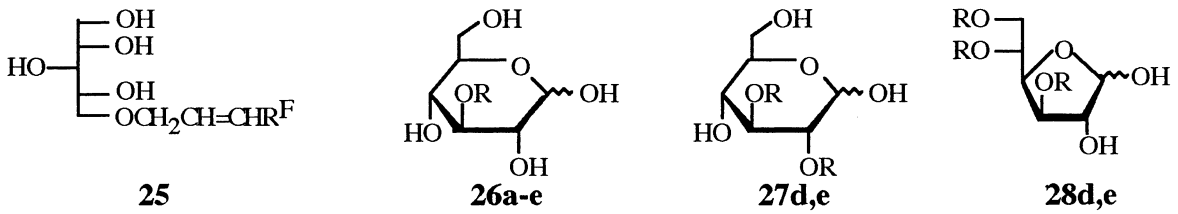
Except for the *F*-methyl group, no well-defined *F*-alkylated ethers or esters have been reported before the mid 1980s. Trifluoroacetylation has found extensive application in chromatography [71], for preparing intermediates [72], and for isolation, modification and specific degradation of the carbohydrate part of glycoconjugates [73a]. Trifluoroacetyl esters are very susceptible to hydrolysis and methanolysis, and similar susceptibility is expected of *F*-acyl esters. However, one report relates the preparation of *F*-butanoyl esters of arabinose obtained by lipase-catalyzed transesterification of the corresponding arabinose derivative with 2,2,2-trifluoroethyl perfluorobutanoate [73b]. Carboxylic and phosphoric esters of *N*-(2-hydroxyethyl)-D-glucamine were prepared, which derived from mixtures of 2-(*F*-alkyl)ethanols with *F*-alkyl chain length with odd carbon numbers between 9 and 19 [74]. A few examples of sugar-derived ethers with the *F*-alkyl chain directly grafted on the oxygen of sugars were synthesized either through a reaction between a nucleophilic *F*-alkoxide anion and an electrophilic carbohydrate [40], or by the use of the familiar addition–elimination process known for nucleophiles reacting on *F*-alkenes [75].

2.2.1 Ethers.

All the ethers reported that have a hydrocarbon spacer between the sugar (or its polyol derivative) and the *F*-alkyl chain were prepared by the linear synthesis strategy (cf. Section 2.1). Thus, a series of *F*-alkylated galactose (**22a–c** and **24b** in Scheme 9) [76], glucose (**26a–e**, **27d** and **27e**, and **28d** and **28e** in Scheme 10) [77,78], rhamnose [78] and xylitol (**25** in Scheme 10) [79] derivatives was synthesized by addition of *F*-alkyl iodides to the appropriate *O*-propenyl-protected sugar. After dehydroiodination [76,79] or reductive removal of the iodo group [77] and deprotection, the expected amphiphiles were obtained. Depending on the experimental conditions, it was possible to graft the *F*-alkyl chain onto the double bond of the sugar **19** in a one-step



Scheme 9. Access to *F*-alkylated galactose ethers.



Scheme 10. Various other *F*-alkylated ethers prepared.

addition–elimination procedure, directly affording **21a–c** in about 80% yield. The protected *F*-alkylated galactopyranose **21a–c** consisted of *Z*/*E* mixtures (3:17 by ^{19}F NMR).

Hydrogenation of the double bond of **21b** led to significant hydrogenolysis, affording the desired (*F*-hexyl)propyl ether **23b** in 25% yield only, accompanied by 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (21%) (Scheme 9) [76]. It was also reported that treatment of intermediate iodides by zinc powder and ammonium chloride readily cleaved the ether bond ($\sim$90% yield); the 2-iodo-3-(*F*-alkyl)propyl group can thus be considered as a 'secondary' protecting group [78]. A further report observes that an attempt at nucleophilic substitution of the tosylate group in 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl tosylate by trifluoroethanol failed [80a]. Recently, in a 'fluorous synthesis approach' [84], an *F*-alkylated benzyl-protected glucal intermediate was prepared that was used for the synthesis of a disaccharide [80b].

2.2.2 Esters — carboxylic esters.

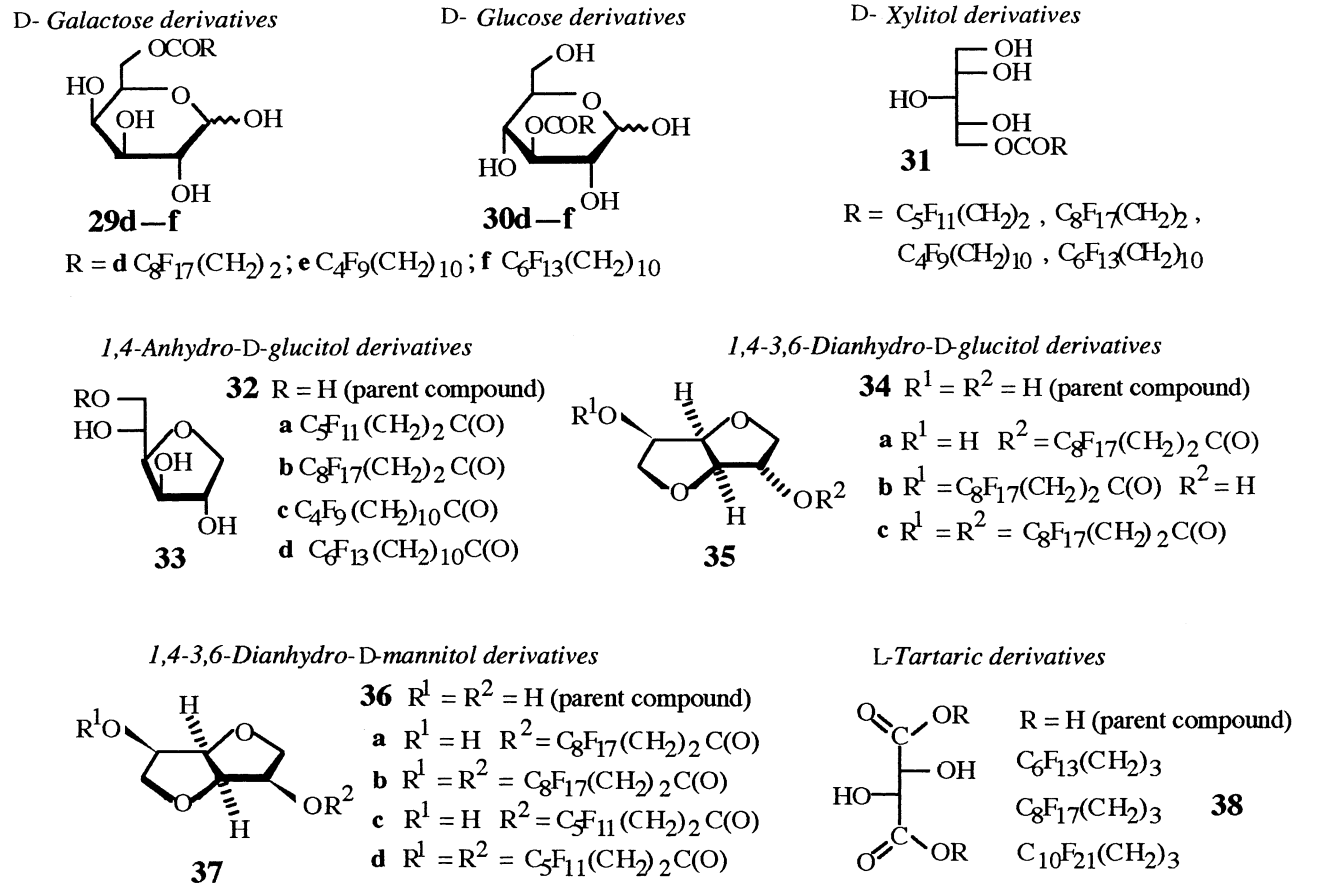
Specific esterification, after partial protection, activation, acylation, then deprotection, is conceivable for monosaccharides, but unattractive for disaccharides because of expected low overall yields. Esterification of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in positions 6 and 3, respectively, and of 1,2:3,4-di-*O*-isopropylidenexylitol with (*F*-alkyl)alkanoyl chlorides was carried out in $\geq$80% (Scheme 11) [76,79,81]. No migration of the acyl group occurred during deacetalation (aqueous trifluoroacetic acid; 50–84%). The recrystallized sugar esters were single anomers with an α-structure, except for **30d**, which had a β-structure. Further studies showed that on standing at room temperature in dimethylsulfoxide, the *F*-alkylated esters of glucose were anomerized to an α/β mixture, whereas, in the same solvent, the esters of galactose gave four products, the mutarotated 6-*O*-acyl esters and probably another set of mutarotated compounds having esters in unknown positions.

A two-step approach (or pseudo-one-step approach, since there was no protection of the hydroxyl groups) was chosen (Scheme 11) in which the mono- and dianhydroglucitol and mannitol **32**, **34** and **36** were first prepared and purified, then esterified [82]. Esterification of 1,4-anhydro-D-glucitol (**32**) (50% excess) using acyl chlorides occurred essentially on the primary hydroxyl group (60–74% yield). Both the exo and endo hydroxyl groups of **34** underwent esterification, the ester of the former being formed predominantly (53 versus 20% yield).

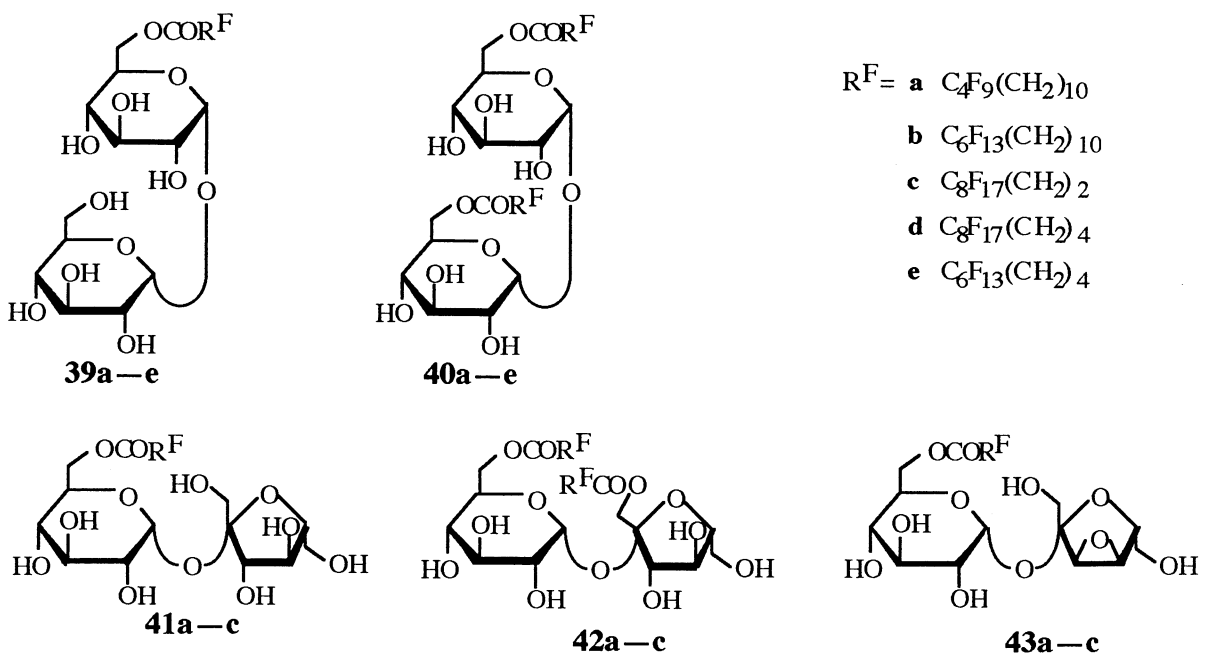
A one-step preparation of 3-(*F*-alkyl)propyl esters of L-tartaric acid **38** ($\sim$80% yield) was recently reported [83]. These compounds have potential as chiral agents for catalytic enantioselective transformations under 'fluorous biphasic system' conditions [84].

Regioselective acylation of unprotected sugars such as α,α-trehalose and sucrose was achieved using the Mitsunobu reaction [59] (Scheme 12). This esterification procedure, which is known to occur essentially on primary hydroxyl groups, allowed the preparation of *F*-alkylated trehalose esters **39** in the 6-position ($\sim$30–45%), along with a small amount of the 6,6′-diesters (3–6%) **40** [85,86]. When the same procedure was applied to su-

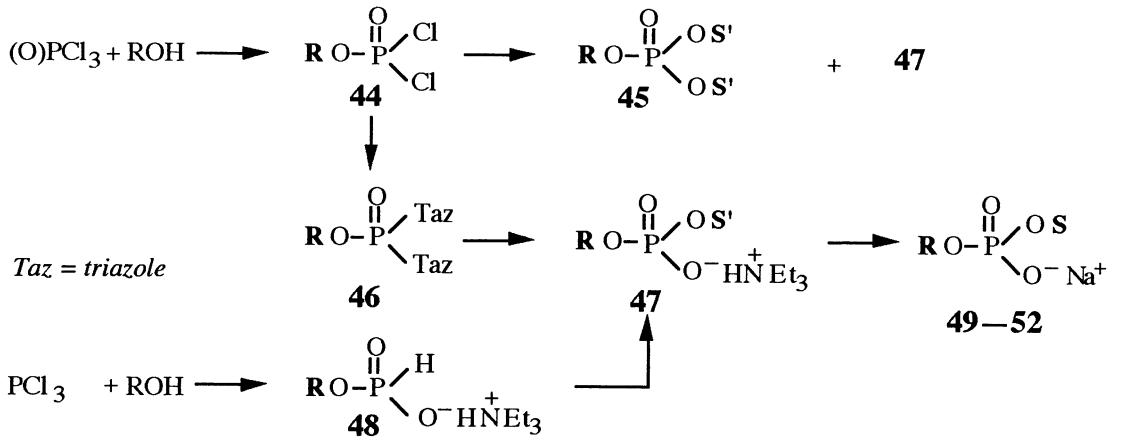
crose, the 6-esters **41** were obtained in ca. 25% yield, along with 6,6′-diesters **42** (6%) and the epoxides **43** (~ 1%). The latter compound is due to the orientation of HO-3′,4′ in the fruc-



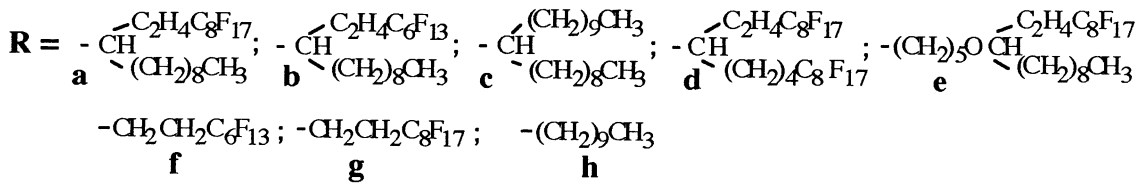
Scheme 11. Various *F*-alkylated esters of sugars and polyols.



Scheme 12. *F*-Alkylated trehalose and sucrose esters.



S: 6-galactose **49a,b,c,d** and **e**; 3-glucose **50a,b** and **g**; 6-glucose **51a,b,c,f,g** and **h**; 6-mannose **52a,b** and **c**.



Scheme 13. Route to single- and double-tailed glycophosphates.

tose part of sucrose, which favors the formation of the tagatose epoxide. It is noteworthy that the presence of the *F*-alkyl chain weakens the C–O bond of the sucrose ester significantly. Thus, ester **41c** led, after a few days of storage in methanol, to sucrose and to the methyl ester of 3-(*F*-octyl)propanoic acid, together with unidentified by-products that probably reflect acyl migration. No such degradation was observed with **41a** and **41b**, which have a much longer hydrocarbon spacer.

2.2.3 Phosphoric esters.

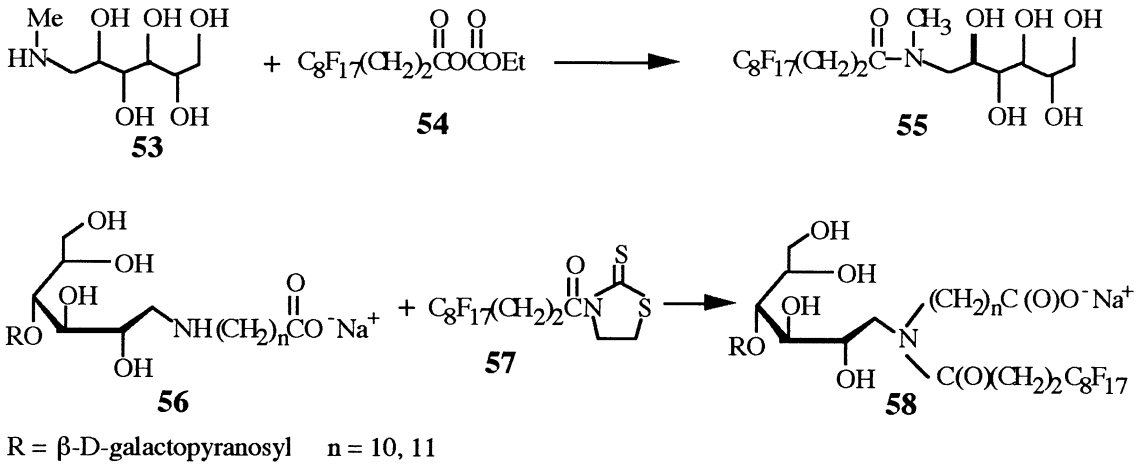
Phosphorylated sugars have been investigated because of their biological importance. Phosphodiesters of carbohydrates with long-chain aliphatic alcohols remain scarce, however, and involve only glucose and galactose derivatives with the phosphate group in either the anomeric position [87] or in the 6-position [88].

The single-chain glucophosphates **50g** and **51f–h** were obtained in 33–60% yield (from suitably protected sugar derivatives) by employing the *F*-alkylated phosphoditriazolide derivatives **46** as the phosphorylating reagent (Scheme 13) [89,90]. In contrast, whatever the experimental conditions tested, phosphorylation of the protected sugar with **44** (from which **46** is obtained) unavoidably led to the triester **45**, together with the expected diester **47**.

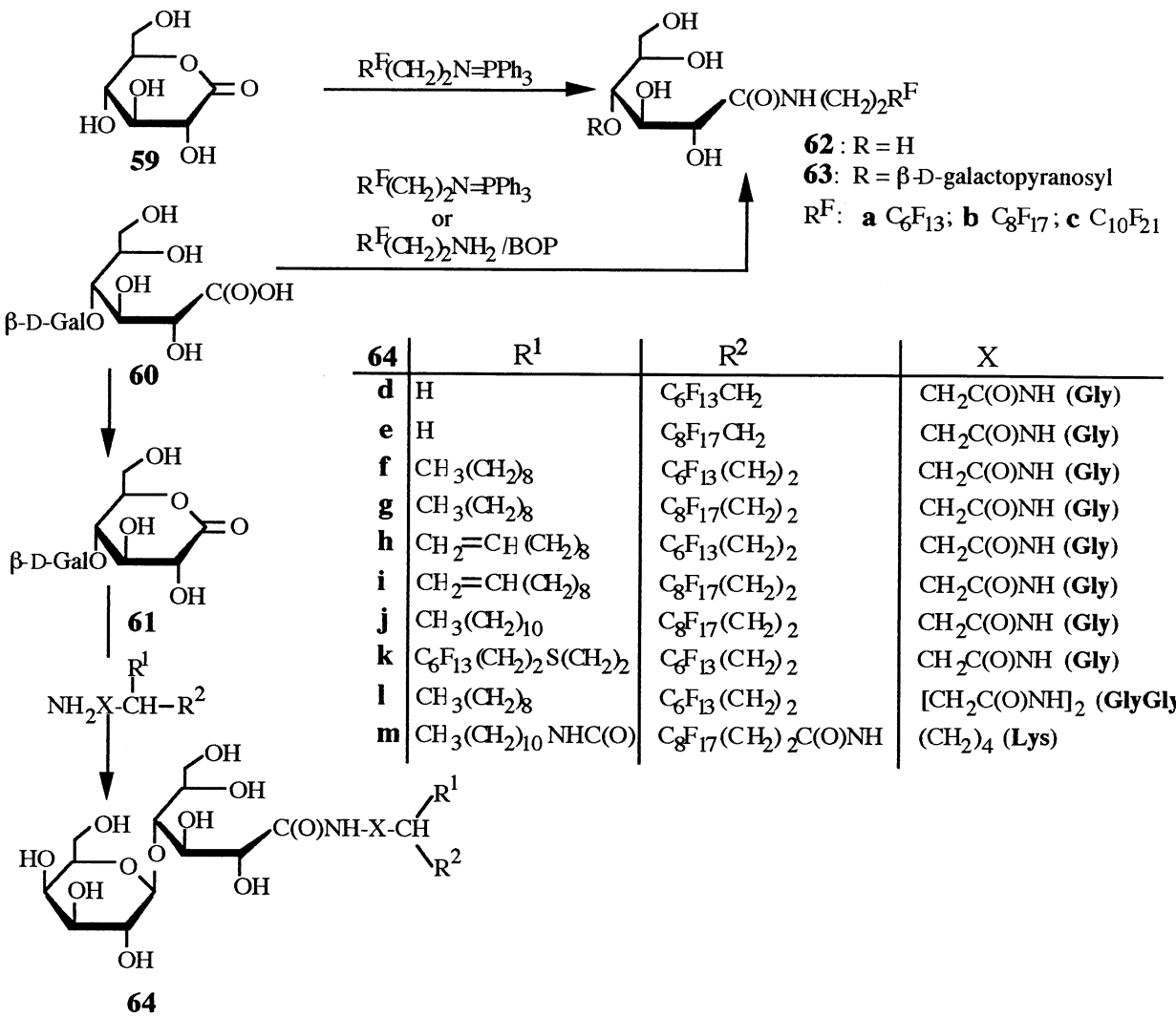
The double-tailed phosphosugars **49a–e**, **50a,b**, **51a–c**, and **52a–c** were prepared in 40–70% yield through a three-step H-phosphonate route [90–92]. The *F*-alkylated phosphonate **48**, prepared via a phosphoramidite intermediate, was condensed on appropriately protected sugar derivatives; oxidation then afforded the glycophosphodiester **47** (Scheme 13). In all cases, complete O-deacetylation and O-deisopropylidenation were readily achieved using conventional procedures without alteration of the phosphodiester linkage.

2.3 Nitrogen-containing polyol or sugar derivatives.

F-Alkylated nitrogen-containing sugars or polyol derivatives, including amides

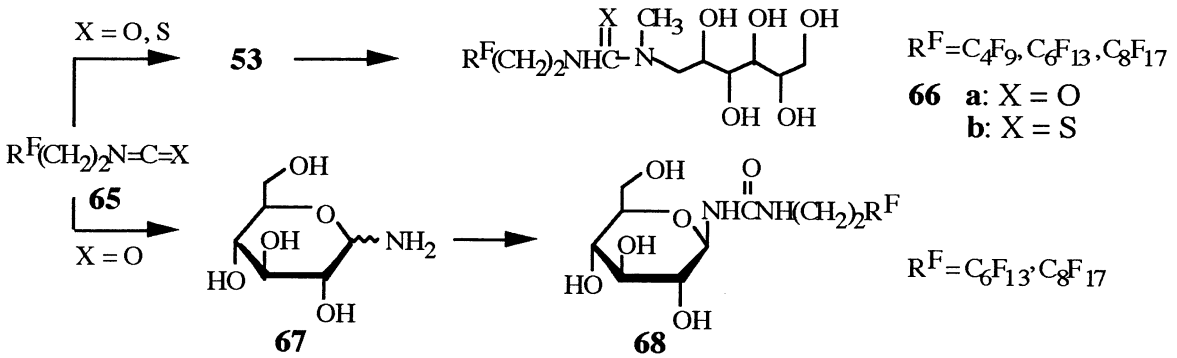


Scheme 14. Preparation of *F*-alkylated amides.

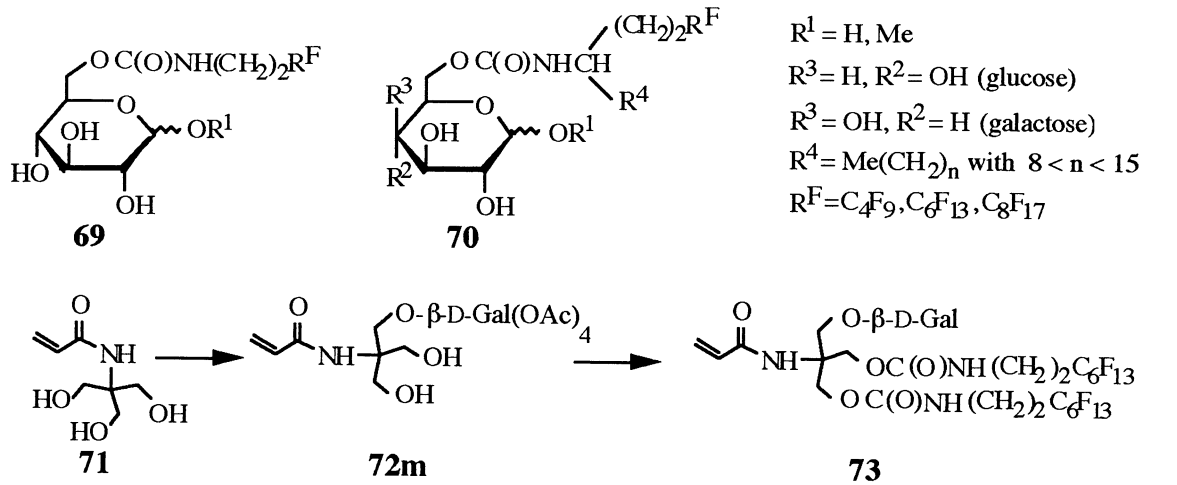


64	R^1	R^2	X
d	H	$C_6F_{13}CH_2$	$CH_2C(O)NH$ (**Gly**)
e	H	$C_8F_{17}CH_2$	$CH_2C(O)NH$ (**Gly**)
f	$CH_3(CH_2)_8$	$C_6F_{13}(CH_2)_2$	$CH_2C(O)NH$ (**Gly**)
g	$CH_3(CH_2)_8$	$C_8F_{17}(CH_2)_2$	$CH_2C(O)NH$ (**Gly**)
h	$CH_2=CH(CH_2)_8$	$C_6F_{13}(CH_2)_2$	$CH_2C(O)NH$ (**Gly**)
i	$CH_2=CH(CH_2)_8$	$C_8F_{17}(CH_2)_2$	$CH_2C(O)NH$ (**Gly**)
j	$CH_3(CH_2)_{10}$	$C_8F_{17}(CH_2)_2$	$CH_2C(O)NH$ (**Gly**)
k	$C_6F_{13}(CH_2)_2S(CH_2)_2$	$C_6F_{13}(CH_2)_2$	$CH_2C(O)NH$ (**Gly**)
l	$CH_3(CH_2)_8$	$C_6F_{13}(CH_2)_2$	$[CH_2C(O)NH]_2$ (**GlyGly**)
m	$CH_3(CH_2)_{10}NHC(O)$	$C_8F_{17}(CH_2)_2C(O)NH$	$(CH_2)_4$ (**Lys**)

Scheme 15. Fluorinated single- and double-tailed D-gluconamides and D-lactobionamides.



Scheme 16. Reactivity of isocyanates with *N*-methyl-D-glucamine and D-glucopyranosyl amine.



Scheme 17. Single- and double-tailed *F*-alkylated 6-*O*-sugar carbamates.

[1,69,70,93–98] ureas or thioureas [99,100] and carbamates [100–105], have been reported. Most of the preparations required no protection, owing to the more pronounced nucleophilic behavior of the amine versus hydroxyl functions and to the higher reactivity of the primary hydroxyl group.

2.3.1 F-Alkylated amides.

3-(*F*-Octyl)propanoic acid was activated by ethyl chloroformate, thus giving the acylating reagent **54** that, by reaction with the *N*-methyl-D-glucamine (**53**), afforded the *N*-[3-(*F*-octyl)propanoyl]-*N*-methyl-D-glucamine (**55**) in 60% yield [1]. Alternatively 3-(*F*-octyl)propanoylthiazolidine-2-thione (**57**), the acylating reagent derived from mercaptothiazoline, when allowed to react with the 1-amino-1-deoxylactitol derivatives (**56**), gave the 'semi-gemini' glycolipids **58** in 16–20% yield [97] (Scheme 14).

A series of single- and double-tailed fluorinated D-gluconamides [70,97] and D-lactobionamides [69,70,93–98] were readily prepared in good yield using three alternative pathways, without prior protection of the hydroxyl groups (Scheme 15). One pathway used an aza-Wittig-type reaction: 2-(*F*-alkyl)ethyl azides were made to react, via an iminophosphorane intermediate, with gluconolactone **59** or lactobionic acid **60**, affording **62a–c** or **63a–c**, respectively, in ≥ 90% yield [69,70,97]. The second pathway utilized the benzotriazolyl-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) activating agent: 2-(*F*-alkyl)ethylamines were allowed to react on benzotriazolyl ester derived from lactobionic acid **60**, giving **63a** and **63b** in 90% yield [98]. The third procedure consisted of condensing 1,5-lactobionolactone **61**, prepared from its acid precursor **60**, with appropriate amines in basic medium, resulting in **63a**, **63b**

and **64** with overall yields of 20–65% [93–96]. In the latter case, the spacer between the hydrophilic and lipophilic/fluorophilic parts was an aminoacid (Gly **64d–k** or Lys **64m**) or a short peptide (Gly–Gly **64l**).

2.3.2 F-Alkylated ureas and thioureas.

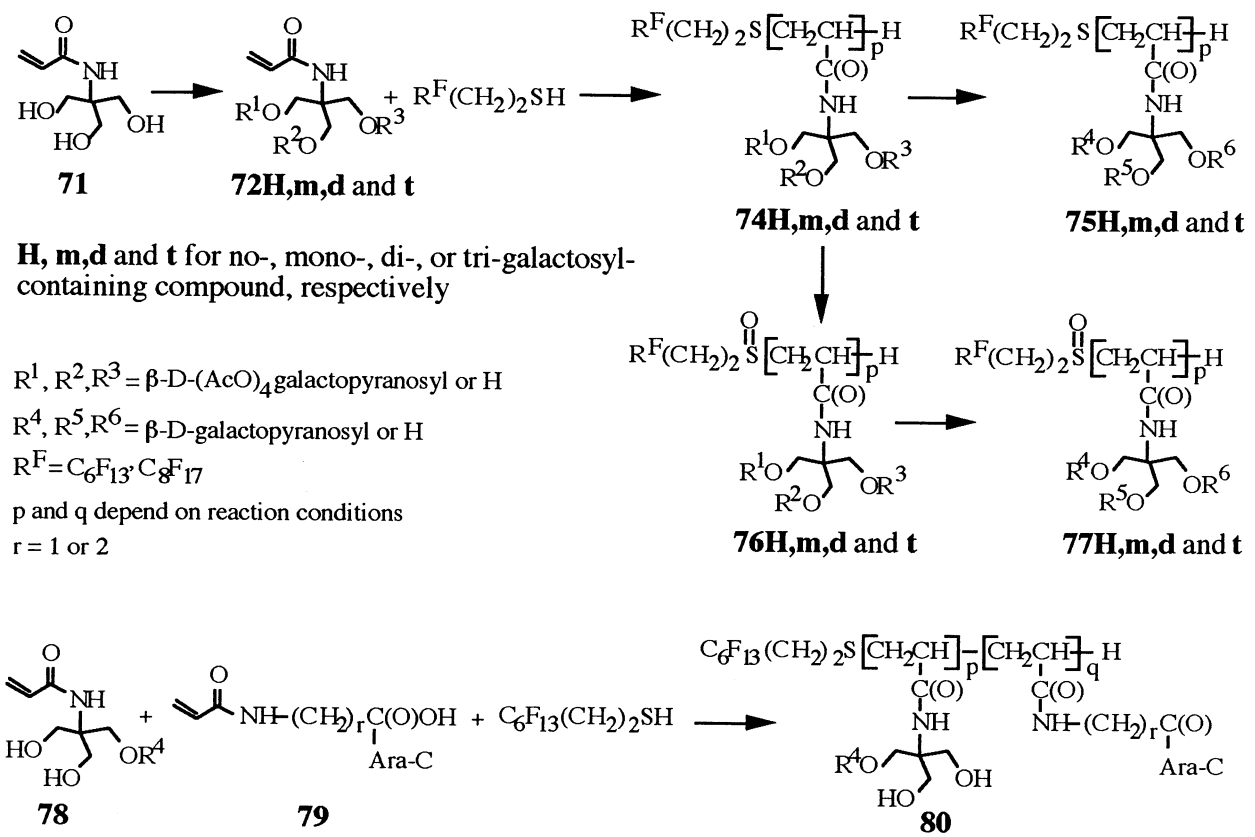
The *F*-alkylated ureas **66a** or thioureas **66b** were readily obtained in 68–78% yield by allowing *F*-alkylated isocyanates or thioisocyanates **65** to react with *N*-methyl-D-glucamine (**53**) [99,100] (Scheme 16). Similarly, the isocyanates, when made to react with D-glucopyranosyl amine (**67**), gave the β anomeric ureas **68** in 80–90% yield [100].

2.3.3 F-Alkylated carbamates.

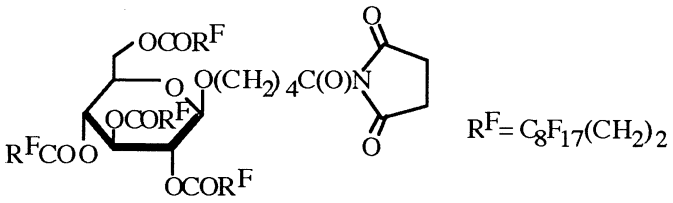
When allowed to react with a D-glycose or a methyl D-glycopyranoside in excess, single- [100,104] and double-tailed [102] *F*-alkylated isocyanates selectively provided the *F*-alkylated 6-*O*-sugar carbamates **69** and **70** in 70% yields [100–102] (Scheme 17). In contrast to the former preparation, a protection/deprotection strategy was needed to prepare 1-*O*-β-D-glycosyl carbamates. The latter were obtained by condensing protected sugars having a free hydroxyl group at the anomeric carbon on isocyanates **65** (X = O) in the presence of DABCO, followed by deprotection [103]. A series of glucose, galactose, mannose, lactose and maltose derivatives was synthesized in 65–95% yield using this two-step approach. The *F*-alkylated double-tailed amphiphile **73** was prepared with the view of allowing the preparation of polymerized vesicles, by condensing 2-(*F*-hexyl)ethyl isocyanate with the monogalactosylated derivative of tris(hydroxymethyl)acrylamidomethane (THAM) **72m**, followed by deprotection [114a]. Related compounds bearing a nitrone groupment as a spin trap were also synthesized [114b].

2.4 Telomers.

Radical telomerization follows the same rules as classical radical polymerization; the major difference arises from the fact that telomerization implies the participation of an additional chemical species, a chain transfer reagent or telogen. A variety of *F*-alkylated



Scheme 18. Access to mono- and polygalactosylated tris(hydroxymethyl)acrylamidomethane telomers.



81

Scheme 19. Poly(*F*-octyl) glucose derivative.

amphiphilic telomers derived from THAM were prepared and tested for biomedical application (vide infra) [104–117].

The tri-*O*-galactosyl derivative **72t** was directly obtained from THAM **71** using the Helferich method (Scheme 18) [116,118]. Mono- and digalactosyl derivatives, **72m** and **72d**, were similarly prepared using appropriately protected THAM derivatives. The yields were significantly improved, from less than 40% to over 60% yields, when ultrasound was applied during glycosylation. Radical telomerization of THAM **72H**, or mono-, di- and tri-*O*-galactosyl THAM **72m**,**d** and **t**, in the presence of 2-(*F*-alkyl)ethanethiols as the transfer reagent and AIBN as the radical initiator, led to various monoadducts ($p = 1$) and/or telomeric ($p > 1$) amphiphiles of the type **74H**,**m**,**d** and **t** which, after deprotection, gave telomers **75H**,**m**,**d** and **t** [116,118]. The number of THAM residues in the polar head (DPn) allows the modulation of the hydrophilic–lipophilic balance (HLB) and depends on the experimental conditions. ^{13}C- and ^{14}C-labelled telomers were synthesized [110]. Controlled oxidation of the sulfide group of monoadducts **74H**,**m**,**d** and **t** ($p = 1$) into a sulfoxide moiety **76H**,**m**,**d** and **t**, then **77H**,**m**,**d** and **t**, was performed in view of enhancing the hydrophilic character of **75H**,**m**,**d** and **t** [115,117]. Bioactive molecules were linked to the telomers in order to increase their persistence in the body and/or target them. This was achieved by co-telomerization of THAM derivative **78**, cytosine arabinoside (Ara-C)-bearing polymerizable groups **79** and (*F*-alkyl)ethanethiols, thus affording **80** [113,119]. Related compounds bearing a fluorescent probe were also synthesized [120].

3. Colloid and surface chemistry of carbohydrate and polyol-derived amphiphiles

3.1 Surface activity and related properties.

F-Alkyl chains are significantly more hydrophobic than their hydrocarbon counterparts. They are also more rigid and bulkier [121]. Grafting *F*-alkyl chains onto a sugar or polyol renders the molecule strongly amphiphilic and surface active. Surface activity increases rapidly with increasing *F*-alkyl chain length, and the surface tension of aqueous solutions can be lowered to 20 mN m^{-1} or less, i.e., to levels that cannot be attained with standard hydrocarbon hydrophobic tails [32–34]. Small amounts of a fluorosurfactant, when added to a standard surfactant, can achieve substantial surface tension reduction [35]. Efficiency also increases when hydrocarbon tails are replaced by fluorocarbon tails, as reflected by very low critical micellar concentrations (CMC). Thus, for example, the trehalose monoester **39c** with a $C_8F_{17}(CH_2)_2$ hydrophobe has a CMC of 0.007 mM as compared with 0.39 mM for its non-fluorinated analog with a linear $C_{10}H_{21}$ hydrophobe; an aqueous solution of the former compound has a surface tension of 21.7 mN m^{-1}, as compared with 38.3 mN m^{-1} for the latter [86]. The difference in fluorocarbon (perfluorodecalin)/water interfacial tension reduction effect is even more marked, with 2.6 mN m^{-1} for the fluorinated compound as compared with 17.4 mN m^{-1} for its hydrocarbon analog. CMC can depend significantly on the polar head. Thus for the same hydrophobic chain, $C_8F_{17}(CH_2)_2$, the CMC is 1.07, 0.17 and 0.007 mM for the glucophosphate **51g**, the maltoside **4c** and the trehalose derivative **39c** [1], respectively. Higher effectiveness and higher efficiency can thus offset the higher cost of fluorosurfactants. Compilations of surface tension and CMC data are provided in Refs. [1,32,34]. Further data can be found in Refs. [81,97,98,100,115,117,118]. Introducing a hydrocarbon spacer between the polar head and the *F*-alkyl tail can also have a considerable impact on a fluorosurfactant's behavior [122]. CMC values depend on too many interrelated structural parameters to allow reliable

predictions to be made at this point, other than within a narrowly defined family of compounds. The poly(*F*-octyl) sugar derivative **81** (Scheme 19) was used to reduce the hydrophobicity of Perflex®, a commercial fluorinated Teflon®-like support (DuPont, Wilmington, DE) for immobilization of *F*-alkylated enzymes, resulting in significantly improved retention of biological activity of the immobilized enzymes [123,124]. Some tris-(hydroxymethyl)acrylamidomethane (THAM) telomers are being investigated for their solubilizing properties, which may be useful in drug formulation [105].

3.2 Self-aggregation.

The strongly enhanced hydrophobic effect developed by *F*-alkyl chains as compared with their hydrocarbon analogs, combined with a definite lipophobic effect, results in a wieldy tendency for fluorinated amphiphiles to self-assemble when dispersed in water and other solvents [2,4,125]. Films and membranes made from fluorinated surfactants are usually better ordered, more stable and less permeable than those made from standard surfactants.

3.2.1 Fluorinated vesicles.

A wealth of fluorinated vesicles have now been reported [125,126]. Fluorinated vesicles were obtained from the double-tailed glycolipids of type **64f**–**m**, with one *F*-alkyl and one alkyl chain. Other self-assemblies were also formed, whose morphology and stability depended, in particular, on the amino acid spacer [94–96]. Derivatives with glycine as a spacer tended to produce multilamellar vesicles; with glycylglycine small unilamellar vesicles were readily formed, with lysine a mixture of stacked disk-like assemblies, tubular and helical structures, and rare vesicles was obtained (Fig. 1). The short single-chain fluorinated glycolipid **63b** arranged into helical structures by simple shaking with water, while its hydrogenated analogue only provided spherical micelles [96]. The single chain compound **64e** gave disk-like structures [95].

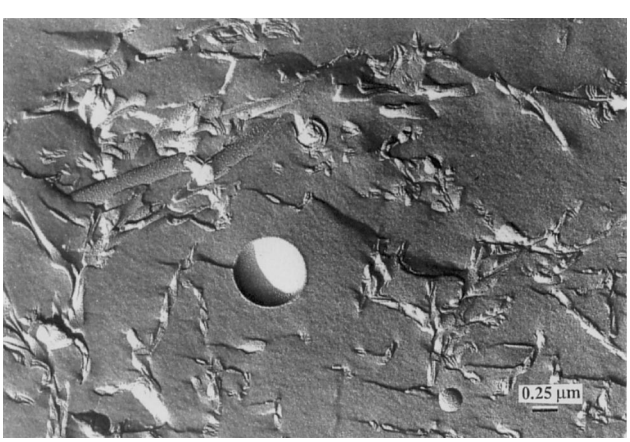


Fig. 1. Freeze-fracture electron micrograph showing a mixture of stacked disks, vesicles, helically twisted tapes and tubules obtained from glycolipid **64m** (from [95] with permission).

The double-tailed anionic galactose and mannose-derived glycophospholipids **49** and **52** readily produced clear dispersions of highly stable, heat sterilizable, unilamellar vesicles upon sonication in water; less stability was seen for the vesicles made from the glucose derivatives **50** and **51**; for **51** vesicles formed only at higher temperatures [127]. Where drug encapsulation stability is concerned, the presence of two *F*-alkyl chains in **49d** effectively prolonged carboxyfluorescein (CF) encapsulation stability ($t_{1/2} = 82$ h compared to 0.7 h for one fluorinated and one hydrogenated chain, and less than 1 min when both chains were hydrogenated). The sugar moiety had a significant effect on encapsulation stability (calcein: galactose-6 16 h > mannose-6 3.8 h > glucose-3 0.8 h for the same hydrophobe; Fig. 2), which probably reflects decreasing head group interactions related to increasing hydration. Serum had a considerable destabilization effect. In the best case (two *F*-alkyl chains), the half-life for CF was about 270 times shorter than in the absence of serum; in the other cases release was too fast for measurement. This may reflect the affinity of certain serum components for the glycosylated residues present at the vesicle's surface. Combinations of amphiphiles having mixed *F*-alkyl/alkyl chains with those bearing either two *F*-alkyl or two alkyl chains resulted in similar or higher shelf stability, but in lesser encapsulation stability [127]. Polymerized vesicles were obtained from compound **73**, which bears the polymerizable moiety on the polar headgroup [114]. Further vesicle formation was reported in Refs. [46,57,70,97].

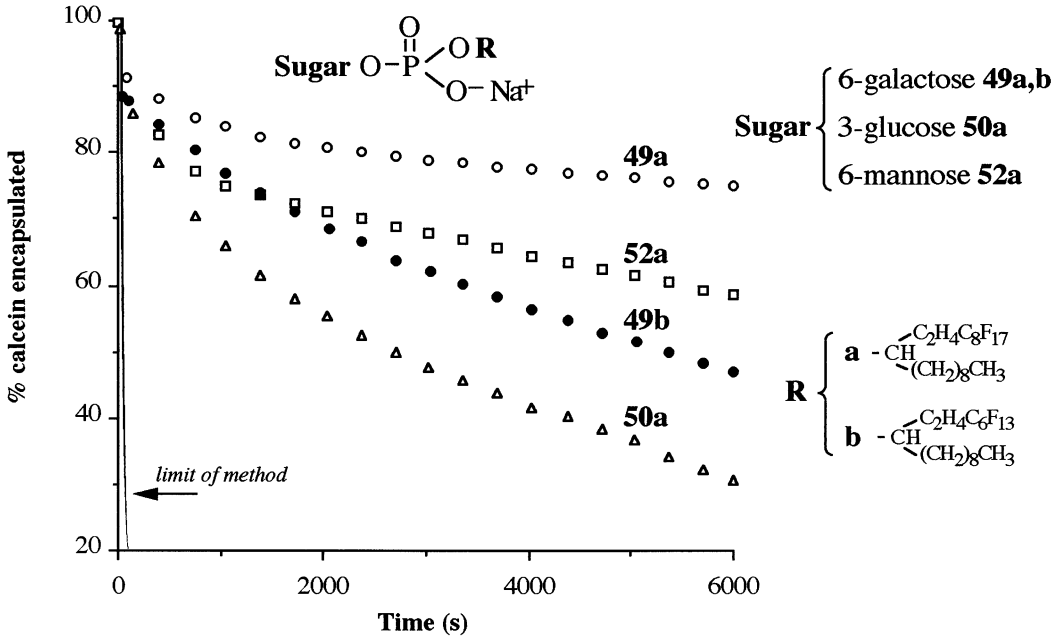


Fig. 2. Release of calcein from vesicles made from *F*-alkylated glycophosphates **49a**, **49b**, **50a** and **52a** in buffer vs. time at 37 °C (from data collected for [127]).

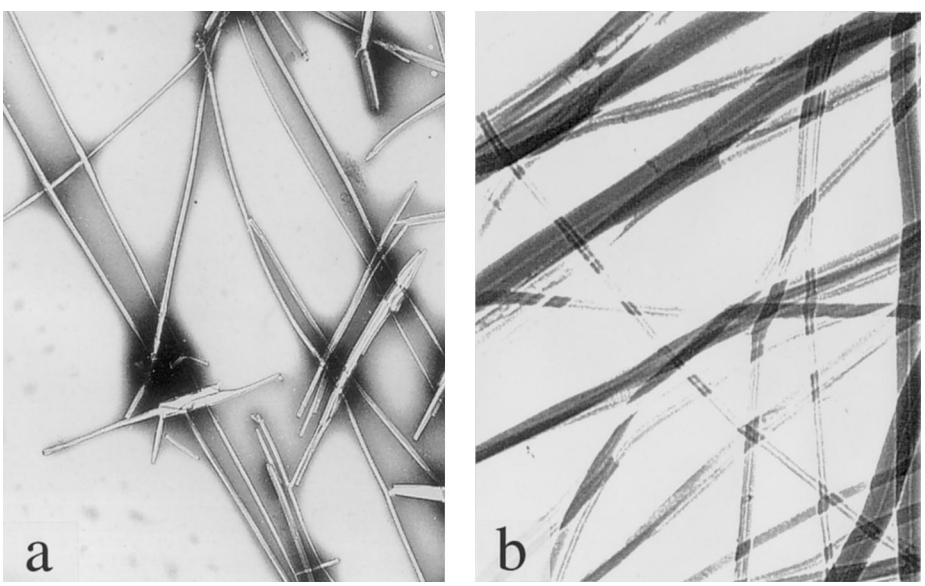


Fig. 3. Tubules made of glucophosphate **51a**: (a) freeze-fracture electron microscopy (from [16]); (b) cryotransmission electron microscopy [128] (courtesy of Dr Krafft, Strasbourg).

3.2.2 Fluorinated tubules and other aggregates.

Stable tubules (i.e., hollow cylindrical bilayer-based microstructures) were obtained when either the partly fluorinated double-tailed anionic glucophospholipid **51a** or its fully hydrogenated analog **51c** were dispersed in water and cooled below the crystal-to-liquid crystal transition temperature (Fig. 3(a)) [16]. These tubules convert into giant vesicles when heated; they spontaneously form again upon cooling. Tubule formation from **51** is pH-dependent and favored at higher pH, indicating the existent of hydrogen bonds between polar head groups. Introducing one *F*-alkyl tail allowed the vesicle–tubule transition to occur above room temperature, it also had a significant impact on tubule diameter, which became five–ten times smaller. The structure of these tubules has been further investigated using cryo-transmission electron microscopy (Fig.

3(b)), and X-ray and neutron small-angle scattering [128]. A tubule wall thickness of about 105 Å has been determined, which represents three bilayers in which the amphiphile is probably in a tilted and/or interdigitated configuration. Transmission electron microscopy indicates that the transparent gel that forms when the maltoside **4c** ($R^F = C_8F_{17}$) is dispersed in water at a higher than 10 g L^{-1} concentration, consists primarily of small bilayer sheets [129]. Related sugar-derived amphiphiles produced similar behavior; the formation of stable gels in the structured non-aqueous solvent formamide was demonstrated [97]. The presence of twisted long lamellae was seen by negative staining electron microscopy.

3.3 Emulsion stabilization capacity.

Stability is obviously a vital issue when emulsions are destined for pharmaceutical use [130,131]. Fluorosurfactants are particularly apt at reducing the interfacial tension, γ_i, between fluorocarbons and water; hence, the free energy of a fluorocarbon-in-water emulsion. Low γ_i values can also stabilize such emulsions by reducing the rate of diffusion of fluorocarbon molecules through the aqueous phase [21]. Low γ_i values alone do not, however, guarantee emulsion stability. Thus, for example, the trehalose derivatives **39c** proved very effective in stabilizing fluorocarbon emulsions (Fig. 4), while the closely related maltoside derivative **4c** ($R^F = C_8F_{17}$), with the same hydrophobic chain, would not even allow the formation of an emulsion [132a]. Molecular modeling indicated that the conformations and relative cross-sections of head and tail are significantly different in the two molecules [132b]. Strong synergistic stabilization was observed when **4c** was combined with a poloxamer (Pluronic® F-68), indicating the formation of hydrogen bonds between polar headgroups [133]. Similar results were obtained with *F*-alkylated xylitol compounds. The negatively charged glucose phosphate esters **50g** and **51f,g** were potent fluorocarbon emulsion stabilizers at very low doses, probably reflecting electrostatic repulsion between charged headgroups; a significant reduction in particle size was observed [134–136]. The same fluorosurfactants were highly effective when used in combination with egg yolk phospholipids (EYP), but not with Pluronic F-68. On the other hand, no improvement was found in terms of emulsion stability when *F*-alkylated telomers of the type **75H** were used instead of, or along with EYP [107].

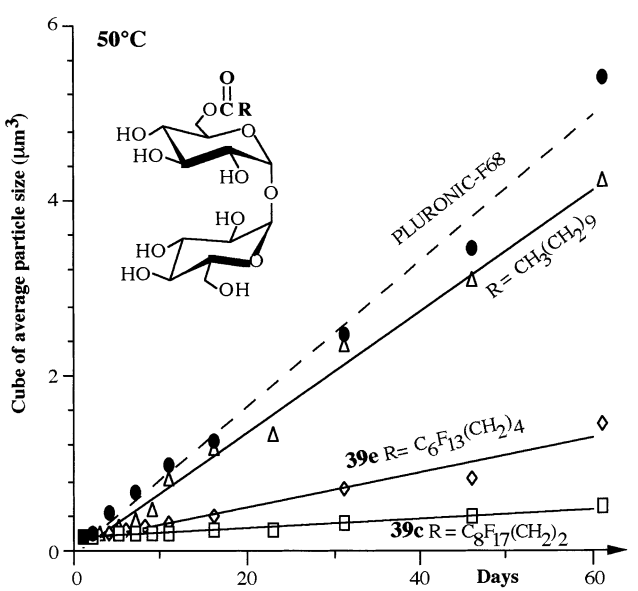
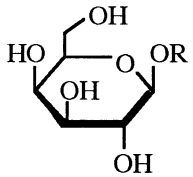


Fig. 4. Effect of the degree of fluorination on fluorocarbon emulsion stability: aging curves $d^3 = f(t)$ at 50 °C for 50% w/v *F*-decalin-in-water emulsions prepared with 5% w/v of a 1:1 mixture of Pluronic F-68 and diverse fluorinated and non-fluorinated trehalose fatty acid esters (from [132] with permission).

The use of fluorosurfactants for stabilizing injectable fluorocarbon emulsions, although it can be highly effective, is less straightforward from a development standpoint than the use of lipophilic heavier molecular diffusion-reducing fluorocarbons, or of (*F*-alkyl)alkyl diblock molecules [21,137]. A notable exception is the stabilization of dispersions of volatile fluorocarbons (for which the molecular diffusion-driven particle size increase is considerably accelerated), as for the preparation of the aforementioned injectable emulsion of perfluoropentane [25]. Water-in-fluorocarbon emulsions [138] with chiral bis(*F*-alkyl) L-tartaric acid **38** are being prepared [83] with the perspective of using them for enantioselective catalysis in fluorous biphasic system conditions [84].



R = $CH_2(CF_2)_3CO_2Me$

R = $CH_2CH_2NHC(O)(CF_2)_3CO_2Me$

82

Scheme 20. Galactose intermediates used in conjugating haptens or drugs to carriers.

4. Biological aspects

There is no indication that the introduction of an *F*-alkyl chain in a molecule increases its acute toxicity [32]. Maximum tolerated doses (MTD) are typically in the 120–500 mg kg^{-1} body weight, but attain almost 4000 mg kg^{-1} for certain telomers of type **75H** ($R^F = C_6F_{13}$, $p \approx 6$) [108]. Also remarkable is the LD_{50} value of 750 mg kg^{-1} body weight in mice found for the single-tailed anionic surfactant **51f** [136]. Hemolytic activity was found to be suppressed or strongly decreased, in spite of high surface activity [32,126,139]. For example, a 40 g L^{-1} dispersion of the maltoside **4c** ($R^F = C_8F_{17}$) causes no detectable hemolysis, while its much less surface active hydrocarbon analog is significantly hemolytic at a 1 g L^{-1} concentration. Hemolytic activity reappears when a long hydrocarbon spacer is inserted between the sugar and the *F*-alkyl tail, as in **4c** ($R^F = C_6F_{13}$, but with a $CH{=}CH(CH_2)_9$ spacer instead of $(CH_2)_2$), which is hemolytic at 0.1 g L^{-1} (similar to **4c**, with a $C_{12}H_{25}$ hydrophobe). No hemolysis was found for **75H** ($R^F = C_8F_{17}$, $p = 6$) at concentrations up to 200 g L^{-1} [108].

Fluorosurfactants show little aptitude for extraction of membrane proteins [104,118,-140]. Lower protein solubilization was, for example, observed for compound **75H** ($R^F = C_{10}F_{21}$, $p = 4$), when compared with its hydrocarbon analog or to Triton® X-100 [141]. Likewise for compound **77H** ($R^F = C_6F_{13}$, $p = 5.4$), a sulfoxide analog of **75H**, introduction of the *F*-alkyl chain strongly decreased the detergent efficiency of the amphiphile when assayed on rat liver cells [115].

Reports on the pharmacology of fluorosurfactants are still scarce. One study involving both iv and po administration in rats of the CO(amide) ^{14}C-labeled telomeric polyol **75H** ($R^F = C_6F_{13}$, $p = 5–6$) indicated wide distribution, long half-life in plasma and tissues, and that metabolism occurred. There was no evidence, however, that the *F*-alkyl chain was metabolized [142]. Studies using both normal rat skin fibroblasts and malignant murine melanoma cells showed that the telomer easily crosses the cell membrane and distributes homogeneously within the cytoplasm of both cell lines, but has difficulty crossing the nuclear membrane [143].

In spite of its interest, little is known yet about the influence sugar-derived fluorosurfactants may have on the in vivo recognition of particles. Lower in vitro uptake of polystyrene microspheres by macrophages was observed when coated with certain *F*-alkylated THAM telomers of type **75H** [144a]. Monolayers made from steroidal amphiphiles **5**, which bear cellobiose or maltose polar heads and two *F*-alkyl hydrophobes, were compressed above a cellulase-containing subphase. Distinct pressure–area behavior was observed, which was related to the specific (with cellobiose) and non-specific (maltose) interactions with the enzyme at the air–water interface, the non-specific interactions being the strongest [52]. Agglutination of vesicles made from the *F*-alkylated glucosyl derivatives **7** occurred when concanavalin A (a lectin extracted from plants) was added to the aqueous phase, indicating recognition between the two types of compounds [46]. Contrary to agglutination caused by non-sugar-based anionic amphiphiles, agglutination induced by **7** was reversed by addition of glucose. Reversible concanavalin A-induced agglutination/recognition effects were also observed when surface pressure–area isotherms of monolayers made from **7** were investigated. The affinity of galactosylated THAM telomers of type **75** ($R^F = C_8F_{17}$) for lectins was estimated by measuring the inhibition of yeast cell aggregation [116]. The affinity was significantly increased when the *F*-alkyl hydrophobe was introduced.

Fluorocarbon chain-containing linking arms, such as **82** (Scheme 20), were prepared to be used to conjugate to protein carriers such as BSA, HSA, or antibodies; ^{19}F atoms

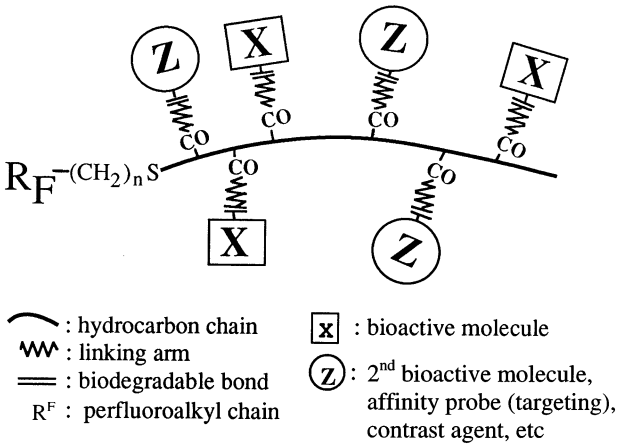


Fig. 5. Derivatization of polyhydroxylated telomers of type **75H** into versatile prodrugs and targeting devices (schematic; from [145] with permission).

would serve as markers for quantitative estimation of bound haptens [144b].

Use of the hydroxyl functions of *F*-alkylated telomers or co-telomers such as **75H** or **80** for covalent binding of a drug and/or other bioactive entity via a biodegradable bond, thus yielding a prodrug, has been proposed (Fig. 5) [118,145]. This principle has been applied to the preparation of telomers bearing cytosine arabinoside moieties linked by a peptide spacer [113]. Cytotoxicity of the telomers was higher than that of monoadducts (one THAM group) and comparable with that of free arabinose cytosine; the *F*-alkyl derivatives were slightly less active than the alkyl analogs.

Some sugar-derived fluorosurfactants were also investigated for their own drug activity. The *F*-alkylated polyol derivative **66a** was shown to inhibit spontaneous platelet aggregation, suggesting applications as an anti-thrombogenic agent [99]. Sulfated laminarioligosaccharides with *F*-alkylated chains were shown to display anti-HIV activity, although not significantly different from that of the non-fluorinated compounds, and comparable with the activity of dextran sulfate [11,146]. Some galactolipid mimics of galactosylceramide **6** have been proposed as inhibitors of the HIV cellular penetration [44,58].

In conclusion, the synthesis and investigation of carbohydrate and related polyol-derived fluorinated amphiphiles has been expanding in the recent years. Such compounds may constitute valuable components of pharmaceuticals and drug delivery systems [147,148]. However, our basic knowledge of their pharmacology needs to be significantly improved before such use can be considered in a clinical situation.

Acknowledgements

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