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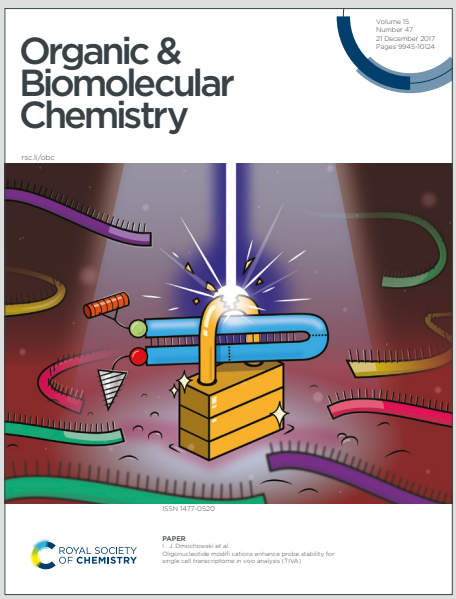

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Photocatalyzed reductive fluoroalkylation of 2-acetoxyglycals towards the stereoselective synthesis of α–1-fluoroalkyl-*C*-glycosyl derivatives

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Electronic Supplementary Information (ESI) available: General Information and Experimental section (Preparation of substrates, Mechanistic Probe Experiments, Calculation of Thermodynamic Parameters, Schemes S1-S5, Figures S1–S6, Tables S1-S4, and NMR and HRMS spectra of compounds **2** – **9**. See DOI: xxx/xxx

ABSTRACT

A benign, efficient, regio- and stereoselective protocol for the syntheses of α–1-fluoroalkyl-*C*-glycosyl compounds bearing CF_3, C_4F_9, and C_6F_{13} substituents on the anomeric carbon has been developed by a new methodology starting from 2-acetoxyglycals for the first time. Remarkably, the reactions proceeded in only one step, through the visible light-photocatalyzed reductive fluoroalkylation of 2-acetoxyglycals by means of an Ir photocatalyst and employed commercially available fluoroalkyl iodides *n*-C_nF_{2n+1}-I (n = 1, 4, 6) as source of fluoroalkyl radicals.

INTRODUCTION

C-glycosyl compounds belong to a particular class of glycomimetics in which the glycosidic oxygen has been replaced by a carbon atom.[1] This structural feature makes them resistant to acid and enzymatic hydrolysis, and thus, they have been envisaged as potential tools in the Glycobiology field as inhibitors of glycosidases and/or glycosyltransferases.[2]

The synthesis of *C*-glycosyl derivatives has largely been addressed over the years and has been extensively reviewed.[3,4,5] Polar and concerted mechanisms and a variety of cross-coupling reactions are shown to be excellent alternatives to obtain this particular class of sugar derivatives. Radical mechanisms promoted by AlBN and/or Bu_3SnH using suitable precursors were also explored,[6] among other approaches.

Another alternative to obtain modified carbohydrates is related to the substitution of a hydroxyl group by a fluorine atom. This strategy provided a variety of modified glycomimetics useful as probes of glycosidase mechanisms, as enzyme inhibitors and also, as lectin ligands.[7] Derivatives having one or several fluorine atoms attached to the *C*-linked moieties of either pyranose or furanose monosaccharides have also been synthesized. In this respect, regio- and stereoselective fluorination reactions of exo-glycals were carried out by Vincent and coworkers,[8,9] and their activities as inhibitors of glycosyltransferases were extensively studied.[10,11]

Perfluoroalkyl carbohydrates,[12] in turn, display a variety of interesting properties to be used as emulsifiers in colloidal systems, as they form self-assembled supramolecular structures. Thus, they are considered as promising compounds in the biomedical field.[13,14] Some of them showed excellent properties as co-surfactants for microemulsions.[15,16]

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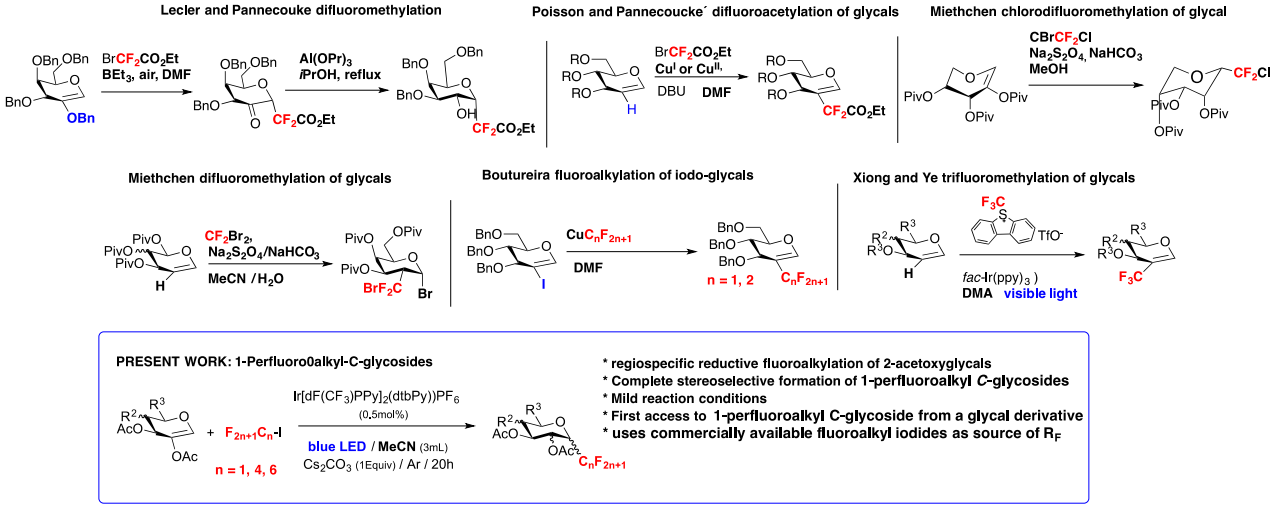
On the other hand, sugar derivatives in which the anomeric carbon bears a fluoroalkyl group through a C-C bond, have also been studied and reviewed.[17] Their syntheses mostly involve reduction of the fluoroalkenyl exoglycals.

Glycals and, to lesser extent 2-acetoxyglycals, have been used as building blocks in glycosylation reactions.[18] As they are easily obtained from glycosylbromides,[19,20] they are valuable precursors at the gram-scale for the synthesis of natural and also modified carbohydrates. The fluoroalkylation of glycals, which comprises the incorporation of fluoroalkyl groups onto the carbon-carbon double bonds, has been achieved by the groups of Ye (trifluoromethylthiolation),[21] Miethchen,[22] Poisson and Pannecoucke,[23] and Boutureira,[24,25] (Scheme 1); in all cases affording fluoroalkyl functionalization at the 2-position. Interestingly, Leclerc and Pannecoucke[26] achieved the preparation of α-CF_2-galactosides through an oxygen-to-carbon acyl migration. Particularly, the method from Boutureira requires 2-iodoglycals as starting material to achieve 2-fluoroalkylglycals in reasonable yields while the group of Xiong and Ye[27] has achieved a facile Ir-photocatalyzed trifluoromethylation of glycals employing the Umemoto´s reagent affording 2-trifluoromethylated glycals in good yields (Scheme 1).



Scheme 1. Approaches to fluoroalkylation of glycals

The results shown here combine our joint interests in photocatalyzed fluoroalkylation reactions[28] with the development of new synthetic methods towards glycomimetics resistant to biological degradations.[29] Inspired by the results from Xiong and Ye[21,30] on the photocatalyzed trifluoromethylation of glycals which are reported to afford 2-trifluoromethyl-substituted glycals, we began our initial investigation on 2-acetoxyglycals.[31] We decided to explore the possibility of obtaining *C*-perfluoroalkylated

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glycosyl compounds, by treatment 2-acetoxyglycals with commercially-available fluoroalkyl iodides under visible light photocatalysis. Fluoroalkyl iodides having 1, 4 and 6 carbon atoms were used.

RESULTS AND DISCUSSION

An initial assessment employing 2,3,4,6-tetra-*O*-acetyl galactal **1a** under Rose Bengal (5 mol%) visible-light photocatalysis using a commercial compact fluorescent lamp (CFL), in the presence of *n*-C_4F_9-I and Cs_2CO_3 in Ar-deoxygenated MeCN, afforded the 1-*C*-nonafluorobuthyl 2,3,4,6-tetra-*O*-acetyl-α-galactosyl compound **2** as a single anomer in 24% yield, although approximately half of the starting glycal was recovered unchanged. The α-*galacto* configuration was confirmed by ^{1}H-NMR spectroscopy, as detailed below (Figure 1). Thus, the photocatalytic addition of the C_4F_9 moiety took place at the anomeric carbon while a hydrogen atom was incorporated on carbon 2. No perfluoroalkylated glycal-derivatives were detected in the reaction mixture.

We then embarked on the optimization of the reaction conditions under photocatalysis (Table 1). The crucial role of light was first demonstrated as no product was obtained in the dark (entry 32, Table 1). Then, the effect of different photocatalysts, solvents, bases and additives on the transformation of 2-acetoxygalactal to the α-1-*C*-perflurobutyl-peracetylated galactose **2** was explored (Table 1) in an attempt to improve the yield of **2**.

As stated above, when Rose Bengal (RB) was used as photocatalyst (entry 1, Table 1), **2** was obtained in 24% yield. Photocatalyst Eosin Y afforded 28 % yield of **2** (entry 16, Table 1), whereas with the iridium-complex (i.e.: $Ir[dF(CF_3)PPy]_2(dtbPy))PF_6$, entry 17), a 53% yield of the product was observed. Taking into consideration that part of starting glycal **1a** was recovered unchanged by column chromatography, a corrected yield value of 87% for compound **2** is re-calculated under these conditions. Using 2,4,6-tri (9*H*-carbazol-9-yl)-5-chloroisophthalonitrile (3CzCIIPN) as photocatalyst, the yield was 11% yield (Table 1, entry 19). In the absence of photocatalyst, product **2** was not detected (Table S1, entry 30). Also, the presence of air led to a decrease in product yield (Table S1, entry 33), in agreement with the presence of open-shell radical species.

Both CFL (compact fluorescent lamp) and blue LEDs (λ_{max} = 470 nm) (entries 17 and 18), resulted in suitable irradiation sources as their emission maxima match with the absorption range of the selected iridium photocatalyst.

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Among the solvent systems explored (i.e.: DMF, DMA, MeCN, MeOH, and THF, see Table S1, ESI), MeCN (Table 1, entries 1 and 17) showed to be the most appropriate one (entry 17). The use of MeOH (Table 1, entry 3), DMA, THF, or DMF (see Table S1, ESI) as solvents afforded no product or low product **2** yields.

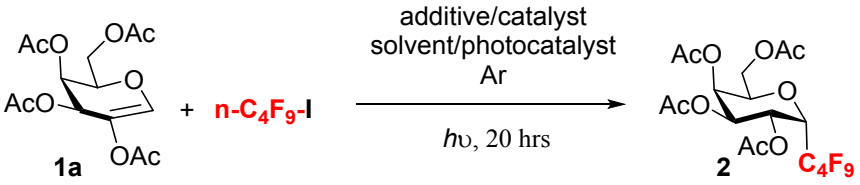
Experiments involving the addition of hydrogen atom donors to the reaction mixture were performed, with the aim to improve the yield of the reduced *C*-perfluorobutylated product. Thus, the use of tris(trimethylsilyl)silane, $(Me_3Si)_3SiH$, THF), or H_2PO_3 (see Table S1, ESI) afforded lower yields of product **2** when using the Ir-photocatalyst. Similar experiments were attempted with diverse hydrogen atom donors using Rose Bengal as photocatalyst (entries 5-12), obtaining lower yields or discrete yield enhancements of product **2**. In the presence of thiols as hydrogen atom donors, the corresponding perfluorobutylthio ethers were obtained. These products were characterized by standard spectroscopic techniques (see below and SI).[32]

By addition of oxidant species (entries 13-15) such as $K_3[Fe(CN)_6]$ or $Cu(AcO)_2$, the α-1-*C*-perflurobutyl-peracetylated galactose **2** was not formed. This result indicated that the presence of an oxidant species in the reaction medium did not promote the re-generation of the glycal double bond. All these attempts ultimately led to diminished yields of **2** or even prevent its formation.

The sequential use of inorganic bases M_2CO_3 (where M = Li^+, Na^+, K^+, Cs^+) and organic bases such as *N,N,N′,N′*-tetramethylethylethylenediamine (TMEDA) were then introduced in the optimization of the reaction conditions. The use of Li^+, K^+, or Na^+ counterions in the carbonate salt afforded very low reaction yields (< 10%) of product **2** (Table S1, ESI). However, the presence of cesium carbonate salt turned out to be beneficial in terms of product yield. The use of TMEDA as organic base (entry 4), was not effective.

In summary, the optimal reaction conditions found entail the use of 2-acetoxyglycals (0.2 mmol), *n*-C_nF_{2n+1}-I (4 equiv.), Cs_2CO_3 (1 equiv.), $(Ir[dF(CF_3)PPy]_2(dtbPy))PF_6$ (0.5 mol%) as photocatalyst, in Ar-deoxygenated MeCN as solvent, irradiating with blue LEDs (λ_{max} = 470nm, 10 watts) under vigorous stirring for 20 hrs. at room temperature (Table 1, entries 16 and 17). Thus, a 87% yield of α-perfluorobutyl-2,3,4,6-tetra-*O*-acetyl-galactose **2** was obtained under the optimized conditions (Table 1, entries 17 and 18).

Table 1. Reaction Optimizations. Reactions of substrate **1a** (0.2 mmol) with C_4F_9-I (4 equiv) in the presence of additives (1 equiv), photocatalyst (RB, Eosin Y, and 3CzClIPN, 5 mol%, Ir-photocatalyst, 0.5 mol%) under irradiation or otherwise noted in indicated solvent (3 mL) for 20 hrs under Ar-atmosphere or otherwise specified



0.2 mmol 4.0 equiv

Entry	Additive (equiv)/ Catalyst[a]	Irradiation sources	Solvent	Yield (%)[b1]
	PC: RB, base[b2] & solvent			
1	Cs_2CO_3 (1)/RB	CFL	**MeCN**	24% (82%)
2	Cs_2CO_3 (1)/RB	CFL	MeCN	20%[c] (57%)
3	Cs_2CO_3 (1)/RB	CFL	**MeOH**	0%
4	TMEDA (1)/RB	CFL	MeCN	0%
	PC RB, H donor			
5	Cs_2CO_3 (1), TTMSS[d] (0.3)/RB	CFL	MeCN	33% (78%)
6	Cs_2CO_3 (1), TTMSS[d] (1)/RB	CFL	MeCN	37% (86%)
7	Cs_2CO_3 (1), *iso*propanol (1)/RB	CFL	MeCN	16%
8	Cs_2CO_3 (1), methanol (1)/RB	CFL	MeCN	8%
9	Cs_2CO_3 (1), acetone (1)/RB	CFL	MeCN	22%
10	Cs_2CO_3 (1), 1-adamantanethiol (1)/ RB[e]	CFL	MeCN	0%
11	Cs_2CO_3 (1), 2-mercaptoethanol (1)/ RB	CFL	MeCN	7%
12	Cs_2CO_3 (1), H_2PO_3 (1)/RB	CFL	MeCN	4%
	Oxidant & PC			
13	Cs_2CO_3 (1), $K_3[Fe(CN)_6]$ (1)/RB	CFL	MeCN	5%
14	Cs_2CO_3 (1), $Cu(AcO)_2$ (1)/ RB	CFL	MeCN	0%
15	Cs_2CO_3 (1), $Cu(AcO)_2$ (1)/ Ir PC	Blue LED	MeCN	2%[f]
	PC / light source			
16	Cs_2CO_3 (1)/EY	CFL	MeCN	28%
17	**Cs_2CO_3 (1)/ Ir PC**	**CFL**	**MeCN**	**53%[g] (87%)**
18	**Cs_2CO_3 (1)/ Ir PC**	**Blue LED**	**MeCN**	**53%[g] (87%)**
19	Cs_2CO_3 (1)/ 3CzClIPN PC	Blue LED	MeCN	11%

[a]RB: Rose Bengal (3 mol%), EY: Eosin Y (3 mol%), Ir PC: (Ir [dF(CF_3)PPy]$_2$(dtbPy))PF_6 (0.5 mol%). [b]The yields of chromatographically isolated products are indicated, corrected values obtained after subtraction of remaining unreacted glycals are indicated in brackets. [c]48h-reaction. [d]TTMSS = tris(trimethylsilyl)silane.. [e]Yields obtained with Ir PC: 2%, with RB PC: 0%.

Having established the optimum reaction conditions, we subsequently proceeded to study the scope of the photocatalyzed perfluoroalkylation reactions of other easily available 2-acetoxyglycals (Table 2).

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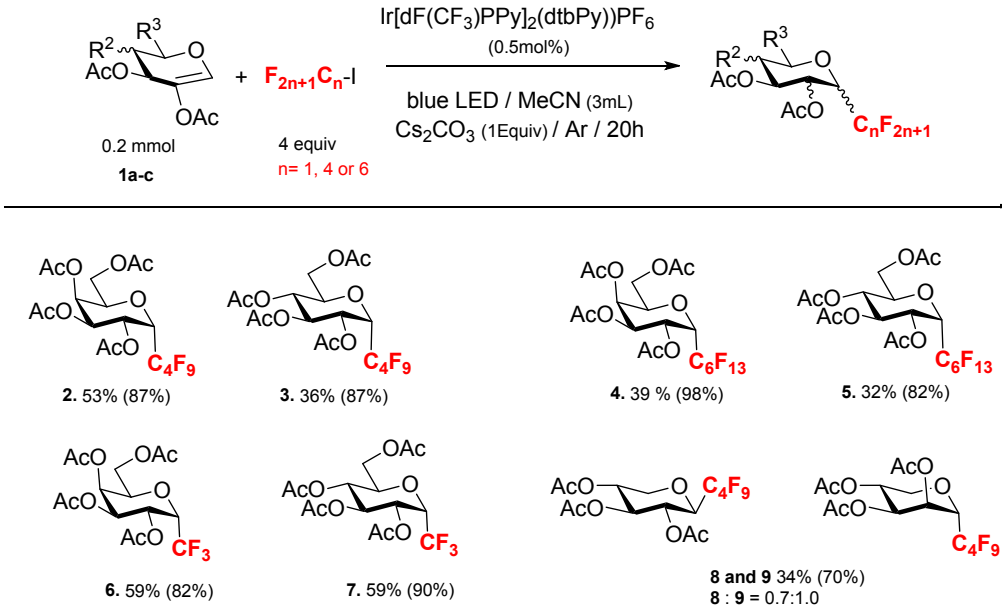
Table 2. Substrate scope of perfluoroakylation of 2-acetoxyglycals. Reaction time 20 hrs. The yields of chromatographically isolated products are indicated, corrected values obtained after subtracting the remaining unreacted glycals are indicated in brackets



The photocatalyzed perfluorobutylation and perfluorohexylation reactions of peracetylated galactal **1a** afforded products **2** and **4** in 53, and 36% yields respectively, as single α-anomers (Figure 1, *C*-perfluoroalkylated glycosyl derivatives). Accordingly, the photocatalyzed perfluorobutylation and perfluorohexylation reactions of peracetylated glucal **1b** gave products **3** and **5** in 39, and 32% yields respectively, also as unique α anomers. In accordance with Miethchen's report,[22b] the purification of these perfluoroalkyl derivatives was difficult to achieve and a final purification step by preparative TLC was required. Yields of products in brackets (Table 2), calculated based on recovered starting materials, attest to the excellent mass balance of the reactions.

The α-configuration together with the equatorial disposition of the *O*-acetate group at C-2, were confirmed by observing the coupling constant values of products **2** - **7**. For example, in the case of **2**, the values for $J_{1,2}$ = 5.2 Hz and a $J_{2,3}$ = 9.7 Hz were consistent with equatorial-axial and axial-axial disposition, respectively. Also, they were in good agreement with those observed for other *gluco*-configured α-*C*-glycosyl compounds.[33,34] Moreover, H-1 appeared as a complex multiplet at 4.87 ppm, deshielded as a result of the effect of the perfluoroakyl chain. Strong heteronuclear coupling of H-1 with the two proximal diastereotopic fluorine atoms was observed ($^3J_{1,F} \approx 5.2$ and $^3J_{1,F'} =$ 28.3 Hz).[35] Similar values were obtained for galactosyl derivatives **4** and **6**, and for the glucosyl derivatives **3**, **5** and **7**.

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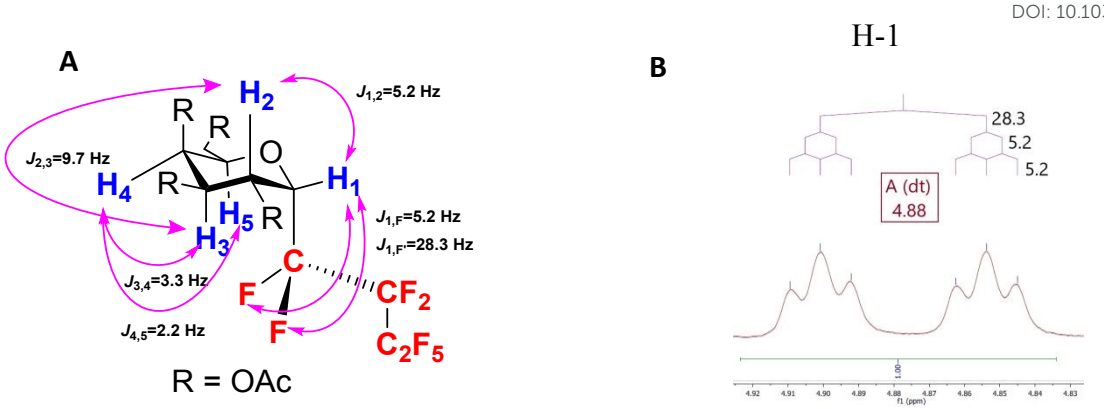


Figure 1. **A**.-Coupling constants (^3J) analysis for the α-*galacto*-configured compound **2.** **B**.-Multiplicity observed for H-1**.**

When we treated the 2-acetoxy glycal derived from xylose **1c** with *n*-C_4F_9-I under the above reaction conditions (Table 2), a mixture of the β-*xylo* and α-*lyxo* pyranoses **8** and **9** in 0.7 : 1.0 ratio was obtained in a combined 34% yield.

Efforts at separating products **8** and **9** from the reaction mixture failed, as standard column chromatography techniques were ineffective, nor preparative HPLC methods achieved separation. Nevertheless, ulterior purification of the mixture of **8** and **9** and thorough spectroscopic characterization allowed the full spectral identification of each anomer in the mixture.

The β-*xylo* configuration of the minor component **8**, was determined based on their ^{1}H-^{1}H coupling (Figure 2). The ^{1}H-^{1}H COSY experiment was crucial to determine the coupling pattern of both compounds **8** and **9**. The large constant values between H-2 and both, H-1 and H-3 ($J_{1,2} \approx J_{2,3}$ = 9.4 Hz) were consistent with their *trans*-diaxial disposition.[36] Thus, H-2 at 5.41 ppm was axially disposed in the $^4C_1$ conformation, which is stabilized in this case by all the substituents equatorially located.

The α-*lyxo* configuration of the major component **9**, instead, was determined as the axially disposed H-3, appeared as a doble-doublet with $J_{3,4}$ = 10.2 Hz (due to the coupling with the axial H-4) and $J_{2,3}$ = 3.3 Hz indicating an equatorial disposition of H-2. On the other hand, the $J_{3,4}$, $J_{4,5eq}$, $J_{4,5ax}$ and $J_{5eq,5ax}$ (10.2, 5.8, 10.4 and 11.3 Hz, respectively), are in good agreement with those described by Durette and Horton for peracetylated α-lyxopyranosides and consistent with a $^4C_1$ conformation.[37]

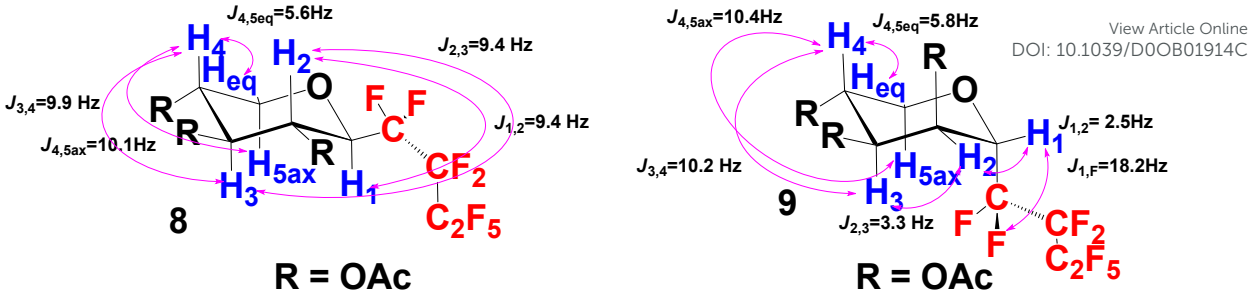


Figure 2. Figure 2. Coupling constants (^3J) analysis for the β-*xylo*-configured compound **8** and for the α-*lyxo*-configured compound **9.**

The pyranose flexibility in xylose **1c** could account for the mixture of the α-*lyxo* and β-*xylo* diastereoisomers found in the Ir-photocatalyzed reactions Also, **1c** can suffer fluoroalkyl radical attack from both faces of the double bond, as compared to hexose-derived 2-acetoxyl glycals **1a** and **1b** (Table 2). Noteworthy, the OAc at 2-position and the anomeric R_F group maintain a *trans*-disposition in the products derived from xylose **1c** (products **8** and **9** Table 2).

Considering the relevance of trifluoromethylated compounds in industry and medicinal chemistry, we undertook the analogous trifluoromethylation reactions of 2-acetoxy-glycal derivatives of galactose and glucose employing this time commercially-available CF_3-I (see ESI for handling of this reagent).

The trifluoromethylation reaction of peracetylated galactal **1a** afforded product **6** in 64% yield, again as a single α-anomer, where the incorporation of the CF_3 moiety took place at the anomeric carbon, and a H atom at carbon-2. The Ir-photocatalyzed trifluoromethylation of peracetylated glucal **1b** gave product **7** in 59% yield, also as a single α-anomer.

We pursued deprotecting products **2** and **3** under the standard Zemplén's conditions (MeONa/MeOH).[38] However, an unidentified product mixture was recovered.

Intrigued by the different reaction course shown in the photocatalyzed trifluoromethylation of glycals reported by Ye and colleagues[21,30] employing the Umemoto´s reagent and *fac*-Ir(ppy)$_3$ as photocatalyst in an oxidative quenching cycle towards the synthesis of *2*-trifluoromethylglycosides, we decided to explore the reaction mechanism of our 2-acetoxyglycals with commercial *n*-perfluoroalkyl iodides and Ir[(dF(CF_3)ppy]$_2$(dtbbpy)$^+$ (PC-1) as photocatalyst. The redox properties of Ir[(dF(CF_3)ppy]$_2$(dtbbpy)$^+$, and similar metal-organo-photoredox catalysts,[39] can behave both in oxidative or reductive quenching manners, or simultaneously in both.[40] However, as fluorescence of PC-1* does not seem to be suppressed by addition of *n*-C_4F_9-I (Figures

S4 and S5), electron transfer oxidation of Ir(III)* to Ir(IV) and concomitant reduction of *n*-C_4F_9-I to C_4F_9 radicals is precluded, ruling out an oxidative photocatalytic quenching cycle with PC-1. On the other hand, the emission spectra of PC-1* are quenched upon addition of a DMF solution of Cs_2CO_3 (Figure 1 below, and Figures S2 & S3), indicating that an electron transfer takes place between PC-1* and Cs_2CO_3, affording Ir(II) and the radical anion of $CO_3^{\bullet-}$, with a Stern Volmer rate constant K_{SV} = 402 M^{-1}.

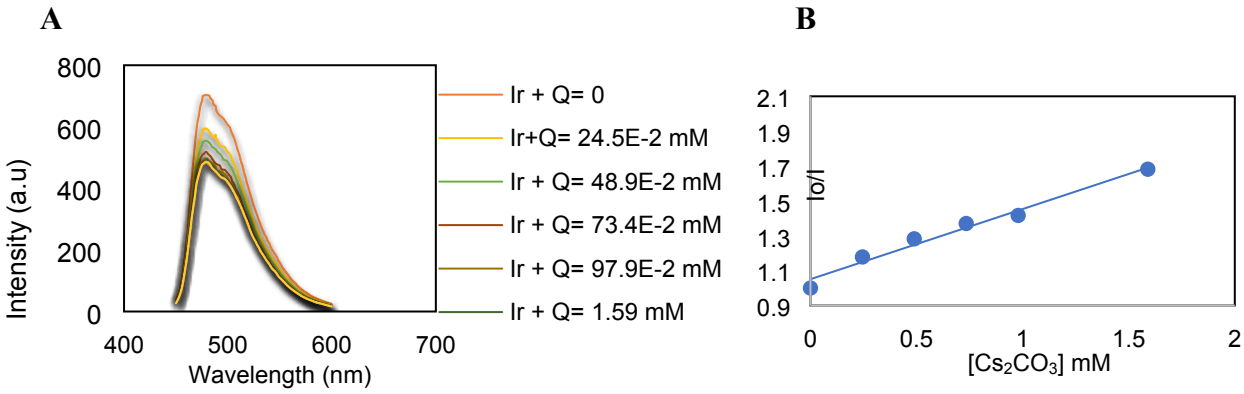
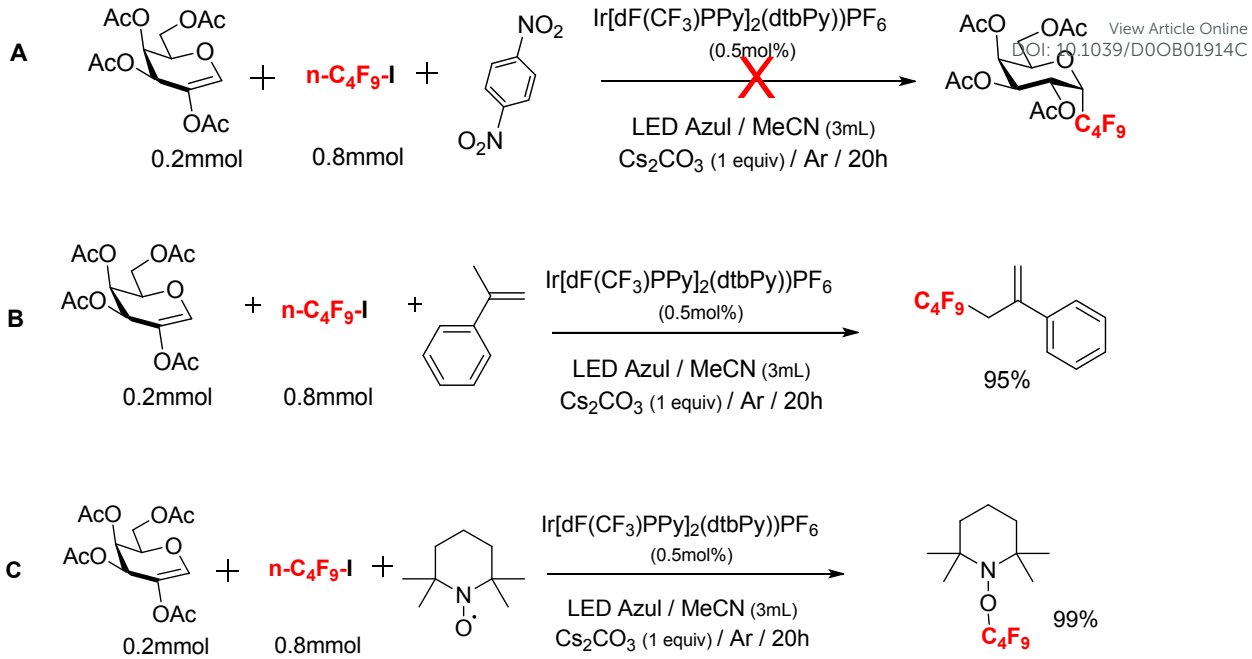


Figure 1. **A.** Suppression of the fluorescence of the photocatalyst, in the presence of DMF solution of Cs_2CO_3 (Q**) B**. Fluorescence Quenching. Stern-Volmer Plot

The photocatalytic reactions of **1** with PC-1 is suppressed in the presence of 1,4-dinitrobenzene (Scheme 2A), confirming the presence of an electron transfer process involving reducing species. Mechanistic evidence, such as the quenching of the photoreactions with 1-methyl-1-phenyl-ethylene, a good radical acceptor, (Scheme 2B) and TEMPO (Scheme 2C), are also in accordance with the presence of radicals (Table S2).



Scheme 2. **Mechanistic** probe experiments

The reaction of **1a** according to the standard reaction conditions in CD_3CN as solvent afforded 3 % yield of product **2**, purporting that a large isotope effect is operating, and that the H-transfer step from the solvent can be rate-determining. Other sources of H-atom donor in the reaction medium cannot be discarded at this time, and this step of the reaction mechanism is being thoroughly investigated at present in our laboratory.

We also measured the quantum yield of the reaction, and found a value of 0.196 ± **0.05**, suggesting the lack of a reaction propagation chain (see ESI for quantum yield calculation). According to the results from Yoon and co-workers[41] we estimated the length of the propagation chain in our photoinitiated reaction and found a value of 0.20, well below that expected in a self-propagation chain mechanisms (see ESI).

We also conducted an on/off light experiment (Figure S1) aimed at revealing/discarding the presence of chains in photoredox processes. A plot of product formation versus photoreaction time revealed that during dark periods (absence of irradiation), no accumulation of product was encountered, indicating the necessity of constant illumination.[39,42] However, ordinary lifetimes for radical chain events may commonly be on the second or sub-second time scale;[43] therefore, the lack of product accumulation during dark intervals is only consistent with chains ceasing faster than the timescale of the analytical measurement employed.[44,45]

The proposed mechanism is illustrated in Scheme 3.

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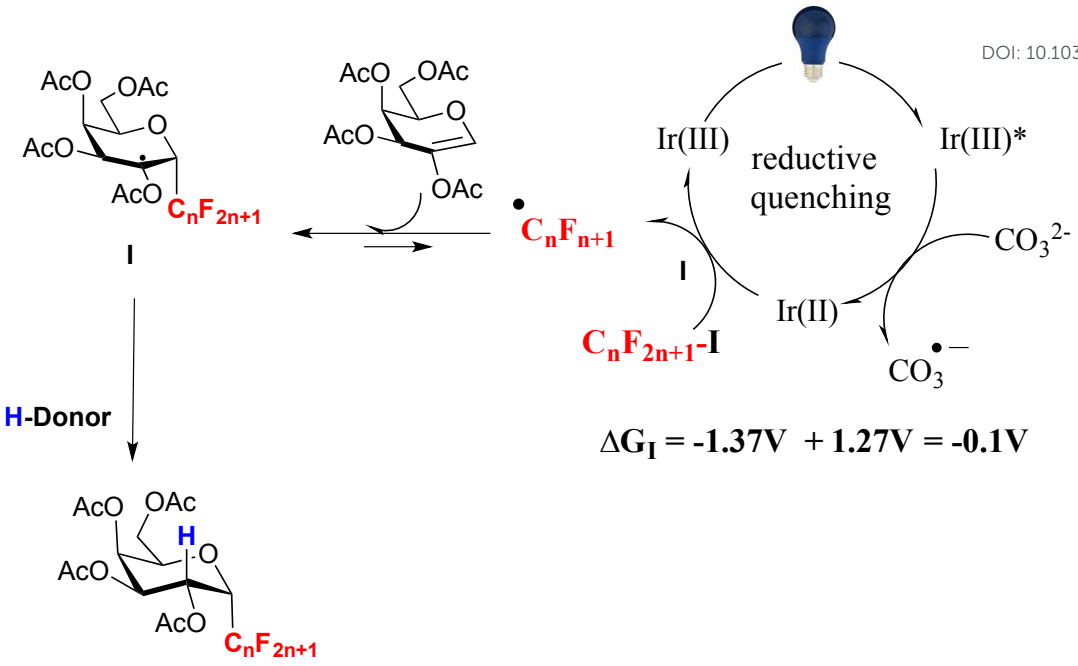

Scheme 3. Proposed reaction mechanism

In the proposed mechanism, the visible-light -excited photocatalyst PC-1* accepts an electron from Cs_2CO_3, affording the PC in its reduced form (Ir(II)). The reductive quenching cycle for the production of C_4F_9 radicals has a Gibbs energy value of –0.1 V, as calculated from the Rehm Weller equation (Figure S7). This Ir(II) has enough reductive potential to reduce the perfluoroalkyl iodide R_F-I to R_F radicals (see section 2.4.2.- ESI), which add to the C-1 position of **1** affording radical adduct intermediate **I**. This intermediate **I** cannot be oxidized to a carbocation intermediate (no Ir(IV) present), as in the case of the work by Ye and co-workers[21,30] but instead traps a H atom to afford the C_{RF}-glycoside product. This H-atom donation step is being investigated at the moment. This latter is probably a sluggish process, with a slow rate determining step, as opposed to the trifluoromethylation of glycals with the Umemoto´s reagent, where oxidation of the intermediate radical adduct to an oxonium ion by Ir(IV) regenerates the PC in its original oxidation step. In the present case, two-bimolecular steps are involved in the generation of product **2**, i.- radical addition and ii.- subsequent H-abstraction. The lack of an ATRA (atom transfer radical addition) reaction product, that would result from concomitant introduction of an iodine atom and a R_F group into the double bond moiety, re-enforces the lack of chain propagation, the low quantum yield observed and the short length chain obtained.

It should be noted that despite that two stereogenic centers are formed in the reductive fluoroalkylation of 2-acetoxygalactal and glucal derivatives, only one mayor

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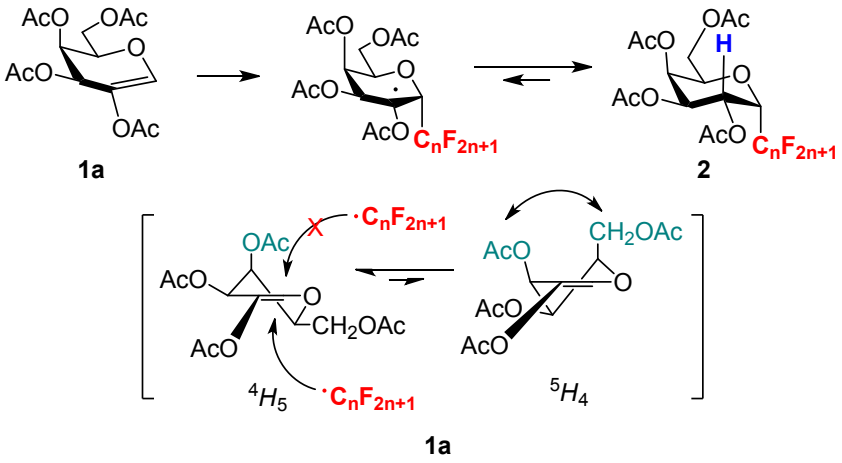
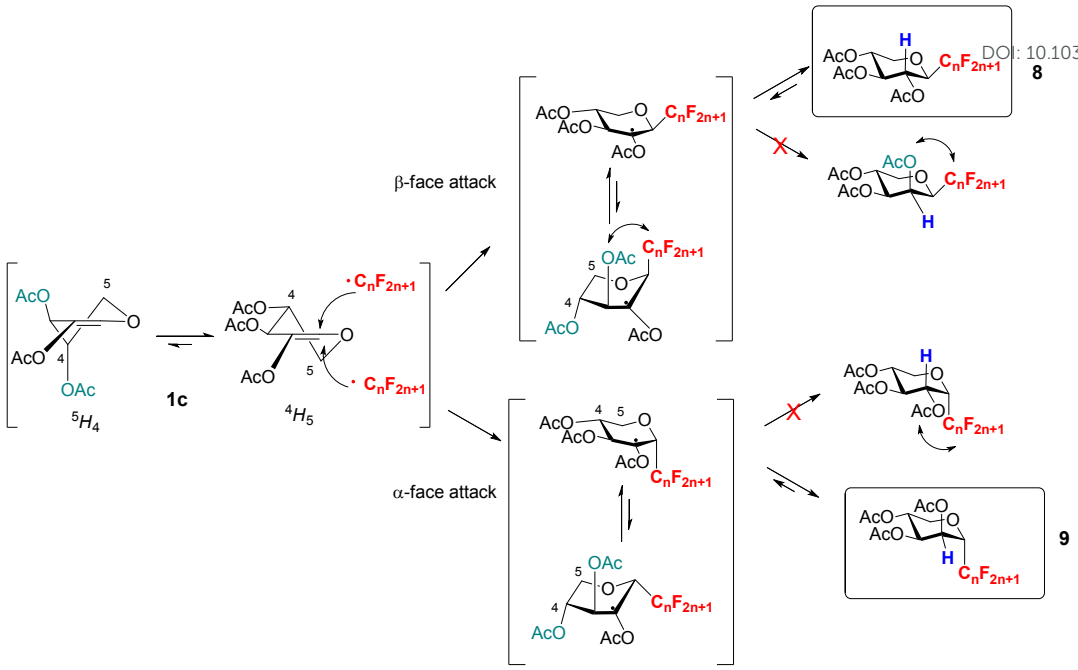
product is obtained in each case (i.e.: **2** and **3**, respectively), as strong selectivity towards the α-*galacto*/α-*gluco*-configured products was observed. These results can be interpreted on the basis of steric effects, also called the α-effect. In the preferred $^4H_5$ conformation of the substrates (*vide infra* Scheme 4), the quasi-equatorial disposition adopted for the -CH_2OAc substituents at position 5-, permits the in-coming R_F radical to approach from the bottom α-face, a fact that is reinforced in the *galacto*-derivative (53% of product **2**) which bears an axial OAc group at position 4 exerting remarkable steric influence towards the R_F radical approximation from the upper β-face. Moreover, an addition on the β-face would lead to an unfavorable twist-boat transition state. Finally, the incoming hydrogen atom-donor occurs from the β-face, leaving the AcO-group in equatorial disposition (Scheme 4).



Scheme 4. α-Attack of the perfluoroakyl radical to **1a** in the preferred $^4H_5$ conformation.

On the other hand, the higher flexibility of the pyranose **1c** could account for the mixture of the α-*lyxo* and β-*xylo* diastereoisomers found in the Ir-photocatalyzed reactions. **1c,** in the preferred $^4H_5$ conformation, can suffer unimpeded fluoroalkyl radical attack at C-1 from both faces of the double bond as a result of absence of any substituent at C-5 (allowing bottom approach of R_F radical) or the advantageous equatorial disposition of the substituent at C-4 (which permits approximation of R_F radical from the top face), as compared to *galacto*-derived glycal **1a**. H-atom donation in the resulting radical intermediates takes place from the same face leading to compounds **8** and **9.**



Scheme 5. α- and β-attack of the perfluoroakyl radical to **1c.**

CONCLUSIONS

Perfluoroalkylation of 2-acetoxy-glycals towards the synthesis of α–1-fluoroalkyl-*C*-glycosyl compounds was achieved through visible-light photocatalytic techniques employing an Ir(F) photocatalyst (PC-1) and commercially available perfluoroalkyl iodides *n*-C_nF_{2n+1}-I (n = 1,4,6) in reasonably good yields.

The synthetic strategy studied in this work represents important advantages over the reported methods for obtaining *C*-fluoroalkylglycosides, as it involves a single process starting from laboratory-available 2-acetoxyglycals, employs inexpensive commercial sources of perfluoroalkylated chains, and uses light in the visible region of the electromagnetic spectrum to initiate the reaction. The reactions were clean and proceeded with good yields and excellent mass balance.

As for the reaction mechanism, we provide evidence on the fact that PC-1 acts in a reductive quenching cycle producing R_F radicals as determined by fluorescence quenching experiments in a non-chain radical process as evidence by the lower-than-unity quantum yield observed (i.e.: 0.196).

The reactions showed to be highly stereoselective since for the 2-acetoxygalactal and 2-acetoxyglucal substrates, only α-*galacto*/α-*gluco*-configured products were observed, respectively. On the other hand, in the case of the pentopyranose-derived glycal

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1c, a mixture of the α-*lyxo* and β-*xylo* diastereoisomers were obtained in the Ir-photocatalyzed reactions.

In summary, we herein report the first visible-light-photocatalyzed one-step- *C*-fluoroalkylation procedure of glycal derivatives towards the synthesis of C-perfluoroalkylated-glycosyl compounds. These results encourage further investigations on alternative radical methods for the introduction of fluorinated groups into glycals and 2-acetoxyglycals.

EXPERIMENTAL

General Procedure for Photocatalytic Reactions

In a 5 mL-reaction vial provided with a screw-cap septum and a micro stir bar, the glycal (**1a-c**, 0.2 mmol), Cs_2CO_3 (65 mg, 0.2 mmol), and the selected photocatalyst (0.36 mol%, 4.5 × 10-2 mmol Eosin Y), 4.5 × 10-2 mmol RB (0.36 mol%), or Iridium catalyst, (1 × 10-3 mmol, 0.5 mol%) were suspended in deoxygenated acetonitrile (3 mL). The mixture was stirred and an Argon atmosphere was flushed into the solution for 3 min. Then, the perfluoroalkyl iodide (*n*-C_4F_9I, 138 µL (0.8 mmol); n-$C_6F_{13}I$, 173 µL (0.8 mmol); or CF_3I, 283 µL (0.8 mmol) of the stock solution) was introduced through the septum with a syringe. After brief ulterior deoxygenation with Argon, the vial was placed on a stir plate and the solution stirred vigorously for 24 hrs at room temperature under constant illumination under 5-Watt-blue LEDs (10-Watt total, distance from the lamp: 1 cm from a blue LED). The mixture was then extracted with DCM or Et_2O (3 × 5 mL), and the extracts, dried over $MgSO_4$ (anh.) and concentrated in vacuo. TLC analyses were performed employing ethyl acetate:iso-octane (1:1) as the mobile phase. The crude residues were analyzed by ^{1}H-NMR, and a ^{19}F-NMR by adding benzotrifluoride as internal standard for quantification of the products. Yields were also determined by weight after purification of the products, under the conditions described above.

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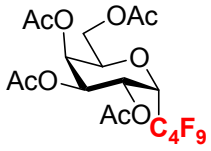
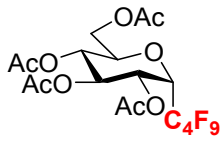
1-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-1,1,2,2,3,3,4,4,4-nonafluorobutane (2)



Purification by column chromatography (8:2 Hexane / EtOAc) followed by preparative TLC, gave compound **2** (58 mg, 53%) as a white powder, 26 mg of starting glycal **1a** were recovered from the column (87% corrected yield for **2**). R_f = 0.50 (1.5:1 iso-octane / EtOAc). $[\alpha]^{20}_D$= –5.81 (*c* 0.97, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.53 (dd, 1 H, $J_{3,4}$ = 3.3, $J_{4,5}$ = 2.2 Hz, H-4), 5.50 (dd, 1 H, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.3 Hz, H-3), 5.46 (dd, 1 H, $J_{1,2}$ = 5.2, $J_{2,3}$= 9.7, H-2), 4.88 (ddd, 1 H, $J_{1,2}$ = 5.2, $J_{1,F}$ = 5.2, $J_{1,F'}$= 28.3 Hz, H-1), 4.30 (m, 1 H, H-5) 4.22 (dd, 1 H, $J_{5,6'}$ = 7.5, $J_{6,6'}$ = 11.7 Hz, H-6'), 4.11 (dd, 1 H, $J_{5,6}$ = 5.2, $J_{6,6'}$ = 11.7 Hz, H-6), 2.16, 2.13, 2.07, 2.05 (4 s, 3 H each, C*H*$_3$CO). ^{13}C {^{1}H} NMR (150.9 MHz, $CDCl_3$) δ: 170.3, 169.9, 169.7, 169.4 (*C*O), 71,6 (C-5), 69.0 (dd, $^2J_{C\text{-}F}$ = 20.0, $^2J_{C,F'}$ = 27.5 Hz, C-1), 67.4 (d, $^4J_{C,F'}$ = 3.2 Hz, C-3) 66.6 (C-4), 65.5 (d, $^3J_{C,F'}$ = 7.8 Hz, C-2), 60.9 (C-6), 20.6, 20.5, 20.4 (×2) (*C*H$_3$CO). ^{19}F NMR (470.592 MHz, $CDCl_3$) δ: –80.9 (t, 3F, *J* = 10.6 Hz, C*F*$_3$), –112.1, –116.1 (2brd, 1 F each, *J* = 302.4 Hz, C$^{1'}$*F*$_2$), –123.4 (m, 2 F, C^3*F*$_2$), –124.6 (m, 1 F, *J* = 5.1, *J* = 23.9, *J* = 293 Hz, C$^{2'}$*F*$_2$), –127.6 (m, 1 F, *J* = 8.5, *J* = 17.5 Hz, C$^{2'}$*F*$_2$). ESI-HRMS: [M+H$^+$] calcd for $C_{18}H_{20}F_9O_9$: 551.0958, Found: 551.09636, [M+Na$^+$] calcd for $C_{18}H_{19}F_9NaO_9$: 573.07776, Found: 573.07870, [M+K$^+$] calcd for $C_{18}H_{19}F_9KO_9$: 589.05169, Found: 589.05194.

1-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-1,1,2,2,3,3,4,4,4-nonafluorobutane (3)



Purification by column chromatography (8:2 Hexane / EtOAc) followed by preparative TLC, gave compound **3** (40 mg, 32%) as white syrup, 40 mg of starting glycal **1b** were recovered from the column (87% corrected yield for **3**). R_f = 0.60 (1:1 Hexane / EtOAc). $[\alpha]^{20}_D$ = +4.3 (*c* 1, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.55 (t, 1 H $J_{2,3}$ = 9.1, $J_{3,4}$= 9.6 Hz, H-3), 5.26 (dd, 1 H, $J_{1,2}$ = 6.1, $J_{2,3}$ = 9.1 Hz, H-2), 5.05 (dd, 1 H, $J_{3,4}$ =9.6, $J_{4,5}$ 8.5, H-4), 4.84 (ddd, 1 H, $J_{1,2}$ = 6.1, $J_{1,F}$ = 5.4, $J_{1,F'}$ = 27.5 Hz, H-1), 4.30 (dd, 1 H, $J_{5,6}$ = 5.8, $J_{6,6'}$ = 13.0, Hz H-6) 4.12 (m, 1 H, H-5, H-6'), 2.12, 2.09 (×2), 2.08 (4 s, 3 H each, C*H*$_3$CO). ^{13}C {^{1}H} NMR (150.9 MHz, $CDCl_3$) δ: 170.4, 169.6, 169.4, 169.3 (*C*O), 72.7 (C-5), 69.7 (C-3), 69.0 (t, $^2J_{C\text{-}F}$ = 24.0 C-1), 67.6 (×2, C-2, C-4), 61.6 (C-6), 20.5, 20.4

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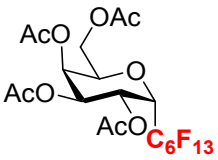
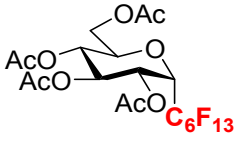
(×2), 20.3 (CH_3CO). ^{19}F NMR (470.592 MHz, $CDCl_3$) δ: –80.9 (t, 3F, J = 10.7 Hz, CF_3), –113.0, –115.2 (2brd, 1 F each, J = 304.3 Hz, $C^{1'}F_2$), –123.4 (m, 2 F, $C^{3'}F_2$), –124.6 (m, 1 F, J = 22.7, J = 293.1 Hz, $C^{2'}F_2$), –127.5 (m, 1 F, J = 4.5, J = 293.1 Hz, $C^{2'}F_2$). ESI-HRMS: [M+Na^+] calcd for $C_{18}H_{19}F_9NaO_9^+$: 573.0778, Found: 573.0784.

1-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane (4)



Purification by preparative thin-layer chromatography (8:2 Hexane / EtOAc) followed by preparative TLC, gave compound **4** (52 mg, 39%) as yellowish syrup, 40 mg of starting glycal **1a** were recovered from the column (98% corrected yield for **4**). R_f = 0.60 (1:1 *iso*-octane / EtOAc). $[\alpha]^{20}_D$ = +14.8 (*c* 1, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ: 5.53 (dd, 1 H, $J_{3,4}$ = 3.5, $J_{4,5}$ = 2.5 Hz, H-4), 5.51 (dd, 1 H, $J_{2,3}$ = 9.6, $J_{3,4}$ = 3.5 Hz, H-3), 5.46 (dd, 1 H, $J_{1,2}$ = 5.2, $J_{2,3}$ = 9.6, H-2), 4.88 (ddd, 1 H, $J_{1,2}$ = 5.2, $J_{1,F}$ =5.2, $J_{1,F'}$ = 28.2 Hz, H-1), 4.30 (m, 1 H, H-5) 4.23 (dd, 1 H, $J_{5,6'}$ = 7.5, $J_{6,6'}$ = 11.7 Hz, H-6'), 4.11 (dd, 1 H, $J_{5,6}$ = 5.2, $J_{6,6'}$ = 11.7 Hz, H-6), 2.16, 2.13, 2.07, 2.06 (4 s, 3 H each, CH_3CO). ^{13}C {^1H} NMR (150.9 MHz, $CDCl_3$) δ: 170.4, 170.0, 169.8, 169.5 (*C*O), 71.5 (C-5), 69.2 (C-1), 67.4 C-3) 66.6 (C-4), 65.5 (C-2), 61.0 (C-6), 20.6, 20.5, 20.4 (×2) (CH_3CO). ^{19}F NMR (470.592 MHz, $CDCl_3$) δ: –80.8 (t, 3 F, J = 10.6 Hz, CF_3), –112.5, –124.2 (m, 6 F, 3× CF_2), –125.4, –126.9 (2m, 1 F each, $C^{2'}F_2$). ESI-HRMS: [M+H^+] calcd for $C_{20}H_{20}F_{13}O_9$: 651.0894, Found: 651.0909.

1-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane (5)



Purification by preparative thin-layer chromatography (8:2 Hexane / EtOAc) followed by preparative TLC, gave compound **5** (42 mg, 32%) as yellowish syrup, 40 mg of starting glycal **1b** were recovered from the column (82% corrected yield for **5**). R_f = 0.60 (1:1 Hexane / EtOAc). $[\alpha]^{20}_D$ = +3.7 (*c* 1, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ: 5.52 (t, 1

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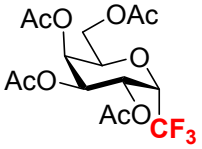
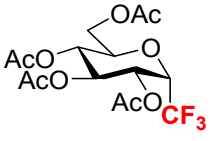
H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 5.24 (dd, 1 H, $J_{1,2} = 6.0$, $J_{2,3} = 9.6$ Hz, H-2), 5.03 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$, H-4), 4.81 (ddd, 1 H, $J_{1,2} = 5.4$, $J_{1,F} = 5.4$, $J_{1,F'} = 27.5$ Hz, H-1), 4.31 (dd, 1 H, $J_{5,6} = 5.7$, $J_{6,6'} = 12.9$ Hz H-6) 4.13 (m, 1 H, H-5, H-6'), 2.12, 2.10 (×2), 2.08 (4 s, 3 H each, CH_3CO). ^{13}C {^{1}H} NMR (150.9 MHz, $CDCl_3$) δ: 169.5, 169.4, 169.3 (×2) (*C*O), 72.6 (C-5), 69.7 (C-3), 69.0 (t, $^2J_{C\text{-}F} = 54.4$ C-1), 67.6 (C-2), 67.5 (C-4), 61.5 (C-6), 20.6, 20.5, 20.4, 20.3 (*C*H$_3$CO). ^{19}F NMR (470.592 MHz, $CDCl_3$) δ: –80.7 (t, 3 F, $J = 10.1$ Hz, CF_3), –120.0, –124.2 (m, 6 F, 3× CF_2), –125.2, –126.9 (2m, 1 F each, $J = 293$ Hz, C$^{2'}F_2$). ESI-HRMS: [M+H$^+$] calcd for $C_{20}H_{19}F_{13}NaO_9$: 673.0714, Found: 673.0707.

(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)trifluoromethane (6)



Purification by preparative thin-layer chromatography (8:2 Hexane / EtOAc) followed by preparative TLC, gave compound **6** (48 mg, 59%) as a yellowish syrup, 19 mg of starting glycal **1a** were recovered from the column (82% corrected yield for **6**). $R_f = 0.70$ (1:1 Hexane / EtOAc). $[\alpha]^{20}_D = -4.5$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.49 (dd, 1 H, $J_{3,4} = 3.3$, $J_{4,5} = 1.8$ Hz, H-4), 5.38 (dd, 1 H, $J_{1,2} = 6.2$, $J_{2,3} = 9.6$, H-2), 5.20 (dd, 1 H, $J_{2,3} = 9.6$, $J_{3,4} = 3.3$ Hz, H-3), 4.65 (ddd, 1 H, $J_{1,2} = 6.2$, $J_{1,F} = 8.7$, $J_{1,F} = 11.7$ Hz, H-1), 4.22 (m, 2 H, H-5 + H-6'), 4.10 (dd, 1 H, $J_{5,6} = 8.4$, $J_{6,6'} = 14.3$ Hz, H-6), 2.14, 2.09, 2.06, 2.04 (4 s, 3 H each, CH_3CO). ^{13}C {^{1}H} NMR (150.9 MHz, $CDCl_3$) δ: 170.4, 170.1, 169.9, 169.6 (*C*O), 71.2 (C-5), 70.2 (q, $J_{C\text{-}F} = 29.2$, C-1), 67.3 (C-3), 66.74 (C-4), 65.0 (C-2), 61.1 (C-6), 20.6 (×2), 20.5 (×2) (*C*H$_3$CO). ^{19}F NMR (470.592 MHz, $CDCl_3$) δ: –67.6 (s, 3 F, CF_3). ESI-HRMS: [M+Na$^+$] calcd for $C_{15}H_{19}F_3NaO_9$: 423.0873, Found: 423.0885.

(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)trifluoromethane (7)



Purification by preparative thin-layer chromatography (8:2 Hexane / EtOAc) followed by preparative TLC, gave compound **7** (47 mg, 59%) as white syrup, 23 mg of starting glycal **1b** were recovered from the column (90% corrected yield for **7**). $R_f = 0.70$ (1:1 *iso*-octane / EtOAc). $[\alpha]^{20}_D = +6.3$ (*c* 1, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.51 (t, 1 H, $J_{2,3} =$

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$J_{3,4}$ = 8.9 Hz, H-3), 5.19 (dd, 1 H, $J_{1,2}$ = 7.1, $J_{2,3}$= 8.9, H-2), 5.05 (t, 1 H, $J_{3,4}$ = $J_{3,4}$ = 8.9 Hz, H-4), 4.60 (ddd, 1 H, $J_{1,2}$ = 7.0, $J_{1,F}$ = 8.7, $J_{1,F}$ = 17.3 Hz, H-1), 4.29 (m, 1 H, $J_{5,6'}$ = 5.0, $J_{6,6'}$ = 12.5 Hz, H-6'), 4.12 (dd, 1 H, $J_{5,6}$ = 2.4, $J_{6,6'}$ = 12.5 Hz, H-6), 4.02 (m, 1 H, H-5), 2.10, 2.09, 2.05, 2.04 (4 s, 3 H each, C*H*$_3$CO). ^{13}C {^{1}H} NMR (150.9 MHz, $CDCl_3$) δ: 170.6, 169.7, 169.5, 169.4 (*C*O), 72.3 (C-5), 70.4 (C-1), 69.8 (C-3), 67.7 (C-4), 67.2 (C-2), 61.6 (C-6), 20.7 (×2), 20.6, 20.4 (*C*H$_3$CO). ^{19}F NMR (470.592 MHz, $CDCl_3$) δ: –67.3 (s, 3 F, C*F*$_3$). ESI-HRMS: [M+Na$^+$] calcd for $C_{15}H_{19}F_3NaO_9$: 423.0873, Found: 423.0863

1-(2,3,4-tri-*O*-acetyl-β-xylopyranosyl)-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorobutane (8) and 1-(2,3,4-Tri-*O*-acetyl-α-lyxopyranosyl)-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorobutane (9)

Isomeric compounds **8** and **9** were obtained from 2-acetoxy-xylal **1c** (52 mg) as an unresolved mixture. The mixture was purified from other minor contaminants by preparative thin-layer chromatography (8:2 Hexane / EtOAc) and 33 mg (34% combined yield) were obtained as a white syrup, 26 mg of starting glycal **1c** were recovered from the column (70% corrected yield for **8** + **9**). R_f = 0.60 (1:1 Hexane / EtOAc).

Further attempts to separate both compounds by HPLC (RP-18 column, MeOH / H_2O mixtures) were unsuccessful. Nevertheless, the signals of both compounds could be clearly seen in the ^{1}H-NMR spectrum, and a 0.7 : 1.0 ratio of **8** : **9** could be determined by integration of the signals. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.77 (br. dd., 1 H, $J_{1,2}$ = 2.5, $J_{2,3}$ = 3.3 Hz, H-2-*lyxo*), 5.41 (t, 0.7 H, $J_{1,2}$ = $J_{2,3}$ = 9.4 Hz, H-2-*xylo*), 5.30 (ddd, 1 H, $J_{4,5eq}$ = 5.8, $J_{4,5ax}$ = 10.4 Hz, $J_{3,4}$ = 10.2, H-4-*lyxo*), 5.28 (m, 0.7 H, H-3-*xylo*), 5.05 (dd, 1 H, $J_{2,3}$ = 3.3, $J_{3,4}$ = 10.2 Hz, H-3-*lyxo*), 5.01 (dd, 0.7 H, $J_{4,5eq}$ = 5.6, $J_{4,5ax}$ = 10.1 Hz, $J_{3,4}$ = 9.9, H-4-*xylo*), 4.33 (dd, 1 H, $J_{4,5eq}$ = 5.8, $J_{5eq,5ax}$ = 11.3 Hz, H-5eq-*lyxo*), 4.22 (dd, 0.7 H, $J_{4,5eq}$ = 5.6, $J_{5eq,5ax}$ = 11.3 Hz, H-5eq-*xylo*), 4.07 (m, 1 H, $J_{H,F}$ = 18.2 Hz, H-1-*lyxo*), 3.93 (m, 0.7 H, H-1-*xylo*), 3.33 (t, 1.7 H, $J_{4,5ax}$ = 10.4, $J_{5eq,5ax}$ = 11.3 Hz, H-5ax-*lyxo* + H-5-ax-*xylo*), 2.16 (s, 2.1 H, C*H*$_3$CO, *xylo*), 2.15, 2.05 (2 s, 3 H each, 2 × C*H*$_3$CO, *lyxo*), 2.04, 2.03 (2 s, 2.1 H each, 2 × C*H*$_3$CO, *xylo*), 2.02 (s, 3 H, C*H*$_3$CO, *lyxo*). ^{13}C {^{1}H} NMR (150.9 MHz, $CDCl_3$) δ: 170.3, 170.2, 169.9, 169.7, 169.6, 169.3 (*C*O), 74.2 (m, C-1-*xylo*), 73.5 (m, C-1-*lyxo*), 73.0 (C-3-*xylo*), 71.0 (C-3-*lyxo*), 68.0 (C-4-*xylo*), 67.6 (C-5-*xylo*), 66.9 (C-5-*xylo*), 66.2 (m, C-2-*xylo*), 65.6 (C-5-*lyxo*), 65.3 (m, C-2-*lyxo*), 21.07,

20.88, 20.81, 20.73, 20.71, 20.54, 20.29 ($CO\mathit{C}H_3$). ^{19}F NMR (470.592 MHz, $CDCl_3$) δ: –80.92 (t, 3 F, J = 10.7 Hz, $C\mathit{F}_3$), –116.5 - –128.0 (m, 6 F, 3 × $C\mathit{F}_2$). ESI-HRMS: [M+H$^+$] calcd for $C_{15}H_{15}F_9NaO_7$: 501.0566, Found: 501.0568

CONFLICTS OF INTEREST

There are no conflicts to declare.

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