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FULL PAPER

Exploring the chemistry of non-sticky sugars: Synthesis of polyfluorinated carbohydrate analogs of D-allopyranose

Vincent Denavit, Jacob St-Gelais, Thomas Tremblay and Denis Giguère*[a]

Abstract: There is a growing interest in the preparation of polyfluorinated carbohydrates. A limited number of fluorohexopyranosides have been used in biological investigations because of the synthetic challenge they present. Hence, we report the synthesis of fluorinated homodimer, fluorodisaccharides, *C*-terminal fluoroglycopeptides, lipoic acid fluoroglycoconjugate and trifluoroallopyranoside derivatives functionalized at C-6. Our strategy uses levoglucosan as inexpensive starting material and unveil an approach to complex carbohydrate analogs with multiple C–F bonds. The challenge of our synthetic route was centered around an efficient preparation of crucial 1,6-anhydro-2,4-dideoxy-difluoroglucopyranose and focused on successfully achieving difficult glycosylation of trifluoroallopyranose donor. These results clearly highlight challenges related to the preparation of polyhalogenated complex organic molecules and pave the way to access novel medically relevant tools.

During the last few decades, research in the field of molecular biology allowed the discovery of valuable medicinally relevant tools derived from carbohydrates. The synthesis of novel glycomimetics is hampered by the complexity of the hydroxylated pyran rings (requiring many hydroxyl groups' protection/deprotection steps), thereby new synthetic method must be developed. As such, fluorinated carbohydrates are invaluable tools as mechanistic probes to study lectin-carbohydrate interactions and to decipher the mechanisms of glycosidases.[1] Undoubtedly, the most widespread application of fluorinated carbohydrates is related to ^{18}F-positron emitting tomography agents for cancer imaging technique.[2]

The replacement of hydroxyl groups by fluorine atoms is no coincidence since there are similarities between OH and F atom in regard to polarity and isosteric relationship.[3] Although, incorporation of fluorine atoms on a hydroxylated pyran ring might lead to greater lipophilicity and increase cell permeability.[4] Finally, the loss of hydrogen donating capacity for the F atom and the high C–F bond energy is another important feature to point out.

Only a limited number of polyfluorinated carbohydrates have been used in biological investigations so far. This is a direct consequence of the long multisteps synthetic sequences used in *de novo* approaches.[5] Representative examples of polyfluorinated carbohydrates with unique properties are presented in **Figure 1**. First of all, the group of DiMagno prepared the hexafluorinated pyran **1**[6] in the late 90's. This compound crosses red blood cell membrane at a tenfold higher rate than glucose. Similarly, the group of O'Hagan synthesize 2,3,4-trifluoroglucose **2** using a *de novo* strategy.[7] This compound is transported less efficiently than D-glucose through the erythrocyte membrane, but the α-anomer is preferred for efficient transport as compared to the β-anomer. Also, our group recently prepared trifluoroglucose derivative **2** using a Chiron approach from levoglucosan.[8] The flexibility of this strategy allowed us to also achieve the preparation of 2,3,4-trideoxy-2,3,4-trifluoro mannose, talose, fucose, allose, and galacturonic acid methyl ester. Moreover, we were the first group to access a 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluorohexopyranoside, represented by molecule **3**. Analogs of the latter compound display weak antiproliferative activity with no selectivity towards normal and cancer cell lines.[9] Recently, the group of Linclau reported the synthesis of trifluoroglucose **2** also using a Chiron approach.[10] Also, the group of Linclau prepared a tetrafluoroethylene-containing monosaccharide **4**, which gained affinity to UDP-galactopyranose mutase from *Mycobacterium tuberculosis* as compared to unmodified analogs.[11] This example clearly suggests that increasing the polar hydrophobicity may help improve biological activity. Furthermore, the group of Hoffmann-Röder made a significant contribution in the preparation of various fluorinated MUC1 glycopeptide antigens,[12] along with the preparation of the corresponding conjugate vaccines.[13] Trifluorinated Thomsen-Friedenreich (TF) analog **5** was used in immunization studies and binding experiments with antiserum obtained from immunization

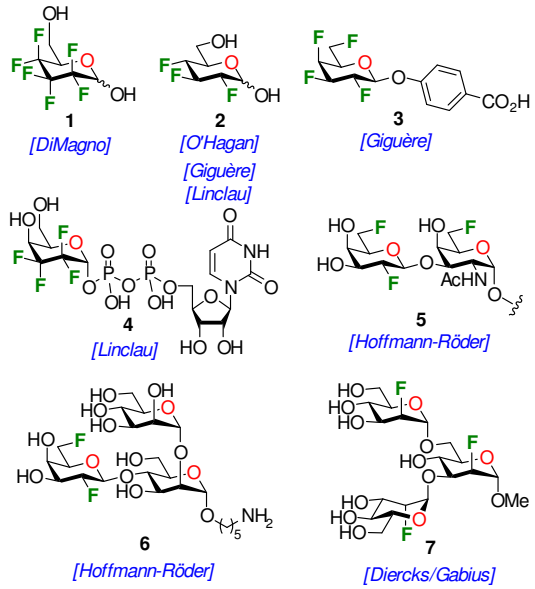

Figure 1. Heavily fluorinated pyrans as carbohydrate mimics: hexafluorinated carbohydrates analog **1**, trifluorinated glucopyranose analog **2**, tetrafluorinated galactopyranoside **3**, tetrafluorinated UDP-galactopyranose **4**, fluorinated MUC1 glycopeptide antigen **5**, fluorinated *Leishmania* cap trisaccharide **6**, and fluorinated *N*-glycan core trimannoside **7**.

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with a conjugate vaccine carrying the TF antigen glycan. The antisera derived from fluoroglycoconjugates showed small differences in binding to the fluorinated antigens. This work showed that fluorinated tumor associated carbohydrate antigens could be used for the design of vaccines with enhanced metabolic stability. This idea was demonstrated with the preparation of fluorotrisaccharide **6** based on the lipophosphoglycan capping structure of *Leishmania donovani*.[14] The amine linker will allow future conjugation reactions to carrier proteins in order to unveil novel immunological properties. It is important to point out that the preparation of such fluorinated immunogenic tools is highly challenging and a flow procedures was developed to allow a scale up synthesis of fluorinated antigens.[15] Finally, the groups of Diercks/Gabius prepared a fluoro-*N*-glycan core trimannoside **7**.[16] Its recognition to *Pisum sativum* was confirmed to be *via* the two terminal mannose residues. Examples presented in **Figure 1** strongly suggests that more research should be directed toward the development of new strategies for the design of fluorinated carbohydrate mimetics.

We aimed to access original polyfluorinated allopyranose analogs using a Chiron approach. The proposed synthetic sequences enable a minimal usage of protection/deprotection cycles, avoid tedious purification, and allows excellent regio- and stereocontrols. Levoglucosan (1,6-anhydro-β-D-glucopyranose) was chosen as the ideal inexpensive starting material since the 1,6-anhydro bridge prevents protection of both O-6 and anomeric position. Moreover, the 6,8-dioxabicyclo[3.2.1]octane core allows navigation on the pyran ring to install fluorine atoms or other functional groups. **Figure 2** shows our retrosynthetic analysis to complex polyfluorinated carbohydrate mimetics. Thus, fluorinated homodimer **8**, disaccharide **9**, *C*-terminal fluoroglycopeptide **10**, allopyranoside derivatives **11**, could be accessible from derivatization of 2,3,4-trideoxy-2,3,4-trifluoroallopyranose **12**. The latter is available from intermediate **13** through acetolysis and nucleophilic deoxyfluorination at C-3. Moreover, 2,4-difluoroglucopyranose **13** is readily accessible from levoglucosan **17** and could be the ideal precursor for lipoic acid fluorinated glycoconjugate **14**, 3-amino-bridged fluorinated disaccharide **15** and *C*-terminal fluoroglycopeptide **16**. Beyond its versatility, this strategy unveils an approach to complex carbohydrate analogs with multiple C–F bonds.

The synthesis of 1,6-anhydro-2,4-dideoxy-difluoro-glucopyranose **13** from levoglucosan **17** is summarized in **Scheme 1**. Three routes were evaluated to prepare the target compound **13**. The first route was initiated with a mono-*O*-*p*-toluenesulfonylation at C-4 as previously described.[17] Nucleophilic fluorination on tosylate **18** yielded the corresponding fluorinated intermediate in a disappointing 12% yield after selective mono-*O*-*p*-toluenesulfonylation at C-2.[18] The fluorination occurred in complete retention of configuration probably *via* formation of a 3,4-anhydro intermediate, followed by a regioselective *trans*-diaxial epoxide opening.[19] However, the selectivity of the opening was impaired by the migration of epoxide.[20] Nevertheless, compound **19** was converted to 1,6:2,3-dianhydro-mannopyranose **20** under basic conditions and treated with potassium hydrogen fluoride affording the desired 2,4-difluoroglucopyranose **13** in low yield. The second route started with tosylate **21**,[17] which was a suitable intermediate for the synthesis of compound **23** *via* intermediate 2,3-anhydro **22** (49% yield over 2 steps). Then, 2,4-difluoroglucopyranose **13** was formed in a 8% yield using potassium hydrogen fluoride.[21] Due to these disappointing results, we explored a third route starting with formation of a *bis*-tosylate intermediate[22] followed by treatment under basic conditions leading to 1,6:3,4-dianhydro-2-*O*-*p*-toluenesulfonyl-β-D-galactose **24** in 93% yield over 2 steps. The latter compound represented the perfect candidate for a dual nucleophilic fluorination. We first used KHF_2 in ethylene glycol and the reaction failed. Consequently, we evaluated other fluorination methods. Efforts towards this end are presented in **Table 1**. We used as initial attempt a neat mixture of 2 equivalents of KHF_2 and 4 equivalents of TBAF·$3H_2O$ at 120 °C for 18 hours (entry 1).[23] A 7% yield was obtained for product **13**,

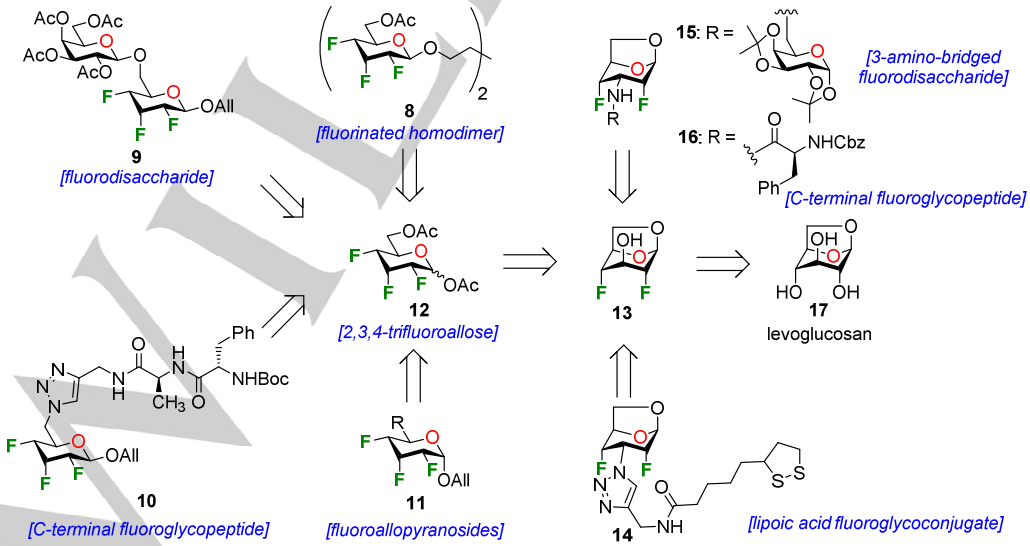

Figure 2. Retrosynthetic analysis to fluorinated homodimer **8**, fluorodisaccharide **9** and **15**, *C*-terminal fluoroglycopeptide **10** and **16**, trifluoroallopyranoside derivatives **11**, and lipoic acid fluoroglycoconjugate **14**.

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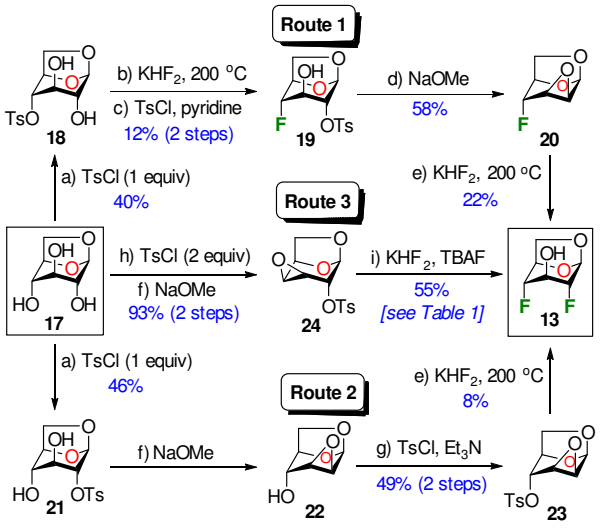
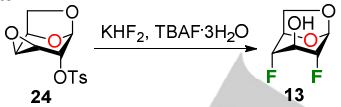


Scheme 1. Approaches to 2,4-difluoroglucopyranose **13** from levoglucosan **17**. Reagents and conditions: a) TsCl (1.1 equiv), pyridine, toluene, 0 °C to rt, 16 h, 40% for **18**, 46% for **21**; b) KHF_2 (8 equiv), butoxyethanol, 200 °C, 24 h; c) TsCl (4 equiv), pyridine, 60 °C, 5 days, 12% over 2 steps; d) 1 M NaOMe, MeOH, rt, 20 h, 58%; e) KHF_2 (8 equiv), ethylene glycol, 200 °C, 3 h, 22% from **20**, 8% from **23**; f) NaOMe (1.3 equiv), $MeOH/CH_2Cl_2$, rt, 1 h, 93% over 2 steps for **24**; g) TsCl (2 equiv), Et_3N (2 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 16 h, 49% over 2 steps; h) TsCl (2 equiv), pyridine, $CHCl_3$, 0 °C to rt, 18 h; i) KHF_2 (4 equiv), $TBAF{\cdot}3H_2O$ (8 equiv), 180 °C, 18 h, 55%.

so we increased the temperature to 180 °C and we achieved a 41% yield for the desired product (entry 2). Then, shortening the reaction time resulted in a lower yield (entry 3), however doubling the amount of $KHF_2/TBAF{\cdot}3H_2O$ allowed formation of compound **13** in a satisfactory 55% yield (entry 4). Hence, based on these results, it is obvious that the third route was the most promising for large scale preparation of 1,6-anhydro-2,4-dideoxy-difluoroglucopyranose **13**.

Table 1. Synthesis of 1,6-anhydro-2,4-dideoxy-difluoroglucopyranose **13** from intermediate **24**.



Entry	$KHF_2/TBAF$ (equiv/equiv)	Temperature (°C)	Time (h)	Yield[a] (%)
1	2/4	120	18	7
2	2/4	180	18	41
3	2/4	180	6	31
4	4/8	180	18	55

[a]Yields refer to isolated pure products after flash column chromatography.

With the continuous objective of shortening the amount of steps to prepared valuable *bis*-fluorinated compound **13**, we tried our optimized conditions (Table 1, entry 4) on *bis*-tosylate **25**[22] (**Scheme 2**).[24] To our delight, compound **13** was isolated in 60% yield (~88% yield per step) starting with 25 grams of intermediate **25**, in one single batch. This process involved the breakage of 2 C–O bonds and the formation of 2 C–F bonds in a stereoselective fashion, through a series of epoxide formation and epoxide opening sequence. With compound **13** in hand, activation of the free hydroxyl group as a triflate was possible *via* exposure to trifluoromethanesulfonic anhydride allowing isolation of bench stable colorless crystals **26**. Treatment of the latter with $Et_3N{\cdot}3HF$ generated volatile intermediate **27** that could be isolated in 52% yield (76% based on recovered starting material). Compound **27** was treated under acetolysis conditions affording 2,3,4-trideoxy-2,3,4-trifluoroallopyranose **12** in 80% yield (α/β = 1:1.7). We next turned our attention to the preparation of 2,3,4-trideoxy-2,3,4-trifluoroglucopyranose **30**. This compound was previously described by the group of O'Hagan,[7] by us,[8] and recently by the group of Linclau.[10] Our proposed route is similar to the one described by the latter group[25] (**Scheme 2**). To this end, we first planned epimerization of the hydroxyl group at C-3 on compound **13** for further nucleophilic fluorination with inversion of configuration allowing the generation of the corresponding 1,6-anhydro-D-glucopyranose product. Initial attempts involving a Lattrell-Dax epimerization[26] starting from triflate **26** failed, at best provided trace amounts of the desired 1,6-anhydro-2,4-dideoxy-2,4-difluoroallopyranose **28**. Epimerization at C-3 succeeded *via* a Dess-Martin oxidation followed by *in situ* ketone reduction with $NaBH_4$ allowing the preparation of compound **28** in 61% yield over 2 steps. Nucleophilic fluorination at C-3 proceeded using TBAF *via* a triflate derivative and furnished volatile intermediate **29** which was subsequently treated under acetolysis conditions providing 2,3,4-trideoxy-2,3,4-trifluoroglucopyranose **30** in 14% yield (α/β = 5.2:1) over 3 steps (~52% yield per steps). Additionally, with this highly efficient synthetic sequence, it is possible to rapidly access novel difluorinated analogs of D-glucopyranose and D-allopyranose. Thus, a simple acetolysis of intermediate **13** and **28** furnished 2,4-dideoxy-2,4-difluoroglucopyranose **31** and 2,4-dideoxy-2,4-difluoroallopyranose **32**, respectively in 94% and 63% yield. Moreover, with triflate **26** in hand and in order to explore the reactivity and increase the molecular diversity of fluorinated 1,6-anhydro-hexopyranose, we introduced an azide functional group at C-3. Thus, compound **26** was treated with sodium azide at 70 °C, for 36 h allowing a challenging nucleophilic substitution leading to 2,3,4-trideoxy-3-azido-2,4-difluoroallopyranose **33** in 60% yield. Then, a click procedure was used to prepare a lipoic acid fluorinated glycoconjugate.[27] Thus, azide **33** reacted with alkyne **34** leading to product **14** in 89% yield. Glyco-nanoparticules conjugated through lipoic acid moiety have been used as tools to study lectin-carbohydrate interactions,[28] as in vitro imaging platform[29] and as agents for controlling nonspecific adsorption of blood serum.[30] We can now consider to use fluorinated carbohydrates in these medically relevant systems. Also, azide **33** was reduced with H_2 gas and a catalytic amount of palladium generating amine **35**. The latter was directly subjected to a reductive amination with 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose **36**[31] and $NaBH_3CN$ affording the first 3-amino-bridged fluorinated disaccharide **15** in 47% over 2 steps. Unnatural disaccharides are needed as potential drug candidates and for investigation of biochemical processes. Finally, amine **35** was also coupled

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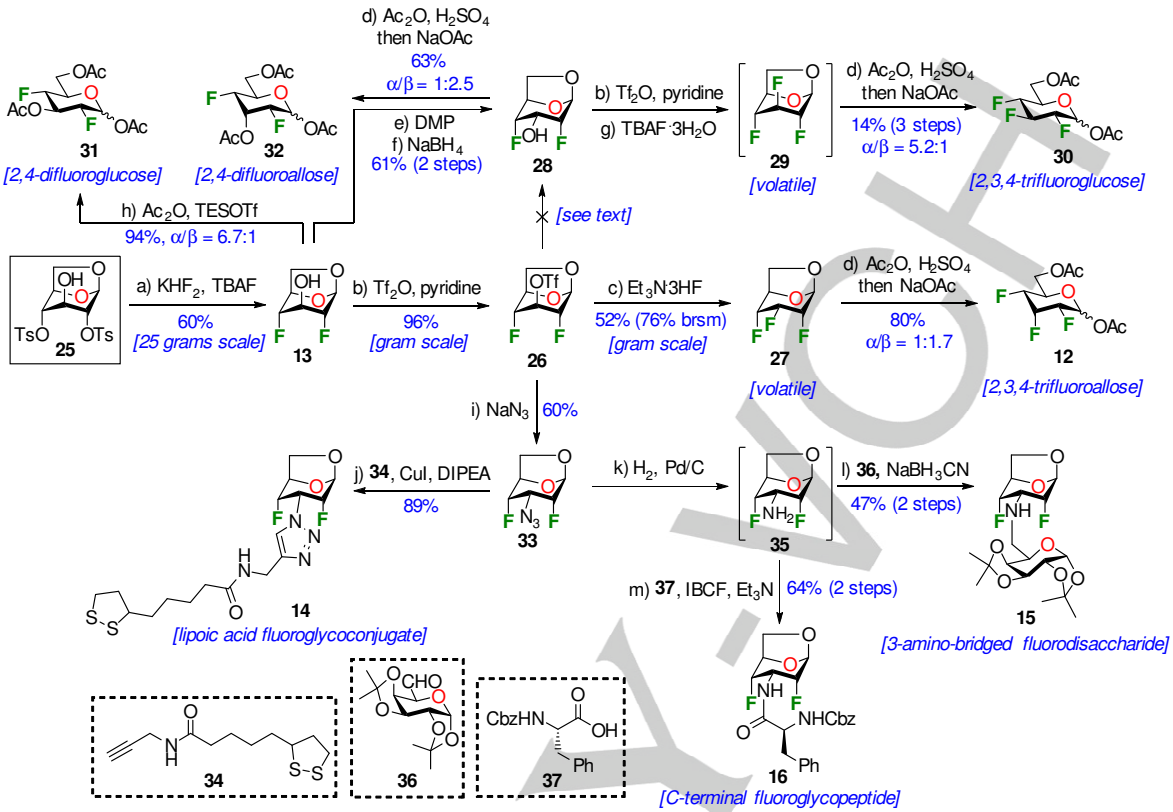

Scheme 2. Stereoselective synthesis of fluorinated glucopyranose and allopyranose analogs from intermediate **25**. Reagents and conditions: a) KHF_2 (4 equiv), TBAF·3H_2O (8 equiv), 180 °C, 24 h, 60%; b) Tf_2O (1.5 equiv), pyridine (3 equiv), CH_2Cl_2, rt, 0.5h, 96% for **26**; c) Et_3N·3HF (75 equiv), 120 °C, 64 h, 52% (76% brsm); d) Ac_2O (30 equiv), H_2SO_4 (10 equiv), 0 °C to rt, 16 h, then NaOAc (20 equiv), rt, 0.3 h, 80% (α/β = 1:1.7) for **12**, 14% over 3 steps (α/β = 5.2:1) for **30**, 63% (α/β = 1:2.5) for **32**; e) DMP (1.5 equiv), CH_2Cl_2, 0 °C, 1 h; f) $NaBH_4$ (8 equiv), MeOH, –20 °C, 6 h, 61% over 2 steps; g) TBAF·3H_2O (3 equiv), 50 °C, 18 h; h) TESOTf (cat.), Ac_2O (110 equiv), rt, 1.5 h, 94% (α/β = 6.7:1); i) NaN_3 (10 equiv), DMF, 70 °C, 36 h, 60%; j) **34** (2 equiv), DIPEA (2 equiv), CuI (0.5 equiv), CH_3CN, 40 °C, 12 h, 89%; k) H_2, Pd/C, MeOH, rt, 2 h; l) **36** (1.2 equiv), molecular sieves, CH_2Cl_2, AcOH (1M in MeOH), 0 °C to rt, 4 days, then $NaBH_3CN$, rt, 24 h, 47% over 2 steps; m) **37** (1.2 equiv), Et_3N (1.5 equiv), IBCF (1 equiv), THF, 0 °C to rt, 16 h, 64% over 2 steps. Ac_2O = acetic anhydride, BRSM = based on recovered starting materials, DIPEA = *N,N*-diisopropylethylamine; DMP = Dess-Martin periodinane; IBCF = isobutyl chloroformate; NaOAc = sodium acetate, TBAF = tetrabutylammonium fluoride, Tf_2O = trifluoromethanesulfonic anhydride; TESOTf = triethylsilyl trifluoromethanesulfonate.

with *N*-(carbobenzyloxy)-*L*-phenylalanine **37**, treated beforehand with isobutyl chloroformate,[32] allowing the preparation of *C*-terminal fluoroglycopeptide (linked at C-3) **16** in 64% over 2 steps. These results clearly demonstrate the usefulness of levoglucosan as starting material for the synthesis of di- and trifluorinated analogs of D-glucopyranose and D-allopyranose.

With the long-term goal of exploring the physical and biological properties of these new fluorinated analogs of hexopyranoses, we explored the feasibility of functionalization of the anomeric position. In our case, this is non-trivial since the polyfluoroalkyl group destabilizes adjacent carbocation center.[33] We first opted for a phase-transfer nucleophilic displacement as previously described on 2,3,4-trideoxy-2,3,4-trifluorogalactopyranose analog.[8] The α-allosyl bromide **38** was slowly generated using a mixture of HBr/AcOH from intermediate **12** in 81% yield (α/β = 3.3:1) based on ^{19}F NMR spectroscopy (**Scheme 3**). To our surprise, the desired β-allopyranoside **39** was not isolated when treated with methyl *p*-hydroxybenzoate under standard basic conditions.[34] Instead, we isolated trace amounts of volatile 2,3,4-trideoxy-2,3,4-trifluoro-D-allal **40**. In parallel, we also evaluated the possibility to treat bromide **38** with thioglucoside donor **41** facilited with TBAF to generate glucosylthioalloside **42**.[35] Mass spectrometry of the crude mixture revealed formation of the desired compound **42** (m/z $C_{22}H_{33}F_3NO_{12}S$ $[M+NH_4]^+$; calcd: 592.1670; found: 592.1684). Unfortunately, we were only able to recover side-product **40** in 56% yield over 2 steps after flash column chromatography. At this point, we were compelled to change strategy and focus on other glycosylation protocol. Treatment of **12** with allyltrimethylsilane and TMSOTf in acetonitrile at 100 °C led exclusively to the formation of α-*C*-allyl glycoside **43** in 34% yield. Additionally, microwave heating can increase reaction rates and only a handful of research groups reported this technique for glycosylation reactions.[36] This approach also allowed us to install a functional group that could be used for further synthetic transformations. For that purpose, an *O*-allyl moiety was ideal. Upon extensive experimentations, we discovered that treatment of compound **12** with allyloxytrimethylsilane and TMSOTf in CH_3CN under microwave heating at 100 °C allowed formation of α-*O*-allyl allopyranoside **33** and β-*O*-allyl allopyranoside **34** (α/β

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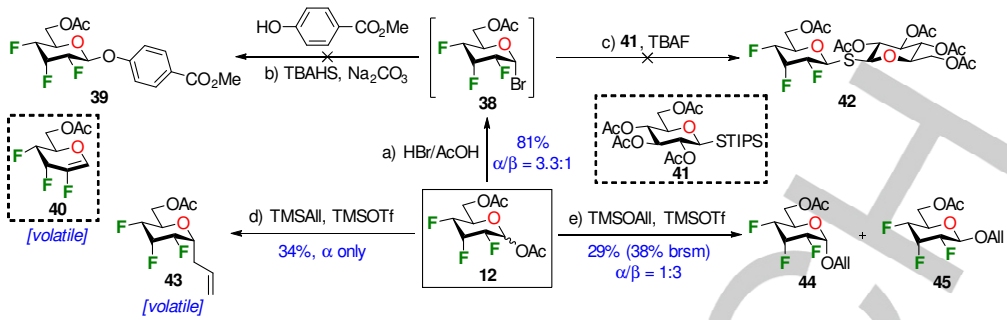
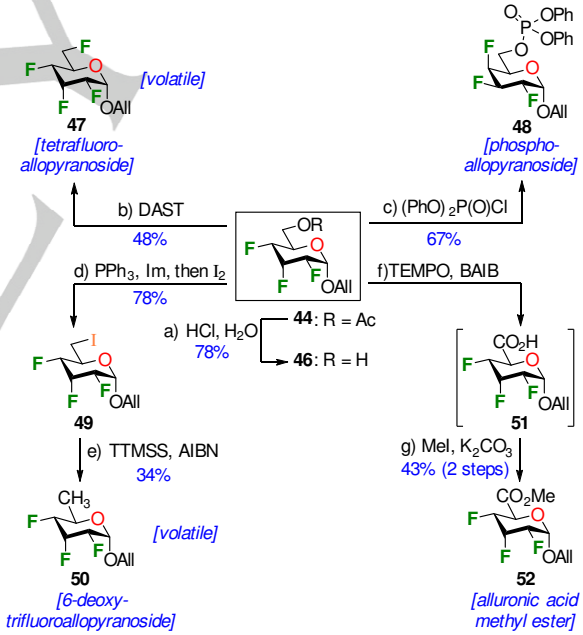


Scheme 3. Functionalization of the anomeric position allowing access to 2,3,4-trideoxy-2,3,4-trifluoroallopyranoside **43**–**45**. Reagents and conditions: a) 33% HBr in AcOH, rt, 76 h, 81%, α/β = 3.3:1; b) methyl *p*-hydroxybenzoate (3.0 equiv), TBAHS (1.0 equiv), EtOAc, 1M Na_2CO_3, rt, 18 h; c) 41 (1.2 equiv), 1M TBAF in THF (1.5 equiv), 40 min, rt; d) TMSAll (9 equiv), TMSOTf (5 equiv), MeCN, 85 °C, 18 h, 34%, α only; e) TMSOAll (10 equiv), TMSOTf (6 equiv), MeCN, microwave heating, 100 °C, 0.75 h, 29% (38% brsm), α/β = 1:3. BRSM = based on recovered starting materials, TBAHS = tetrabutylammonium hydrogen sulfate, TMSAll = allyltrimethylsilane, TMSOAll = allyloxytrimethylsilane, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

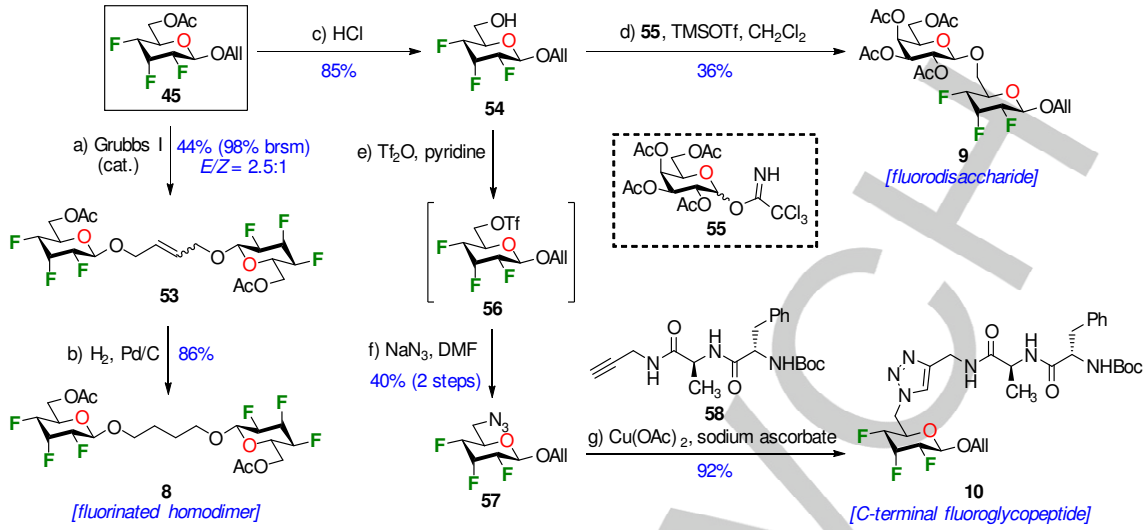
= 1:3). To the best of our knowledge, this is a rare example of glycosylation involving microwave heating with an acetyl glycosyl donor.

With the challenging glycosylation successfully completed, the next hurdle, involving functionalization at C-6, was addressed. Reaction of α-*O*-allyl allopyranoside **44** under acidic conditions generated the corresponding free alcohol **46** in 78% yield. Then, hydroxyl **46** was treated with DAST and generated volatile 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluoroallopyranoside **47** in 48% isolated yield. Then, direct phosphorylation afforded phospho-allopyranoside **48** in 67% yield. Also, iodine installation from hydroxyl **46** afforded the tetrahalogenated pyran **49** in 78% yield and radical deiodination allowed the isolation of volatile 2,3,4,6-tetradeoxy-2,3,4-trifluoroallopyranoside **50**. Lastly, oxidation of hydroxyl **46** generated the corresponding alluronic acid **51**, which was subsequently treated *in situ* with methyl iodide under basic conditions providing trifluorinated alluronic acid methyl ester **52**. These results highlight challenges related to the preparation of volatile polyhalogenated complex organic molecules.

We next turned our attention to the expansion of the molecular diversity starting from key-synthon **45**. First of all, a ruthenium-catalyzed olefin metathesis[37] of *O*-propenyl **45** allowed the preparation of homodimer **53** (*E*/*Z* = 2.5:1) in 44% yield (98% based on recovered starting material). The latter was subjected to a hydrogen atmosphere with a catalytic amount of palladium, generating unprecedented trifluorinated pyran dimer (linked at the anomeric position) **8** in 86% yield. Subsequently, de-*O*-acetylation under acidic conditions provided intermediate **54** that was used for further derivatization at C–6. We proposed that compound **54** could stand as a unique glycosyl acceptor. To test this hypothesis, we subjected hydroxyl **54** under glycosylation conditions with known tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **55**.[38] To our delight, fluorinated β-(1→6)-disaccharide **9** was isolated in 36% yield as the sole β-anomer. Finally, glycopeptides and glycoproteins are a large family of bioactive molecules[39] and fluoroglycoproteins have been utilized for some time as interesting fluorine label glyco-amino acids.[12, 40] Thus, we intended to install an azide moiety on the trifluorinated allopyranoside scaffold and perform a copper-catalyzed Huisgen cycloaddition with an alkynic-amino acid partner. This strategy is common for introduction of sugars into proteins since 1,2,3-triazoles are considered hydrolytically stable bioisosteres of the amide bond for glycine amino acid.[41] Accordingly, compound **54** was activated as triflate **56** and subjected to nucleophilic displacement with sodium azide leading to compound **57** in 40% yield over 2 steps. Click chemistry was successfully used to link azide **57** with BOC-Ala-Phe-NH-C_3H_3 **58** affording the corresponding triazole-linked *C*-terminal fluoroglycopeptide (linked at C-6) **10** in excellent yield.



Scheme 4. Synthesis of allopyranoside analogs: 2,3,4,6-tetradeoxy-2,3,4,6-tetrafluoroallopyranoside **47**, phospho-allopyranoside **48**, 2,3,4,6-tetradeoxy-2,3,4-trifluoroallopyranoside **50**, and alluronic acid methyl ester **52**. Reagents and conditions: a) HCl (37% in water), water, rt, 1 h, 78%; b) DAST (3 equiv), 2,4,6-collidine (6 equiv), microwave irradiation, 100 °C, 1 h, 48%; c) $ClP(O)(OPh)_2$ (2 equiv), DMAP (2 equiv), CH_2Cl_2, rt, 4 h, 67%; d) PPh_3 (1.5 equiv), imidazole (2 equiv), THF, 68 °C, 0.5 h, then I_2 (1.5 equiv), 68 °C, 2 h, 78%; e) TTMSS (2 equiv), AIBN (0.1 equiv), toluene, 110 °C, 18 h, 34%; f) TEMPO (0.2 equiv), BAIB (2.5 equiv), CH_2Cl_2/H_2O, rt, 1 h, g) MeI (40 equiv.), K_2CO_3 (1.1 equiv.), CH_3CN, rt, 18 h, 43% over 2 steps. AIBN = 2,2'-azobis(2-methylpropionitrile), BAIB = (diacetoxyiodo)benzene, DMAP = 4-(dimethylamino)pyridine, Im = imidazole; PPh_3 = triphenylphosphine, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, THF = tetrahydrofuran, TTMSS = tris(trimethylsilyl)silane.



Scheme 5. Synthesis of allopyranoside analogs: fluorinated homodimer **8**, fluorodisaccharide **9**, and *C*-terminal fluoroglycopeptide **10**. Reagents and conditions: a) Grubbs 1st generation (0.1 equiv), 1,2-DCE, 40 °C, 72 h, 44% (98% brsm), *E*/*Z* = 2.5:1; b) H_2, Pd/C (10% by weight), EtOAc, rt, 18 h, 86%; c) HCl (37% in water), water, rt, 1 h, 85%; d) **55** (2 equiv), TMSOTf (0.25 equiv), molecular sieves, CH_2Cl_2, –20 °C, 2 h, 36%; e) Tf_2O (2 equiv), pyridine (3 equiv), CH_2Cl_2, rt, 0.5 h, f) NaN_3 (5 equiv), DMF, 80 °C, 18 h, 40% over 2 steps; g) **58** (2 equiv), $Cu(OAc)_2$ (0.2 equiv), sodium ascorbate (0.4 equiv), *t*-BuOH/H_2O/CH_3CN (1:1:2), rt, 6 h, 92%. BRSM = based on recovered starting materials, DCE = dichloroethane, Pd/C = palladium on carbon, Tf_2O = trifluoromethanesulfonic anhydride, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

The preparation of organofluorine compounds have attracted attention over the past years. The synthesis of a set of fluorinated analog of allopyranoses was accomplished using a Chiron approach. The versatility of our strategy allowed a rapid access to fluorinated homodimer, fluorodisaccharides, *C*-terminal fluoroglycopeptides, and lipoic acid fluoroglycoconjugate. The usefulness of organofluorine presented herein are not limited to biological systems. The developed compounds could be useful in material sciences to modulate key physical properties, namely lipophilicity. We strongly believe that the resulting molecules could serve as tools to deepen investigations on the use of intriguing fluorine-containing carbohydrate analogs and to underscore their relevance to several science fields.

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Keywords: carbohydrates • fluorinated glycoside • allopyranose • fluoroglycopeptide • fluorodisaccharide

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[24] A prolonged reaction time was necessary for optimal conversion of *bis*-tosylate **25**.

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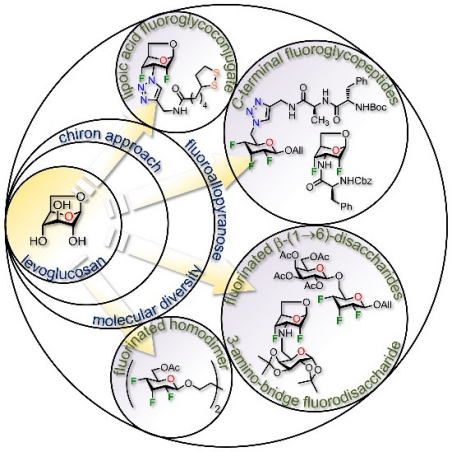
FULL PAPER

Non-stick sugars! The synthetic preparation of heavily fluorinated carbohydrates was achieved. A Chiron approach was used to access novel analogs of D-allopyranose that could be useful in biology or material sciences.



*Vincent Denavit, Jacob St-Gelais, Thomas Tremblay, and Denis Giguère**

Page No. – Page No.

Exploring the chemistry of non-sticky sugars: Synthesis of polyfluorinated carbohydrate analogs of D-allopyranose