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COPPER-MEDIATED VINYLIC AND BENZYLIC FLUOROALKYLATIONS AND STEREOSELECTIVE SYNTHESIS OF 2-TRIFLUOROMETHYLGLYCOSIDES

Jordi Mestre Ventura

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Copper-Mediated Vinylic and Benzylic Fluoroalkylations and Stereoselective Synthesis of 2-Trifluoromethylglycosides

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DOCTORAL THESIS

2017

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Copper-Mediated Vinylic and Benzylic Fluoroalkylations and Stereoselective Synthesis of 2-Trifluoromethylglycosides

PhD Thesis

Supervised by Prof. Sergio Castillón Miranda and

Dr. Omar Boutureira Martín

Department of Analytical Chemistry and Organic Chemistry

Tarragona 2017

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Prof. Sergio Castillón Miranda and Dr. Omar Boutureira Martín from Department of Analytical Chemistry and Organic Chemistry, University Rovira i Virgili,

We STATE that the present study, entitled "Copper-Mediated Vinylic and Benzylic Fluoroalkylations and Stereoselective Synthesis of 2-Trifluoromethylglycosides", presented by Jordi Mestre Ventura for the award of the degree of Doctor, has been carried out under our supervision at the Department of Analytical Chemistry and Organic Chemistry of this university.

Tarragona, 28 March, 2017.

Prof. Sergio Castillón Miranda

Dr. Omar Boutureira Martín

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Abbreviations and Acronyms

A	
Ac	Acetyl
Ar	Aryl
B	
b	Broad singlet
BHT	*tert*-Butyl hydroxytoluene
Bn	Benzyl
Boc	*tert*-Butyl carbamate
b.p.	Boiling point
BTB	1,3-Bis(trifluoromethyl)benzene
Bu	Butyl
Bz	Benzoyl
C	
Calc.	Calculated
Conv.	Conversion
COSY	Proton homonuclear correlation
D	
d	Doublet
2D	Two dimensional
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet doublet of doublets
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMSO	Dimethyl sulfoxide
E	
equiv	Equivalent(s)
ESI-TOF	Electrospray ionitzation-time of flight

Et	Ethyl
EWG	Electron withdrawing group
F	
FTIR	Fourier transform infrared spectroscopy
G	
gCOSY	Gradient correlation spectroscopy
gHMBC	Gradient Heteronuclear multiple bond correlation
gHSQC	Gradient heteronuclear single quantum coherence
H	
h	Hour(s)
HRMS	High-resolution Mass Spectrometry
Hz	Hertz
I	
i-Pr	Isopropyl
IR	Infrared
J	
J	Coupling constant
L	
L	Ligand
M	
m	Multiplet
Me	Methyl
m.p.	Melting point
Ms	Mesyl
m/z	Mass under charge
N	
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMR	Nuclear magnetic resonance

Nu	nucleophile
P	
Ph	Phenyl
Piv	Pivaloyl
pKa	Acid dissociation constant
ppm	Parts per million
Py	Pyridine
Q	
q	Quartet
quint	Quintet
R	
RDS	Rate-determining step
rt	Room temperature
S	
s	Singlet
T	
t	Triplet
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Trifluoromethylsulfonyl
Tf_2O	Trifluoromethylsulfonyl anhydride
THF	Tetrahydrofurane
TLC	Thin layer cromatography
TS	Transition state
Ts	Tosyl
TTBP	2,4,6-Tri-*tert*-butylpyrimidine
U	
UV/Vis	Ultraviolet/visible

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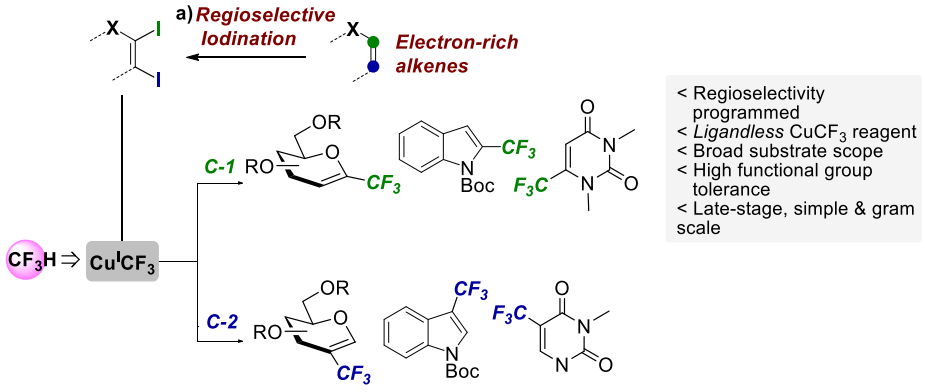
Summary

The work presented in this PhD thesis is divided in two main topics: 1) development of Cu-mediated (Csp^2)–X and (Csp^3)–X perfluoroalkylation methodologies and; 2) studying the diastereoselective glycosylation using directing groups (CF_3 and I) at C-2.

The first main topic starts in Chapter III with the synthesis of electron-rich trifluoromethylated alkene derivatives following a two-step strategy. The first step comprises the regioselective positioning of iodine at C–1 or C–2 of electron-rich double bonds present in many naturally occurring and drug-containing relevant scaffolds including glycals, benzofused heterocycles, nitrogeneous bases, and nucleosides (Scheme 1a). The key step was performed by a cross-coupling trifluoromethylation using the "ligandless" $CuCF_3$ reagent derived from fluoroform (Scheme 1b). This late-stage functionalization occurred satisfactorily affording the trifluoromethyl-derivatives in high yields and purity. Other advantages include broad functional group tolerance, easy reaction set-up & work-up and scalability of the reaction to the gram scale.



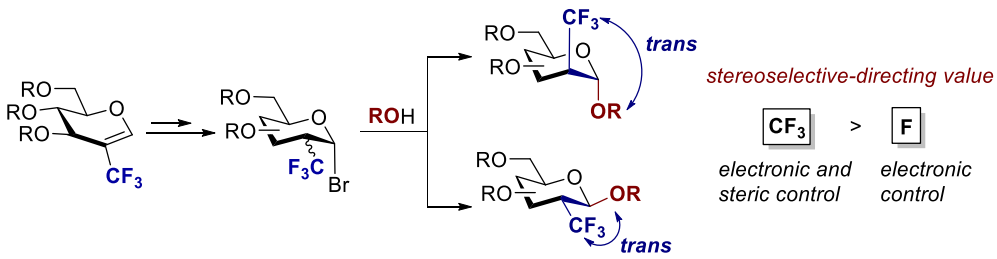
Scheme 1

The results included in chapter IV are protected due to the possibility of generation of patents.

Summary

The results included in chapter V are protected due to the possibility of generation of patents.

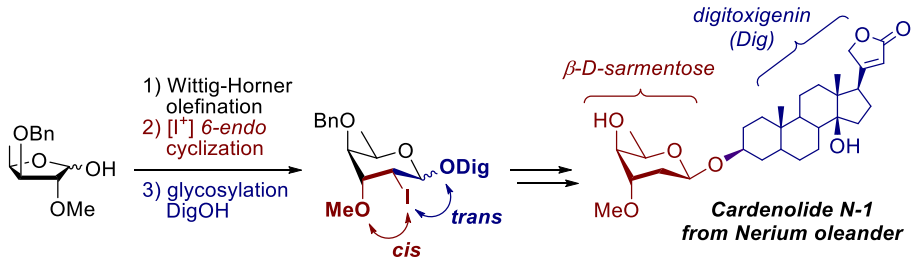
The second topic started in chapter VI with the diastereoselective glycosylation of 2-deoxy-2-trifluoromethylpyranoses derived from 2-trifluoromethylglycals. Screening of protecting groups and configuration of the CF_3 revealed the stereoselectivity was largely affected by the CF_3 group, affording mainly 1,2-*trans* glycosides. The results were compared with the studies of Ryan Gilmour on "fluorine directed glycosylations", which suggested that CF_3 imparts a higher disatereocontrol when compared to F, and the latter relies on the nature of the protecting groups for achieving good stereoselectivities. The stereoelectronic properties of the CF_3 presumably impart better control on the stereoselectivity due to the higher steric hindrance of the trifluoromethyl group.



Scheme 3

In the same context, chapter VII deals with the stereoselective access to 2-deoxyglycosides. This strategy exploits a methodology developed in our group which herein is applied in the synthesis of Cardenolide N-1, a cardiotonic glycoside extracted from *Nerium Oleander,* which also displays antitumoural activity. The synthetic plan features the following key steps: Wittig-Horner olefination of a furanose precursor, iodonium-promoted *6-endo* cyclization affording a pyranose derivative with a 2,3-*cis* relationship by virtue of the *inside-alkoxy effect*. Finally, the iodine atom controls the glycosylation favoring the 1,2-*trans*

β-glycoside. Final elaboration of the glycoside afforded the synthetic Cardenolide N-1, which characterization data was compared with that of the natural product providing unequivocal proof of its structural validation.



Scheme 4

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CHAPTER I

General Introduction

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1.1. Importance of fluorine chemistry

Fluorine chemistry has become a hot topic in many areas of chemical sciences and, in the last 20 years has grown in importance especially in the field of medicinal chemistry mainly due to the pioneering research launched by Fréderic Swarts in the 1980s.[1] Although some fluorinated minerals such as fluorite (CaF_2) and fluoroapatite ($Ca_5(PO_4)_3$)F are widely present in nature, fluorine-containing organic molecules are scarce in naturally occurring compounds. Nowadays about 20% of all pharmaceuticals on the market contain fluorine moieties and this number is increasing.[2] 5-Fluorouracil (an antineoplastic agent, Figure 1.1) was one of the first fluorinated drugs synthesized (1957). It is used for cancer treatment as it shows inhibition activity against the enzyme thymidylate synthase, preventing the production of thymidine.[3]

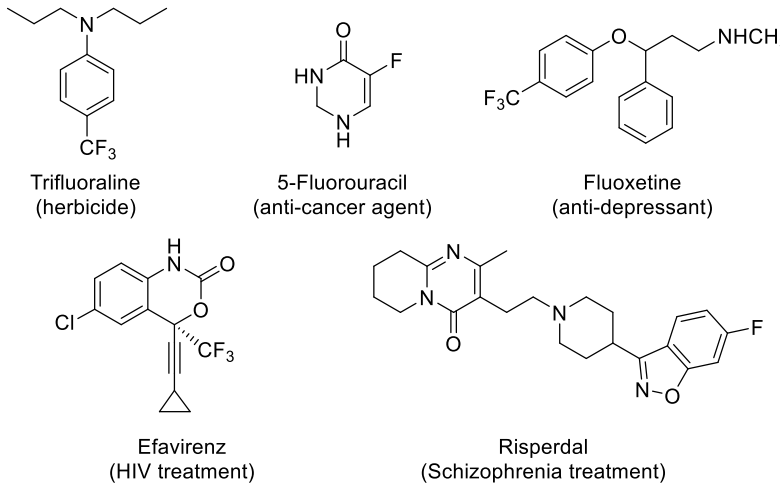

Figure 1.1. Examples of fluorinated agrochemicals and drugs.

Since the first discoveries in this field, fluorine and fluorine-containing groups have been incorporated into many pharmaceuticals by

[1] Filler, R; Saha, R. *Future Med. Chem.* **2009**, *1*, 777–791.
[2] Thomas, E. M. C. *Electrophilic fluorination methodology*. Ph. D. Thesis, Durham University, England, 2002.
[3] Swinson, J. *Manuf. Chemist*. **2005**, 35–36.

virtue of improving metabolic stability and physicochemical properties and enabling the possibility to modulate protein-ligand interactions and opening new mechanisms of action. Other applications of fluorinated compounds include inhalational anesthetics, steroids (especially anti-inflammatory agents), central nervous system (CNS) medications and anti-cancer drugs.[4]

1.1.1. Physical properties of fluorine

The small size and high electronegativity of fluorine (Figure 1.2) in conjunction with the fact that 2s and 2p orbitals of the fluorine atom overlap efficiently with the corresponding orbitals of carbon, determine the general inertness of C–F bond.[5] The carbon-fluorine bond is highly polarized due to the high electronegativity of fluorine (4.0 on the Pauling scale). Thus, its high strength can be understood in terms of both $C^{\delta+}$–$F^{\delta-}$ electrostratic attraction and covalent electron sharing bond.[6] The high strength of the C–F bond makes organofluorine compounds more stable towards oxidation than their non–fluorinated analogues and F is frequently used as an isostere of hydrogen and even of hydroxy groups, attending that the van der Waals radius of fluorine (1.47 Å) is intermediate to that of oxygen (1.52 Å) and hydrogen (1.2 Å). The low polarizability of fluorine also contributes to the overall inertness of C–F moieties which also lowers intermolecular interactions.

The stability of the carbon-fluorine bond increases in accordance with the number of fluorine atoms, CH_3F being the least stable (C–F bond length 1.384 Å) and CF_4 the most stable (C–F bond length 1.335 Å). The

[4] For key reviews see: a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330; b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369; c) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029.

[5] For selected books see: a) Ojima, I. In *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley–Blackwell, Chichester, 2009; b) Bégué, J.–P.; Bonnet–Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley; Hoboken, 2008; c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley–VCH. Weinheim, 2004.

[6] Launay, G. Ph. D. Thesis, St Andrews University, Scotland, 2010.

reason for this stabilization emerges from the above commented nearly perfect fit of the carbon and fluorine orbitals and the appearance of ionic ressonance structures (Figure 1.3).[5c]

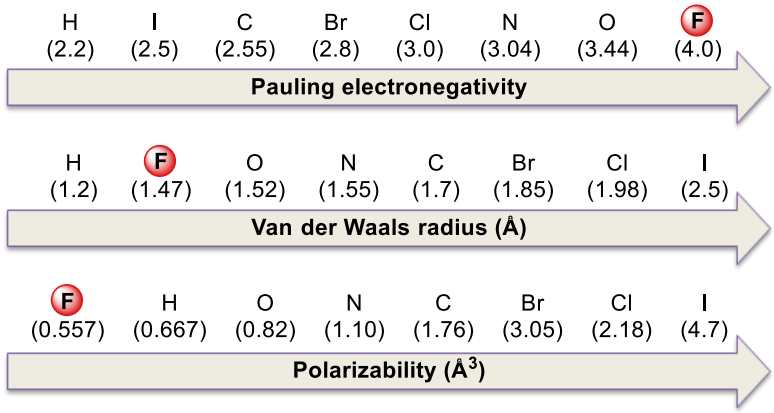

Figure 1.2. Comparison of atomic physical properties of the two first rows elements and halogens.

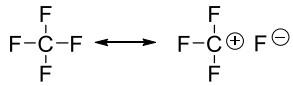

Figure 1.3. Ressonance stabilization in tetrafluoromethane.

1.1.2. Chemical properties of organofluorine compounds

Fluorine has become important not solely in medicine, but also in many agrochemicals (about 30–40% of agrochemicals are fluorinated)[7] since active ingredients benefit from the incorporation of fluorine or fluorinated groups that drastically change their chemical, physical, and biological properties (Figure 1.4).[5] Likewise F, CF_3 and even C_2F_5 are the most used groups for the preparation of lightly fluorinated-modified compounds, the physical properties and reactivity of these motifs are better understood assuming the following statement by Ritter and coworkers: "The trifluoromethyl group should be considered more

[7] Thayer, A. N. *Chem. Eng. News*. **2006**, *84*, 15–24.

appropriately as a distinct functional group rather than as a substituted methyl group".[8]

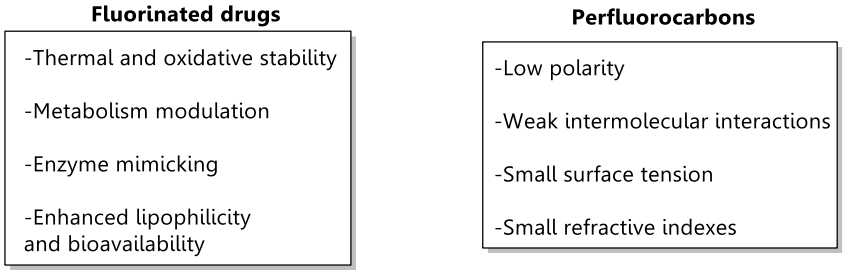

Figure 1.4. Fluorine effects upon incorporation into pharmaceuticals and perfluorocarbons.

As commented above, fluorine is widely used as a hydrogen mimic since their Van der Waals radii are similar. In those pharmaceuticals, where a fluorine atom replaces hydrogen, the geometry of the molecule often remains unperturbed. Despite the conservation of the steric hindrance, fluorine can affect the electronic environment of the molecule without affecting its geometry. On the other hand, the trifluoromethyl group, which have similar electronegativity compared to fluorine,[9] displays a high steric hindrance (–2.40 in Taft's steric parameters, E_S)[10] comparable to that of isopropyl (–2.17) or even *tert*-butyl (–2.78) and its incorporation affects not only the electronic profile but also the geometry of the parent molecule, (Table 1.1).[11] Furthermore, the three lone pairs of fluorine can act as an electrostatic and steric shield for carbon against nucleophilic attacks, thereby increasing the overall stability of the compound.

[8] Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature*. **2011**, *473*, 470–477.
[9] Huheey, J. E. *J. Phys. Chem*. **1965**, *69*, 3284–3291.
[10] Schlosser, M.; & Michel, D. *Tetrahedron*, **1996**, *52*, 99–108,
[11] Kitazume, T.; T. Yamazaki. *Experimental Methods in Organic Fluorine Chemistry, Gordon,* Breach Publishing Group, Newark, NJ, **1999**.

Table 1.1. Comparison of selected properties of F *vs.* CF_3.

Group	Pauling electronegativity	Steric hindrance (E_s)[a]	Lipophilicity (logP)[b]
F	4.0	–0.46	0.14
CF_3	3.5	–2.40	0.88

[a]Taft's steric parameters; [b]logP calculated by partition coeficients between *n*–octanol and water

Fluorine substitution can alter the reactivity and stability pattern of functionalities in adjacent positions.[12] For instance, α-fluorinated carbocations are stabilized by the donation of the lone electron pairs on the fluorine atom (Figure 1.5a). In the case of α-fluorinated carbanions, π–n repulsion between the anionic center and the lone electron pairs of fluorine is present, destabilizing the formation of such anionic center (Figure 1.5a). In contrast, the high inductive effect exerted by CF_3 destabilizes α-trifluoromethyl cations whereas α-trifluoromethylated carbanions are stabilized upon hyperconjugation between the negative and the low lying σ^* C–F orbital (Figure 1.5b). In fluorinated arenes and alkenes, the lone electron pairs of F push the π-electrons and resonate with the conjugated systems (Figure 1.5c). In the case of trifluoromethylated π-systems, only the inductive effect is mainly observed and the overall contribution is a decrease of the electron density of the system (Figure 1.5d).[13] This effect explains why the σ_p^+ of F and CF_3 have values of –0.07 and +0.63 respectively, indicating that F enables moderate resonance stabilization of a positive charge in the aromatic system whereas CF_3 disfavors the formation of these species.[14]

[12] a) Hiyama, T; Shimizu, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; b) Dixon, D. A.; Fukunaga, T.; Smart, B. E. *J. Am. Chem. Soc.* **1986**, *108*, 4027–4031.
[13] Siodła, T.; Ozimiński, W. P.; Hoffmann, M.; Koroniak, H.; Krygowski, T. M. *J. Org. Chem.* **2014**, *79*, 7321−7331.
[14] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

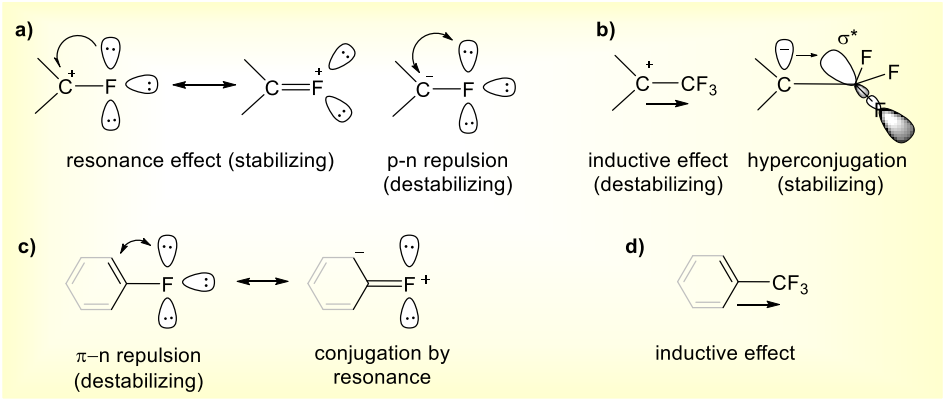

Figure 1.5. Fluorine effects in carboacation, carbanions, and conjugated systems.

1.1.3. The effect of fluorine on physicochemical properties of bioactive molecules

1.1.3.1. The effect of fluorine on pKa and lipophilicity

Passive transport is the principal mechanism of drug distribution in organism. Thus, drug lipophilicity and its modulation become very important as it affects the pharmacokinetic properties.[15] The introduction of trifluoromethyl (Table 1.1) and other fluorinated groups usually increase the lipophilicity of the final molecule.[16] The bioavailability of a drug (% of the dose reaching the circulatory system)[4a] depends on the absorption process and is affected by the pKa. In this context, fluorine can change the pKa of the functional groups close to it (see Table 1.2), thus increasing the acidity of acidic functional groups and reducing the basicity of basic groups. Drugs bearing basic functionalities such as nitrogen–containing groups are often troubled by low bioavailability. The incorporation of fluorine or a trifluoromethyl group adjacent to the basic group decreases its basicity, thus enhancing the bioavailability of the

[15] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 237–432.
[16] Leroux, F. R.; Manteau, B.; Vors, J.–P.; Pazenok, S. *Beilstein J. Org. Chem.* **2008**, *4*, 13.

drug.[17] On the other hand, the acidity of trifluoroacetic acid (pKa = 0.51) is much higher compared to that of acetic acid (pKa = 4.76, Table 1.2).[18] The inductive effect of fluorine also reduces the basicity of organic bases by approximately the same order of magnitude (see pKa values of fluorinated ethylamines, Table 1.2).[19]

Table 1.2. pKa of acetic acids derivatives and ethylamines at 25 ºC in water.

Compound	K_a	Compound	K_a
CH_3COOH	4.76	$CH_3CH_2NH_2$	10.58
CH_2FCOOH	2.60	CH_2FCH_2N	9.19
CHF_2COOH	1.40	CHF_2CH_2N	7.45
CF_3COOH	0.51	$CF_3CH_2NH_2$	5.40

1.1.3.2. The effect of fluorine substitution on molecular conformation

Frequently, the substitution of hydrogen and oxygen by fluorine is tolerated since they are similar in size. The steric volume of the trifluoromethyl group is roughly twice the bulk that of the methyl group, being slightly larger than that of isopropyl group.[1,11,20] Therefore the introduction of CF_3 not only affects the electronic properties of the compound but also may change the geometry of the molecule. Furthermore, electronic modification can also affect the conformation. For example, 1,2-difluoroethane adopts a *gauche* conformation instead of the less sterically demanding *anti* conformation (Figure 1.6). This observation is explained by the appearance of hyperconjugation between the σ_{C-H} bonding orbital with the σ^*_{C-F} anti–bonding orbital displayed in the *gauche* conformation.

[17] Fuglseth, E. Ph. D. Thesis. Norwegian University of Science and Technology, Norway, 2010.
[18] Gelb, R. I.; Schwartz, L. M.; Laufer, J. *J. Am. Chem. Soc.* **1981**, *103*, 5664–5673.
[19] Wodzinska, J.; Kluger, R. *J. Org. Chem.* **2008**, *73*, 4753–4754.
[20] a) Hagmann. W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369; b) Chem. Katagiri, T.; Yamaji, S.; Handa, M.; Irie, M.; Uneyama, K. *Chem. Commun.* **2001**, 2054–2055

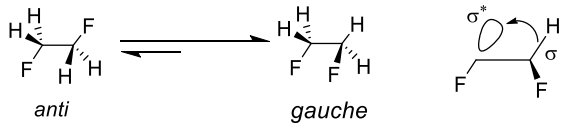

Figure 1.6. Stabilization of the gauche conformation of 1,2-difluorethane by hyperconjugation effect.

Although fluorine is the most electronegative atom and the C–F bond is highly polarized, hydrogen bond interactions with F are generally weak.[21] It is in fact the large electronegativity that renders the three lone electron pairs of fluorine highly attracted to the nucleus, thus reducing the availability to participate in F····H interactions. It has been reported that the hydrogen bonding energy in organofluorine compounds is usually 2.0–3.2 Kcal/mol for a C(sp^3)–F····H–O, compared to 5.0–10.0 Kcal/mol for C=O····H–O interactions.[22,23] Hydrogen bond interactions with F have been observed in fluoronorepinephrine which can adopt two different conformations (2F-NE and 6F-NE, Figure 1.7, a).[5c] Although only weak hydrogen bonding interactions are observed in organofluorine compounds, other interactions such as C–F····C=O dipolar interactions have been observed, for example, in a set of trombin inhibitors.[24] Conformational changes are also observed in some α-fluorocarbonyl compounds, which set the C–F bond antiparallel to the carbonyl bond in order to avoid destabilizing dipolar interactions (Figure 1.7, b). This stabilization energy depends on the nature of the carbonyl moiety, the most polarized amide functionality being the most stable.[25]

[21] a) Dalvit, C.; Invernizzi, C.; Vulpetti, A. *Chem. Eur. J.* **2014**, *20*, 11058–11068; b) Dunitz, J. D. *Chem. Eur. J.* **1997**, *3*, 89–98.
[22] oward, J. A. K; Hoy, V. J.; O'Hagen, D.; Smith, G. T. *Tetrahedron.* **1996**, *52*, 12613–12622.
[23] Murray–Rust, P.; Stallings, W.C.; Monti C. T.; Preston. R. K.; Glusker, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 3206–3214.
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[25] Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 38.

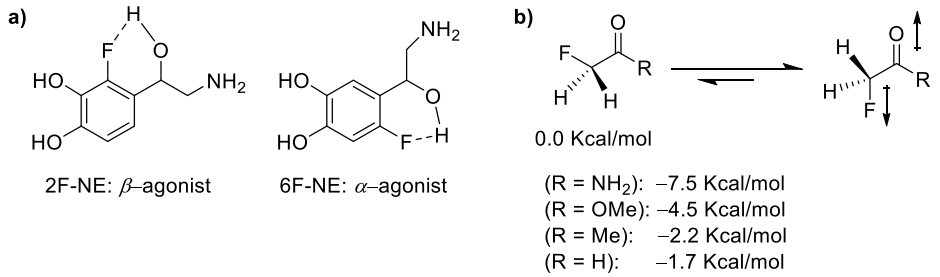

Figure 1.7. Conformational changes caused by hydrogen bonding and dipole–dipole interaction.

When fluorine is introduced to replace a hydroxyl unit, this results in loss of the acidic hydrogen, thus disabling the hydrogen bond donating ability of the original molecule. This change has proven usefull to understand the role of hydrogen bonding interactions in some biological structures.[26,27]

1.2. Importance of fluorosugars

Fluorinated carbohydrates are used in many biochemical and medicinal applications since they play important roles as enzyme inhibitors[28] and as tools for evaluating protein-carbohydrate interactions and recognition processes,[29] serve as diagnostic agents[30] and they are

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[28] André, S.; Cañada, F. J.; Shiao, T. C.; Largartera, L.; Diercks, T.; Bergeron–Brlek, M.; el Biari, K.; Papadopoulos, A.; Ribeiro, J. P.; Touaibia, M.; Solis, D.; Menéndez, M.; Jiménez–Barbero, J.; Roy, R.; Gabius, H.–J. *Eur. J. Org. Chem.* **2012**, 4354–4364.
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present in antiviral and antitumoural drugs. Below are commented some application of fluorine-containing sugars.

1.2.1. Glycosidic bond stability

Introduction of fluorine atoms adjacent to the anomeric carbon (*e. g.* fluorine and/or perfluoroalkyl groups) results in the improvement of glycosidic bond stability. One classical example of the application of such strategy into bioactive molecules accounts for the development of more stable 2'-fluorodeoxynucleosides such as Clorafabine (Figure 1.8a),[31] a drug used in the pediatric leukemia treatment. In this sense, Dhama[32] and coworkers studied the relative acidic stability in enzyme-free simulated gastric fluid conditions of DNA, 2'F-ANA, RNA and 2'F-RNA (Figure 1.8, b). Whereas short half-lives of purine–based DNA ($t_{1/2}$ = 2 min) and RNA ($t_{1/2}$ = 3 h) were obtained, 2'F–ANA showed only about 5% degradation after 48 h. A pyrimidine-based 2'F–ANA and 2'F-RNA sequences were substantially more stable than purine analogs and only about 10% degradation was observed after 3 months at 55 ºC, compared to the half–life of 2–3 weeks measured for the isosequential DNA under similar conditions.

1.2.2. NMR probes

^{19}F has a 100% natural abundance with a spin ½ and a high gyromagnetic ratio value (25.181 x 10^{-7} rad s^{-1} T^{-1}) which confers large nuclei sensitivity (83% sensitivity of ^{19}F based on ^{1}H NMR sensitivity). Additionally, small changes in fluorinated molecules are observable by ^{19}F chemical shift changes in the wide ^{19}F NMR spectral window. Therefore, introduction of fluorinated motifs provides additional structural and conformational information to be used as a valuable tool

[31] Bonate, P. L.; Arthaud, L.; Cantrell, W. R.; Stephenson, K.; Secrist, J. A.; Weitman, S. *Nat. Rev. Drug Discov.* **2006**, *5*, 855–863.
[32] Watts, J. K.; Katolik, A.; Viladoms, J.; Damha, M. J. *Org. Biomol. Chem.* **2009**, *7*, 1904–10.

for molecular recognition studies and for monitoring interaction of fluorinated ligands with proteins.[33]

Gabius, Gronenborn and coworkers[34] used ^{19}F NMR studies to quantify protein-carbohydrate interactions. Fluorinated dimannoside and trimannoside were used as fluoroprobes to determine the interaction with cyanovirin, a lectin with anti-HIV activity. The signals of the bound and unbound glycan were easily discernible, with about 1 ppm chemical shift difference. Moreover dissociation constant (K_d) could be obtained from the titration shifts (chemical shift $\Delta\delta$ (ppm) *vs* the ratio of ligand to protein concentration).

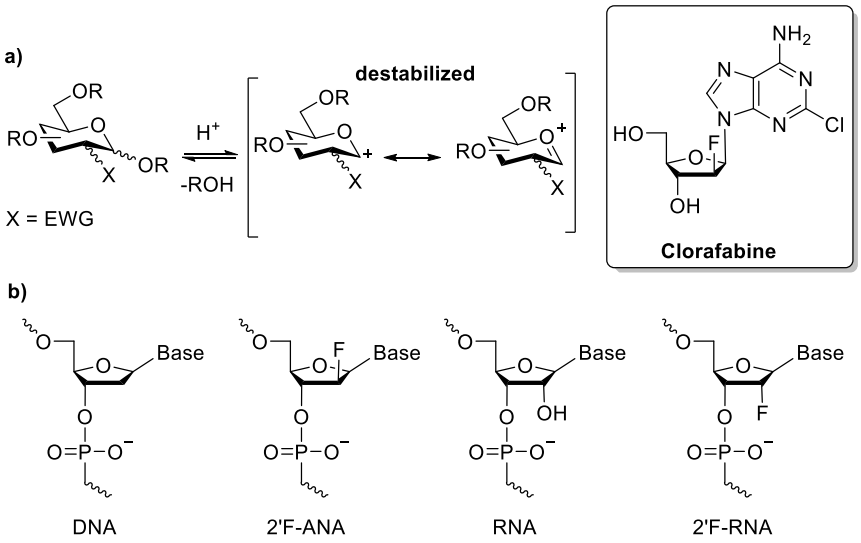

Figure 1.8. Effect of fluorinated motifs to the anomeric bond stability.

[33] a) Calle, L. P.; Echeverria, B.; Franconetti, A.; Serna, S.; Fernández–Alonso, M. C.; Diercks, T.; Cañada, F. J.; Ardá, A.; Reichardt, N.–C.; Jiménez–Barbero, J. *Chem. Eur. J.* **2015**, *21*, 11408–11416; b) Braitsch, M.; Kählig, H.; Kontaxis, G.; Fischer, M.; Kawada, T.; Konrat, R.; Schmid, W. *Beilstein J. Org. Chem.* **2012,** *8,* 448–455; c) Dalvit, C.; Vulpetti, A. *ChemMedChem.* **2011**, *6*, 104–114; d) Allman, S. A.; Jensen, H. H.; Vijayakrishnan, B.; Garnett, J. A.; Leon, E.; Liu, Y.; Anthony, D. C.; Sibson, N. R.; Feizi, T.; Matthews, S.; B. G. Davis. *ChemBioChem* **2009**, *10*, 2522–2529; e) Kumar, K.; d' Alarcao, M.; Dafik, L. PCT Int. Appl. WO 2007/106886, 2007.

[34] Matei, E.; André, S.; Glinschert, A.; Infantino, A. S.; Oscarson, S.; Gabius, H.–J.; Gronenborn, A. M. *Chem. Eur. J.* **2013**, *19*, 5364–5374

Saturation transfer difference (STD) is another useful NMR technique to study protein-carbohydrate interactions. STD is based on the magnetic irradiation of a protein and subsequent magnetic transference to the coordinated ligands. The spectra obtained in this operation is called *on-resonance* spectrum, I_{Sat} (I_{Sat} shows increased intensities of ^{1}H or ^{19}F nuclei of the coordinated molecule). I_{Sat} is then subtracted from an *off-ressonance* spectrum, $I_{0,}$ so that $I_{STD} = I_0 - I_{Sat}$.[35] Thus, the signals with the same intensity in I_{sat} and I_0 are suppressed and only signals corresponding to coordinated ligands are shown. Moreover, the most intense ^{1}H or ^{19}F signals are those related to H or F closer to the binding site. Professors Jesús Jiménez–Barbero and Hans–Joachim Gabius integrated the use of STD with ^{19}F NMR for the study of protein–carbohydrate interactions using a modified STDreF spectroscopy technique.[28,36] Figure 1.9 shows an off–resonance spectrum of 2-deox-2-fluoro-D-glucose (2–FDG), displaying a higher proportion of the β-anomer. The bottom spectrum shows the STD spectrum in which appears the α–anomer more intense, indicating a selective binding of this anomer to the leguminous lectin ConA.[36]

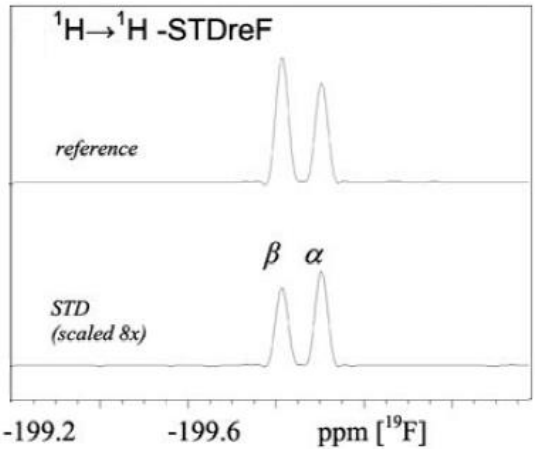

Figure 1.9. Top: Fluorine NMR spectra without saturation (I_0); Bottom: Saturation transfer difference (I_{STD}).[36]

[35] M. Mayer, B. Meyer. *Angew. Chem. Int. Ed.* **1999,** *38*, 1784–1788**.**
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1.2.3. Positron emission tomography (PET)

Positron emission tomography is a diagnostic technique that produces a 3D picture of metabolic processes provided by a radiotracer. Radiotracers (unstable isotopes with a determined radioactive decay) emit gamma rays which are recognized by a detection system. The commonly used tracer isotopes and their half-life time include ^{11}C (20.4 minutes), ^{13}N (9.98 minutes), ^{15}O (2.03 minutes), and the most important, ^{19}F (109.8 minutes).[37] 2-[Fluorine-18]-fluoro-2-deoxy-D-glucose [^{18}F]FDG is widely used as a cancer diagnostic agent.[38] Its usefulness is devoted to the abnormally increased glucose uptake of cancer cells, which in the presence of [^{18}F]FDG results in accumulation of the radiotracer in the cancer cells adverting metabolic irregularities in the body.

1.2.4. Miscellaneous applications

Fluorinated carbohydrates are also used for different and diverse purposes including mechanistic probes of enzymes,[39] lectin ligands,[28] are metabolic and oxidative stable,[40] as antiviral and antitumoural agents[41] and represent building blocks to construct fluorinated glycoconjugates including glycopeptides[42] and glycoproteins.[43]

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[37] Peller, P.; Subramaniam, R.; Guermazi, A. *PET–CT and PET–MRI in Oncology: A Practical Guide,* Springer, Heidelberg, 2012.

[38] a) Baschnagel, A. M.; Wobb, J. L.; Dilworth, J. T.; Williams, L.; Eskandari, M.; Wu, D.; Barbara L. Pruetz, B. L.; Wilson, G. D. *Radiother. Oncol.* **2015**, *117*, 118–124; b) Nensa, F.; Tezgah, E.; Poeppel, T. D.; Jensen, C. J.; Schelhorn, J.; Kohler, J.; Heusch, P.; Bruder, O.; Schlosser, T. Nassenstein, K. *J. Nucl. Med.* **2015**, *56*, 255–260; c) Kubik–Huch, R. A.; Dörffler, W.; von Schulthess, G. K.; Marincek, B.; Köchli, O. R.; Seifert, B.; Haller, U.; Steinert, H. C. *Eur. Radiol.* **2010**, *10*, 761–767.

[39] Hartman, M. C. T.; Coward, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 10036–10053.

[40] Ioannou, A.; Cini, E.; Timofte, R. S.; Flitsch, S. L.; Turner, N. J.; Linclau, B. *Chem. Commun.* **2011**, *47*, 11228–11230

[41] a) Parrish, J. P.; Lee, S. K.; Boojamra, C. G.; Hui, H.; Babusis, D.; Brown, B.; Shih, I.; Feng, J. Y.; Ray, A. S.; Mackman, R. L. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3354–3357. b) Withers, S.; Chen, H.; Resende, R. PCT Int. Appl. WO 2013/106937, 2013. c) Lavaire, S.; Plantier, R. R.; Portella, C.; Monte, M.; Kirn, A.; Aubertin, A.–M. *Nucleosides Nucleotides.* **1998**, *17*, 2267–2280.

[42] a) Johannes, M.; Reindl, M.; Gerlitzki, B.; Schmitt, E.; Hoffmann–Röder, A. *Beilstein J. Org. Chem.* **2015**, *11*, 155 – 161; b) Lamandé–Langle, S.; Collet, C.; Hensienne, R.; Vala, C.;

Chrétien, F.; Chapleur, Y.; Mohamadi, A.; Lacolley, P.; Regnault, V. *Bioorg. Med. Chem.* **2014**, *22*, 6672–6683; c) Lang, C.; Maschauer, S.; Hübner, H.; Gmeiner, P.; Prante, O. *J. Med. Chem.* **2013**, *56*, 9361–9365.

[43] a) Salvadó, M.; Amgarten, B.; Castillón, S.; Bernardes, G. J. L.; .; Boutureira, O. *Org. Lett.* **2015**, *17*, 2836–2839; b) Huo, C.–X.; Zheng, X.–J.; Xiao, A.; Liu, C.–C.; Sun, S.; Lv, Z.; Ye, X.–S. *Org. Biomol. Chem.* **2015**, *13*, 3677–3690; c) Lee, H.–Y.; Chen, C.–Y.; Tsai, T.–I.; Li, S.–T.; Lin, K.–H.; Cheng, Y.–Y.; Ren, C.–T.; Cheng, T.–J. R.; Wu, C.–Y.; Wong, C.–H. *J. Am. Chem. Soc.* **2014**, *136*, 16844–16853; d) Boutureira, O.; Bernardes, G. J. L.; Fernández–González, M.; Anthony, D. C.; Davis, B. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1432–1436.

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COPPER-MEDIATED VINYLIC AND BENZYLIC FLUOROALKYLATIONS AND STEREOSELECTIVE SYNTHESIS OF 2-TRIFLUOROMETHYLGLYCOSIDES
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CHAPTER II

General Objectives

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2.1. General objectives

The present PhD work is composed of different, complementary areas of organic chemistry including fluorine and carbohydrate chemistry, organic synthesis and organometallic chemistry. Chapters are classified according to two main objectives:

1) To develop new procedures to introduce trifluoromethyl and pentafluoroethyl moieties into alkenes, allylic and benzylic positions (chapters III, IV and V).

2) To perform stereoselective glycosylations with the aid of CF_3 and I as permanent and temporary directing groups respectively (chapters VI and VII).

a) The research described in **Chapter III** aims to develop a novel and general synthetic methodology for the regiocontrolled introduction of CF_3 into glycals, nucleosides, nitrogenous bases, and heterocyclic benzoderivatives. This strategy exploits the regioselective pre–introduction of an halogen followed by chemoselective Cu–promoted trifluoromethylation. The specific objectives of this chapter are:

- The regioselective preparation of vinyl halides, especially iodoglycals, as key intermediates.
- Optimization of the conditions for the trifluoromethylation of haloglycals using the fluoroform-derived "ligandless" $CuCF_3$ reagent.
- To study the substrate scope and the functional group tolerance of this method with different glycal derivatives.
- To explore a preliminary derivatization of trifluoromethylglycals.
- To apply the selected conditions in the trifluoromethylation of other valuable scaffolds or re-optimize the reactions conditions when required.

The work presented in this chapter has been developed in collaboration with Dr. Vladimir Grushin and Dr. Anton Lishchynskyi at the Institute of Chemical Research of Catalonia (ICIQ).

b) The research described in **Chapter IV** aims to apply the strategy used in the previous chapter to introduce the pentafluoroethyl moiety. The specific goals of this chapter are:

- To prepare optimal coupling partners found during the trifluoromethylation screening.
- To use the a suitable reagent to effect the pentafluoroehylation step.
- To explore the scope of this methodology to demonstrate its general utility.

c) The research described in **Chapter V** focus exploring the pentafluoroethylation of benzylic and allylic positions. The specific objectives are:

- To find a suitable reagent to introduce the C_2F_5 moiety into allylic and benzylic positions.
- To identify suitable coupling partners.
- To study the functional group tolerance of the reaction.
- To perform mechanistic studies to gain insight into this transformation.

d) The research described in **Chapter VI** aims to explore a synthetic route to prepare 2-trifluoromethylglycosides from 2-trifluoromethylglycals. The specific objectives are:

- To identify convenient conditions to functionalize 2-trifluoromethylglycals and access to suitable glycosyl donors.
- To prepare *manno*- and *gluco*- 2–trifluoromethylglycosyl donors bearing both electron–donating and electron-withdrawing groups.
- To determine the stereoselectivity under S_N1 glycosylation conditions and study the stereoelectronic effects of the CF_3 moiety.

- To compare the results found with a similar study reported by Ryan Gilmour using 2-fluoroglycosyl donors.

e) The research described in **Chapter VII** plans to perform the first total synthesis of Cardenolide N-1. The specific objectives are:

- To stablish a convenient synthethic route, highlighting the strategy developed in our group for the stereoselective synthesis of 2-deoxyglycosides using iodine as temporary stereocontrolling substituent.
- To optimize key steps of the synthesis including the WH olefination, iodine-induced cyclization, and glycosylation.
- To confirm the structure proposed for Cardenolide N-1 by comparison of spectroscopic data collected from the total synthesis with those recorded upon extraction from Nerium Oleander twigs

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CHAPTER III

Trifluoromethylation of Electron-Rich Vinyl iodides with Fluoroform-Derived "Ligandless" $CuCF_3$

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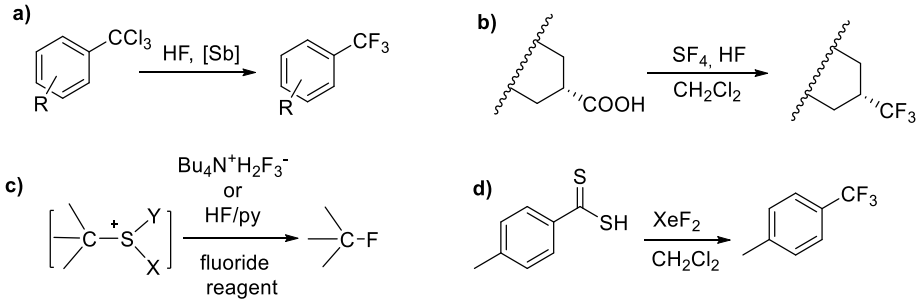
3.1. Introduction

3.1.1. Synthesis of trifluoromethylated compounds

Fluorine chemistry is one of the most exploited fields in chemical research and is in the spotlight, especially, in the design of new drugs and agrochemicals. Year after year increasing number of reports dealing with the synthesis of fluorinated ingredients are published. There are two main different approaches for the preparation of challenging fluorinated molecules: 1) Starting from a fluorinated building block; and 2) introducing fluorine or fluorinated groups in the late stage of the synthesis. Regarding late-stage transformation, construction of CF_3 unit can be performed by fluorination of a reactive functional group already present in the molecule or by direct trifluoromethylation of a precursor involving C–CF_3 bond formation.



Scheme 3.1. Indirect methods for the preparation of CF_3-containing compounds.

Several indirect methods to construct the CF_3 moiety by fluorinating another functional group are available, for instance: from a trichloromethyl unit using anhydrous hydrogen fluoride and a catalytic amount of Sb^V chloride or in the presence of an excess of Sb^{III} fluoride (so-called Swarts reaction, Scheme 3.1a);[1] from a carboxyl group by treatment with hydrogen fluoride and sulfur tetrafluoride (Scheme 3.1b);[2] by oxidative desulfurization-fluorination with amine-HF complexes and a

[1] Quirmbach, M.; Steiner, H. *Chim. Oggi.* **2009**, *27*, 23–25.
[2] Lin, P; Jiang, J. *Tetrahedron*. **2000**, *56*, 3635–3671.

source of electrophilic halogen (Scheme 3.1c);[3] and from a dithiocarboxylic acid and xenon difluoride (Scheme 3.1d).[4] However, these approaches are unwidely since toxic and dangerous reagents are required, high wastes of hazardous materials are usually produced, reactions occur under harsh conditions, and the application is generally confined to simple substrates due to limited functional group tolerance.

Alternatively, direct introduction of the CF_3 unit is desirable to overcome most of the previous issues. Hence, there are different possibilities to introduce the CF_3 group into the target molecule involving electrophilic, nucleophilic, radical and metal-mediated/catalyzed trifluoromethylations.[5] Depending on the chosen strategy, different sources of the CF_3 synthon may be required. In the following pages, a brief survey of these methods is discussed, focusing particularly on metal-mediated which fall within the scope of this thesis.

3.1.1.1. Nucleophilic trifluoromethylation

Among all the methods available, nucleophilic trifluoromethylation has been the most popular since the discovery of the Ruppert's reagent (Me_3SiCF_3) which enables the synthesis of many trifluoromethylated compounds by reaction with carbonylic motifs and other electrophiles leading to a variety of trifluoromethylated scaffolds.[6] The trifluoromethylation mechanism with Me_3SiCF_3 described by Prakash *et al.* in 1989 is depicted in Scheme 3.2.[7] The first step involves activation of Me_3SiCF_3 to liberate the $^-CF_3$ anion with a fluoride-based activator including tetra-*n*-butylammonium fluoride hydrate (TBAF), tetramethylammonium fluoride (TMAF), tetra-*n*-butylammonium difluorophenylsilicate (TBAT), CsF and KF. The trifluoromethyl anion then nucleophilically adds to the carbonyl group. During the propagation

[3] Shimizu, M; Hiyama, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231.
[4] Cech, D.; Holy, A. *Collect. Czech. Chem. Commun.* **1976**, *1*, 3335–3342.
[5] Ma, J.–A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996.
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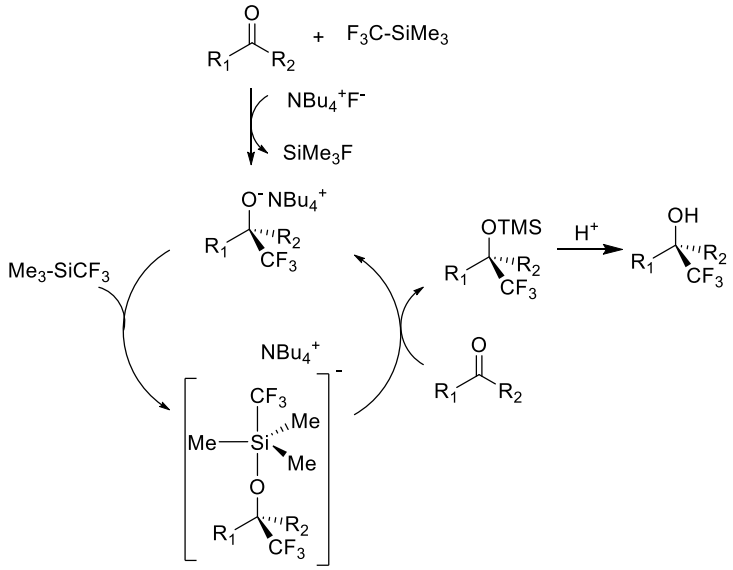
[7] Prakash, G. K. S.; Krishnamurti, R. Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393–395.

stage, the resultant alkoxide activates another molecule of Me_3SiCF_3 which transfers the $^-CF_3$ to another carbonyl group and the alkoxide is regenerated.



Scheme 3.2. Mechanism for the trifluoromethylation of carbonyl groups with $TMSCF_3$.

Methods for the preparation of the Ruppert's reagent have been described from CF_3 sources including CF_3Br[8], CF_3I[9] or CHF_3.[10] Fluoroform has also been used directly as a trifluoromethide, generated from electroreduction of 2-pyrrolidone,[11] or with the aid of strong bases.[12] Other CF_3 sources for nucleophilic trifluoromethylation include

[8] a) Grobe, J.; Hegge, *J. Synlett* **1995**, 641–642; b) Prakash, G. K. S.; Deffieux, D.; Yudin, A. K.; Olah, G. A. *Synlett* **1994**, 1057; c) Ruppert, I.; Schlich, W. V. *Tetrahedron Lett.* **1984**, *24*, 2195–2198.
[9] Pawelke, G. J. *Fluorine Chem.* **1989**, *42*, 429–433.
[10] Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338*, 1324–1327.
[11] Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1996**, *56*, 2–4.
[12] a) Folléas, B.; Marek, I.; Normant, J.–F.; Jalmes, L. S. *Tetrahedron Lett.* **1998**, *39*, 2973–2976; b) Russell, J.; Roques, N. *Tetrahedron*, **1998**, *54*, 13771–13782; c) Folle´as, B.; Marek, I.; Normant, J.–F.; Saint–Jalmes, L. *Tetrahedron,* **2000**, *56*, 275–283.

hemiaminals of fluoral,[13] trifluoroacetate derivatives,[14] trifluoroacetamide and trifluoromethanesulfinamide derivatives,[15] the trifluoromethylacetophenone *N,N*-dimethyltrimethylsilylamine adduct,[16] and phenyl trifluoromethyl sulfide,[17] sulfoxide and sulfone.[18]

3.1.1.2. Electrophilic/radical trifluoromethylation.

Since in 1984 Yagupolskii[19] developed a series of *S*-(trifluoromethyl)diarylsulfonium salts for the trifluoromethylation of thiophenolates, the design of new electrophilic trifluoromethylating agents have been extensively studied.[20] After these early discoveries, Umemoto[21] and, shortly after, Shreeve[22] designed trifluoromethylchalcogenium salts as CF_3^+ sources (Figure 3.1) and used them for electrophilic trifluoromethylation of a variety of nucleophiles including silyl enol ethers, enamines, thiolates, and electron-rich arenes. The trifluoromethysulfonium salts were poorly effective in *O*-CF_3 and *N*-CF_3 trifluoromethylation. In 2007, Umemoto and coworkers developed a class of thermally unstable *O*-(trifluoromethyl)-dibenzofuranium salts which proved useful in the trifluoromethylation of alcohols and amines.[23]

[13] a) Mispelaere, C.; Roques, N. *Tetrahedron Lett.* **1999**, *40*, 6411–6414; b) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101–2103.
[14] Sbihi, H.; Ouahmi, F.; Beji, M.; Baklouti, A. *Phosphorus. Sulfur Silicon Relat. Elem.* **2013**, *188*, 539–544.
[15] Jablonski, L. Joubert, J.; Billard, T.; Langlois, B. R. *Synlett* **2003**, 230–232.
[16] Motherwell, W.B.; Storey, L. J. *Synlett* **2002**, 646–648.
[17] Yokoyama, Y.; Mochida, K. *Synlett* **1996**, 1191–1192.
[18] Prakash, G. K. S.; Hu, J.; Olah, G. A. *Org. Lett.* **2003**, *5*, 3253–3256.
[19] Yagupolskii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 115–118.
[20] For key reviews see: a) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010,** *6*, 65; b) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1777.
[21] Umemoto, T.; Ishihara, S. J. *Am. Chem. Soc.* **1993**, *115*, 2156–2164.
[22] Yang, J.–J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1998**, *63*, 2656–2660.
[23] Umemoto T.; Adachi K.; Ishihara, S. *J. Org. Chem.* **2007**, *72*, 6905–6917.

Togni *et al.*[24] developed electrophilic trifluoromethylating reagents based on hypervalent iodine compounds. In 2008 Shibata and coworkers developed the trifluoromethyl version of the Johnson-methyl transfer reagent, which was subsequently applied in the electrophilic trifluoromethylation of carbon nucleophiles.[25] Nowadays, the commercially available Umemoto and Togni reagents (**I**–**III**) are the most used $^{+}CF_3$/$^{\bullet}CF_3$ precursors and, during recent years, have been extensively applied in a variety of reactions involving C(sp)–, C(sp^2)–, C(sp^3)– and S-CF_3 bond formation (Figure 3.2).[24,26]

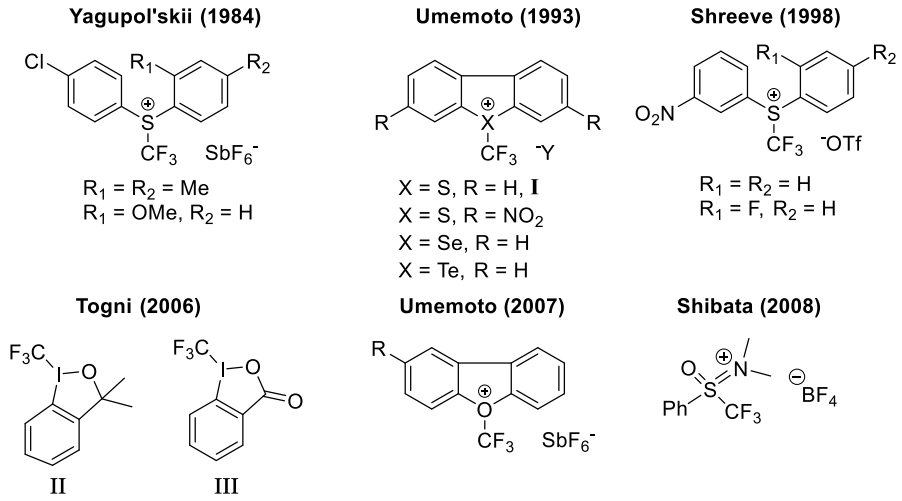


Figure 3.1. Electrophilic/radical trifluoromethylation reagents.

Trifluoromethyl radicals can be generated from CF_3I, $Te(CF_3)_2$, CF_3COCF_3, and $BrCF_3$ by thermal, photolytic, electrochemical, and chemical induction.[27] The CF_3 radical is highly electrophilic and, as a result, radical trifluoromethylation is reminiscent to electrophilic

[24] a) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650–682; b) Kieltsch, I.; b) Eisenberger, P.; Stanek, K.; Togni, A. *Chimia.* **2008**, *62*, 260–263; c) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579–2586.
[25] Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465–3468.
[26] a) Barata–Vallejo, S.; Lantaño, B.; Postigo, A. *Chem. Eur. J.* **2014**, *20*, 16806–16829; b) Kieltsch, I.; Eisenberger, P.; Stanek, K.; Togni, A. *Chimia.* **2008**, *62*, 260–263.
[27] McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555–6666.

trifluoromethylation.[28] For example, CF_3 radical produced from CF_3I adds region- and stereoselectively in the presence of triethylborane (Et_3B) to alkenes and alkynes to afford the corresponding trifluoromethylated alkanes and alkenes respectively (Scheme 3.3).[29] Typically, radical trifluoromethylation affords stereoselectively *E*-alkenes and regioselective addition occurs at the least substituted carbon. Radical trifluoromethylation also occurs in silyl enol ethers and silyl ketene acetals to produce α-trifluromethylated carbonylic compounds (Scheme 3.4).[30]

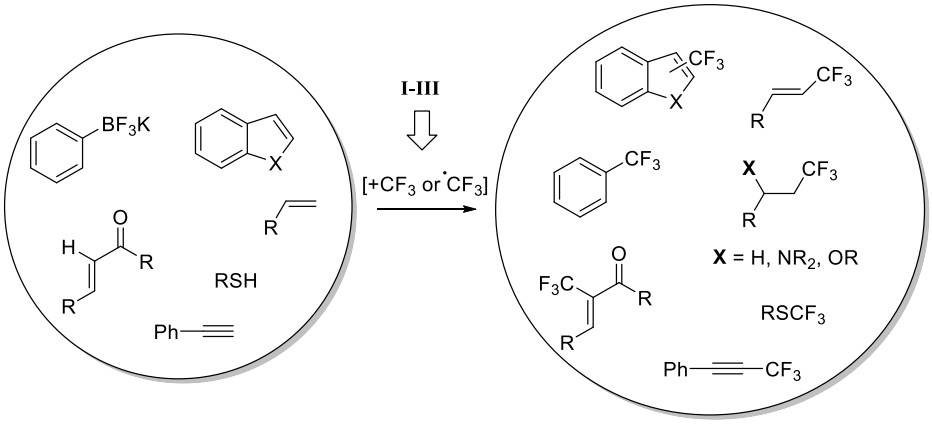
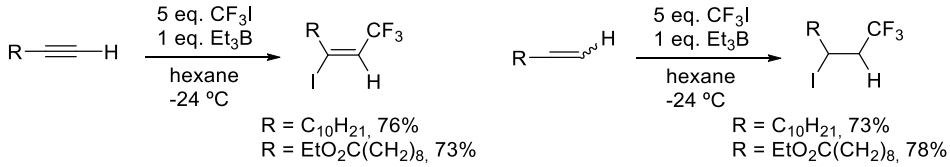


Figure 3.2. Examples of electrophilic/radical trifluoromethylations with Togni and Umemoto's reagents.



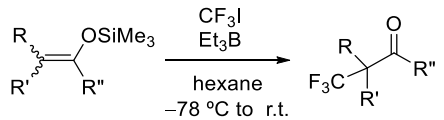
Scheme 3.3. Selected examples of radical trifluoromethylation of alkenes and alkynes with the CF_3I/Et_3B system.

[28] a) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967–974; b) Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 2895–2906; c) Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958.

[29] Takeyama, Y.; Ichinose, Y.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3159–3162.

[30] Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 154–1553.

This reaction has recently received much attention, specially due to the development of new $\cdot CF_3$ precursors such as CF_3SO_2Na, also known as Langlois' reagent[31] (or reagents which also found application as radical sources of CF_3, *e.g.* $TMSCF_3$[32]). Likewise, Umemoto's and Togni's reagents have been extensively used to produce trifluoromethyl radical by the aid of photoredox iridium and rhodium catalysts, or by SET reactions with Cu^{I} or Cu^{II} conditions with the Langolis reagent.[33]



R	R'	R"	Yield
H	H	n-C_9H_{19}	64%
n-C_4H_9	H	n-C_5H_{11}	32%
H	H	O-n-C_8H_{17}	90%
n-C_6H_{13}	H	OMe	66%

Scheme 3.4. Radical addition of CF_3 to silyl enol ethers.

3.1.1.1. Metal mediated/catalyzed trifluoromethylation

Metal-mediated/catalyzed trifluoromethylation is a cross-coupling reaction employing a CF_3 source and a metal, usually copper to produce a new C–CF_3 bond. Other metals, for instance Pd or Zn, have been scarcely used. The M–CF_3 reagents can be produced *in situ* during the reaction or pregenerated before the addition to the coupling partner. The main CF_3 sources used in the Cu-mediated trifluoromethylation are classified as follows:[34]

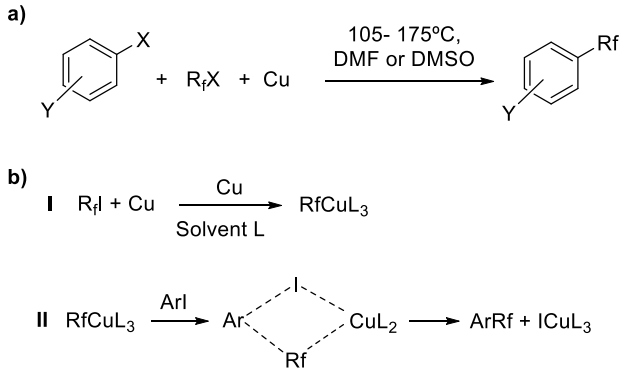
- Polyfluorinated methanes (CF_3I, CF_3Br, CF_2Br_2, CF_3H, etc).
- Derivatives of trifluoroacetic and fluorosulfonyldifluoroacetic acids.
- $CuCF_3$ species generated from Hg^{II}, Zn^{II}, and Cd^{II} *via* metal metathesis.
- Ruppert's reagent (CF_3SiMe_3) and the ethyl analogue CF_3SiEt_3.
- Well-defined trifluoromethyl copper complexes.

[31] Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 2895–2906.
[32] Studer, A. *Chem. Rev.* **2015**, *115*, 683–730.
[33] a) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967–974; b) Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958.
[34] Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475–4521.

A brief chronology of the advances on Cu-mediated (or catalyzed) trifluoromethylation are listed below, paying especial attention on the development of new CF_3 sources, the reaction composition, structural information of the $CuCF_3$ species involved, and mechanistic information.

Undoubtedly, the groundbreaking discovery by McLoughlin and Thrower[35] on Cu-mediated reductive coupling of perfluoroalkyl iodides with aromatic iodides in the 1960s, laid the foundations on the field of Cu-mediated trifluoromethylation (Scheme 3.5a). The authors noticed the participation of RfCu species in the reaction: "It was apparent that fluoroalkylcopper compounds were involved when it was found that these fluoroalkylations could be conducted in two separate stages." The first stage comprised metalation of RfI with Cu^0 in solution and the second involved treatment of an haloarene with the previous reactive solution. In this seminal work, other valuable information was revealed. The reaction was successful in polar aprotic solvents and, although best results were obtained in DMSO and DMF, pyridine, hexamethylphosphoramide (HMPA) or dimethylacetamide (DMA) also gave good results. Thus, coordinating solvents were required to stabilize CuRf species, however, perfluoroalkylation yields were higher using diluted amounts of DMSO or DMF. The reactivity order for ArX was I>Br>>Cl. This transformation was only accomplished with copper since perfluoroalkyl transfer from other metals (Zn and Hg) able to produce stable MRf reagents proved unsuccessful. A mechanism was proposed involving a four-centered transition state (Scheme 3.5b) although no evidence supporting this mechanism has been provided in that or posterior reports.

[35] a) McLoughlin, V. C. R.; Thrower, J. U.S. Patent 3408411, 1968; b) McLoughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25,* 5921–5940.

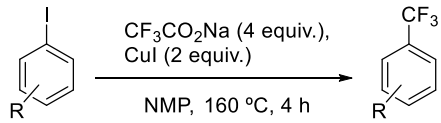


Scheme 3.5. Copper-mediated perfluroalkylation of aryl iodides.

After this revolutionary work, other chemists joined the field. Kobayashi and Kumadaki studied specifically the trifluoromethylation of aryl iodides with CF_3I,[36] and shortly after using cheaper CF_3Br,[36b] to obtain 72% and 11% yield of benzotrifluoride, respectively. In these reports, the reactive CuRf species were produced *in situ* during the reaction. In 1980, trifluoromethylation of iodonucleosides were achieved with a pregenerated and filtered $CuCF_3$ solution.[36c] This operation provided various advantages mainly derived from the removal of metallic copper, for instance: reduction of hydrodehalogenation byproducts and the use of typical glass apparatus enabled the reaction monitoring by g.l.c. and t.l.c and the trifluoromethylation could be performed at lower temperatures ranging from room temperature to 60 ºC (preparation of $CuCF_3$ solution in the previous stage required 120 ºC). These improvements were also observed by Yagupolskii[37] who reported the first example of $CuCF_3$ generated by transmetalation from $Hg(CF_3)_2$ using *N*-methylpyrrolidone (NMP) and DMA as solvents. Moreover one example of benzylic trifluoromethylation was described therein.

[36] a) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, 4095–4096; b) Kobayashi, Y.; Kumadaki, I. *Chem. Pharm. Bull.* **1972**, *20*, 1839–1839; c) Kobayashi, Y.; Yamamoto, K.; Asai, T.; Nakano, M.; Kumadaki, I. *J. Chem. Soc.; Perkin Trans. 1* **1980**, 2755–2761.
[37] Kondratenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. *Synthesis* **1980**, 932–933.

$CuCF_3$ can be generated by decarboxylation of sodium trifluoroacetate. Kondo[38] in 1981 and Osuka in 1982[39] applied this approach to prepare a variety of aryl iodides to obtain trifluoromethylated aryl derivatives in good yields (Scheme 3.6). Unlike other CF_3 sources, sodium trifluoroacetate is an easy-handling and cheap reagent that avoids the use of toxic elements. Although CF_3CO_2M (M = Na, K or NR_4), have been extensively used up to now,[40] important disadvantages (aggravated for large scale applications) are still present: decarboxylation requires temperatures as high as 180 ºC, large excess of CF_3 source is needed and the trifluoroacetic salts are highly hygroscopic and have limited solubility in certain solvents. In an attempt to reduce the loading of the CF_3 source, CF_3CO_2Me was used in place of CF_3CO_2Na, although with limited efficiency.[41]

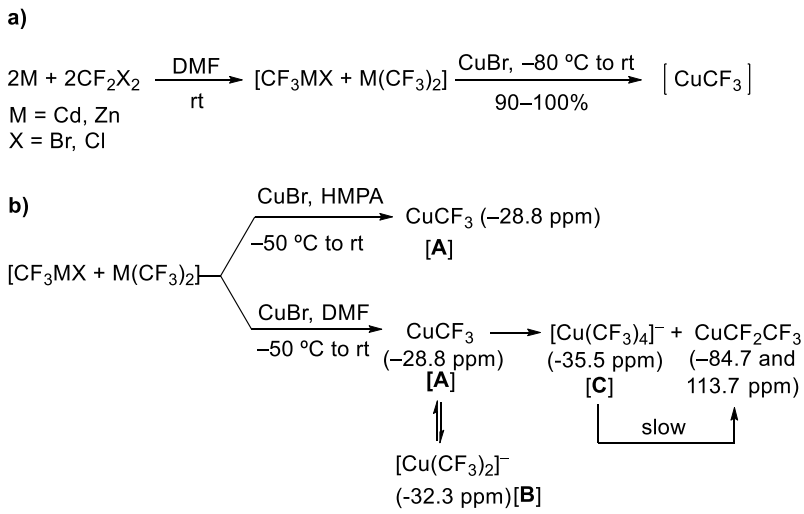


Scheme 3.6. Trifluoromethylation of aryl iodides *via* copper-promoted decarboxylation of sodium trifluoroacetate.

At that time, it was believed that putative $CuCF_3$ species had an important role in the trifluoromethylation but it was not until 1986 when they were detected by ^{19}F NMR. Burton and Wiemers prepared $CuCF_3$ by transmetalation from Cadmium and Zinc trifluoromethyl compounds which, in turn, were prepared from difluorodihalomethanes used for the

[38] Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981**, *10*, 1719–1720.
[39] Suzuki, H.; Yoshida, Y.; Osuka, A. *Chem. Lett.* **1982**, *11*, 135–136.
[40] a) Traynelis, S. F.; Liebeskind, L. S.; Liotta, D. C.; Garnier–Amblard, E. C.; PavanKumar Reddy, G. PCT Int. Appl. WO 2016081649, 2016; b) Akama, T.; Jarnagin, K.; Plattner, J. J.; Pulley, S. R.; White, W. H.; Zhang, Y.–K.; Zhou, Y. PCT Int. Appl. WO 2014149793, 2014; c) Larghi, E. L.; Operto, M. A.; Torres, R.; Kaufman, T. S. *Eur. J. Med. Chem.* **2012**, *55*, 74–84; d) Barbosa, H. J.; Collins, E. A.; Hamdouchi, C.; Hembre, E. J.; Hipskind, P. A.; Johnston, R. D.; Lu, J.; Rupp, M. J.; Takakuwa, T.; Thompson, R. C. U. S. Patent 7612067, 2009; e) Lin, R. W.; Davidson, R. I. Eur. Pat. Appl. EU 307519, 1989; Davidson, R. I. U. S. Patent 4814480, 1989.
[41] Langlois, B. R.; Roques, N. J. *Fluorine Chem.* **2007**, *128*, 1318–1325.

first time as CF_3 sources (Scheme 3.7a).[42] Striking observations revealed that the composition of the reagent was more complex than expected. The authors noticed a different behavior of "$CuCF_3$" depending on the solvent. In HMPA, only one signal [A] was observed in the ^{19}F NMR at –28.8 ppm. When DMF was used, two additional signals at –32.8 [**B**] and –35.5 ppm [**C**] appeared and their concentration was increasing while concentration of [**A**] was decreasing. At the same time, $CuCF_2CF_3$ was continuously produced, and after 11 h at room temperature, this was the main compound detected by ^{19}F NMR (Scheme 3.7b).



Scheme 3.7. a) Pregeneration of $CuCF_3$ species prepared by transmetalation; b) Observation of the species in the composition of the reagent solution.

Soon later, it was discovered that [**A**] equilibrates with [**B**] which were assigned to $[(CF_3)Cu]\cdot L$ (L = "metal halide") and $[(CF_3)_2Cu]^-$ respectively and [**C**] was revealed as the oxidized $[Cu^{III}(CF_3)_4]^-$.[43] The $CuCF_3$

[42] a) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832–834; b) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014–5015.

[43] a) Kuett, A.; Movchun, V.; Rodima, T.; Dansauer, T.; Rusanov, E. B.; Leito, I.; Kaljurand, I.; Koppel, J.; Pihl, V.; Koppel, I.; Ovsjannikov, G.; Toom, L.; Mishima, M.; Medebielle, M.; Lork, E.; Roeschenthaler, G.–V.; Koppel, I. A.; Kolomeitsev, A. A. *J. Org. Chem.* **2008**, *73*,

prepared following the Burton's procedure was used in the trifluoromethylation of aryl chlorides.[44] Owing to the C–Cl bond strength, strongly Cu-coordinating groups (especially nitro groups) in the *ortho* position were required and reaction with less reactive substrates gave hydrodehalogenation and pentafluoroethylation as main byproducts.

Fluorosulfonyl difluoromethyl iodide, FSO_2CF_2I, was introduced as CF_3 source able to generate $CuCF_3$.[45] The authors proposed the following mechanism: a single electron transfer (SET) event between Cu and FSO_2CF_2I produces $[FSO_2CF_2I]^-$ which is followed by fragmentation to difluorocarbene and fluoride anion with coproduction of SO_2 (Scheme 3.8). Combination of these species affords a trifluoromethyde which, in the presence of CuI, yields $CuCF_3$. Similarly, fluorosulfonyldifluoroacetic acid derivatives undergo decarboxylation and desulfurization in the presence of CuI. Chen and Wu reported trifluoromethylation of a variety of organic compounds using $FSO_2CF_2CO_2Me$ and a catalytic amount of CuI in DMF which produces $CuCF_3$ *via* a similar mechanism (Scheme 3.8).[46] This CF_3 source has been extensively used,[47] for instance, Duan and Dolbier presented the selective monotrifluoromethylation of a series of *trans*-1,2-diiodoalkenes achieving high regioselectively at terminal positions with 1.1 equivalents of $FSO_2CF_2CO_2Me$ and 1 equivalent of *trans*-α,β-diiodostyrene in the presence of 10 molar % CuI in DMF. The reaction proceeded with good to excellent yields in all cases (Scheme 3.9).[48]

2607–2620; b) Willert–Porada, M. A.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc.; Chem. Commun.* **1989**, 1633–1634.

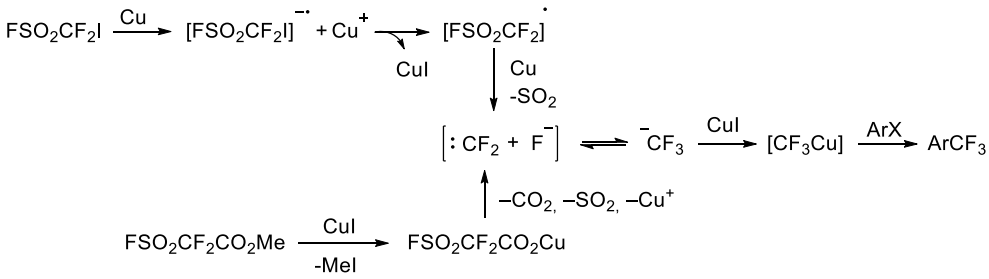
[44] a) Clark, J. H.; McClinton, M. A.; Blade, R. J. J. *Chem. Soc.; Chem. Commun.* **1988**, 638–639; b) Clark, J. H.; Denness, J. E.; McClinton, M. A.; Wynd, A. J. *J. Fluorine Chem.* **1990**, *50*, 411–426.

[45] Chen, Q.–Y.; Wu, S–W. *J. Chem. Soc.; Perkin Trans. 1* **1989**, 2385–2387.

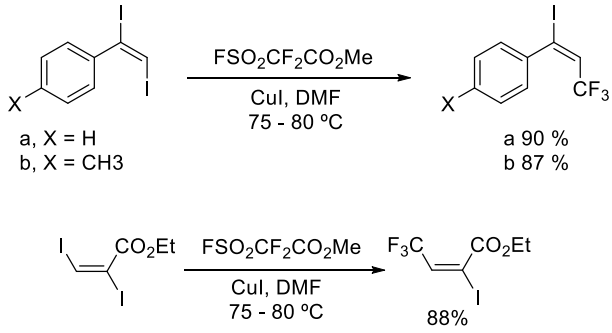
[46] Chen, Q.–Y.; Wu, S–W. *J. Chem. Soc.; Chem. Commun*. **1989**, 705–706.

[47] a) Grunewald, G. L.; Lu, J.; Criscione, K. R.; Okoro, C. O. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5319–5323; b) Wang, C.–L.; Li, H.–Q.; Meng, W.–D.; Qing, F.–L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4456–4458; c) Zheng, X.; Meng, W.–D.; Xu, Y.–Y.; Cao, J.–G.; Qing, F.–L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 881–884; d) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701–2704; e) Veliz, E. A.; Stephens, O. M.; Beal, P. A. *Org. Lett.* **2001**, *3*, 2969–2972; f) Qing, F.–L.; Fan, J. *J. Fluorine Chem.* **1999**, *96*, 159–161.

[48] Duan, J.; Dolbier, W. R.; Chen, Q. *J. Org. Chem.* **1998,** *63,* 9486–9489.



Scheme 3.8. CF_3Cu formation from methyl FSO_2CF_2I and $FSO_2CF_3CO_2Me$.



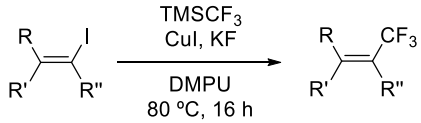
Scheme 3.9. Regioselective monotrifluoromethylation of terminal alkenyl diiodides with methyl fluorosulfonyldifluoroacetate.

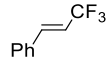
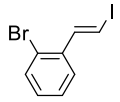
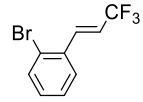
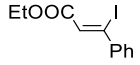
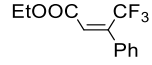
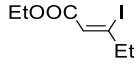
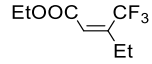
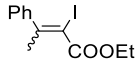
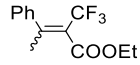
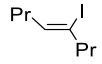
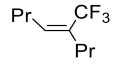
While trifluorometylation of iodoarenes has been widely explored, direct methods to introduce the trifluoromethyl group into alkenyl halides have been less developed. Urata and Fuchikami[49] reported the trifluoromethylation of terminal bromo- and iodoalkenes with KF/CuI in a 1:1 mixture of DMF and NMP using Et_3SiCF_3 as the CF_3 source. They observed the formation of perfluoroethyl side-products that are produced upon α-fluoride elimination from $CuCF_3$ and latter formation of CF_3CF_2Cu which pentafluoroethylates the olefinic substrate. Hafnera and Bräse optimized the reaction conditions to improve the selectivity.[50] The best results were obtained when the strong coordinating solvent DMPU

[49] a) Urata, H.; Fuchikami, *T. Tetrahedron Lett.* **1991**, *32*, 91–94; b) Fuchikami, T.; Urata, H. JP 03218325, 1991.
[50] Hafner, A.; Bräse, S. *Adv. Synth. Catal.* **2011**, *353*, 3044–3048.

was used in order to stabilize the $CuCF_3$ species and Me_3SiCF_3 was slowly added to the reaction mixture at 80 ºC during 2 h. With these optimized conditions, the scope was expanded to a variety of alkenyl iodides (Table 3.1).

Table 3.1. Selected examples of trifluoromethylation of alkenyl iodides with TMS-CF_3 and CuI.



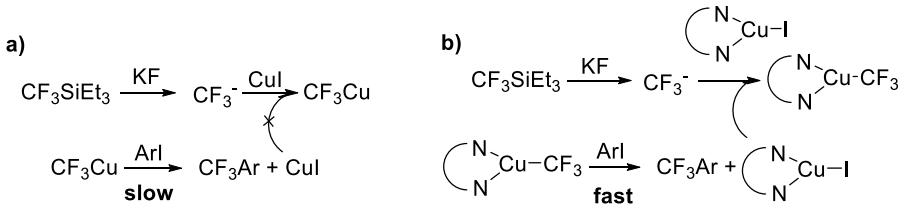
Entry	Alkenyl iodide	Product	Yield (%)
1			>99
2			>99
3			86
4			88
5			78
6			>99

[a]General conditions: alkenyl iodide (0.40 mmol). Me_3SiCF_3 (0.48 mmol), CuI (0.68 mmol), KF (0.60 mmol), DMPU (1.5 mL), 80 ºC, 16 h.

Stoichiometric amounts of copper were required for the aforementioned strategies but, in 2008, Oishi, Kondo, and Amii reported the first example of aromatic trifluoromethylation catalytic in copper.[51] Typically, a fluoride-based initiator is required to liberate the CF_3^- anion which in the presence of CuI generates $CuCF_3$. The later reacts with the aromatic substrate to afford the trifluoromethylated product. In this last

[51] Oishi, M; Kondo, H; Amii, H. *Chem. Commun.* **2009**, 1909–1911.

step, CuI is co-produced, which cannot be recycled in the reaction because the generation of CF_3^- is much faster than the formation of CuI and resulting in decomposition of CF_3^- (Scheme 3.10a). In the presence of diamine ligands, however, copper complexes are produced. The enhanced solubility and nucleophilicity of these *N,N*-ligated-Cu species accelerates the second step, Scheme 3.10b.

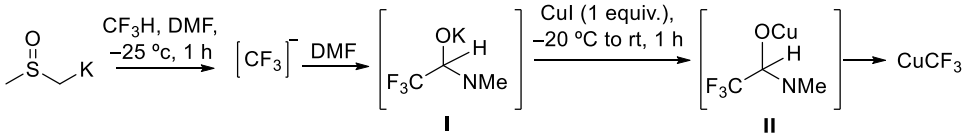


Scheme 3.10. a) Trifluoromethylation under stoichometric conditions, b) Catalytic trifluoromethylation enabled by diamine-ligand copper.

$TMSCF_3$[52] is the most popular reagent used in nucleophilic trifluoromethylations and, arguably, also in copper-mediated trifluoromethylations. Numerous examples are reported in the literature using the $TMSCF_3$/CuX system in: trifluoromethylation of aryl and heteroaryl iodides[43] and bromides,[53] allylic[54] and propargylic[55] halides, arenediazonium salts,[56] boronic acids,[57] terminal alkynes[57a,58] and arylpropiolic acids.[59]

[52] Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683−730.
[53] a) Kremlev, M. M.; Mushta, A. I.; Tyrra, W.; Yagupolskii, Y. L.; Naumann, D.; Möller, A. *J. Fluorine Chem.* **2012**, *133*, 67–71; b) Parker, M. F.; Bronson, J. J.; Silva, M.V.; Gillman, K. W. PCT Int. Appl. WO 2009096941, 2009.
[54] Miyake, Y.; Ota, S.; Nishibayashi, Y. *Chem. Eur. J.* **2012**, *18*, 13255−13258.
[55] Miyake, Y.; Ota, S.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, *49*, 7809−7811.
[56] Bayarmagnai, B.; Matheis, C.; Risto, E.; Goossen, L. J. *Adv. Synth. Catal.* **2014**, *356*, 2343–2348.
[57] a) Jiang, X.; Chu, L.; Qing, F.–L. *J. Org. Chem.* **2012**, *77*, 1251−1257; b) Chu, L.; Qing, F.–L. *Org. Lett.* **2010**, *12*, 5060–5063.
[58] a) Zhang, K.; Qiu, X.–L.; Huang, Y.; Qing, F.–L. *Eur. J. Org. Chem.* **2012**, 58–61; b) Chu, L.; Qing, F.–L. *J. Am. Chem. Soc.* **2010**, *132*, 7262–7263.
[59] Yang, L.; Jiang, L.; Li, Y.; Fu, X.; Zhang, R.; Jin, K.; Duan, C. *Tetrahedron* **2016**, *72*, 3858–3862.

Fluoroform (CF_3H), a side product of Teflon manufacturing, represents a tempting surrogate as CF_3 source. To the best of our knowledge, the first use of CHF_3 as CF_3 source to prepare $CuCF_3$ complex was shown in 2000.[60] The activation of fluoroform occurs at low temperature using metallated dimethylsulfoxide (dimsyl-K) as a base in DMF to produce adduct **I,** which after addition of CuI, produces complex **II** and eventually $CuCF_3$ species (Scheme 3.11). This method was indeed used in the trifluoromethylation of 4-iodoanisole in DMF/DMI (1:1) solvent system. Deprotonation of CHF_3 has long been used as the chosen strategy to activate the C–H bond[10,61] however, when the reaction with electrophiles is not fast enough, $^{-}CF_3$ readily decomposes to difluorocarbene and fluoride.[62]



Scheme 3.11. Preparation of $CuCF_3$ by deprotonation of CHF_3.

A revolutionary strategy for the activation of CHF_3 was reported in 2011, when Grushin described the preparation of $CuCF_3$ by the so-called "direct cupration of fluoroform".[63] Simple and cheap reagents are required for the preparation of [K(DMF)][Cu(OtBu)$_2$] which readily activates CHF_3 in a concerted manner, thus avoiding the participation of $^{-}CF_3$ or difluorocarbene species, thus suppressing unwanted side reactions (Scheme 3.12).

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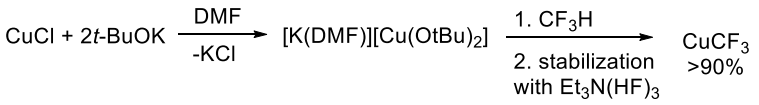
[60] Folleas, B.; Marek, I.; Normant, J.–F.; Saint–Jalmes, L. *Tetrahedron* **2000**, 56, 275–283.

[61] a) Zhang, Y.; Fujiu, M.; Serizawa, H.; Mikami, K. *J. Fluorine Chem.* **2013**, *156*, 367–371; b) Kawai, H.; Yuan, Z.; Tokunaga, E.; Shibata, N. *Org. Biomol. Chem.* **2013**, *11*, 1446–1450; c) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848–8856; d) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2–4; e) Russell, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771–13782.

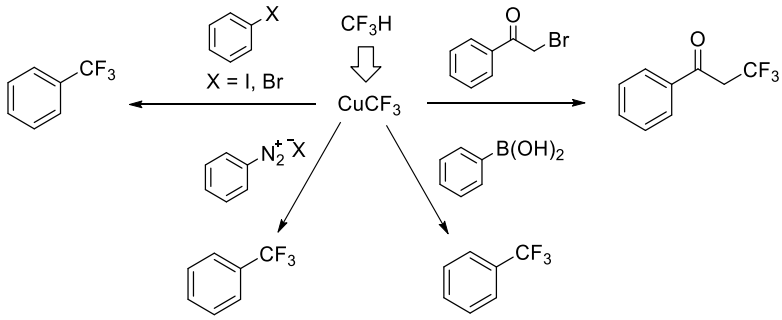
[62] Okusu, S.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2015**, *17*, 3802–3805.

[63] a) Konovalov, A. I.; Benet–Buchholz, J.; Martin, E.; Grushin, V. V. *Angew. Chem.* **2013**, *125*, 11851–11855; b) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet–Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133,* 20901–20913.



Scheme 3.12. Direct cupration of fluoroform.

Trifluoromethylation using this new reagent system has found broad application in the trifluoromethylation of aromatic halides aryl boronic acids, α-bromoketones and arenediazonium salts (Scheme 3.13).[64]

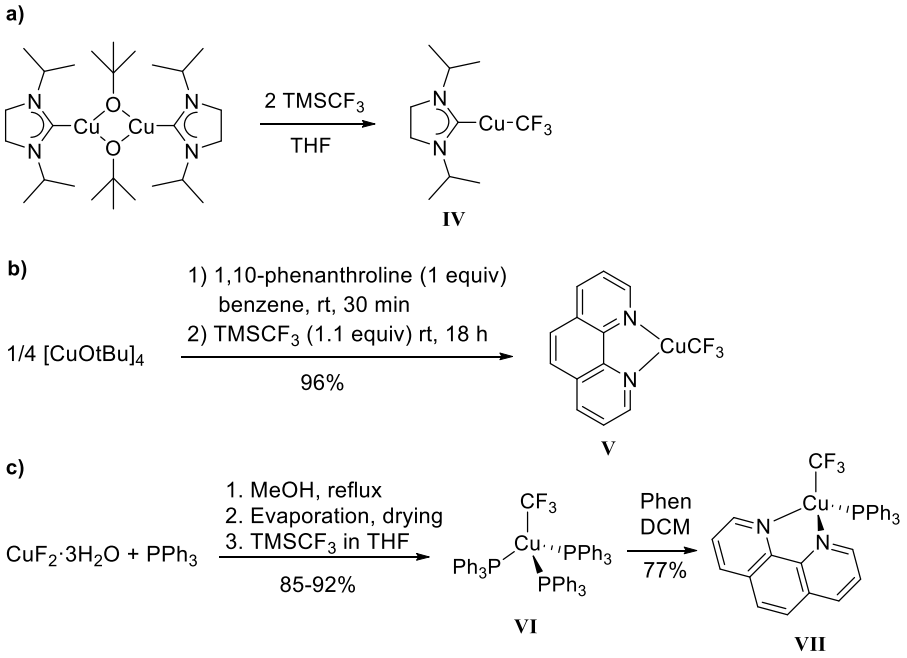


Scheme 3.13. Trifluoromethylation with $CuCF_3$ derived from fluoroform.

In the last years, well-defined $CuCF_3$ complexes have been described providing valuable structural information. The first fully characterized $CuCF_3$ complex **IV** was reported in 2008 by Vicic and coworkers (Scheme 3.14a).[65] This air-sensitive complex indeed was useful in providing high trifluoromethylation yields (>90%) based on Cu, however, 5 equivalents of the organic partner were required.

[64] a) Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero–Adán, E. C.; Novák, P.; Grushin. V. V. *J. Org. Chem.* **2013**, *78*, 11126–11146; b) Novák, P.; Lishchynskyi, A.; Grushin. V. V. *J. Am. Chem. Soc.* **2012**, *134*, 16167–16170; c) Novák, P.; Lishchynskyi, A.; Grushin. V. V. *Angew. Chem. Int. Ed.* **2012**, *51*, 7767–7770; d) Lishchynskyi, A.; Berthon, G.; Grushin, V. V. *Chem. Commun.* **2014**, *50*, 10237–10240.

[65] Dubinina, G. G.; Furutachi, H.; Vicic, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 8600–8601.



Scheme 3.14. Preparation of well-defined $CuCF_3$ complexes.

Soon after, several $CuCF_3$ complexes[63b,66,67] were characterized by X–Ray diffraction, most of them bearing phosphine, nitrogen or alkoxide ligands. Hartwig developed the synthesis of **V** and, although no structural crystallographic data was provided, this robust reagent was characterized by NMR techniques, elemental analysis, and was launched in the market under the brand name Trifluoromethylator®.[68] The same research group has recently reported trifluoromethylation of arylsilanes using **V** (Scheme 3.14b).[69] Grushin optimized the preparation of **VI** and

[66] a) Jover, J.; Miloserdov, F. M.; Benet–Buchholz, J.; Grushin, V. V.; Maseras, F. *Organometallics* **2014**, *33*, 6531–6543; b) Konovalov, A. I.; Benet–Buchholz, J.; Martin, E.; Grushin, V. V. *Angew. Chem.; Int. Ed.* **2013**, *52*, 11637–11641; c) Tomashenko, O. A.; Escudero–Adán E. C.; Martínez Belmonte, M.; Grushin, V. V. *Angew. Chem.; Int. Ed.* **2011**, *50*, 7655–7659.

[67] Weng, Z.; Lee, R.; Jia, W.; Yuan, Y.; Wang, W.; Feng, X.; Huang, K.–W. *Organometallics* **2011**, *30*, 3229–3232.

[68] Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793–3798.

[69] Morstein, J.; Hou, H.; Cheng, C.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 8054–8057.

disclosed a derivatization to **VII** (Scheme 3.14c).[70] These air-stable complexes efficiently trifluoromethylate a variety of aryl iodides in the range of 60–90% yield based on copper with only 1.1 equivalents of the organic coupling partner. Although the use of well-defined complexes may seem attractive, (some are even commercially available) they are cost-prohibitive for large scale operations, require laborious preparation which concerns their synthetic utility and previously commented CF_3 sources, mainly $TMSCF_3$, are required for its preparation. Last but not least, stoichiometric amount of ligands are required.

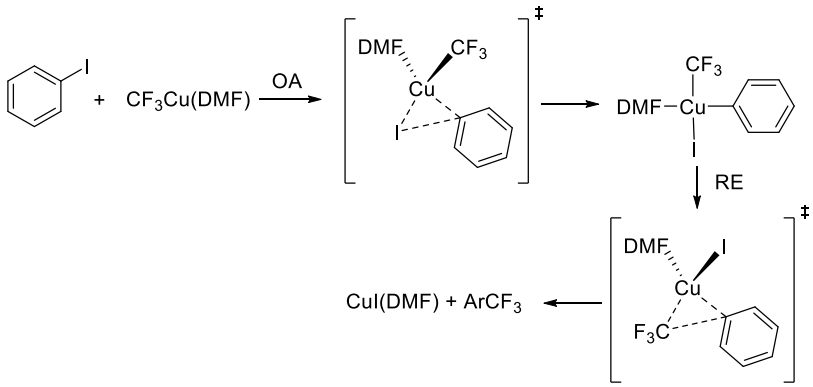
Very recently, phenyl trifluoromethyl sulfoxide has been introduced as a CF_3 source able to produce CF_3Cu species.[71] In that work, the conditions used are similar to that of Grushin's method in terms of reagents (CuCl, *t*-BuOK, and DMF) and stabilizers ($Et_3N{\cdot}HF$). Other methods using alternative CF_3 sources to prepare the copper complexes have been published recently including the Umemoto's reagent,[72] $Cu(O_2CCF_2SO_2F)_2$[73] and cyclic-protected Hexafluoroacetone.[74] Despite the high development on new CF_3 sources, the application and reaction scope is generally limited to simple aryl precursors and trifluoromethylation of more complex scaffolds (*e.g.* motifs widely present in natural products or biological active ingredients) remain underdeveloped.

Since the first tentative mechanistic proposal by McLoughlin and Thrower, suggesting that the trifluoromethylation of aryl halides operates under σ-bond metathesis (SBM),[35] other mechanistic alternatives have been scarcely proposed. The groups of Holmes and Buchwald performed Hammett studies providing σ values of +0.46,[75] and +0.52[76] respectively, supporting the nucleophilic character of the $CuCF_3$ species involved.

[70] Usui, Y.; Noma, J.; Hirano, M.; Komiya, S. *Inorg. Chim. Acta* **2000**, *309*, 151–154.
[71] Li, X.; Zhao, J.; Zhang, L.; Hu, M.; Wang, L.; Hu, *J. Org. Lett.* **2015**, *17*, 298−301
[72] Zhang, C.–P.; Wang, Z.–L.; Chen, Q.–Y.; Zhang, C.–T.; Gu, Y.–C.; Xiao, J.–C. *Angew. Chem. Int. Ed.* **2011**, *50*, 1896–1900.
[73] Zhao, G.; Wu, H.; Xiao, Z.; Chen, Q.–Y.; Liu, C. *RSC Adv.* **2016**, *6*, 50250–50254.
[74] Negishi, K.; Aikawa, K.; Mikami, K. *Eur. J. Org. Chem.* **2016**, 4099–4104.
[75] Carr, G. E.; Chambers, R. D.; Holmes, T. F. J. *Chem. Soc.; Perkin Trans. 1* **1988**, 921–926.
[76] Chen, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 11628–11631.

Moreover, in other reports, the absence of cyclized products in radical clock experiments[68,77] dissuaded to justify radical pathways.

In 2014, Grushin and coworkers presented a detailed mechanistic study of the trifluoromethylation of aryl halides with "ligandless" $CuCF_3$ including radical clock, kinetic and Hammett correlation experiments in combination with computational calculations.[78] Their investigations indicated that the reaction occurs through an associative oxidative addition followed by reductive elimination (AOARE) mechanism (Scheme 3.15). Shortly after, Li published computational studies using a well-defined [(NHC)$CuCF_3$] complex, corroborating the findings of Grushin.[79] In both works other reaction pathways were proposed, for instance S_NAr, SBM, halogen atom transfer (HAT) and SET mechanisms, but were ruled out because they were prohibitively high in energy or were in contradiction with experimental observations.



Scheme 3.15. Simplified mechanism proposed by Grushin and coworkers.

[77] a) Sanhueza, I. A.; Nielsen, M. C.; Ottiger, M.; Schoenebeck, F. *Helv. Chim. Acta* **2012**, *95*, 2231–2236.
[78] Konovalov, A. I.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 13410–13425.
[79] Yu, D.–H.; Shao, J.–N.; He, R.–X.; Li, M. *Chinese Chem. Lett.* **2015**, *26*, 564–566.

3.2. Objectives

As stated in chapter I, fluorinated carbohydrates are used in many biochemical and medicinal applications. There are few examples of CF_3 containing sugars which were prepared either starting from a trifluoromethylated synthon (building block approach)[80] or through the nucleophilic trifluoromethylation of oxosugars with the Ruppert's reagent.[81] Recent reports exploit late-stage transformations for the introduction of perfluoroalkyl motifs, for instance, Cu-catalyzed difluoroacetylation[82] and radical trifluoromethylation[83] of glycals (Scheme 3.16a). Nevertheless, flexible and regiocontrolled introduction of such motifs at the desired position of electron-rich double bonds present in natural products, including glycals and other heterocycles is challenging. In this regard, trifluoromethylation of indoles has been extensively studied,[84] although generally giving poor regioselectivity and directed to the synthesis of 2-trifluormethylindoles,[85] the introduction at C–3 has been much less explored (Scheme 3.16b).[72]

---

[80] a) Brown, K.; Dixey, M; Weymouth–Wilson, A.; Linclau, B. *Carbohydr. Res*. **2014**, *387*, 59–73; b) Miethchen, R. *J. Fluorine Chem*. **2004**, *125*, 895–901; c) Eilitz, U.; Böttcher, C.; Sieler, J.; Gockel, S.; Haas, A.; Burger, K. *Tetrahedron* **2001**, *57*, 3921–3925.

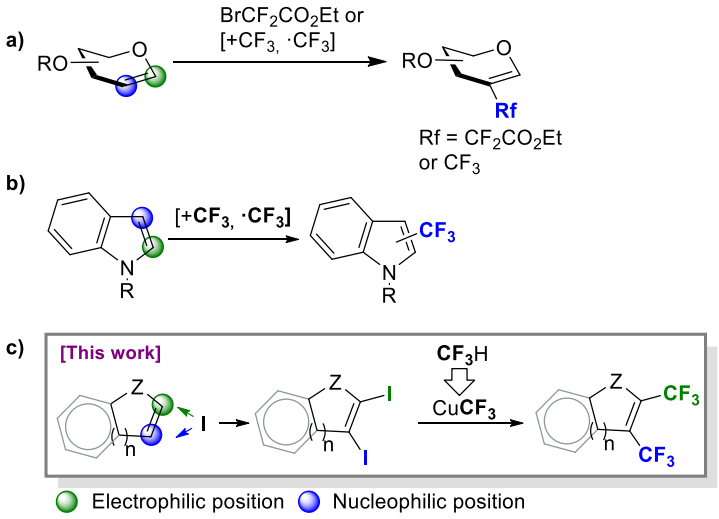
[81] a) Kollatos, N.; Manta, S.; Dimopoulou, A.; Parmenopoulou, V.; Triantakonstanti, V. V.; Kellici, T.; Mavromoustakos, T.; Schols, D.; Komiotis, D. *Carbohydr Res*. **2015**, *407*, 170–178; b) *Jeannot, F.; Gosselin, G.; Mathé, C. Org. Biomol. Chem.* **2003**, *1*, 2096–2102; c) Jeannot, F.; Gosselin, G.; Standring, D.; Bryant, M.; Sommadossi, J. P.; La Colla, P.; Mathé, C. *Bioorg. Med. Chem*. **2002**, *10*, 3153–3161; d) Lavaire, S.; Plantier–Royon, R.; Portella, C. *Tetrahedron: Asymm*. **1998**, *9*, 213–226; e) Munier, P; Giudicelli, M.–B.; Picq, D. Anker, D. *J. Carbohydr. Chem*. **1996**, 15, 739–762; f) Munier, P; Giudicelli, M.–B.; Picq, D. Anker, D. *J. Carbohydr. Chem.* **1994**, *13*, 1225–1230.

[82] Belhomme, M.–C.; Poisson, T.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 3428–3431.

[83] Wang, B.; Xiong, D.–C.; Ye, X.–S. *Org. Lett.* **2015**, *17*, 5698–5701.

[84] a) Ge, G.; Huang, X.; Ding, C.; Li, H.; Wan, S.; Hou, X. *Chin. J. Chem.* **2014**, *32*, 727–733; b) Zhang, X.–G.; Li, J.–H.; Dong, S.–X.; Liu, Q.; Tang, R.–Y.; Zhong, P. *Synthesis* **2010**, 1521–1525; c) Bastos, M. M.; Mayer, L. M. U.; Figueira, E. C. S.; Soares, M.; Boechat, N.; Kover, W. B. *J. Heterocyclic Chem*. **2008**, *45*, 969–973; d) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008,** *10*, 625–628; e) Iqbal, N.; Choi, S.; Ko, E.; Cho, E. J. *Tetrahedron Lett.* **2012**, *53*, 2005–2008.

[85] a) Shimizua, R.; Egami, H.; Nagi, T.; Chaea, J.; Hamashimaa, Y.; Sodeoka M. *Tetrahedron Lett.* **2010**, *51*, 5947–5949; b) Liu, T.; Shen, Q. *Org. Lett.* **2011**, *13*, 2342–2345; c) Mu, X.; Chen, S.; Zhen, X.; Liu, G. *Chem. Eur. J.* **2011**, *17*, 6039–6042.



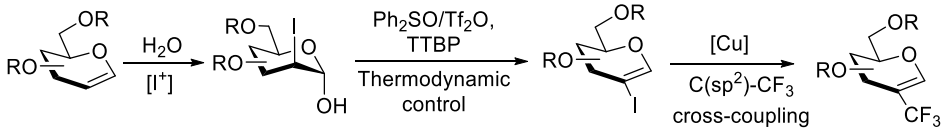
Scheme 3.16. Previous methods to prepare CF_3-containing a) glycals and b) indoles and our c) general strategy.

To overcome problems on regioselectivity and to have access to regioisomers against the substrate control observed in electrophilic trifluoromethylations, we envisioned a general two-step strategy for the selective introduction of CF_3 into glycals, indoles and nucleosides (Scheme 3.16, c). The first step of the strategy comprises the regioselective preparation of suitable vinyl halides as key intermediates from commercially available precursors (or prepared using reported protocols). This section will be specially focused in the preparation of haloglycals since the preparation of halonucleosides and haloindoles is well documented. The second step involves a $C(sp^2)$–X trifluoromethylation using "ligandless" $CuCF_3$ derived from fluoroform (preparation of $CuCF_3$ was performed by Dr Anton Lishchynskyi in the laboratory of Vladimir Grushin at the ICIQ). Then, trifluoromethylation is optimized for different structural scaffolds. Finally, the generality of the method is explored with different structures, carbohydrate configurations, functional groups and reaction sites with opposite electronic properties.

3.3. Results and discussion

3.3.1. Synthesis of haloglycals

Since we were especially interested in the synthesis of 2-trifluoromethylglycals, the corresponding 2-iodoglycals precursors were firstly prepared following a protocol developed in our group comprising the following steps: 1) treatment of easily accessible or commercially available glycals with iodonium reagents in aqueous media to provide the corresponding 2-iodolactols, and 2) subsequent dehydrative elimination with Ph_2SO/Tf_2O system under thermodynamic control in the presence of TTBP to afford 2-iodoglycals (Scheme 3.17).[86]



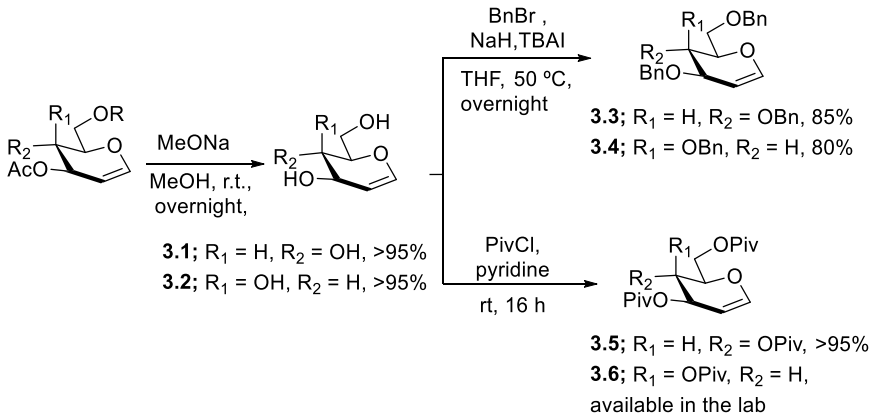
Scheme 3.17. Proposed strategy for the synthesis of 2-trifluoromethyl glycals.

First, benzyl- and pivaloyl-protected glycals **3.3**–**3.6** were prepared from the corresponding peracetylated glycals using standard protocols (Scheme 3.18).[87] With these starting materials in hands, the aforementioned strategy was applied to obtain the corresponding vinyl iodides. In the first step, reaction with NIS in CH_3CN/H_2O afforded the corresponding 2-deoxy-2-iodopyranoses giving predominantly α-*manno* (from glucal) and α-*talo* (from galactal) configurations according to the preferred 1,2-*trans* addition (Scheme 3.18).[88]

[86] a) Cobo, I.; Matheu, M. I.; Castillón, S.; Boutureira, O.; Davis, B. G. *Org. Lett.* **2012**, *14*, 1728–1731; b) Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S.; Seeberger, P. H. *J. Org. Chem.* **2007**, *72*, 8998–9001.

[87] a) Vedachalam, S.; Tan, S. M.; Teo, H. P.; Cai, S.; Liu, X.–W. *Org. Lett.* **2012**, *14*, 174–177; b) Yongyat, C.; Ruchirawat, S.; Boonyarattanakalin, S. *Bioorg. Med. Chem.* **2010**, *18*, 3726–3734; c) Hudson, R. H. E.; Ghorbani–Choghamarani, A. *Org. Biomol. Chem.* **2007**, *5*, 1845–1848; d) Walvoort, M. T. C.; Kallemeijn, W. W.; Willems, L. I.; Witte, M. D.; Aerts, J. M. F. G.; Marel, G. A. van der, Codée, J. D. C.; H. S. Overkleeft. *Chem. Commun.* **2012**, *48*, 10386–10388.

[88] a) Gammon, D. W.; Kinfe, H. H.; De Vos, D. E.; Jacobs, P. A.; Sels, B. F. *J. Carbohydr. Chem.* **2007**, *26*, 141–157; b) Gammon, D. W.; Kinfe, H. H.; De Vos, D. E.; Jacobs, P. A.;



Scheme 3.18. Preparation of benzyl- and pivaloyl-protected glycals.

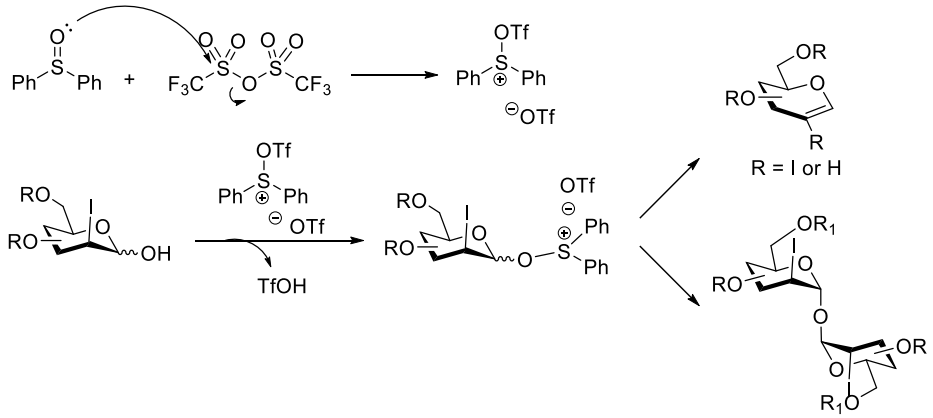
The second step involves an elimination reaction which occurs under modified dehydrative glycosylation conditions replacing a nucleophile by the strong base, 2,4,6-tri-*tert*-butylpyrimidine (TTBP), and driving the reaction under thermodynamic control to favor elimination over self-glycosylation (Scheme 3.19). First, activation of the anomeric hydroxyl of 2-iodopyranoses takes place with the Ph_2SO/Tf_2O system which was developed by Gin *et al.* and applied in the glycosylation of lactols.[89] Thus, base-assisted elimination with the strong non-nucleophilic base TTBP gives 2-iodoglycals along with variable amounts of trehaloses (produced by the incomplete activation of pyranoses which can then act as nucleophiles reacting with the activated counterparts).

When the strategy was applied to a series of glucal and galactal scaffolds bearing different protecting groups, the reaction outcome was highly dependent on the stereochemistry and the nature of substituents (Table 3.2). Thus, the *talo* series gave higher selectivity for the formation of 2-iodoglycals than the *manno* equivalents. The increasing bulkiness of the protecting group, in contrast, favored the formation of the trehalose, and thus, 2-iodoglycal selectivity decreases in the order

Sels, B. F. *Tetrahedron Lett.* **2004**, *45*, 9533–9536; c) Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett.* **1999**, *1*, 895–897.

[89] Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597–7598.

OBn>OPiv>OTIPS. Unfortunately, more labile acetyl and triethylsilyl (TES) protecting groups showed no tolerance under the reaction conditions. Substitution of TTBP by *t*-BuOK or DBU proved unsuccessful, the first gave no reaction products[86b] and DBU produced exclusive formation of glycals through a base-assisted E1 elimination.

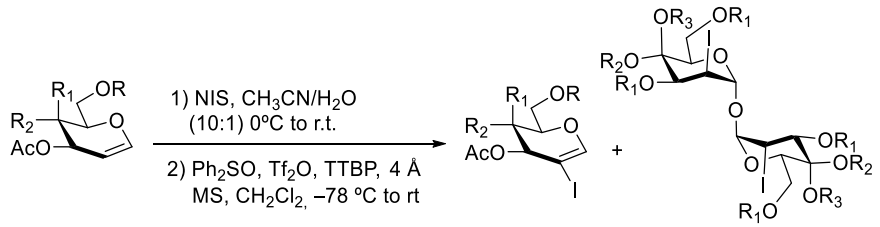


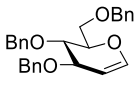
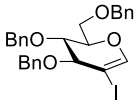
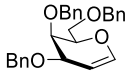
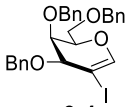
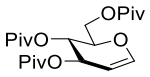
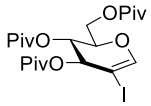
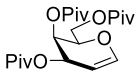
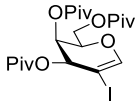
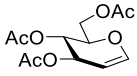
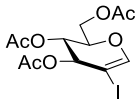
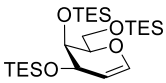
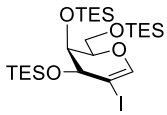
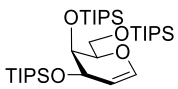
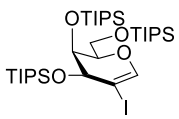
Scheme 3.19. Activation of hydroxyl with Ph_2SO/Tf_2O system.

The remarkable difference in the reaction outcome depending on the configuration and steric properties of the protecting groups called for a selectivity rationale. Since the group to be eliminated must be in axial position, elimination from conformers **A** leads to formation of 2-iodoglycals whereas conformers **B** are prone to undergo addition from non-activated halohydrines yielding 1,1'-disaccharides (Scheme 3.20).[86b] Hence, $^4H_3$ half-chair conformations (transition state B) bearing axial I are stabilized by hyperconjugation between the σC–I and σ*C–O bonds of the oxocarbenium.[90] Moreover, benzyl-protecting groups at C–3 and C–4 prefer pseudoaxial positions,[91] thus stabilizing conformation **A** whereas ester groups favor conformers **B** to avoid destabilizing 1,3-interactions.

[90] Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171.
[91] a) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195–1201; b) Antoinette, J.; Romero, C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168–169; c) Woods, R. J.; Andrews, C.W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 850 – 858

Table 3.2. Iodohydroxylation/dehydrative elimination sequence of glycals.



Entry	Glycal	2-iodoglycal	Yield of iodoglycal (%)[a]	Iodoglycal/ trehalose ratio[b]
1	 **3.3**	 **3.3a**	45	1:1
2	 **3.4**	 **3.4a**	55	3:1
3	 **3.5**	 **3.5a**	10	1:6.3
4	 **3.6**	 **3.6a**	52	1:1
5[c]	 **3.7**	 **3.7a**	–[c]	–
6[d]	 **3.8**	 **3.8a**	–[d]	–
7	 **3.9**	 **3.9a**	–	0 : 1

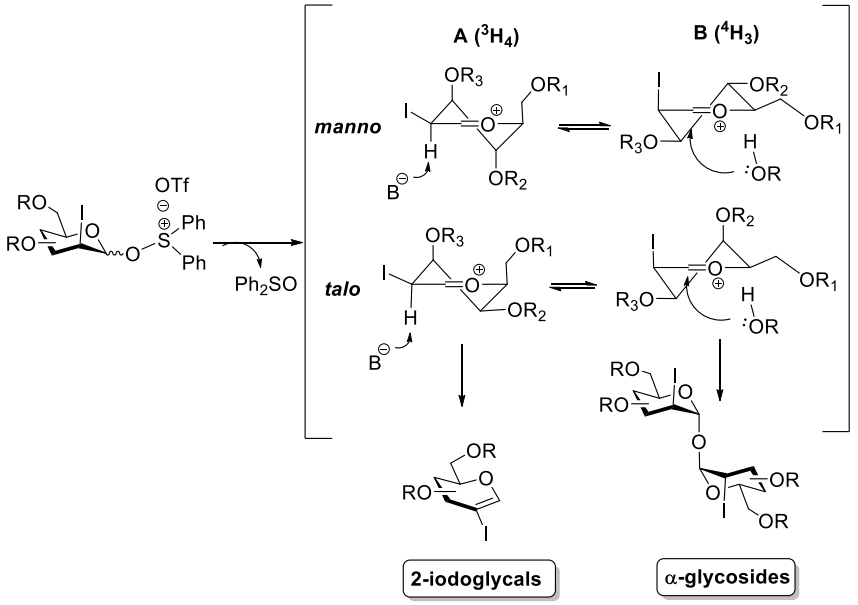
[a]Isolated yield after column chromatography; [b]Ratio determined by ^{1}H NMR; [c]Ferrier products observed; [d] Decomposition observed.

2-Iodoglycal formation in the *manno* configuration through intermediate **A** is disfavored due to steric repulsions between the approaching base and the substituent on C–4. It is noteworthy that *talo* series gives better yields for 2-iodoglycals compared to the *manno* counterparts since the substituent at C–4 is pointing away from the base approach t

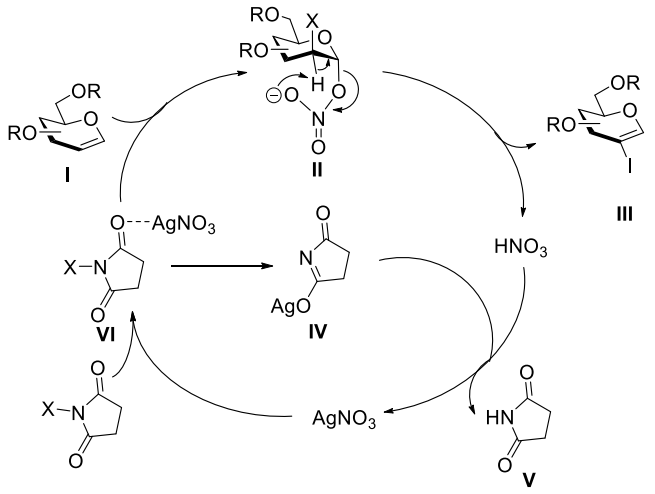
The previous methodology lacks from acetyl-group tolerance, one of the most used and versatile protecting groups in carbohydrate chemistry. Furthermore, only moderate yields using this strategy are usually obtained. Therefore a different and more efficient methodology to prepare 2-iodoglycals would be highly appreciated. Fortunately, during the course of our investigations, a new method for the synthesis of 2-haloglycals using iodosuccinimide and catalytic $AgNO_3$ in CH_3CN was reported by Dharuman and Vankar.[92] The authors proposed a mechanism as follows (Scheme 3.21): Firstly, an electrophilic addition of halide to glycal **I** is followed by nucleophilic attack of NO_3^- to the anomeric carbon, thus producing an unstable intermediate **II** which, after *in situ* elimination of HNO_3, affords the corresponding 2-haloglycal **III** Finally, acid-base equilibrium between **IV** and HNO_3 produces **V** and regenerates $AgNO_3$ which is reintroduced in the catalytic cycle.

Using the Vankar's methodology, previously inaccessible peracetylated 2-iodoglycals including 2-iodogalactal **3.10a** and more complex 2-iodolactal **3.11a** were successfully prepared in good yields (Scheme 3.22). Moreover, **3.10a** was hydrolyzed to 2-iodogalactal **3.12a** for assaying the trifluoromethylation step in the absence of protecting groups (Scheme 3.23).

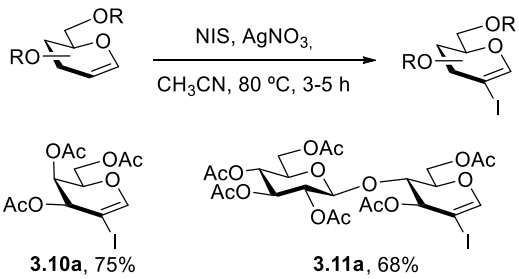
[92] Dharuman, S.; Vankar, Y. *Org. Lett.* **2014**, *16*, 1172–1175.



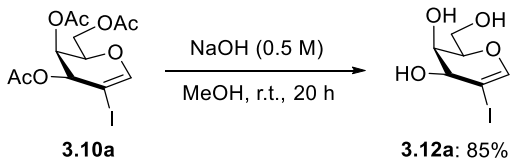
Scheme 3.20. Mechanism of dehydrative elimination of activated 2-halopyranoses.



Scheme 3.21 Mechanism of the one pot synthesis of 2-haloglycals with NIS and $AgNO_3$.[92]



Scheme 3.22. Synthesis of 2-iodoglycals bearing acetyl protecting groups.

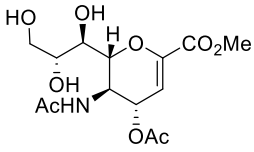


Scheme 3.23. Synthesis of 2-iodglycal **3.12a**.

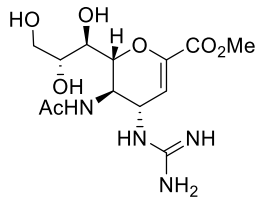
More complex substrates with interesting biological properties such as those derived from Neu5Ac2en (sialidase inhibitor) were also considered as substrates. We envisaged that application of the I-tagging>cross strategy to Ne5Ac2en could serve for accessing to the corresponding trifluoromethylated derivatives at C–3 and as a potential divergent method to prepare diverse C–3 substituted analogs *via* a variety of cross-coupling reactions. Sialidases, also known as neuramidases, are glycosidase enzymes that catalyze the hydrolysis of terminal sialic acid (or neuraminic acid) residues present in glycoproteins, glycolipids or oligosaccharides expressed by various organisms including bacteria, viruses and fungi.[93] Sialidase inhibitors of influenza viruses, *e.g.*; Neu5AC2en and two well-known commercialized drugs, Zanamivir (Relenza®)[94] and Oseltamivir (Tamiflu®),[95] are well recognized drugs in

[93] Buschiazzo, A.; Alzari, P. M. *Curr. Opin. Struct. Biol.* **2008**, *12*, 565–572.
[94] M. Vonitzstein, W. Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, B. Jin, T. V. Phan, M. L. Smythe, H. F. White, S. W. Oliver, P. M. Colman, J. N. Varghese, D. M. Ryan, J. M. Woods, R. C. Bethell, V. J. Hotham, J. M. Cameron and C. R. Penn, *Nature*, **1993**, *363*, 418–423.

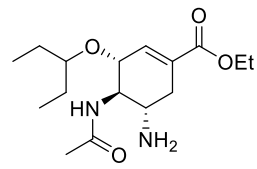
this area (Figure 3.3). Synthesis of Neu5Ac2en analogues is desirable to improve inhibitory activity of parent scaffolds and to establish an efficient methodology to develop a library of compounds for the treatment of influenza virus which easily develop drug resistance. In this sense, the research groups of Itzstein[96] and Anastasia[97] have been working on the synthesis of C–3 and C–4 substituted analogues of Neu5Ac2en.



Neu5Ac2en



Zanamivir (Relenza®)



Oseltamivir (Tamiflu®)

Figure 3.3. Sialidase inhibitors.

Although commercially available, Neu5Ac2en is cost-prohibitive for synthetic purposes and we decided to perform a preparative synthesis from more economical sialic acid, **3.13**, following reported protocols:[96,98] Firstly, Dowex®-catalyzed esterification of **3.13** afforded **3.14** which was converted to peracetylated analog **3.15**. Substitution of the anomeric acetate using AcCl afforded chloride **3.15a** and, finally, NaH_2PO_4 promoted elimination rendered **3.16** in 68% global yield (Scheme 3.24, route a). In contrast, when Ac_2O/Py system was substituted by AcCl in the presence of a catalytic amount of methanol to *in situ* produce anhydrous HCl, chloride derivative **3.15a** was produced in one-pot (Scheme 3.24, route b). The total yield was increased from 68% (route a) to 87% yield (route b). It should be noted that transformation from **3.14** to **3.16** was

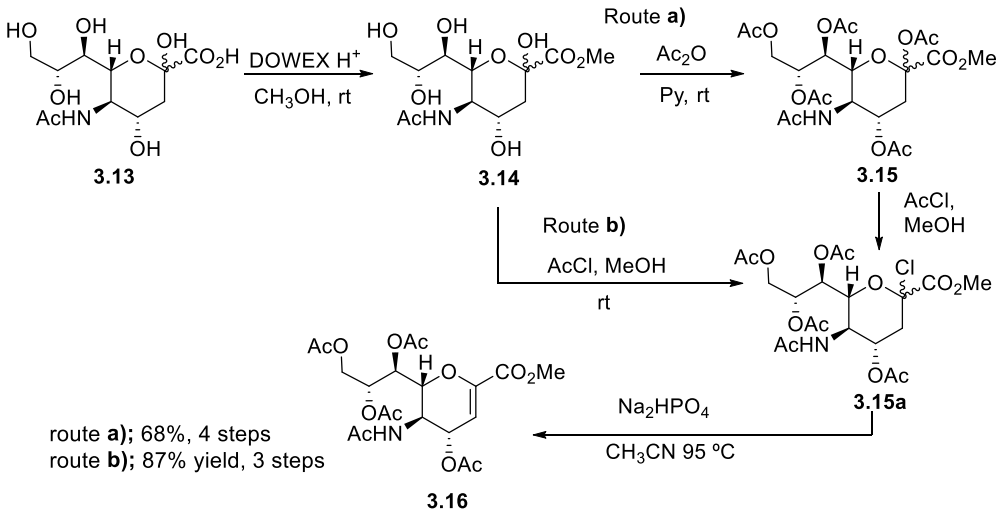
[95] C. U. Kim, W. Lew, M. A. Williams, H. T. Liu, L. J. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver and R. C. Stevens, *J. Am. Chem. Soc.* **1997**, *119*, 681–690.

[96] Rudrawar, S.; Pascolutti, M.; Bhatt, B.; Thomson, R. J.; von Itzstein, M. *Tetrahedron Lett.* **2013**, *54*, 1198–1201.

[97] Allevi, P.; Rota, P.; Agnolin, I. S.; Gregorio, A. Anastasia, M. *Eur. J. Org. Chem.* **2013**, 4065–4077.

[98] Malapelle, A.; Coslovi, A.; Doisneau, G.; Beau, J.–M. *Eur. J. Org. Chem.* **2007**, 3145–3157.

performed on the same flask and the overall transformation from **3.13** to **3.16** only required two extractions and one column chromatography).



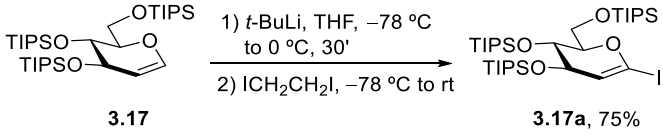
Scheme 3.24. Preparation of Neu5Ac2en.

With **3.16** in hand, we prepared the corresponding iodoglycal **3.16a** following Vankar's methodology. The reaction was notably slower compared to the previous peracetylated glycals since, in this case, the double bond is comparatively more electron-deficient resulting from conjugation with the methyl ester. However, **3.16a** was obtained in a moderate 47% yield after 12 h, Scheme 3.25.

Scheme 3.25. Preparation of 2-iodoNeu5Ac2en.

After the preparation of 2-iodoglycals, we also decided to synthesize 1-iodoglycals in order to introduce the trifluoromethyl group

at the electron-poor C–1 position. Thus, 1-Iodoglycal **3.17a** was prepared by lithiation of **3.17** with *t*-BuLi followed by metal-halogen exchange using ICH_2CH_2I.[99] Although a little amount of starting material was recovered unreacted, the product was obtained in good 75% yield (Scheme 3.26).



3.17 **3.17a**, 75%

Scheme 3.26. Preparation of 1-iodoglycal **3.17a.**

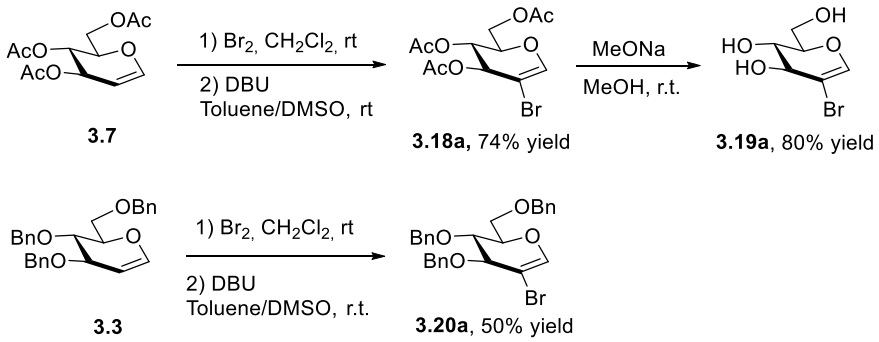
Next, we considered other 2-haloglycals to examine the scope and/or limitations in the trifluoromethylation step. For this purpose, different 2-bromoglycals were prepared. The bromoglycals will predictably show lower reactivity than the iodinated analogs.

3,4,6-Tri-*O*-acetyl-D-glucal **3.7** and the corresponding perbenzylated glycal **3.3** were subjected to bromination with Br_2 to obtain a mixture of dihalogenated *manno* and *gluco* bromoglycosides. DBU promoted elimination afforded 2-bromoglycals **3.18a** and **3.20a** in 74% and 50% yield respectively (Scheme 3.27).[100] Furthermore, unprotected 2-bromo-D-glucal **3.19a** was smoothly obtained after acetyl deprotection using NaOMe in MeOH.

The products obtained in the bromination step are produced under kinetic control and the stereoselectivity is affected by the solvent polarity,[101] the enol ether structure, and the halogen nature.[102] It has been reported[103] that bromine addition to glycals in aprotic solvents takes place through a two-step mechanism which involves the

[99] Liu, M.; Niu, Y.; Wu, Y.–F.; Ye, X.–S. *Org. Lett.* **2016**, *18*, 1836–1839.
[100] Leibeling, M.; Koester, D. C.; Pawliczek, M.; Schild, S. C.; Werz, D. B. *Nat. Chem. Biol.* **2010**, *6*, 199–201.
[101] a) Igarashi, K.; Honma, T.; Imagawa, T. *J. Org. Chem.* **1970**, *35*, 610–616; b) Boullanger, P.; Descotes, G. *Carbohydr. Res.* **1976**, *51*, 55–63.
[102] Horton, D.; Priebe, W. Varela, O. *J. Org. Chem.* **1986**, *51*, 3479–3485.
[103] Boschi, A.; Chiappe, C.; De Robertis, A.; Ruasse, M. F. *J. Org. Chem.* **2000**, *65*, 8470–8477.

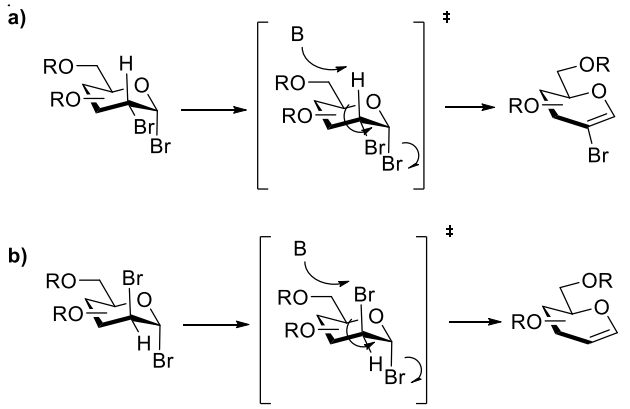
irreversible formation of an oxocarbenium ion by electrophilic addition of bromine followed by the nucleophilic attack of bromide giving the corresponding α-glycosyl bromides.



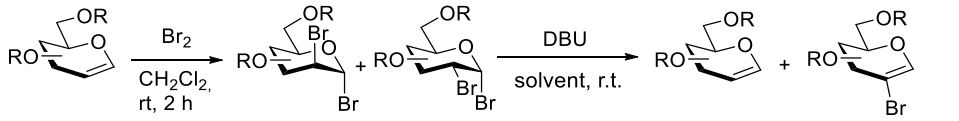
Scheme 3.27. Synthesis of 2-bromoglycals *via* bromination/elimination sequence.

Generally, elimination with strong non-nucleophilic bases such as DBU proceeds through an E2 elimination mechanism.[104] Thus, E2 elimination from 2-bromo-α–bromoglycosides must involve the groups in relative *trans-diaxial* disposition. Hence, elimination from 2-bromo-α-bromoglucoside would lead to the formation of 2-bromoglucal, Scheme 3.28a, whereas elimination from manno analog would afford glucal, Scheme 3.28b. This implies that stereoselectivity in the bromine addition step should determine the glucal/2-bromoglucal selectivity in the consecutive elimination. However, Results showed that the expected correlation of selectivities did not occur, suggesting that elimination do not proceed through a purely E2 mechanism and rather a E1 mechanism is plausible.

[104] a) Bruckner, R. In *Advanced Organic Chemistry: Reaction Mechanisms.* Academic Press, 2001, 143; b) Sun, X. In *Organic Mechanisms: Reactions, Methodology, and Biological Applications.* John Wiley Sons, 2013, 271–274 c)Cho, B. R.; Cho, N. S.; Chung, H. S.; Son, K. N.; Han, M. S.; Pyun, S. Y. *Bull. Korean Chem. Soc.* **1997**, *18*, 1301–1304.



Scheme 3.28. E2 products from a) *manno*-2-bromo-α-bromopyranoside, and b) *gluco*-2-bromo-α-bromopyranoside.



R = OAc,	1	:	2.7	[a]1 (**3.7**)	:	6 (**3.18a**)
				[b]1 (**3.7**)	:	12 (**3.18a**)
R = OBn,	1	:	1.80	[b]1 (**3.3**)	:	3.5 (**3.20a**)

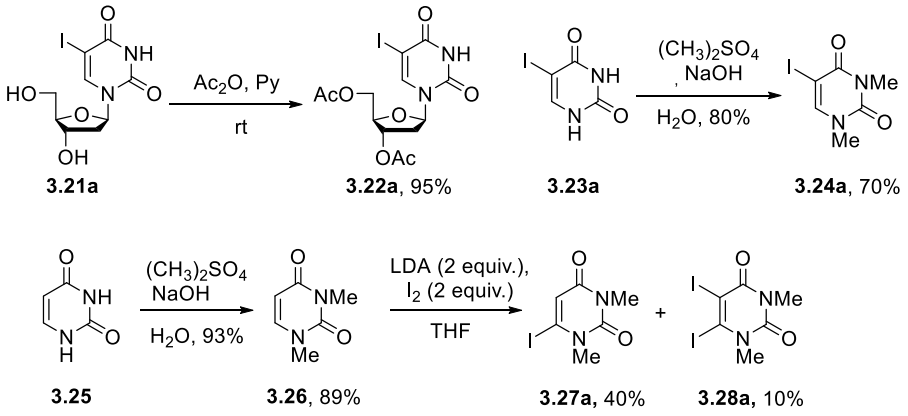
Scheme 3.29. Selectivities observed after bromination/elimination sequence; [a]Toluene/DMSO (1:1); [b]Toluene/DMSO (4:1).

3.3.2. Synthesis of iodonucleosides

Trifluoromethyl-containing nucleosides displaying biological activity have found application in medicine mainly as antiviral agents.[105] Various 5-iodonucleosides are commercially available and additionally, we considered preparing uracil derivatives with I at different positions. Protection of 5-iodo-2′-deoxyuridine **3.21a** using Ac_2O occurred smoothly under conventional conditions and **3.22a** was produced in 95%

[105] a) Guess, S.; Stone, D. U.; Chodosh, *J. Ocul. Surf.* **2007**, *5*, 240–250; b) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115–133.
[105] a) Greer, S. B. U. S. Patent 8252768, 2012; b) Mekras, J. A.; Boothman, D. A.; Greer, S. B. *Cancer Res.* **1985**, *11*, 5270–5270.

yield.[106] 5-Iodouracil **3.23a** and uracil **3.25** were converted in *N*-Me derivatives **3.24a** and **3.26** respectively,[107] and the latter was finally subjected to lithiation followed by Li/I exchange to obtain two different products consisting of 6-iodouracil **3.27a** and 5,6-diiodouracil **3.28a** (Scheme 3.30).[108]

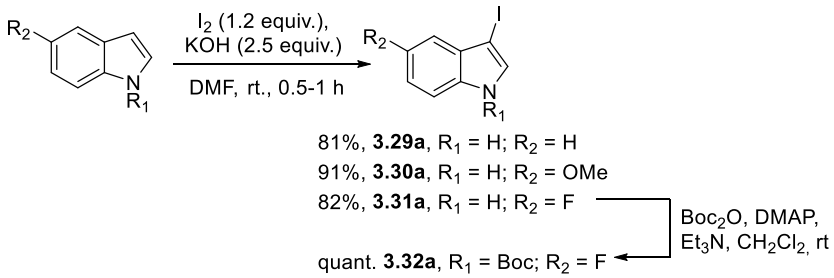


Scheme 3.30. Preparation of iodonucleoside and iodouracil precursors.

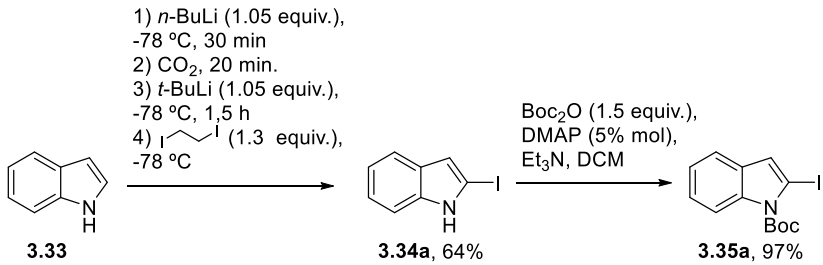
3.3.3. Synthesis of iodoindoles

As discussed in the introduction, trifluoromethylation of other structures having electron-rich double bonds, especially indoles, are of interest. A set of 3-iodoindoles **3.29**–**3.31a** and Boc-protected iodoindole **3.32a** were prepared following reported protocols (Scheme 3.31).[109] Moreover, preparation of **3.35a** was accomplished by the one pot *in situ* formation of an *N*-carboxylate, lithiation and consecutive Li/I exchange to afford **3.34a** followed by final nitrogen protection with Boc (Scheme 3.32).[110]

[106] Hudson, R. H. E.; Ghorbani–Choghamarani, A. *Org. Biomol. Chem.* **2007**, *5*, 1845–1848.
[107] Seley, K. L.; Salim, S.; Zhang, L.; O'Daniel, P. I. *J. Org. Chem.* **2005**, *70*, 1612–1619.
[108] Saito, I.; Ikehira, H.; Matsuura, T. *J. Org. Chem.* **1986**, *51*, 5148–5153.
[109] Tasch, B. O. A.; Antovic, D.; Merkul, E. and Müller, T. J. J. *Eur. J. Org. Chem.* **2013**, 4564–4569.
[110] Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495–2497.



Scheme 3.31. Preparation of various 3-iodoindoles.

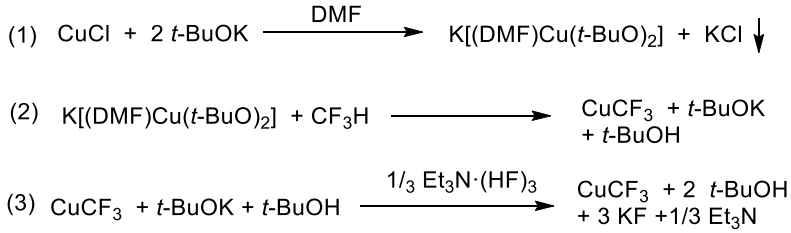


Scheme 3.32. Preparation of 2-iodoindole **3.27a**.

3.3.4. Trifluoromethylation of haloglycals

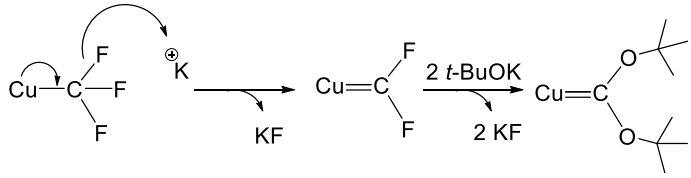
The new trifluoromethylation reagent developed by Grushin and coworkers consists of a "ligandless" trifluoromethyl copper(I) organometallic species generated from CF_3H, CuCl and *t*-BuOK in DMF and subsequent stabilization with $Et_3N{\cdot}(HF)_3$, also called TREAT–HF, Scheme 3.33). Treatment of CuCl with 2 equivalents of *t*-BuOK in DMF produces a K[(DMF)Cu(*t*-BuO)$_2$] complex (Scheme 3.33, eq. 1) that readily reacts with CF_3H at room temperature to produce $CuCF_3$ (Scheme 3.33, eq. 2). This fluoroform-derived $CuCF_3$ reagent is decomposed due to α-elimination of fluoride producing a Cu^I difluorocarbene specie that undergo extremely facile[111] nucleophilic displacement of the fluorines with the remaining amount of *t*-BuOK (Scheme 3.34).

[111] For reviews, see: a) Hughes, R. P. Eur. *J. Inorg. Chem.* **2009**, 4591–4606; b) Torrens, H. Coord. *Chem. Rev.* **2005**, *249*, 1957–1985; c) Brothers, P. J.; Roper, W. R. *Chem. Rev.* **1988**, *88*, 1293–1326.



Scheme 3.33. Synthesis of $CuCF_3$ from *t*-BuOK, CuCl and CF_3H in DMF and stabilization with TREAT–HF.[63b,64a]

The degradation is thermodynamically favored by the formation of an insoluble KF salt. From Scheme 3.34, it can be observed that 3 potassium cations decompose 1 molecule of $CuCF_3$. The addition of 1/3 equivalents of TREAT–HF relative to the amount of initial CuCl is enough to neutralize the remaining *t*-BuOK since 3 mols of HF are contained in each mol of TREAT–HF. Furthermore, addition of "extra" amount of TREAT–HF improves the reactivity of the $CuCF_3$ as well as its stability.



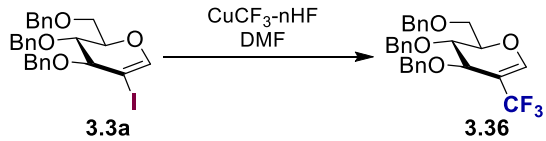
Scheme 3.34 Mechanism of the degradation of $CuCF_3$ reagent

We started our study by exploring the selective incorporation of the CF_3 moiety into carbohydrate scaffolds reacting fluoroform-derived "ligandless" $CuCF_3$ reagent ($CuCF_3$-nHF) with 2-iodoglycals as representative examples of building blocks derived from structurally complex natural sources. 3,4,6-Tri-*O*-benzyl-2-iodo-D-glucal **3.3a** was selected for the optimization studies (Table 3.3). Treatment of **3.3a** with stabilized $CuCF_3$ in DMF afforded expected coupling product **3.36** in 57% yield after 27 h at room temperature (entry 1). In an attempt to improve yield, the effect of "extra" TREAT–HF was evaluated (entries 2–4), being

the addition of 0.2 "extra" equiv optimal (81%) in terms of balance between reagent's reactivity and stability (entries 2–4). No significant differences were observed when moving from 1.2 to 2 equiv of $CuCF_3$-0.6HF (entries 5 to 7). Increasing the temperature up to 50 ºC accelerated substantially the reaction rate (entries 8–11). While the use of 1.2 equiv of $CuCF_3$-0.6HF afforded **3.36** in 92% yield after 5 h (entry 8) and the same reaction with 1.6 equiv resulted in nearly quantitative yield after 13 h (entry 9), optimal conditions with 2 equiv reduced the time to 7 h (entry 10). The yield and stability of the final vinyl-CF_3-product was not compromised upon extending the reaction time from 7 to 13 h once the reaction is completed (entry 11). Notably, the formation of undesired by-products such as those found in many metal-mediated reactions with glycals (*e.g.,* Ferrier)[112] and 2-iodoglycals (*e.g.,* hydrodehalogenation) [86b] is suppressed. These findings, together with the fact that microwave-assisted trifluoromethylation at 100 ºC (entry 12) reduced the time to *only 10 min* while maintaining practical yields (81%), reinforces the potential application of this strategy as a late-stage trifluoromethylation protocol suitable, for example, in the preparation of challenging ^{18}F–radiolabelled carbohydrates with [^{18}F]$CuCF_3$.[113] This is further supported by the *operational simplicity* of the purification step (only an aqueous extraction and/or filtration through a short path of SiO_2 was sufficient to afford **3.36** in *high-purity* (Figure 3.4, a) and the *scalability* of this reaction as demonstrated for **3.40** and **3.59** (Scheme 3.35 and 3.38), which also makes our protocol using fluoroform-derived "ligandless" $CuCF_3$ amenable for gram-scale applications.

[112] a) Vankar, Y. D.; Linker, T. *Eur. J. Org. Chem*. **2015**, 7633–7642; b) Gómez, A. M.; Lobo, F.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2013**, 7221–7262.
[113] a) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.* **2016**, *116*, 719–766; b) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. *Chem. Sci*. **2014**, *5*, 4545–4553; c) Campbell, M. G.; Ritter, T. *Chem. Rec.* **2014**, *14*, 482–491; d) Cole, E.; Stewart, M.; Littich, R.; Hoareau, R.; Scott, P. *Curr. Top. Med. Chem*. **2014**, *14*, 875–900; e) Van der Born, D.; Sewing, C.; Herscheid, J. K. D. M.; Windhorst, A. D.; Orru, R. V. A.; Vugts, D. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11046–11050; f) Rühl, T.; Rafique, W.; Lien, V. T.; Riss, P. J. *Chem. Commun*. **2014**, *50*, 6056–6059; g) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chem.* **2013**, *5*, 941–944.

Table 3.3. Optimization of trifluoromethylation of **3.3a**.



3.3a 3.36

Entry[a]	$CuCF_3$-nHF (equiv)	"Extra" $Et_3N{\cdot}3HF$ (equiv)[b]	T [ºC]	t [h]	Yield [%][c]
1	$CuCF_3$ (2)[d]	–	rt	27	57
2	$CuCF_3$–0.3HF (2)	0.1	rt	27	73
3	$CuCF_3$–0.6HF (2)	0.2	rt	21	81
4	$CuCF_3$–0.9HF (2)	0.3	rt	21	80
5	$CuCF_3$–0.6HF (1.2)	0.2	rt	39	82
6	$CuCF_3$–0.6HF (1.6)	0.2	rt	39	87
7	$CuCF_3$–0.6HF (2)	0.2	rt	39	90
8	$CuCF_3$–0.6HF (1.2)	0.2	50	5	92
9	$CuCF_3$–0.6HF (1.6)	0.2	50	13	>95
10	$CuCF_3$–0.6HF (2)	0.2	50	7	>95
11	$CuCF_3$–0.6HF (2)	0.2	50	13	>95
12[e]	$CuCF_3$–0.6HF (2)	0.2	100	10 min	81

[a]General conditions: Reactions were performed in a sealed NMR tube with $CuCF_3$-nHF (up to 2 equiv) in DMF and 2-iodoglucal **1a** (1 equiv) unless otherwise indicated. [b]mol $Et_3N{\cdot}3HF$/mol CuCl added to stabilized $CuCF_3$. [c]Determined by ^{19}F NMR of the crude reaction mixture using 1,3-bis(trifluoromethyl)benzene as internal standard. [d]Stabilized $CuCF_3$. [e]The reaction mixture was microwave irradiated in a sealed tube at 100 ºC for 10 min using a CEM–Discover™ single-mode synthesizer (temperature control, fixed hold time off, normal absorption mode, 300 W).

The identity of the resulting product was first confirmed by MS analysis, which showed a mass shift (from 542 to 484 Da) corresponding to the loss of I and the addition of a single CF_3 unit (Δmass –58 Da). As expected, ^1H, ^{13}C, and ^{19}F NMR analysis revealed the trifluoromethylation proceed at C–2. Besides the characteristic CF_3 peak at –62.6 ppm in the ^{19}F NMR (Figure 3.4, a) and the presence of two quaternary centres

corresponding to C–2 (q, $^2J_{C,F}$ = 30.7 Hz) and CF_3 (q, $^1J_{C,F}$ = 269.9 Hz) in the ^{13}C NMR (Figure 3.4, b), 2D–HMBC experiments also showed key H1–C–2/CF_3 cross-peaks that unequivocally confirms the structure of **3.36**. Finally, the impact of the CF_3 group in the conformation of **3.36** was evaluated analysing the characteristic coupling constants $^3J_{3,4}$ and $^3J_{4,5}$ ~ 3.2 Hz. These small values are indicative of a 2-substituted D-glucal adopting the "inverted" $^5H_4$ conformation,[114] probably due to the destabilizing 1,2-allylic ($A^{1,2}$) strain introduced by the bulky CF_3 group.

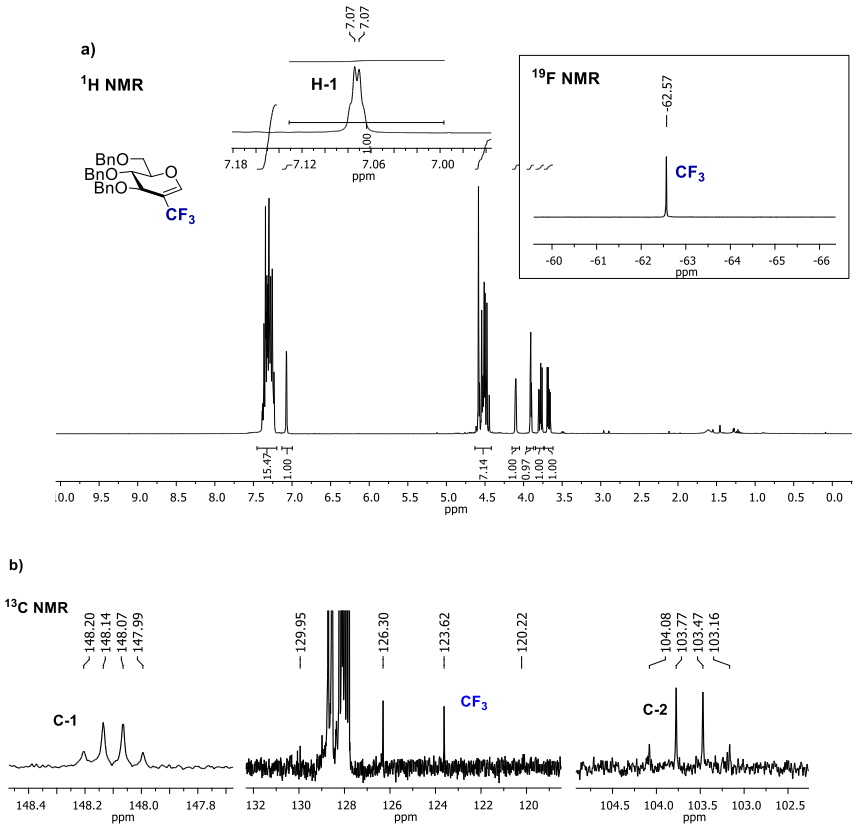


Figure 3.4. a) ^{1}H NMR and ^{19}F NMR spectra of the crude after trifluoromethylation of **3.3a**; b) ^{13}C NMR signals of C–1, CF_3 and C–2 of **3.36**.

[114] Chalmers, A. A.; Hall, R. H. *J. Chem. Soc. Perkin Trans. 2*, **1974**, 728–732.

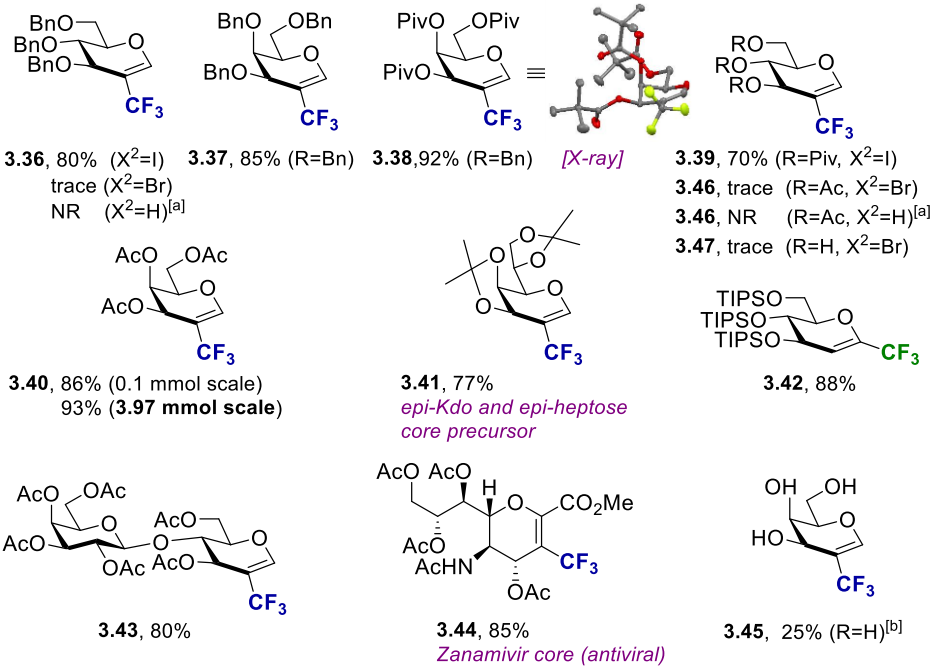
With the optimal conditions in hand, the scope of this transformation was evaluated with a series of haloglycals featuring representative protecting groups (Bn, Ac, Piv, and TIPS), multiple stereocenters/configurations (D-gluco, D-galacto, etc.), and high degree of complexity (disaccharides) (Scheme 3.35). Generally, CF_3-products were consistently obtained in high isolated yields and purity. Benzyl 2-iodoglycals **3.4a** (D-*Glc*) and **3.4a** (D-*Gal*) afforded **3.36** and **3.37** in good yields (up to 85%). Unlike protocols using nucleophilic R_3SiCF_3 reagents that react with the electrophilic C(sp^2) of carbonyl moieties,[115] the combination of mild reaction conditions and specific cross-coupling allowed $CuCF_3$ to react in the presence of acetyl and pivaloyl esters **3.38–40** and **3.43–44** (up to 93%), even in gram scale for **4.40** (93%).

Diagnostic coupling constants $^3J_{3,4}$ and $^3J_{4,5}$ in 2-CF_3-D-galactals **3.37–38** and **3.40** ranged from 4.3 to 3.0 Hz,[116] indicating certain ring-flattening induced by the 2-CF_3 (distorted between $^4H_5$ and $^5H_4$) as evidenced by X–ray analysis of **3.38**. Acid-sensitive isopropylidene moiety was also well tolerated in **3.41** (77%). Indeed, this represents a successful example of a complex carbohydrate CF_3-building block that contains the core structure of important heptosides found in bacterial glycolipids such as the epimers of 3-deoxy-D-*manno*-2-octulosonic acid (Kdo) and L-*glycero*-D-*manno*-heptopyranose (heptose).[117]

We next evaluated the reactivity (I *vs.* Br) and selectivity (C–1 *vs.* C–2) of this transformation. Since 2-bromoglucals **3.18–20a** (potential precursors of **3.36**, **3.46** and **3.47** in Scheme 3.35) were unreactive under the conditions used for iodides,[118] this pronounced difference in reactivity enables the selective modification of electron-rich vinyl iodides over bromides. Moreover, the selective introduction of I at C–1 enables access to 1-CF_3-glucal **3.42** in 88% yield. The method also tolerates

[115] Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2014**, *115*, 683–730.
[116] Chalmers, A. A.; Hall, R. H. *J. Chem. Soc. Perkin Trans. 2*, **1974**, 728–732; Lemieux, R. U.; Nagabhushan, T. L.; O'Neill, I. K. *Can. J. Chem.* **1968**, *46*, 413–418.
[117] Dohi, H.; Périon, R.; Durka, M.; Bosco, M.; Roué, Y.; Moreau, F.; Grizot, S. ; Ducruix, A. ; Escaich, S.; Vincent, S. P. *Chem. Eur. J.* **2008**, *14*, 9530–9539.
[118] Hafner, A.; Bräse, S. *Adv. Synth. Catal.* **2011**, *353*, 3044–3048.

fluoride-labile silyl ethers (TIPS) as protecting groups. Controls to further confirm the importance of I using D-glucals **3.3** and **3.3'** resulted in recovery of starting materials. Again, no Ferrier products were observed with neither iodoglycals nor glycals. Collectively, the synthetic flexibility of the overall transformation has been validated with 2-CF_3 **3.36**, **3.39** and 1-CF_3 **3.42** since this strategy allows the selective preparation of complementary 1/2-CF_3-regioisomers from a single/common-configuration precursor in a diversity-oriented manner.

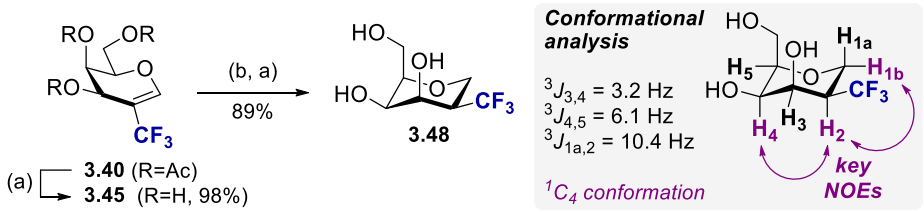


Scheme 3.35. Trifluoromethylation scope with haloglycals and control reactions. Isolated yields given. [a]Reactions conducted with 3,4,6-tri-*O*-benzyl and 3,4,6-tri-*O*-acetyl-D-glucal **3.3** and **3.3'**, respectively. [b]Degradation of **3.45** observed. X^1 and X^2 refer to I unless otherwise indicated. NR=no reaction, Piv=pivaloyl, TIPS=triisopropylsilyl. ORTEP drawing of **3.38** with thermal ellipsoids drawn at the 50% probability level (H atoms omitted for clarity).

Of benefit is also the smooth preparation of complex D-lactose **3.43** (80%) with an acid-sensitive glycosidic linkage and Neu5Ac2en **3.44** (85%), containing the core structure of the antiviral zanamivir (Relenza®). The fast kinetics for **3.44** under very mild conditions (without "extra" TREAT–HF, rt, 1 h), probably due to the strongly coordinating and/or electron-withdrawing ester at C–2,[64a,78] and the fast product isolation (filtration through a short path of SiO_2) suggests a good potential for large-scale operations. Finally, a key advantage of our method is the specificity of the cross-coupling between the $CuCF_3$/C(sp^2)–I pair that prevents, unlike methods using electrophilic/radical–CF_3 sources, the generation of reactive glycosyl oxocarbenium ions incompatible with many free nucleophiles (OH, NH_2), which are indeed frequent in many late-stage protocols.[119] Thus, trifluoromethylation of unprotected 2-iodogalactal **3.12a** afforded **3.45** albeit in 25% yield. However, the inertness of 2-bromo **3.19a** (precursor of **3.47**, Scheme 3.35) and the successful results with unprotected nucleosides **3.49** and **3.51** (Scheme 3.37) suggest the reduced yield is due to the instability of the starting unprotected vinyl iodide moiety under the conditions tested.

A second round of scaffold elaboration further demonstrated the synthetic value of the vinyl-CF_3 motif (Scheme 3.36). While conventional Zemplén deacetylation afforded **3.45** in excellent yield (98%), consecutive hydrogenation (10% Pd/C, 10 atm H_2) and deacetylation yielded 1,5-anhydro-2-CF_3-2-deoxy alditol **3.48** (89%) as sole diastereoisomer ($^1C_4$ conformation) as indicated by the analysis of diagnostic coupling constants and key NOE signals.

[119] a) Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 3216–3221; b) Campbell, M. G.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474–480.
a) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.* **2016**, *116*, 719–766; b) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. *Chem. Sci.* **2014**, *5*, 4545–4553; c) Campbell, M. G.; Ritter, T. *Chem. Rec.* **2014**, *14*, 482–491; d) Cole, E.; Stewart, M.; Littich, R.; Hoareau, R.; Scott, P. *Curr. Top. Med. Chem.* **2014**, *14*, 875–900; e) Van der Born, D.; Sewing, C.; Herscheid, J. K. D. M.; Windhorst, A. D.; Orru, R. V. A.; Vugts, D. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11046–11050; f) Rühl, T.; Rafique, W.; Lien, V. T.; Riss, P. J. *Chem. Commun.* **2014**, *50*, 6056–6059; g) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chem.* **2013**, *5*, 941–944.



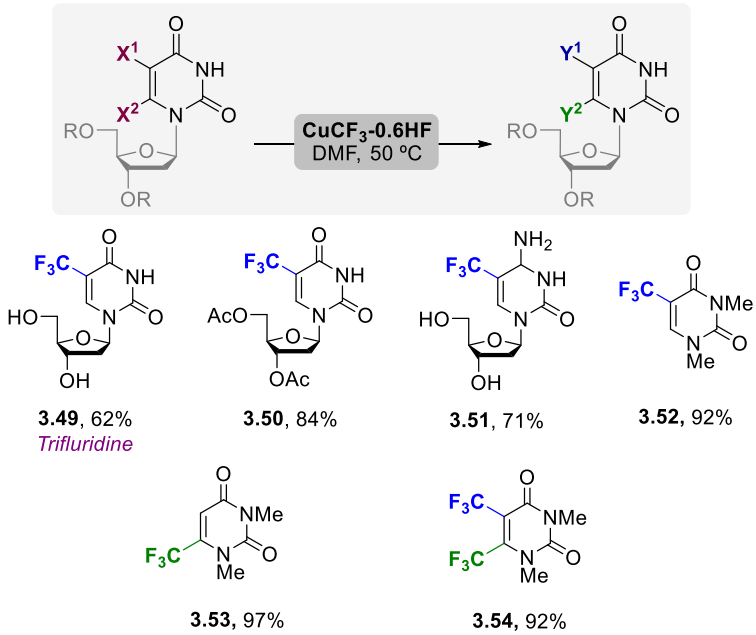
Scheme 3.36. Elaboration of 2e. *Conditions:* (a) NaOMe, MeOH, rt, 12 h, 98%; (b) H_2 (10 atm), 10% Pd/C, MeOH, rt, 72 h.

3.3.5. Trifluoromethylation of iododinated nucleosides and nitrogenous bases

Having established conditions for the efficient site-selective trifluoromethylation of iodoglycals, we next extended the scope of this approach to iodinated nucleosides and nitrogenous bases. Trifluoromethyl-containing nucleosides are attractive motifs in medicinal chemistry owing to their applications as antivirals, including the well-known commercialized 2′deoxy-5-trifluoromethyluridine **3.49** (Viroptic®) used in the treatment of herpes simplex virus-1 and -2 (HSV–1 and HSV–2),[120] and 5-CF_3-2′-deoxycytidine **3.51** which displays activity against pancreatic tumor cells.[121] Thus, late-stage trifluoromethylation of commercially available 5-iodonucleosides using CHF_3-derived $CuCF_3$ reagent would represent an interesting alternative for the preparation of such products. Viroptic®, **3.49** was prepared in a fair 53% isolated yield and the acetylated analog **3.50** was also obtained in a very good 84% yield using our methodology. Yield of **3.49** was slightly improved to 62% by portionwise additions of the $CuCF_3$ reagent. Reaction with 5-iodo-2′-deoxycytidine smoothly afforded **3.51** in a good 71% yield in contrast to the 3.3% isolated yield achieved using a $CF_3I/FeSO_4$ system in presence of H_2O_2 and H_2SO_4.[122] Our results are however comparable to the radical

[120] a) Guess, S.; Stone, D. U.; Chodosh, *J. Ocul. Surf.* **2007**, *5*, 240–250; b) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115–133.
[121] a) Greer, S. B. U. S. Patent 8252768, 2012; b) Mekras, J. A.; Boothman, D. A.; Greer, S. B. *Cancer Res.* **1985**, *11*, 5270–5270.
[122] Yamakawa, T.; Yamamoto, K.; Uraguchi, D.; Tokuhisa, K. PCT Int. Appl. WO/2007/055170, 2007.

trifluoromethylation strategy using CF_3SO_2Na (Langlois reagent).[123] Finally, a successful example of regiocontrol using our method showed the preparation in excellent yields (up to 97%) of the two regioisomers of trifluoro-1,3-dimethyluracil **3.52–53** and a rare example of bis-trifluoromethylation **3.54** obtained from diiodinated precursor **3.28a**.



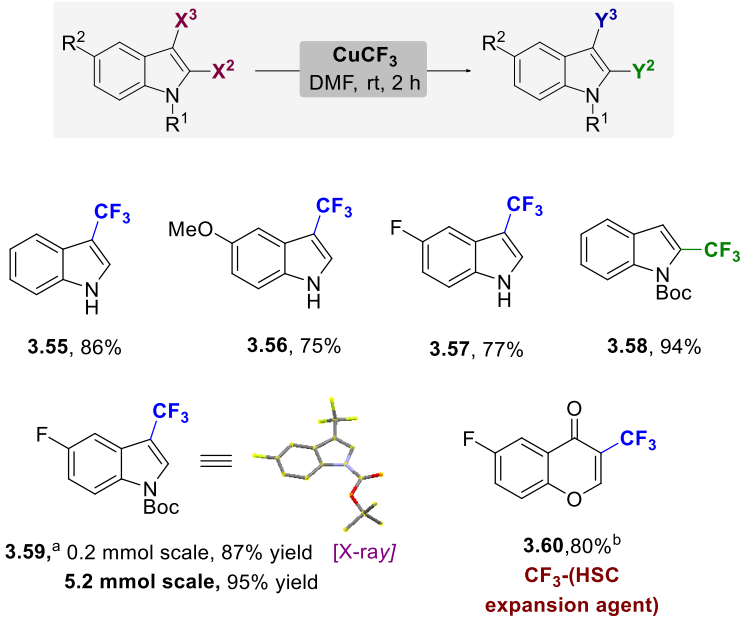
Scheme 3.37. Trifluoromethylation of iodinated nucleosides and nitrogenous bases. Isolated yields given. X^2 and X^3 refer to I.

3.3.6. Trifluoromethylation of benzo-fused heterocycles

The utility of the trifluoromethylation protocol was also extended to iodinated benzo-fused heterocycles (Scheme 3.38). Same reaction conditions used with iodoglycals (0.2 equiv. of "extra" TREAT–HF and 50 °C) were applied to 3-iodoindole **3.29a** and the desired product **3.55** was obtained along with a substantial amount of the hydrodehalogenated product. We were pleased to discover that hydrodehalogenation was nearly suppressed by conducting reactions at room temperature and

[123] Musumeci, D.; Irace, C.; Santamaria, R.; Montesarchio, D. *Med. Chem. Commun.* **2013**, *4*, 1405–1410.

without the addition of "extra" TREAT–HF (stabilized $CuCF_3$). Thus, **3.55**, **3.56** and **3.57** were in good yields (up to 86%) after 2 h at room temperature regardless the electronic properties of their substituents (*e.g.,* F *vs.* OMe). Similarly, 2-CF_3 indole **3.58** was obtained in excellent yield (94%) by regioselective iodination at C–2 and subsequent trifluoromethylation. Unlike previous reactions with unprotected "*N*-free" indoles **3.55–57** that proceed smoothly at room temperature, trifluoromethylation of *N*-Boc **3.32a** required heating up to 50 ºC to afford **3.59** in 87% yield (up to 95% in gram scale, suitable for X–ray). 6-Fluoro-4H-chromen-4-one is an hematopoietic stem cell (HSC) expansion agent,[124] and the corresponding trifluoromethylated derivative **3.60** was smoothly prepared from the commercially available iodoprecursor.



Scheme 3.38. Trifluoromethylation of iodinated benzo-fused heterocycles. Isolated yields given. [a]Conducted from rt to at 50 ºC, 24 h. [b] $CuCF_3$–0.6HF, rt, 15 h. X^2 and X^3 refer to I, Boc=tert-butoxycarbonyl. ORTEP drawing of **3.59** with thermal ellipsoids drawn at the 50% probability level (H atoms are omitted for clarity).

[124] Bouchez, L. C.; Boitano, A. E.; Cooke, M. P.; Schultz, P. G. PCT Int. Appl. WO 2012102937, 2012.

Trifluoromethylation of unprotected "*N*-free" 3-iodoindoles proceeds under milder conditions as compared to those with 2-iodoglycals since no additives neither heating is required. Striking differences were also observed with such substrates including an abnormal color-change to a greenish-blue immediately after mixing. Nonetheless, the most noteworthy remark was probably noticed by the *in situ* ^{19}F NMR monitoring of the reaction course (Figure 3.5). Two signals appeared at –56.5 ppm, assigned to 3-(trifluoromethyl)indole **3.55** and –54.3 ppm, tentatively assigned to a transient intermediate exhibiting N-Cu coordination that after quenching with water, converged to the same peak at –56.5 ppm. Meaningfully, only one signal was observed in the reaction with *N*-Boc indole **3.32a**, which indeed reacted noticeably slower. The improved reaction rate resembles the enhancement observed during the trifluoromethylation of iodoarenes due to the *ortho*-effect[64a,78] although in this case *via* a completely different mechanism. Collectively, the apparent N-Cu coordination probably enhances the trifluoromethylation rate by lowering the electronic density of the indole and increasing that of the metallic center, thus, facilitating the oxidative addition.

We were still interested in the mechanism of the dehydrohalogenation of indole scaffolds, thus, some control experiments and reaction variables were explored. hydrodehalogenation processes can be promoted/favored by the addition of *N*-containing bases and/or phosphines,[86] which are able to stabilize iodonium species, by the presence of potential SET catalysts such as CuX salts[125] (produced during the course of the trifluoromethylation with $CuCF_3$), or initiated/promoted by light-driven processes. Moreover, the presence of proton abstraction sources (including polar protic solvents) favors the hydrodehalogenation reaction and, although DMF has proven to be a good proton source,[64d] the effect of HF has to be considered. Table 3.4 shows the hydrodehalogenation/trifluoromethylation (H/CF_3) ratio is directly

[125] a) Zhang, L.; Zheng, M.; Zhao, F.; Zhai, Y.; Liu, H. *ACS Comb. Sci.* **2014**, *16*, 184–191; b) Biswas, S.; Batra, S. *Eur. J. Org. Chem.* **2012**, 3492–3499.

proportional to the increasing amount of $Et_3N{\cdot}3HF$ (TREAT–HF) whereas the temperature has a negligible effect (entries 1–6). The formation of hydrodehalogenation product is not appreciably favored by exposure to light (entry 1 *vs.* 7) and is not produced when 3-iodoindole **3.29a** is stirred alone in the presence of CuI or Et_3N (entries 8 and 11). Moreover, while no conversion is observed when **3.29a** is stirred alone in the presence of the radical scavenger TEMPO, hydrodehalogenation process is completely inhibited when it is present under trifluoromethylation conditions (entries 9 and 10). Importantly, TEMPO–CF_3 is NOT detected under these conditions.

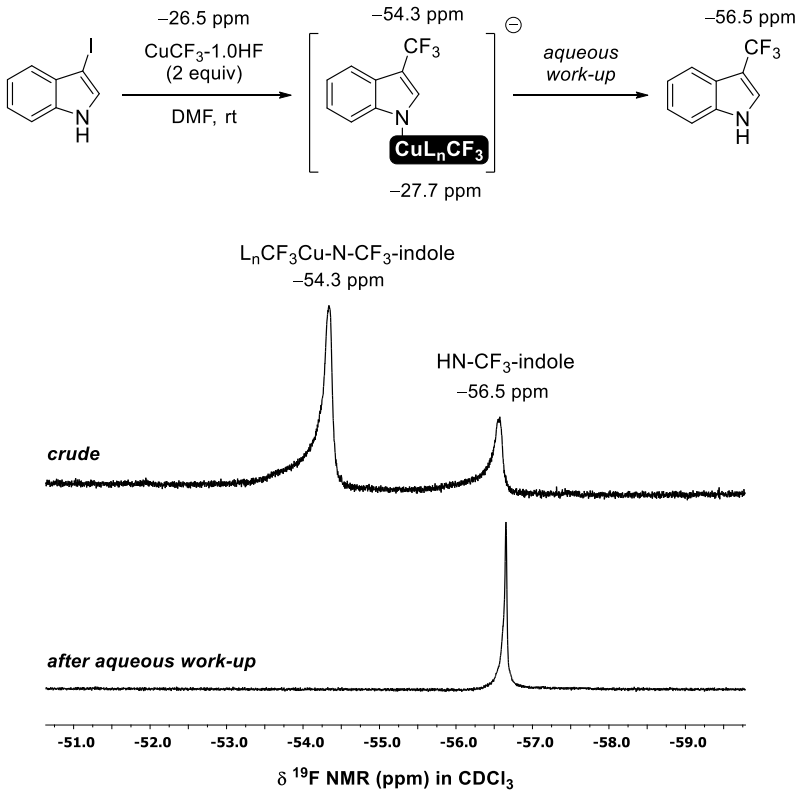
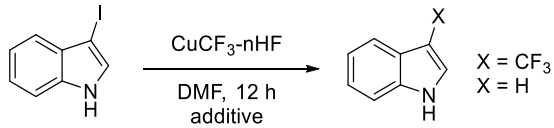


Figure 3.5. Selected region of the ^{19}F NMR showing Cu(I) coordination of unprotected 3-iodoindoles.

Table 3.4. Control experiments in the trifluoromethylation of **3.29a**.

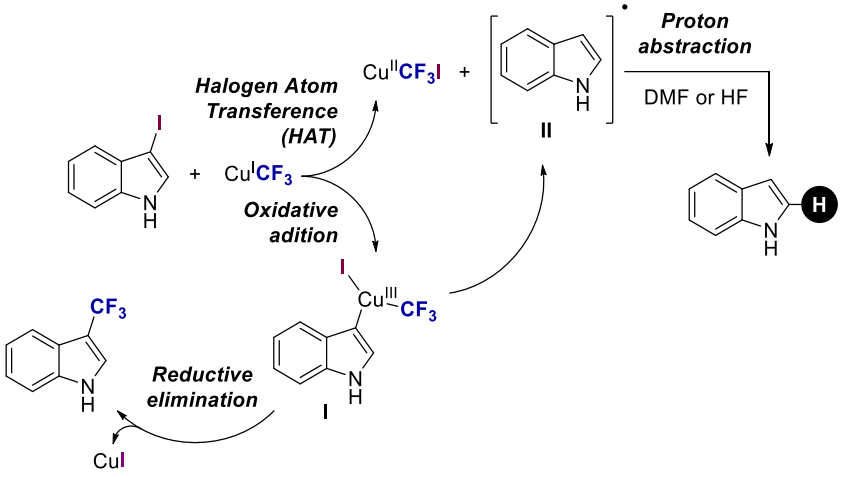


Entry[a]	$CuCF_3$–nHF	$Et_3N{\cdot}3HF$ ("extra" equiv)[b]	Additive (equiv)	*T* [ºC]	Conv. [%][c]	H/CF_3 ratio[d]
1[e]	$CuCF_3$	–	–	rt	>99	0.05
2[e]	$CuCF_3$	–	–	35	>99	0.04
3	$CuCF_3$–0.3HF	0.3	–	rt	>99	0.12
4	$CuCF_3$–0.3HF	0.3	–	35	>99	0.11
5	$CuCF_3$–0.6HF	0.6	–	rt	>99	0.19
6	$CuCF_3$–0.6HF	0.6	–	35	>99	0.17
7[e,f]	$CuCF_3$	–	–	rt	>99	0.06
8	–	–	CuI (1)	rt	<1	–
9[e]	$CuCF_3$	–	TEMPO (1)	rt	>99	0
10	–	–	TEMPO (1)	rt	<1	–
11[g]	–	–	Et_3N (1.2)	rt	<1	–

[a]General conditions: Reactions were performed in a sealed vial with $CuCF_3$–nHF (1 equiv) in DMF and 3-iodoindole **3.29a** (1 equiv) unless otherwise indicated; [b]mol $Et_3N{\cdot}3HF$/mol CuCl; [c]Determined by ^1H NMR of the crude reaction mixture; [d] Determined by integration of H–5 protons; [e]Stabilized $CuCF_3$; [f]Reaction conducted in the darkness; [g]Reaction analyzed after 6 h.

The inhibition of hydrodehalogenation by TEMPO in conjunction with the fact that CuI, light, and Et_3N are not promoting such a detrimental side-reaction critically points out the presence of a radical process during the production of indole, presumably from a reactive intermediate produced after oxidative addition of **3.29a** with $CuCF_3$. Moreover, increasing amounts of "extra" HF could favor the process serving as a proton abstraction source additionally to the inherent presence of DMF. A plausible mechanism is proposed as follows (Scheme 3.39). First, an oxidative addition of $Cu^{I}CF_3$ with 3-iodoindole **3.29a** generates an elusive intermediate Cu^{III} complex **I** that undergoes

reductive elimination to afford 3-(trifluoromethyl)indole **3.55** along with co-production of CuI. On the other hand, complex **I** may react through a HAT mechanism producing a radical indole intermediate **II**, which readily abstracts a proton from either DMF or HF to afford hydrodehalogenated indole by-product. However, alternative mechanistic pathways such as a direct single electron transfer (SET) cannot be ruled out.[126]



Scheme 3.39. Proposed mechanism for hydrodehalogenation of iodoindoles.

3.4. Conclusions

The objectives of the chapter have been met. In conclusion, we have presented a flexible strategy to introduce CF_3 either in the nucleophilic or electrophilic position of electron-rich double bonds. The regioselectivity is governed by regiocontrolled pre-introduction of iodine and subsequent cross-coupling with $CuCF_3$ derived from fluoroform.

The method has proven general and enabled access to valuable trifluoromethylglycals, trifluoromethylindoles and biologically active trifluoromethyl-containing nucleosides. Trifluoromethylation yields are generally high (up to 95%), displaying broad functional group tolerance

[126] Yu, D.–H.; Shao, J.–N.; He, R.–X.; Li, M. *Chinese Chem. Lett.* **2015**, *26*, 564–566.

and generally no by-products are obtained. Trifluoromethylation of bromoglycals was unsuccessful, further demonstrating the high chemoselective for C(sp^2)–I bonds. Typical reaction conditions for iodinated glycals, nucleosides and nitrogenous bases required moderate heating (50ºC) and slight excess of $Et_3N{\cdot}(HF)_3$ whereas *N*–H indoles reacted at ambient temperature under neutral conditions. With the latter scaffolds, substantial amounts of hydrodehalogenatod products were formed under the aforementioned typical conditions. The improved reactivity of *N*–H indoles is attributed to the occurrence of *N*–Cu coordination and the mechanism governing the hydrodehalogenation has been investigated which results suggest a radical mechanism.

3.5. Experimental section

3.5.1. General considerations

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Varian Mercury spectrometer or a Bruker Avance Ultrashield (400 MHz for ^{1}H) and (100.6 MHz for ^{13}C). Fluorine (^{19}F NMR) nuclear magnetic resonance spectra were recorded on a Varian Mercury spectrometer (376.5 MHz for ^{19}F). Spectra were fully assigned using COSY, HSQC, HMBC, and NOESY. All chemical shifts are quoted on the δ scale in ppm using the residual solvent as internal standard (^{1}H NMR: $CDCl_3$ = 7.26, CD_3OD = 3.31 and ^{13}C NMR: $CDCl_3$ = 77.16, CD_3OD = 49.0). Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, and app = apparent. Melting points (m.p.) were recorded on a Reichert apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco FT/IR–600 Plus ATR Specac Golden Gate spectrophotometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1.0 dm and are reported with implied units of 10^{-1} deg cm^2 g^{-1}. Concentrations (*c*) are given in g/100 mL. High–resolution mass spectra (HRMS) were recorded on an Agilent 1100 Series LC/MSD mass spectrometer with electrospray ionization (ESI).

Nominal and exact *m/z* values are reported in Daltons. Thin layer chromatography (TLC) was carried out using commercial aluminium backed sheets coated with $60F_{254}$ silica gel. Visualization of the silica plates was achieved using a UV lamp (λ_{max} = 254 nm), 6% H_2SO_4 in EtOH, and/or cerium molybdate stain. Flash column chromatography was carried out using silica gel 60 A CC (230–400 mesh). Mobile phases are reported in relative composition (*e.g.* 1:1 EtOAc/hexane v/v). HPLC grade dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were dried using standard methods, acetonitrile was dried using activated 3Å molecular sieves, and anhydrous DMF was stored over freshly calcined 4Å molecular sieves in a glove box. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. All reagents were used as received from commercial suppliers. All reactions using anhydrous conditions were performed using flame-dried apparatus under an atmosphere of argon. Brine refers to a saturated solution of sodium chloride. Anhydrous sodium sulfate (Na_2SO_4) was used as drying agent after reaction work-up, as indicated.

3.5.2. Synthesis of 2-iodoglycals

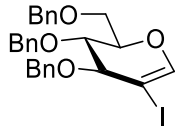
General procedure for the synthesis of 2-iodoglycals

Method A:[86a] *N*-iodosuccinimide, (NIS) (1.50 mmol) was added to a solution of the corresponding glycal (1 mmol) in 10:1 (v/v) CH_3CN/H_2O (20 mL) at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 3 h. The crude was then diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was azeotropically dried with toluene and used in the next step without further purification. The crude was dissolved in dry CH_2Cl_2 (12 mL) and treated with a mixture of Ph_2SO (3.00 mmol), 2,4,6-tri-*tert*-butylpyrimidine (TTBP) (3.00 mmol), and 4 Å molecular sieves (0.8 g) in dry CH_2Cl_2 (12 mL) at –78 ºC for 30 min. Tf_2O (1.5 mmol) was then added

and the reaction gradually warmed up to room temperature and stirred for 5 h. The reaction mixture was quenched with Et_3N and the solvent evaporated. The residue was purified by column chromatography.

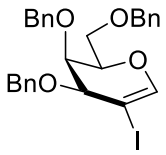
Method B:[92] NIS (1.20 mmol) and $AgNO_3$ (0.20 mmol) were added under argon atmosphere to a solution of glycal (1 mmol) in dry CH_3CN (2 mL) at room temperature. The reaction mixture was warmed up to 80 ºC and stirred for 4 h. The crude was filtered through a short path of Celite® 545 and the solvent evaporated. The residue was purified by column chromatography.

3,4,6-Tri-*O*-benzyl-2-iodo-D-glucal (3.3a)



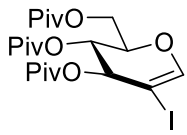
The title compound was prepared following general method A, starting from **3.3** (2 g, 4.80 mmol) and NIS (1.62 g, 7.2 mmol) in 10:1 (v/v) CH_3CN/H_2O (55 mL). After standard workup the crude was dissolved with dry CH_2Cl_2 (50 mL) cooled to –78ºC and transferred to a flask containing 4 Å molecular sieves, Ph_2SO (2.68 g, 13.27 mmol) and TTBP (3.29 g, 13.27 mmol) in CH_2Cl_2 (50 mL) at –78 ºC. Tf_2O (1.10 mL, 7.2 mmol) was then added and after standard workup the crude was purified by column chromatography EtOAc/Hexane (1:9) giving **3.3a** (1.08 g, 45% over two steps) as a yellowish solid. R_f EtOAc/Hexane (1:9): 0.4; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.43–7.19 (m, 15H, ArH), 6.74 (bs, 1H, H–1), 4.74–4.48 (m, 6H, $3CH_2Ph$), 4.30 (m, 1H, H–5), 4.09 (d, $J_{3,4}$ = 4.8 Hz, 1H, H–3), 4.00 (dd, $J_{4,5}$ = 7.0 Hz, $J_{3,4}$ = 4.8 Hz, 1H, H–4), 3.79 (dd, $J_{6a,b}$ = 10.8 Hz, $J_{5,6a}$ = 5.5 Hz, 1H, H–6a), 3.71 (dd, $J_{6a,b}$ = 10.8 Hz, $J_{5,6b}$ = 3.8 Hz, 1H, H–6b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.4 (C–1), 137.8, 137.6, 137.6 (C, Ar), 128.5, 128.4, 128.4, 128.1, 127.9, 127.9, 127.7, 127.7 (CH, Ar), 78.9 (C–3), 76.5 (C–5), 73.4 (C–4), 73.4, 73.1, 72.2 ($3CH_2Ph$), 70.4 (C–2), 67.8 (C–6). Spectroscopic data are in agreement with that reported.[86a,]

3,4,6-Tri-*O*-benzyl-2-iodo-D-galactal (3.4a)



The title compound was prepared following general method A, starting from **3.4** (200 mg, 0.48 mmol) and NIS (172 mg, 0.76 mmol) in 10:1 (v/v) CH_3CN/H_2O (10 mL). After standard workup the crude was dissolved with dry CH_2Cl_2 (5 mL) cooled to –78ºC and transferred to a flask containing 4 Å molecular sieves, Ph_2SO (290 mg, 1.44 mmol) and TTBP (567 mg, 1.44 mmol) in CH_2Cl_2 (5 mL) at –78 ºC. Tf_2O (0.12 mL, 0.72 mmol) was then added and after standard workup the crude was purified by column chromatography EtOAc/Hexane (1:9) giving **3.4a** (1.08 g, 45% over two steps) as a yellowish solid. R_f EtOAc/Hexane (1:9): 0.4; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.44–7.29 (m, 15H, ArH), 6.63 (bs, 1H, H–1), 4.83–4.38 (m, 6H, $3CH_2Ph$), 4.36 (m, 1H, H–5), 4.11 (m, 1H, H–3), 4.05 (m, 1H, H–4), 3.81 (dd, $J_{6a,b}$ = 10.6 Hz, $J_{5,6a}$ = 7.6 Hz, 1H, H–6a), 3.70 (dd, $J_{6a,b}$ = 10.6 Hz, $J_{5,6b}$ = 4.2 Hz, 1H, H–6b); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 147.6 (C–1), 138.1, 138.0, 137.9, (C, Ar), 128.5, 128.5, 128.4, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8 (CH, Ar), 75.9 (C–3), 75.9 (C–5), 74.0, 73.5 ($2CH_2Ph$), 73.3 (C–4), 73.0 (CH_2Ph), 73.0 (C–2), 67.9 (C–6). Spectroscopic data are in agreement with those reported.[86a]

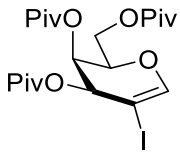
2-Iodo-3,4,6-tri-*O*-pivaloyl-D-glucal (3.5a)



The title compound was prepared following general method A, starting from **3.5** (110 mg, 0.28 mmol) and NIS (110 mg, 0.44 mmol) in 10:1 (v/v) CH_3CN/H_2O (5.5 mL). After standard workup the crude was dissolved with dry CH_2Cl_2 (7 mL) cooled to –78ºC and transferred to a

flask containing 4 Å molecular sieves, Ph_2SO (190 mg, 0.92 mmol) and TTBP (230 mg, 0.92 mmol) in CH_2Cl_2 (5 mL) at –78 ºC. Tf_2O (78 µL, 0.46 mmol) was then added and after standard workup the crude was purified by column chromatography EtOAc/Hexane (1:60) giving **3.5a** (15 mg, 10% over two steps) as a pale yellow solid. R_f (1:9 EtOAc/hexane): 0.68; m.p: 104–105 ºC; $[\alpha]_D^{20}$: +53.5 (2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.78 (d, $J_{1,3}$ = 1.1 Hz, 1H, H–1), 5.57–5.55 (m, 1H, H–3), 5.27 (dd, $J_{4,5}$ = 7.9 Hz, $J_{3,4}$ = 5.8 Hz, 1H, H–4), 4.38 (ddd, $J_{4,5}$ = 7.9 Hz, $J_{5,6a}$ = 5.5 Hz, $J_{5,6b}$ = 2.8 Hz, 1H, H–5), 4.30 (dd, $J_{6a,b}$ = 12.3 Hz, $J_{5,6a}$ = 5.5 Hz, 1H, H–6a), 4.19 (dd, $J_{6a,b}$ = 12.3 Hz, $J_{5,6b}$ = 2.8 Hz, 1H, H–6b), 1.23, 1.20, 1.17 (s, 27H, 9CH_3, Piv); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 178.1, 177.3, 176.4 (3C=O, Piv), 149.6 (C–1), 74.6 (C–5), 70.6 (C–3), 67.2 (C–4), 67.0 (C–2), 61.1 (C–6), 39.2, 39.0, 38.9 (3C, *t*-Bu), 27.4, 27.2, 27.1 (9CH_3, *t*-Bu); FT–IR (neat) ν in cm^{-1}: 2960, 2923, 2852, 1742, 1480, 1280, 1135; HRMS (TOF ES+) for ($M+Na^+$) $C_{21}H_{33}INaO_7^+$ (*m/z*): calc. 547.1163; found 547.1156.

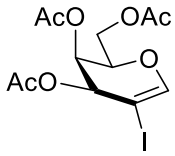
2-Iodo-3,4,6-tri-*O*-pivaloyl-D-galactal (3.6a)



The title compound was prepared following general method A, starting from **3.6** (500 mg, 1.25 mmol) and NIS (423 mg, 1.88 mmol) in 10:1 (v/v) CH_3CN/H_2O (22 mL). After standard workup the crude was dissolved with dry CH_2Cl_2 (12 mL) cooled to –78ºC and transferred to a flask containing 4 Å molecular sieves, Ph_2SO (758 mg, 3.75 mmol) and TTBP (932 mg, 3.75 mmol) in CH_2Cl_2 (12 mL) at –78 ºC. Tf_2O (0.25 mL, 1.5 mmol) was then added and after standard workup the crude was purified by column chromatography EtOAc/Hexane (1:20) giving **3.6a** (344 mg, 52% over two steps) as a pale yellow solid. R_f (1:9 EtOAc/hexane): 0.51; m.p: 53–55 ºC; $[\alpha]_D^{20}$: +17.7 (9.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.72 (d, $J_{1,3}$ = 1.5 Hz, 1H, H–1), 5.57 (dd, $J_{3,4}$ = 4.4 Hz, $J_{1,3}$ = 1.5 Hz,

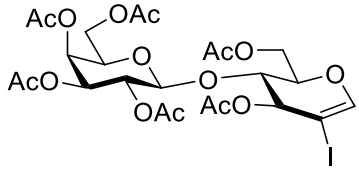
1H, H–3), 5.46 (dd, $J_{3,4}$ = 4.4 Hz, $J_{4,5}$ = 2.5 Hz, 1H, H–4), 4.46–4.43 (m, 1H, H–5), 4.26 (dd, $J_{6a,b}$ = 12.0 Hz, $J_{5,6a}$ = 8.2 Hz, 1H, H–6a), 4.06 (dd, $J_{6a,b}$ = 12.0 Hz, $J_{5,6b}$ = 5.0 Hz, 1H, H–6b), 1.20, 1.17, 1.15 (s, 27H, $9CH_3$, Piv); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 178.0, 177.0, 176.7 (3C=O, Piv), 148.7 (C–1), 73.3 (C–5), 67.0 (C–3), 64.4 (C–4), 61.2 (C–6), 60.4 (C–2), 39.1, 39.0, 38.8 (3C, *t*-Bu), 27.3, 27.14, 27.12 ($9CH_3$, *t*-Bu); FT–IR (neat) ν in cm^{-1}: 2972, 2934, 2871, 1739, 1624, 1480, 1280, 1138, 1036; HRMS (TOF ES+) for ($M+Na^+$) $C_{21}H_{33}INaO_7^+$ (*m/z*): calc. 547.1163; found 547.1149.

3,4,6-Tri-*O*-acetyl-2-iodo-D-galactal (3.10a)



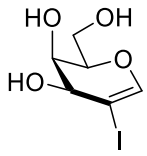
The title compound was prepared following general method B, starting from 3,4,6-tri-*O*-acetyl-D-galactal **3.10** (2.242 g, 8.23 mmol), NIS (2.223 g, 9.88 mmol) and $AgNO_3$ (559 mg, 3.29 mmol) in dry CH_3CN (5 mL). The mixture was heated at 80 ºC under argon atmosphere for 3 h and after standard workup the crude was purified by column chromatography EtOAc/Hexane (2:8) to give **3.10a** (2.46 g, 75%) as a white solid. R_f EtOAc/Hexane (2:8): 0.2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.76 (bd, $J_{1,3}$ = 1.5 Hz, 1H, H–1), 5.57 (m, 1H, H–3), 5.47 (dd, $J_{3,4}$ = 4.6 Hz, $J_{4,5}$ = 2.0 Hz, 1H, H–4), 4.41 (m, 1H, H–5), 4.24 (dd, $J_{6a,6b}$ = 11.8 Hz, $J_{5,6a}$ = 7.6 Hz, 1H, H–6a), 4.17 (dd, $J_{6b,6a}$ = 11.6 Hz, $J_{5,6b}$ = 5.4 Hz, 1H, H–6b), 2.10 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.06 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.0 MHz): δ 170.5, 169.9 (2C=O, Ac), 149.3 (C–1), 73.2 (C–5), 67.3 (C–2), 67.0 (C–3), 64.5 (C–4), 61.6 (C–6), 20.8, 20.7, 20.7 ($3CH_3$, Ac). Spectroscopic data are in agreement with those reported.[92]

1,5-Anhydro-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-iodo-D-*arabino*-hex-1-enitol (3.11a)



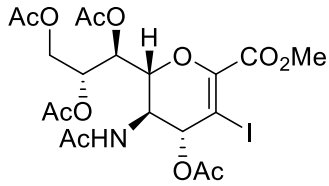
The title compound was prepared following general method B, starting from 3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-D-glucal **3.11** (470 mg, 0.83 mmol), NIS (224 mg, 0.99 mmol) and $AgNO_3$ (42 mg, 0.25 mmol) in dry CH_3CN (2 mL). The mixture was heated at 80 ºC under argon atmosphere for 4 h and after standard workup the crude was purified by column chromatography EtOAc/Hexane (1:1) to give **3.11a** (385 mg, 68%) as a white solid. R_f (1:1 EtOAc/hexane): 0.25; m.p: 43–45 ºC; $[\alpha]_D^{20}$: +5.5 (0.14, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.76 (bs, 1H, H–1), 5.59 (d, $J_{3,4}$ = 4.4 Hz, 1H, H–3), 5.38 (d, $J_{3',4'}$ = 3.3 Hz, 1H, H–4'), 5.19 (dd, $J_{2',3'}$ = 10.7 Hz, $J_{1',2'}$ = 7.8 Hz, 1H, H–2'), 5.00 (dd, $J_{2',3'}$ = 10.7 Hz, $J_{3',4'}$ = 3.3 Hz, 1H, H–3'), 4.62 (d, $J_{1',2'}$ = 7.8 Hz, 1H, H–1'), 4.37–4.31 (m, 2H, H–5,6a'), 4.24 (dd, $J_{6a,b}$ = 12.8 Hz, $J_{5,6a}$ = 7.9 Hz, 1H, H–6a), 4.17–4.01 (m, 2H, H–6b,6b'), 4.02 (appt, $J_{3,4}$ = $J_{4,5}$ = 4.4 Hz, 1H, H–4), 4.94 (appt, $J_{5',6a'}$ = $J_{5',6b'}$ = 6.5 Hz, 1H, H–5'), 2.17, 2.13, 2.11, 2.06, 2.05, 1.98 (s, 18H, $6CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.6, 170.5, 170.4, 170.2, 169.8, 169.3 (6C=O, Ac), 148.8 (C–1), 101.5 (C–1'), 75.4 (C–4), 74.2 (C–5), 71.1 (C–3'), 71.0 (C–5'), 70.8 (C–3), 68.9 (C–2'), 66.9 (C–4'), 65.5 (C–2), 61.3 (C–6), 61.2 (C–6'), 21.1, 20.94, 20.88, 20.83, 20.81, 20.7 ($6CH_3$, Ac); FT–IR (neat) ν in cm^{-1}: 2979, 1740, 1368, 1215, 1170, 1046; HRMS (TOF ES+) for ($M+NH_4^+$) $C_{24}H_{35}INO_{15}^+$ (*m/z*): calc. 704,1046; found 704.1035.

1,5-Anhydro-2-deoxy-2-iodo-D-*lyxo*-hex-1-enitol (3.12a)



To a solution of **3.10a** (78 mg, 0.195 mmol in 1:1 (v/v) MeOH/H_2O (2 mL) was added NaOMe (8.5 mg, 0.16 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 5 h and neutralized with Dowex® (H^+ 50WX8–200). The ion exchanger was filtered off and washed with MeOH. The resulting solution was concentrated under reduced pressure and the residue purified by column chromatography (1:19 MeOH/CH_2Cl_2) to afford **3.12a** (45 mg, 85%) as a white solid. R_f (1:9 MeOH/CH_2Cl_2): 0.13; m.p: 135–137 ºC; $[\alpha]_D^{20}$: +31.5 (1.2, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ in ppm: 6.71 (d, $J_{1,3}$ = 1.5 Hz, 1H, H–1), 4.18–4.16 (m, 1H, H–3), 4.09–4.03 (m, 2H, H–4,5), 3.81 (dd, $J_{6a,b}$ = 11.6 Hz, $J_{5,6a}$ = 6.9 Hz, 1H, H–6a), 3.74 (dd, $J_{6a,b}$ = 11.6 Hz, $J_{5,6b}$ = 5.1 Hz, 1H, H–6b); ^{13}C NMR (CD_3OD, 100.6 MHz) δ in ppm: 149.3 (C–1), 79.6 (C–5), 77.5 (C–2), 69.3 (C–3), 67.6 (C–4), 62.0 (C–2); FT–IR (neat) ν in cm^{-1}: 3343, 2926, 1736, 1627, 1373, 1227, 1164, 1022; HRMS (TOF ES+) for ($M+Na^+$) $C_6H_9INaO_4^+$ (*m/z*): calc. 294.9438; found 294.9434.

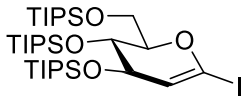
Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-iodo-D-*glycero*-α-D-*galacto*-non-2-enonate (3.16a)



The title compound was prepared following general method B, starting from **3.16** (170 mg, 0.359 mmol), NIS (105 mg, 0.47 mmol) and $AgNO_3$ (18.3 mg, 0.107 mmol) in dry CH_3CN (2 mL). The mixture was heated at 80 ºC under argon atmosphere for 12 h and after standard workup the crude was purified by column chromatography EtOAc/Hexane (8:2) to give **3.16a** (100 mg, 46%) as a white foam. R_f

(EtOAc): 0.42; $[\alpha]_D^{20}$: –0.96 (6.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.30–6.21 (m, 1H, NH), 5.68–5.62 (m, 1H, H–4), 5.47–5.41 (m, 1H, H–7), 5.25–5.17 (m, 1H, H–8), 4.54 (dd, $J_{9a,b}$ = 12.5 Hz, $J_{8,9a}$ = 2.7 Hz, 1H, H–9a), 4.49–4.42 (m, 2H, H–6,5), 4.07 (dd, $J_{9a,b}$ = 12.5 Hz, $J_{8,9b}$ = 6.9 Hz, 1H, H–9b), 3.78 (s, 3H, OCH_3), 2.10, 2.07, 2.03, 2.00, 1.85 (s, 15H, $5CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.7, 170.5, 170.3, 170.1, 169.9 (5C=O, Ac), 161.3 (C=O, CO_2Me), 145.9 (C–2), 77.0 (C–6), 75.3 (C–3), 73.7 (C–4), 70.6 (C–8), 67.1 (C–7), 61.9 (C–9), 52.8 (OCH_3), 47.7 (C–5) 22.9, 20.9, 20.8, 20.7, 20.6 ($5CH_3$, Ac); FT–IR (neat) ν in cm^{-1}: 3274, 3058, 2956, 1739, 1662, 1535, 1436, 1370, 1210, 1029, 734; HRMS (TOF ES+) for ($M+Na^+$) $C_{20}H_{26}INNaO_{12}^+$ calc. 622.0392; found 622.0394.

1-Iodo-3,4,6-tri-*O*-(triisopropylsilyl)-D-glucal (3.17a)



3,4,6-Tri-*O*-(triisopropylsilyl)-D-glucal **3.17** (345 mg, 0.56 mmol) Was azeotropically dried with toluene and dissolved in dry THF (1.8 mL). The mixture was cooled to –78 °C and *t*-BuLi (1.3 mL, 2.24 mmol) was added slowly with a syringe. The reaction was warmed to 0 °C, stirred for 1 h, and then cooled to –78 °C again. 1,2-Diiodoethane (631 mg, 2.24 mmol) was dissolved in THF (1.8 mL) and cannulated under argon atmosphere to the flask containing the sugar. The reaction was warmed to rt, stirred for 1 h and quenched with a saturated solution of $NaHCO_3$, extracted with EtOAc, dried with Na_2SO_4, filtrated and the solvent evaporated under reduced pressure. Purification by column chromatography (hexane) afforded **3.17a** (309 mg, 75%) as a colorless oil. R_f (hexane): 0.25. ^{1}H NMR ($CDCl_3$, 400 MHz): 5.40 (dd, 1H, $J_{2,3}$ = 5.5 Hz, $J_{2,4}$ = 1.4 Hz, H–2); 4.35 (m, 1H, H–5), 4.12 (dd, $J_{6a,b}$ = 11.4 Hz, $J_{5,6a}$ = 7.6 Hz, 1H, H–6a), 4.12 (m, 1H, H–4), 3.90 (dt, $J_{2,3}$ = 5.5 Hz, $J_{3,4}$ = 2.2 Hz, 1H, H–3), 3.86 (dd, $J_{6a,b}$ = 11.4 Hz, $J_{5,6b}$ = 4.2 Hz, 1H, H–6b), 1.13–0.96 (m, 63H, 9CH, $18CH_3$, *i*-Pr); ^{13}C NMR ($CDCl_3$, 100.6 MHz): 111.6 (C–2), 107.5 (C–1), 86.0 (C–5), 69.5 (C–4), 68.0 (C–3), 61.7 (C–6), 18.3, 18.2, 18.2, 18.2 (9CH, *i*-Pr),

12.6, 12.4, 12.2 ($18CH_3$, *i*-Pr). Spectroscopic data are in agreement with those reported.[127]

3.5.3. Preparation of $CuCF_3$ reagents stabilized with different amounts of TREAT–HF

The fluoroform-derived reagent $CuCF_3$ stabilized with $Et_3N{\cdot}3HF$ (TREAT–HF) was prepared in a 0.1 mol scale in DMF following a reported procedure.[63b] At the moment of use the concentration of the reagent (referred to as $CuCF_3$) was 0.34 M. $CuCF_3$ reagents with "extra" TREAT–HF were prepared as follows: in a glove box, three different vials were charged with 5 mL of the $CuCF_3$ solution and different volumes of TREAT–HF (purity 99%) were added to the vials. TREAT–HF (35 μL, 0.215 mmol) to obtain $CuCF_3$–0.3HF, TREAT–HF (70 μL, 0.430 mmol) to obtain $CuCF_3$–0.6HF, and TREAT–HF (105 μL, 0.645 mmol) to obtain $CuCF_3$–0.9HF. All reagents were stored at –30 °C and left undisturbed for several hours prior to use.

3.5.4. Trifluoromethylation of iodoglycals

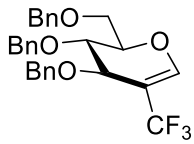
Optimization experiments: in a glove box, the corresponding $CuCF_3$ TREAT–HF reagent was added to **3.3a** (54 mg, 0.1 mmol) in an NMR tube. The tube was sealed, brought out of the glove box, and 1,3-bis(trifluoromethyl)benzene (internal standard; 0.05 mmol, 7.7 μL) was added. The reaction was monitored by ^{19}F NMR at the selected temperature and quenched by extraction with Et_2O. The solvent was evaporated under reduced pressure and the crude analyzed by ^1H NMR to determine the conversion.

General procedure for the trifluoromethylation of electron-rich vinyl iodides: in a glove box, $CuCF_3$–0.6HF (0.34 M, 0.59 mL, 0.2 mmol) was added at room temperature to a vial containing the corresponding vinyl iodide (0.1 mmol). The concentration of $CuCF_3$–0.6HF

[127] Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. 1. Chem.* **1994**, *72*, 1262–1272.

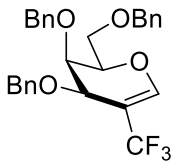
at the moment of use ranged between 0.33–0.38 M, measured before the reaction. The vial was sealed, brought out of the glove box, and stirred at 50 ºC for 7 h. The crude was extracted with Et_2O, the solvent evaporated, and the crude analyzed by ^1H NMR. The residue was purified using chromatographic techniques.

3,4,6-Tri-*O*-benzyl-2-trifluoromethyl-D-glucal (3.36)



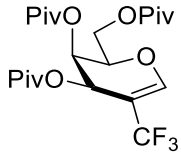
The title compound was prepared following the general procedure above, starting from **3.3a** (200 mg, 0.36 mmol) and $CuCF_3$–0.6HF (2.2 mL, 0.74 mmol). After standard work-up, the crude was purified by column chromatography (1:15 EtOAc/hexane) to afford **3.36** (139 mg, 80%) as a colorless syrup. R_f (1:4 EtOAc/hexane): 0.43; $[\alpha]_D^{20}$: –11.2 (1.26, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.21 (m, 15H, ArH), 7.07 (bq, $J_{1,F}$ = 1.5 Hz, 1H, H–1), 4.59–4.44 (m, 7H, $3CH_2Ph$, H–5), 4.10 (bs, 1H, H–3), 3.90 (appt, $J_{3,4}$ = $J_{4,5}$ = 3.2 Hz, 1H, H–4), 3.78 (dd, $J_{6a,b}$ = 10.5 Hz, $J_{5,6a}$ = 6.9 Hz, 1H, H–6a), 3.67 (dd, $J_{6a,b}$ = 10.5 Hz, $J_{5,6b}$ = 5.1 Hz, 1H, H–6b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.1 (q, $J_{1,F}$ = 7.2 Hz, C–1), 137.8, 137.6, 137.4 (C, Ar), 128.7, 128.6, 128.5, 128.4, 128.2, 128.11, 128.06, 128.0 127.9, 127.8 (CH, Ar), 125.0 (q, $J_{C,F}$ = 269.9 Hz, CF_3), 103.6 (q, $J_{2,F}$ = 30.7 Hz, C–2), 76.5 (C–5), 73.4, 72.4, 72.2 ($3CH_2Ph$), 71.2 (C–4), 68.9 (C–3), 71.2 (C–4), 68.9 (C–3), 67.7 (C–6); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.6 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 3030, 2866, 1667, 1497, 1454, 1323, 1213, 1109; HRMS (TOF ES+) for ($M+Na^+$) $C_{28}H_{27}F_3NaO_4^+$ (*m/z*): calc. 507.1754; found 507.1752. Spectroscopic data were identical to those previously reported.[83]

3,4,6-Tri-*O*-benzyl-2-trifluoromethyl-D-galactal (3.37)



The title compound was prepared following the general procedure above, starting from **3.4a** (63.4 mg, 0.12 mmol) and $CuCF_3$–0.6HF (0.71 mL, 0.23 mmol). After standard work-up, the crude was purified by column chromatography (1:15 EtOAc/hexane) to afford **3.37** (49.6 mg, 85%) as a colorless syrup. R_f (1:4 EtOAc/hexane): 0.53; $[\alpha]_D^{20}$: –20.7 (2.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.21 (m, 15H, ArH), 7.07 (bq, $J_{1,F}$ = 1.5 Hz, 1H, H–1), 4.59–4.44 (m, 7H, 3CH_2Ph, H–5), 4.10 (bs, 1H, H–3), 3.90 (appt, $J_{3,4}$ = $J_{4,5}$ = 3.2 Hz, 1H, H–4), 3.78 (dd, $J_{6a,b}$ = 10.5 Hz, $J_{5,6a}$ = 6.9 Hz, 1H, H–6a), 3.67 (dd, $J_{6a,b}$ = 10.5 Hz, $J_{5,6b}$ = 5.1 Hz, 1H, H–6b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 147.9 (q, $J_{1,F}$ = 7.1 Hz, C–1), 138.2, 138.0, 137.7 (C, Ar), 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8 (CH, Ar), 124.7 (q, $J_{C,F}$ = 269.6 Hz, CF_3), 104.8 (q, $J_{2,F}$ = 30.8 Hz, C–2), 76.6 (C–5), 74.2, 73.5 (2CH_2Ph), 72.9 (C–4), 72.7 (CH_2Ph), 68.5 (C–3), 67.8 (C–6); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.1 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 3063, 3031, 2867, 1662, 1497, 1454, 1326, 1211, 1108, 1063, 1027; HRMS (TOF ES+) for ($M+Na^+$) $C_{28}H_{27}F_3NaO_4^+$ (*m/z*): calc. 507.1754; found 507.1750. Spectroscopic data were identical to those previously reported.[83]

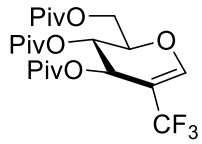
3,4,6-Tri-*O*-pivaloyl-2-trifluoromethyl-D-galactal (3.38)



The title compound was prepared following the general procedure above, starting from **3.6a** (54 mg, 0.10 mmol) and $CuCF_3$–0.6HF (0.57 mL,

0.20 mmol). After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **3.38** (43 mg, 92%) as a white solid. R_f (1:9 EtOAc/hexane): 0.50; m.p: 96–98 ºC; $[\alpha]_D^{20}$: +6.0 (0.17, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.09 (bs, 1H, H–1), 5.86 (bdq, $J_{3,4}$ = 4.1 Hz, $J_{3,F}$ = 0.9 Hz, 1H, H–3), 5.46 (dd, $J_{3,4}$ = 4.1 Hz, $J_{4,5}$ = 3.3 Hz, 1H, H–4), 4.49 (m, 1H, H–5), 4.41 (dd, $J_{6a,b}$ = 11.8 Hz, $J_{5,6a}$ = 8.9 Hz, 1H, H–6a), 4.18 (dd, $J_{6a,b}$ = 11.8 Hz, $J_{5,6b}$ = 4.1 Hz, 1H, H–6b), 1.22, 1.21, 1.20 (s, 27H, 9CH_3, Piv); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 178.2, 177.2, 176.8 (3C=O, Piv), 149.0 (q, $J_{1,F}$ = 7.1 Hz, C–1), 123.8 (q, $J_{C,F}$ = 271.6 Hz, CF_3), 103.0 (q, $J_{2,F}$ = 31.5 Hz, C–2), 74.0 (C–5), 63.5 C–4), 61.3 (C–6), 61.2 (C–3), 39.1, 39.0, 38.9 (3C, *t*–Bu), 27.2, 27.2, 27.1 (9CH_3, *t*-Bu); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.5 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 2975, 1738, 1666, 1481, 1280, 1111; HRMS (TOF ES+) for ($M+Na^+$) $C_{22}H_{33}F_3NaO_7^+$ (*m/z*): calc. 489.2071; found 489.2072.

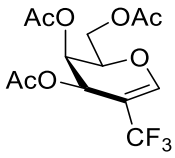
3,4,6-Tri-*O*-pivaloyl-2-trifluoromethyl-D-glucal (3.39)



The title compound was prepared following the general procedure above, starting from **3.5a** (15 mg, 0.028 mmol) and $CuCF_3$–0.6HF (0.16 mL, 0.056 mmol). After standard work-up, the crude was purified by column chromatography (1:40 EtOAc/hexane) to afford **3.39** (9.1 mg, 70%) as a pale yellow syrup. R_f (1:9 EtOAc/hexane): 0.57; $[\alpha]_D^{20}$: –13.3 (0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.18 (bs, 1H, H–1), 5.56 (bd, $J_{3,4}$ = 3.3 Hz, 1H, H–3), 5.13 (bd, $J_{3,4}$ = 3.3 Hz, H–4), 4.53–4.43 (m, 2H, H–5,6a), 4.05 (dd, $J_{6a,b}$ = 17.6 Hz, $J_{5,6b}$ = 7.9 Hz, 1H, H–6b), 1.23, 1.20, 1.19 (s, 27H, 9CH_3, Piv); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 178.1, 176.8, 176.6 (3C=O, Piv), 149.3 (q, $J_{1,F}$ = 6.6 Hz, C–1), 124.0 (q, $J_{C,F}$ = 271.8 Hz, CF_3), 102.3 (q, $J_{2,F}$ = 31.8 Hz, C–2), 74.6 (C–5), 65.6 (C–4), 61.3 (C–3), 61.0 (C–6), 38.98, 38.97, 38.96 (3C, *t*-Bu), 27.3, 27.0 (9CH_3, *t*-Bu); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.5 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 2978, 2963,

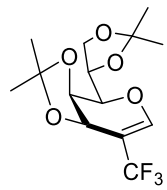
1740, 1669, 1327, 1279, 1122; HRMS (TOF ES+) for ($M+Na^+$) $C_{22}H_{33}F_3NaO_7^+$ (*m/z*): calc. 489.2071; found 489.2092.

3,4,6-Tri-*O*-acetyl-2-trifluoromethyl-D-galactal (3.40)



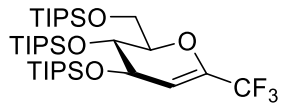
The title compound was prepared following the general procedure above, starting from **3.10a** (1.58 g, 3.97 mmol) and $CuCF_3$–0.6HF (20.9 mL, 7.94 mmol). After standard work-up, the crude was purified by column chromatography (1:4 EtOAc/hexane) to afford **3.40** (1.25 g, 93%) as a white solid. R_f (1:4 EtOAc/hexane): 0.41; m.p: 54–56 ºC; $[\alpha]_D^{20}$: +23.5 (0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.06 (bs, 1H, H–1), 5.80 (d, $J_{3,4}$ = 4.3 Hz, 1H, H–3), 5.41 (dd, $J_{3,4}$ = 4.3 Hz, $J_{4,5}$ = 3.0 Hz, 1H, H–4), 4.43 (m, 1H, H–5), 4.34 (dd, $J_{6a,b}$ = 11.9 Hz, $J_{5,6a}$ = 8.1 Hz, 1H, H–6a), 4.23 (dd, $J_{6a,b}$ = 11.9 Hz, $J_{5,6b}$ = 4.1 Hz, 1H, H–6b), 2.08, 2.06, 2.02 (s, 9H, $3CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.5, 169.8, 169.7 (3C=O, Ac), 149.3 (q, $J_{1,F}$ = 6.9 Hz, C–1), 123.6 (q, $J_{C,F}$ = 270.0 Hz, CF_3), 102.9 (q, $J_{2,F}$ = 31.5 Hz, C–2), 73.8 (C–5), 63.5 (C–4), 61.3 (C–6), 60.8 (C–3), 20.7, 20.5 ($3CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.7 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 2940, 1747, 1666, 1455, 1371, 1328, 1213, 1151, 1112, 1046; HRMS (TOF ES+) for ($M+Na^+$) $C_{13}H_{15}F_3NaO_7^+$ (*m/z*): calc. 363.0662; found 363.0658. Spectroscopic data were identical to those previously reported.[83]

1,5-Anhydro-2-deoxy-2-trifluoromethyl-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-hept-1-enitol (3.41)



The title compound was prepared following the general procedure above, starting from 1,5-anhydro-2-deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-hept-1-enitol[86b] (24 mg, 0.06 mmol) and $CuCF_3$–0.6HF (0.34 mL, 0.12 mmol). After standard work-up, the crude was purified by column chromatography (1:8 EtOAc/hexane) to afford **3.41** (15 mg, 77%) as a pale yellowish oil. R_f (1:8 EtOAc/hexane): 0.37; $[\alpha]_D^{20}$: +0.55 (0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.96 (bq, $J_{1,F}$ = 1.5 Hz, 1H, H–1), 4.86 (d, $J_{3,4}$ = 6.2 Hz, 1H, H–3), 4.54 (dd, $J_{3,4}$ = 6.2 Hz, $J_{4,5}$ = 1.0 Hz, 1H, H–4), 4.41 (ddd, $J_{5,6}$ = 8.1 Hz, $J_{6,7a}$ = 6.1 Hz, $J_{6,7b}$ = 4.6 Hz, 1H, H–6), 4.13 (dd, $J_{7a,b}$ = 9.1 Hz, $J_{6,7a}$ = 6.1 Hz, 1H, H–7a), 4.08 (dd, $J_{7a,b}$ = 9.1 Hz, $J_{6,7b}$ = 4.6 Hz, 1H, H–7b), 3.84 (bd, $J_{5,6}$ = 8.1 Hz, 1H, H–5), 1.44, 1.43, 1.42, 1.38 (s, 12H, $4CH_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.3 (q, $J_{1,F}$ = 6.7 Hz, C–1), 124.6 (q, $J_{C,F}$ = 270.0 Hz, CF_3), 111.7, 109.9 ($2C_{ketal}$), 107.0 (appd, $J_{2,F}$ = 30.5 Hz, C–2), 76.2 (C–5), 73.8 (C–6), 71.5 (C–4), 67.0 (C–3), 66.6 (C–7), 29.9, 27.8, 27.0, 25.3 ($4CH_3$); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.5 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 2986, 2933, 2361, 2331, 1774, 1724, 1668, 1373, 1334, 1225, 1146, 1115, 1043, 993, 844; HRMS (TOF ES+) for ($M+Na^+$) $C_{14}H_{19}F_3NaO_5^+$ (*m/z*): calc. 347.1077; found 347.1082.

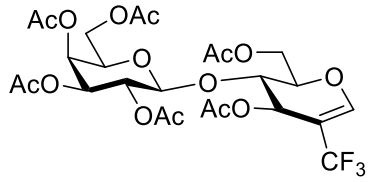
3,4,6-tris-*O*-(triisopropylsilyl)1-trifluoromethyl-D-glucal (3.42)



The title compound was prepared following the general procedure above, starting from **3.17a** (74.1 mg, 0.10 mmol) and $CuCF_3$–0.6HF (0.57 mL, 0.20 mmol).. After standard work-up, the crude was purified by column chromatography (hexane) to afford **3.42** (60 mg, 88%) as a glassy syrup. R_f (hexane): 0.74; $[\alpha]_D^{20}$: –7.9 (0.28, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.47 (dd, $J_{2,3}$ = 5.6 Hz, 1H, H–2), 4.45–4.42 (m, 1H, H–5), 4.15 (bs, 1H, H–4), 4.09–3.86 (m, 1H, H–3), 3.99 (dd, $J_{6a,b}$ = 11.4 Hz, $J_{5,6a}$ = 7.5 Hz, 1H, H–6a), 3.88 (dd, $J_{6a,b}$ = 11.4 Hz, $J_{5,6b}$ =4.8 Hz, 1H, H–6b), 1.13–0.96 (m, 63H, 9CH, $18CH_3$, *i*-Pr); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm:

142.0 (q, $J_{1,F}$ = 35.0 Hz, C–1), 119.9 (q, $J_{C,F}$ = 273.2 Hz, CF_3), 100.9 (q, $J_{2,F}$ = 3.7 Hz, C–2), 82.2 (C–5), 69.4 (C–4), 65.0 (C–3), 61.4 (C–6), 18.2–18.1 (9CH, *i*-Pr), 12.6, 12.4, 12.1 (18CH_3, *i*-Pr); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –72.9 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 2944, 2867, 1735, 1463, 1370, 1192, 1103, 882; HRMS (TOF ES+) for (M+NH_4^+) $C_{34}H_{73}F_3NO_4Si_3^+$ (*m/z*): calc. 700.4794; found 700.4782.

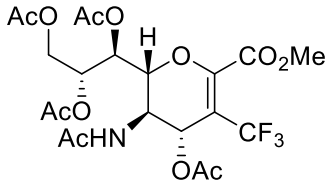
3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-trifluoromethyl-D-glucal (3.43)



The title compound was prepared following the general procedure above, starting from **3.11a** (60.9 mg, 0.087 mmol) and $CuCF_3$–0.6HF (0.45 mL, 0.17 mmol). The reaction mixture was stirred at 50 ºC for 16 h. After standard work-up, the crude was purified by column chromatography (1:1 EtOAc/hexane) to afford **3.43** (44 mg, 80%) as a white solid. R_f (1:1 EtOAc/hexane): 0.15; m.p: 50–52 ºC; $[\alpha]_D^{20}$: +1.9 (0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.13 (bq, $J_{1,F}$ = 1.5 Hz, 1H, H–1), 5.59 (bs, 1H, H–3), 5.37 (dd, $J_{3',4'}$ = 3.6 Hz, $J_{4',5'}$ = 1.0 Hz, 1H, H–4'), 5.18 (dd, $J_{2',3'}$ = 10.5 Hz, $J_{1',2'}$ = 7.5 Hz, 1H, H–2'), 5.01 (dd, $J_{2',3'}$ = 10.5 Hz, $J_{3',4'}$ = 3.6 Hz, 1H, H–3'), 4.69 (d, $J_{1',2'}$ = 7.5 Hz, 1H, H–1'), 4.46 (m, 1H, H–5), 4.31 (dd, $J_{6a,b}$ = 12.0 Hz, $J_{5,6a}$ = 8.1 Hz, 1H, H–6a), 4.18 (dd, $J_{6a,b}$ = 12.0 Hz, $J_{5,6b}$ = 4.8 Hz, 1H, H–6b), 4.15 (dd, $J_{6a',b'}$ = 11.4 Hz, $J_{5',6a'}$ = 6.7 Hz, 1H, H–6a'), 4.11 (dd, $J_{6a',b'}$ = 11.4 Hz, $J_{5',6b'}$ = 6.5 Hz, 1H, H–6b'), 4.02–3.96 (m, 2H, H–4,5'), 2.14, 2.10, 2.05, 2.04, 2.02, 2.00 (s, 18H, 6CH_3, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.6, 170.5, 170.4, 170.2, 169.7, 169.2 (6C=O, Ac), 149.0 (q, $J_{1,F}$ = 6.5 Hz, C–1), 124.2 (q, $J_{C,F}$ = 271.8 Hz, CF_3), 101.7 (C–1'), 101.1 (q, $J_{2,F}$ = 31.3 Hz, C–2), 74.9 (C–5), 73.2 (C–4), 71.4 (C–5'), 70.9 (C–3'), 68.9 (C–2'), 67.0 (C–4'), 61.4 (C–6'), 61.3 (C–3), 61.1 (C–6), 20.9, 20.84, 20.78, 20.77, 20.7, 20.6 (6CH_3, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –64.0 (s, CF_3);

FT–IR (neat) ν in cm^{-1}: 2980, 1740, 1667, 1369, 1328, 1211, 1115, 1047, 1020; HRMS (TOF ES+) for ($M+Na^+$) $C_{25}H_{31}F_3NaO_{15}^+$ (*m/z*): calc. 651.1507; found 651.1509. Spectroscopic data were identical to those previously reported.[83]

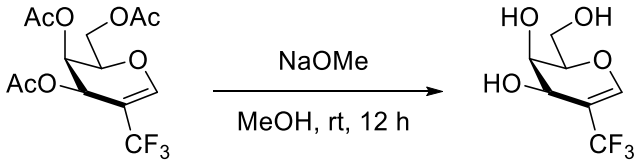
Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-3-trifluoromethyl-D-*glycero*-α-D-*galacto*-non-2-enonate (3.44)



The title compound was prepared following the general procedure above, starting from **3.16a** (40 mg, 0.067 mmol) and $CuCF_3$–0.6HF (0.36 mL, 0.13 mmol). The reaction mixture was stirred at room temperature for 2 h. After standard work-up, the crude was purified by column chromatography (1:4 EtOAc/hexane) to afford **3.44** (30.7 mg, 85%) as a white foam. R_f (1:1 EtOAc/hexane): 0.23; $[\alpha]_D^{20}$: +9.0 (0.62, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.87 (d, $J_{4,5}$ = 7.5 Hz, 1H, H–4), 5.73 (d, *J* = 9.2 Hz, 1H, NH), 5.48 (dd, $J_{7,8}$ = 6.9 Hz, $J_{6,7}$ = 2.7 Hz, 1H, H–7), 5.25 (ddd, $J_{7,8}$ = 6.9 Hz, $J_{8,9b}$ = 6.0 Hz, $J_{8,9a}$ = 2.9 Hz, 1H, H–8), 4.48 (dd, $J_{5,6}$ = 9.7 Hz, $J_{6,7}$ = 2.7 Hz, 1H, H–6), 4.44–3.35 (m, 2H, H–5,9a), 4.09 (dd, $J_{9a,b}$ = 12.5 Hz, $J_{8,9b}$ = 6.0 Hz, 1H, H–9b), 3.86 (s, 3H, OCH_3), 2.11, 2.08, 2.04, 1.92 (s, 15H, $5CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.72, 170.70, 170.6, 170.0, 169.8 (5C=O, Ac), 161.0 (C=O, CO_2Me), 151.2 (q, $J_{2,F}$ = 3.8 Hz, C–2), 122.5 (q, $J_{C,F}$ = 272.3 Hz, CF_3), 104.9 (q, $J_{3,F}$ = 33.0 Hz, C–3), 77.45 (C–6), 69.8 (C–8), 66.7 (C–7), 66.2 (C–4), 61.8 (C–9), 53.6 (OCH_3), 47.3 (C–5) 23.2, 20.92, 20.85, 20.80, 20.78 ($5CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –58.6 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 3273, 3060, 2961, 1746, 1663, 1540, 1370, 1208, 1131, 1008; HRMS (TOF ES+) for ($M+Na^+$) $C_{21}H_{26}F_3NNaO_{12}^+$ (*m/z*): calc. 564.1299; found 564.1307. Spectroscopic data were identical to those previously reported.[83]

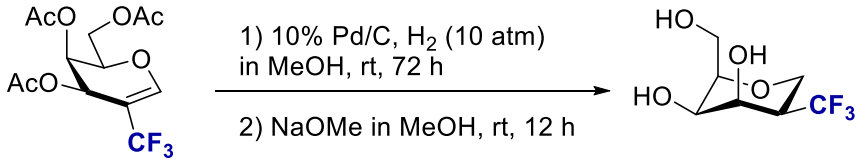
3.1.1.1. Derivatization of 2–trifluoromethylglycals

Deacetylation of 2-trifluoromethylgalactal 3.40



10% Pd/C (90 mg, 0.08 mmol Pd) was added to a solution of **3.40** (55 mg, 0.162 mmol) in dry and deoxygenated methanol (1mL) at room temperature. The mixture was stirred under H_2 (10 atm) at the same temperature for 72 h, filtered through a short path of Celite® 545, and concentrated under reduced pressure. The crude was redissolved in MeOH (2 mL) and NaOMe (4.32 mg, 0.08 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 12 h and neutralized with Dowex® (H^+ 50WX8–200). The ion exchanger was filtered off and washed with MeOH. The crude material was purified by column chromatography (1:9 MeOH/EtOAc) to afford **3.45** (31.0 mg, 89% over two steps) as a white solid. R_f (1:9 MeOH/CH_2Cl_2): 0.15; m.p: 137–139 ºC; $[\alpha]_D^{20}$: +49.3 (0.1, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ in ppm: 4.81 (appt, $J_{2,3}$ = $J_{3,4}$ = 3.2 Hz, 1H, H–3), 4.15 (dd, $J_{6a,b}$ = 12.7 Hz, $J_{5,6a}$ = 8.6 Hz, 1H, H–6a), 4.03 (dd, $J_{1a,b}$ = 11.4 Hz, $J_{1a,2}$ = 10.4 Hz, 1H, H–1a), 3.87 (ddd, $J_{5,6a}$ = 8.6 Hz, $J_{4,5}$ = 6.1 Hz, $J_{5,6b}$ = 2.8 Hz, 1H, H–5), 3.79 (dd, $J_{4,5}$ = 6.1 Hz, $J_{3,4}$ = 3.2 Hz, 1H, H–4), 3.73 (dd, $J_{6a,b}$ = 12.7 Hz, $J_{5,6b}$ = 2.8 Hz, 1H, H–6b), 3.64 (dd, $J_{1a,b}$ = 11.4 Hz, $J_{1b,2}$ = 4.1 Hz, 1H, H–1b), 4.63–4.56 (m, 1H, H–2); ^{13}C NMR (CD_3OD, 100.6 MHz) δ in ppm: 125.2 (q, $J_{C,F}$ = 280.1 Hz, CF_3), 79.3 (C–5), 66.6 (C–4), 69.3 (q, $J_{3,F}$ = 2.3 Hz, C–3), 59.1 (C–6), 55.9 (q, $J_{1,F}$ = 3.1 Hz, C–1), 45.8 (q, $J_{2,F}$ = 25.8 Hz, C–2); ^{19}F NMR (CD_3OD, 376.5 MHz) δ in ppm: –68.0 (d, $J_{2,F}$ = 9.3 Hz, 3F, CF_3); FT–IR (neat) v in cm^{-1}: 3366, 2926, 1664, 1398, 1325, 1262, 1110, 1036; HRMS (TOF ES+) for ($M+Na^+$) $C_7H_{11}F_3NaO_4^+$ (*m/z*): calc. 239.0502; found 239.0506.

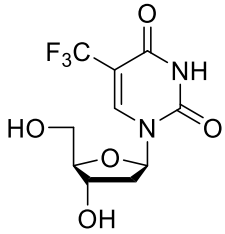
Hydrogenation/deacetylation of 2-trifluoromethylgalactal 3.40



1,5-Anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoromethyl-D-*lyxo*-hex-1-enitol **3.40** (20 mg, 0.058 mmol) was dissolved in MeOH (0.5 mL) and NaOMe (1.6 mg, 0.03 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 12 h and neutralized with Dowex® (H^+ 50WX8–200). The ion exchanger was filtered off and washed with MeOH. The resulting solution was concentrated under reduced pressure to afford **3.48** (12.2 mg, 98%) as a white solid. R_f (1:9 MeOH/CH_2Cl_2): 0.55; m.p: 93–95 ºC; $[\alpha]_D^{20}$: +8.0 (0.1, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ in ppm: 7.03 (bs, 1H, H–1), 4.46 (bdq, $J_{3,4}$ = 4.4 Hz, $J_{3,F}$ = 0.9 Hz, 1H, H–3), 4.08 (m, 1H, H–5), 3.99 (dd, $J_{3,4}$ = 4.4 Hz, $J_{4,5}$ = 2.5 Hz, 1H, H–4), 3.90 (dd, $J_{6a,b}$ = 12.0 Hz, $J_{5,6a}$ = 6.8 Hz, 1H, H–6a), 3.80 (dd, $J_{6a,b}$ = 12.0 Hz, $J_{5,6b}$ = 4.6 Hz, 1H, H–6b); ^{13}C NMR (CD_3OD, 100.6 MHz) δ in ppm: 149.4 (q, $J_{1,F}$ = 7.6 Hz, C–1), 126.4 (q, $J_{C,F}$ = 269.2 Hz, CF_3), 107.0 (q, $J_{2,F}$ = 29.0 Hz, C–2), 80.1 (C–5), 66.3 (C–4), 63.4 (C–3), 61.4 (C–6); ^{19}F NMR (CD_3OD, 376.5 MHz) δ in ppm: –63.0 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 3537, 3349, 3185, 1669, 1346, 1214, 1103, 1040; HRMS (TOF ES+) for ($M+Na^+$) $C_7H_9F_3NaO_4^+$ (*m/z*): calc. 237.0345; found 237.0341.

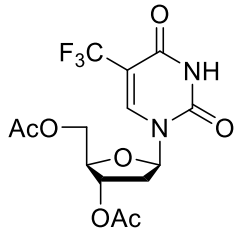
3.5.5. Trifluoromethylation of iodinated nucleosides and nitrogenous bases

5-Trifluoromethyl-2'-deoxyuridine (3.49)



To a vial containing 5-iodo-2′-deoxyuridine **3.21a** (47 mg, 0.13 mmol), three portions of $CuCF_3$–0.6HF (0.36 mL, 0.13 mmol) was added every 2 h and stirred at 50 ºC. After 2 h from the last addition, the residue was azeotropically dried with toluene and the crude purified by column chromatography (1:9 MeOH/CH_2Cl_2) to afford **3.49** (23.8 mg, 62%) as a white solid. R_f (4:1 EtOAc/hexane): 0.38; ^{1}H NMR (CD_3OD, 400 MHz) δ in ppm: 8.80 (bs, 1H, H–6), 6.24 (t, $J_{1',2a'}$ = $J_{1',2b'}$ = 6.2 Hz, 1H, H–1′), 4.42 (m, 1H, H–3′), 3.97 (m, 1H, H–4′), 3.84 (dd, $J_{5a',b'}$ = 11.9 Hz, $J_{4',5a'}$ = 2.9 Hz, 1H, H–5a′), 3.75 (dd, $J_{5a',b'}$ = 11.9 Hz, $J_{4',5b'}$ = 2.9 Hz, 1H, H–5b′), 2.37 (ddd, $J_{2a',b'}$ = 13.7 Hz, $J_{1',2a'}$ = 6.3 Hz, $J_{2a',3'}$ = 4.4 Hz, 1H, H–2a′), 2.27 (m, 1H, H–2b′); ^{13}C NMR (CD_3OD, 100.6 MHz) δ in ppm: 161.2 (C–4), 151.3 (C–2), 143.8 (q, $J_{C,F}$ = 5.9 Hz, C–6), 123.9 (q, $J_{C,F}$ = 268.8 Hz, CF_3), 105.3 (q, $J_{C,F}$ = 32.9 Hz, C–5), 87.3 (C–1′), 87.5 (C–4′), 71.7 (C–3′), 62.1 (C–5′), 42.1 (C–2′); ^{19}F NMR (CD_3OD, 376.5 MHz) δ in ppm: –64.5 (s, CF_3). Spectroscopic data were identical to those previously reported.[128]

5–Trifluoromethyl–3′,5′–di–*O*–acetyl–2′–deoxyuridine (3.50)

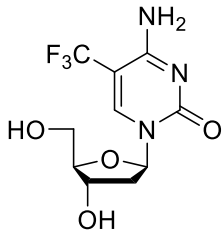


The title compound was prepared following the general procedure above, starting from 3′,5′–di–*O*–acetyl–5–iodo–2′–deoxyuridine **3.22a** (43 mg, 0.10 mmol) and $CuCF_3$–0.6HF (0.55 mL, 0.20 mmol). The reaction mixture was stirred at 50 ºC for 4 h. After standard work–up, the crude was purified by column chromatography (1:30 MeOH/CH_2Cl_2) to afford **3.50** (32 mg, 84%) as a white solid. R_f (4:1 EtOAc/hexane): 0.38; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.08 (bs, 1H, H–6), 6.27 (dd, $J_{1',2b'}$ = 8.1 Hz, $J_{1',2a'}$ = 5.5 Hz, 1H, H–1′), 5.23 (appdt, $J_{2b',3'}$ = $J_{3',4'}$ = 6.2 Hz, $J_{2a',3'}$ = 2.1 Hz,

[128] Fang, Z.; Ning, Y.; Mi, P.; Liao, P.; Bi, X. *Org. Lett.* **2014,** *16*, 1522–1525.

1H, H–3'), 4.42 (dd, $J_{5a',b'}$ = 11.2 Hz, $J_{4',5a'}$ = 2.3 Hz, 1H, H–5a'), 4.36–4.28 (m, 2H, H–4',5b'), 2.62 (ddd, $J_{2a',b'}$ = 14.5 Hz, $J_{1',2a'}$ = 5.5 Hz, $J_{2a',3'}$ = 2.1 Hz, 1H, H–2a'), 2.22–2.07 (m, 7H, H–2b', $2CH_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.5, 170.3 (2C=O, Ac), 158.3 (C–4), 149.4 (C–2), 140.1 (q, $J_{6,F}$= 5.9 Hz, C–6), 121.8 (q, $J_{C,F}$ = 269.8 Hz, CF_3), 105.9 (q, $J_{5,F}$ = 33.2 Hz, C–5), 86.2 (C–1'), 83.2 (C–4'), 74.1 (C–3'), 63.8 (C–5'), 38.7 (C–2'), 21.0, 20.6 ($2CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –63.5 (s, CF_3). Spectroscopic data were identical to those previously reported.[129]

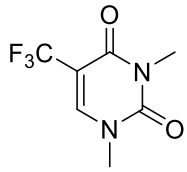
5-Trifluoromethyl-2'-deoxycytidine (3.51)



The title compound was prepared following the general procedure above, starting from 5-iodo-2'-deoxycytidine (16 mg, 0.045 mmol) and $CuCF_3$–0.6HF (0.55 mL, 0.20 mmol). The reaction mixture was stirred at 50 ºC for 4 h. The residue was azeotropically dried with toluene and the crude purified by column chromatography (1:20→1:4 MeOH/CH_2Cl_2) to afford **3.51** (9.5 mg, 71%) as a white solid. ^1H NMR (CD_3OD, 400 MHz) δ in ppm: 8.83 (bs, 1H, H–6), 6.19 (appt, $J_{1',2a'}$ = $J_{1',2b'}$ = 5.9 Hz, 1H, H–1'), 4.38 (m, 1H, H–3'), 3.97 (m, 1H, H–4'), 3.86 (dd, $J_{5a',b'}$ = 12.0 Hz, $J_{4',5a'}$ = 2.9 Hz, 1H, H–5a'), 3.74 (dd, $J_{5a',b'}$ = 12.0 Hz, $J_{4',5b'}$ = 2.9 Hz, 1H, H–5b'), 2.44 (ddd, $J_{2a',b'}$ = 13.6 Hz, $J_{1',2a'}$ = 6.3 Hz, $J_{2a',3'}$ = 5.0 Hz, 1H, H–2a'), 2.21 (m, 1H, H–2b'); ^{13}C NMR (CD_3OD, 100.6 MHz) δ in ppm: 162.5 (C–4), 157.0 (C–2), 144.7 (q, $J_{6,F}$ = 6.1 Hz, C–6), 124.7 (q, $J_{C,F}$ = 268.9 Hz, CF_3), 98.0 (q, $J_{5,F}$ = 34.5 Hz, C–5), 89.2 (C–4'), 88.3 (C–1'), 71.1 (C–3'), 61.9 (C–5'), 42.6 (C–2'); ^{19}F NMR (CD_3OD, 376.5 MHz) δ in ppm: –63.8 (s, CF_3). Spectroscopic data were identical to those previously reported.[123]

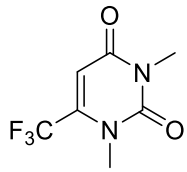
[129] Tanabe, Y.; Matsuo, N.; Ohno, N. *J. Org. Chem.* **1988,** *53*, 4582–4585.

5-Trifluoromethyl-1,3-dimethyluracil (3.52)



The title compound was prepared following the general procedure above, starting from 5-iodo-1,3-dimethyluracil **3.24a** (30 mg, 0.11 mmol) and $CuCF_3$–0.6HF (0.59 mL, 0.22 mmol). The reaction mixture was stirred at 50 ºC for 3 h. After standard work-up, the crude was purified by column chromatography (3:7 EtOAc/hexane) to afford **3.52** (21.1 mg, 92%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.68 (bs, 1H, H–6), 3.48, 3.36 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 158.8, 151.0 (2C=O), 143.2 (q, $J_{6,F}$ = 5.9 Hz, C–6), 122.1 (q, $J_{C,F}$ = 268.8 Hz, CF_3), 104.1 (q, $J_{5,F}$ = 32.9 Hz, C–5), 37.9, 28.1 ($2CH_3$); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –63.9 (s, CF_3). Spectroscopic data were identical to those previously reported.[130]

6-Trifluoromethyl-1,3-dimethyluracil (3.53)

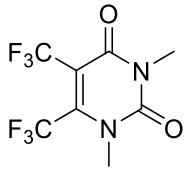


The title compound was prepared following the general procedure above, starting from 6-iodo-1,3-dimethyluracil **3.27a** (84 mg, 0.31 mmol) and $CuCF_3$–0.6HF (1.66 mL, 0.62 mmol). The reaction mixture was stirred at room temperature for 5 h. After standard work-up, the crude was purified by column chromatography (1:4 EtOAc/hexane) to afford **3.53** (63 mg, 97%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.22 (s, 1H, H–5), 3.49 (q, J = 1.3 Hz, 3H, CH_3), 3.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$,

[130] Serizawa, H.; Aikawa, K.; Mikami, K. *Chem. Eur. J.* **2013**, *19*, 17692–17697.

100.6 MHz) δ in ppm: 161.1, 151.7 (2C=O), 140.6 (q, $J_{6,F}$ = 34.3 Hz, C–6), 119.6 (q, $J_{C,F}$ = 275.1 Hz, CF_3), 102.7 (q, $J_{5,F}$ = 5.6 Hz, C–5), 32.6 (q, $J_{C,F}$ = 3.6 Hz, CH_3), 28.5 (CH_3); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –66.0 (s, CF_3). Spectroscopic data was identical to that previously reported.[131]

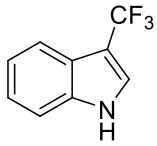
5,6-bis(Trifluoromethyl)-1,3-dimethyluracil (3.54)



The title compound was prepared following the general procedure above, starting from 5,6-diiodo-1,3-dimethyluracil **3.28a** (22 mg, 0.056 mmol) and $CuCF_3$–0.6HF (0.59 mL, 0.22 mmol). The reaction mixture was stirred at 50 ºC for 5 h. After standard work-up, the crude was purified by column chromatography (3:7 EtOAc/hexane) to afford **3.54** (14.3 mg, 92%) as a yellowish syrup. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 3.57 (q, *J* = 2.6 Hz, 3H, CH_3), 3.39 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 157.1, 150.1 (2C=O), 144.2 (q, *J* = 37.0 Hz), 121.0 (q, *J* = 273.5 Hz), 119.2 (q, *J* = 279.6 Hz), 107.9 (q, *J* = 33.7 Hz), 35.8 (m), 29.0 (appd, *J* = 2.1 Hz); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –56.53 (q, *J* = 14.8 Hz, CF_3), –58.45 (qq, *J* = 14.6, 2.15 Hz, CF_3); FT–IR (neat) ν in cm^{-1}: 2960, 2923, 2852, 1732, 1670, 1442, 1366, 1200, 1160; HRMS (EI) for (M^+) $C_8H_6F_6N_2O_2^+$ (*m/z*): calc. 276.0333; found 276.0339.

3.5.6. Trifluoromethylation of iodinated benzo–fused heterocycles

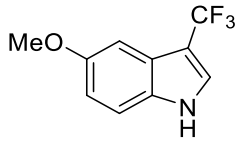
3-(Trifluoromethyl)-1*H*-indole (3.55)



[131] Hocek, M.; Ćerňová, M.; Pohl, R.; Klepetářová, B. *Heterocycles* **2014**, *89*, 1159–1171.

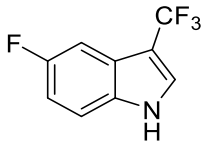
The title compound was prepared following the general procedure above, starting from **3.29a** (37 mg, 0.15 mmol) and $CuCF_3$ (0.82 mL, 0.3 mmol). The reaction mixture was stirred at room temperature for 2 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **3.55** (24 mg, 86%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.36 (bs, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.56–7.52 (m, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.35–7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 135.9, 124.4 (q, $J_{C,F}$ = 5.3 Hz), 124.3 (q, $J_{C,F}$ = 265.9 Hz), 123.68, 123.66 (q, $J_{C,F}$ = 2.1 Hz), 121.7, 119.6, 111.7, 107.9 (q, $J_{C,F}$ = 36.9 Hz); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –57.4 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 2940, 1747, 1666, 1455, 1371, 1328, 1213, 1151, 1112, 1046. Spectroscopic data were identical to those previously reported.[72]

5-Methoxy-3-(trifluoromethyl)-1*H*-indole (3.56)



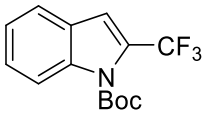
The title compound was prepared following the general procedure above, starting from 5-methoxy-3-iodo-1*H*-indole **3.30a** (69 mg, 0.25 mmol) and $CuCF_3$ (1.6 mL, 0.5 mmol). The reaction mixture was stirred at room temperature for 2 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **3.56** (40 mg, 75%) as a brownish solid. M.p: 62–65 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.30 (bs, 1H), 7.51–7.48 (m, 1H), 7.31 (d, J = 8.9 Hz, 1H), 7.17 (bs, 1H), 6.95 (dd, J = 8.9 Hz, J = 2.4 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 155.4, 130.9, 124.8 (q, $J_{C,F}$ = 5.2 Hz), 124.5 (q, $J_{C,F}$ = 265.9 Hz), 124.2 (q, $J_{C,F}$ = 1.9 Hz), 114.4, 112.6, 107.5 (q, $J_{C,F}$ = 36.8 Hz), 100.7, 55.9; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –57.5 (s, CF_3); FT–IR (neat) ν in cm^{-1}: 3325, 2950, 2843, 1734, 1631, 1595, 1559, 1492, 1450, 1374, 1284, 1216, 1116, 1072, 993, 924, 727; HRMS (TOF ES+) for ($M+H^+$) $C_{10}H_9F_3NO^+$ (*m/z*): calc. 216.0631; found 216.0632.

5-Fluoro-3-(trifluoromethyl)-1*H*-indole (3.57)



The title compound was prepared following the general procedure above, starting from 5-fluoro-3-iodo-1*H*-indole **3.31a** (26 mg, 0.1 mmol) and $CuCF_3$ (0.56 mL, 0.2 mmol). The reaction mixture was stirred at room temperature for 2 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **3.57** (15.6 mg, 77%) as a yellowish solid. M.p: 62–64 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.41 (bs, 1H), 7.59–7.55 (m, 1H), 7.44–7.39 (m, 1H), 7.36 (dd, *J* = 8.9 Hz, *J* = 4.3 Hz, 1H), 7.06 (td, *J* = 9.0 Hz, *J* = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 158.8 (d, *J* = 237.5 Hz), 132.4, 125.9 (q, *J* = 5.1 Hz), 124.2 (dq, *J* = 10.6 Hz, *J* = 2.2 Hz), 124.1 (q, *J* = 266.0 Hz), 112.6, 112.5 (d, *J* = 36.6 Hz), 108.1 (appdd, *J* = 37.3 Hz, *J* = 4.7 Hz), 104.9 (d, *J* = 25.0 Hz); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –57.7 (s, 3F), –121.7 (td, *J* = 9.2 Hz, *J* = 4.3 Hz, 1F); FT–IR (neat) ν in cm^{-1}: 3363, 2977, 1735, 1370, 1096, 992, 801; HRMS (TOF ES–) for ($M+H^-$) $C_9H_4F_4N^-$ (*m/z*): calc. 202.0285; found 202.0285.

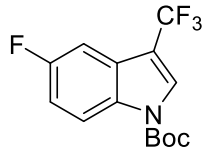
***Tert*-butyl-2-(trifluoromethyl)-1*H*-indole-1-carboxylate (3.58)**



The title compound was prepared following the general procedure above, starting from *tert*-butyl-2-iodo-1*H*-indole-1-carboxylate **3.55a** (46 mg, 0.13 mmol) and $CuCF_3$ (0.73 mL, 0.32 mmol). The reaction mixture was stirred at room temperature for 16 h. After standard work-up, the crude was purified by column chromatography (hexane) to afford **3.58** (36 mg, 94%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm:

8.29 (bdq, *J* = 8.6, 0.8 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.49–7.42 (m, 1H), 7.33–7.27 (m, 1H), 7.14 (s, 1H), 1.68 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.7, 137.8, 127.1, 127.0 (q, *J* = 39.2 Hz) 126.6, 123.7, 122.1, 120.9 (q, *J* = 267.8 Hz, CF_3), 116.2, 113.6 (q, *J* = 5.1 Hz), 85.6, 28.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –58.2 (s, 3F, CF_3). Spectroscopic data were identical to those previously reported.[132]

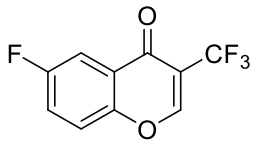
Tert-butyl-5-fluoro-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (3.59)



The title compound was prepared following the general procedure above, starting from *tert*-butyl-5-fluoro-3-iodo-1*H*-indole-1-carboxylate **3.32a** (1.88 g, 5.2 mmol) and $CuCF_3$ (22 mL, 8.32 mmol). The reaction mixture was stirred 16 h at room temperature and 8 h at 50 ºC. After standard work-up, the crude was purified by column chromatography (hexane) to afford **3.59** (1.50 g, 95%) as a white solid. M.p: 81–83 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 8.13 (dd, *J* = 9.1 Hz, *J* = 4.5 Hz, 1H), 7.97 (bd, *J* = 1.2 Hz, 1H), 7.34–7.28 (m, 1H), 7.10 (td, *J* = 9.1 Hz, *J* = 2.6 Hz, 1H), 1.71 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.7 (d, *J* = 241.2 Hz), 148.7, 131.8, 127.5 (q, *J* = 5.4 Hz), 126.3 (dq, *J* = 10.5 Hz, *J* = 1.8 Hz), 123.2 (q, *J* = 267.1 Hz, CF_3), 116.8 (d, *J* = 9.2 Hz), 113.7 (d, *J* = 25.2 Hz), 111.4 (qd, *J* = 37.3 Hz, *J* = 4.2 Hz), 105.4 (d, *J* = 25.2 Hz), 85.6, 28.1; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –59.5 (s, 3F), –118.7 (m, 1F); FT–IR (neat) ν in cm^{-1}: 3133, 2982, 1739, 1454, 1371, 1251, 1138, 1093, 844; HRMS (EI) for (M^+) $C_{14}H_{13}F_4NO_2^+$ (*m/z*): calc. 303.0882; found 303.0872.

[132] Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174–1176.

6-Fluoro-3-(trifluoromethyl)-4*H*-chromen-4-one (3.60)



The title compound was prepared following the general procedure above, starting from 6-fluoro-3-iodo-4*H*-chromen-4-one (54 mg, 0.186 mmol) and $CuCF_3$–0.6HF (0.98 mL, 0.36 mmol). The reaction mixture was stirred at room temperature for 15 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **3.60** (34.5 mg, 80%) as a white solid. M.p: 80–82 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 172.1, 160.3 (d, *J* = 247.8 Hz), 156.0 (q, *J* = 6.8 Hz), 152.3 (d, *J* = 2.1 Hz), 126.0 (appd, *J* = 52.3 Hz), 123.2 (d, *J* = 25.5 Hz), 122.2 (q, *J* = 272.5 Hz), 120.7 (d, *J* = 8.1 Hz), 115.6 (appd, *J* = 30.3 Hz), 111.4 (d, *J* = 24.8 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 159.7 (d, *J* = 241.2 Hz), 148.7, 131.8, 127.5 (q, *J* = 5.4 Hz), 126.3 (dq, *J* = 10.5 Hz, *J* = 1.8 Hz), 123.2 (q, *J* = 267.1 Hz, CF_3), 116.8 (d, *J* = 9.2 Hz), 113.7 (d, *J* = 25.2 Hz), 111.4 (qd, *J* = 37.3 Hz, *J* = 4.2 Hz), 105.4 (d, *J* = 25.2 Hz), 85.6, 28.1; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –64.5 (s, 3F), –112.7 (m, 1F); FT–IR (neat) ν in cm^{-1}: 3086, 2925, 1655, 1479, 1389, 1333, 1139, 1101, 961, 831, 716; HRMS (TOF ES+) for (M+H$^+$) $C_{10}H_5F_4O_2^+$ (*m/z*): calc. 233.0220; found 233.0217.

3.5.7. Mechanistic considerations and hydrodehalogenation of iodoindoles

General procedure: in a glove box, the corresponding $CuCF_3$–nHF reagent in DMF (0.67 mL, 0.2 mmol) was added to 3-iodoindole **1q** (24 mg, 0.2 mmol) and additive (0.2mmol). The vial was sealed, brought out of the glove box, and stirred overnight at the temperature indicated. The reaction was quenched by extraction with Et_2O/H_2O. The solvent was evaporated under reduced pressure and the crude analyzed by ^{1}H NMR to determine the hydrodehalogenation/trifluoromethylation (H/CF_3) ratio.

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Jordi Mestre Ventura

CHAPTER IV

The results included in this chapter are protected due to the possibility of generation of patents.

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CHAPTER VI

Stereoselective Synthesis of 2-Deoxyglycosides. Trifluoromethyl-Directed Glycosylation

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6.1. Introduction

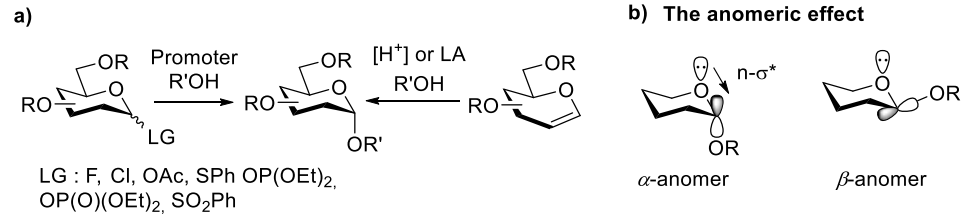
2-Deoxyglycosides are important biological structures present in natural products and, despite their prevalence, chemical synthesis is problematic since the absence of participating groups at position 2 limits the control of the stereoselectivity during the glycosylation reaction. Consequently, α/β anomeric mixtures are usually obtained.[1] Furthermore, given the particular lability of the glycosidic bond in 2-deoxyglycosides, soft reaction conditions are required to avoid its hydrolysis.

6.1.1. 2-Deoxy-α-glycosides

Generally, glycosylation of 2-deoxyglycosil donors under thermodynamic conditions predominantly furnish α-glycosides, which formation is favored by the anomeric effect.[2] This stability feature determines the axial preference of an electronegative substituent which arises from the occurrence of stabilizing n-σ^* hyperconjugation between the lone electron-pairs of the oxygen and the low-lying C–O antibonding orbital (Scheme 6.1b).[3] Different glycosyl donors have been described to produce mainly α-anomers (Scheme 6.1a).[4] A different approach is based on the activation of glycals with protic or Lewis acids to deliver α-anomers after the formation of an oxocarbenium ion intermediate.[5] The acid-catalyst used has to tolerate the newly produced and labile 2-

[1] Ernst, B; Hart, G. W.; Sinaý, P. Special Problems in Glycosylation Reactions: 2–Deoxy Sugars, in Carbohydrates in Chemistry and Biology, Wiley–VCH Verlag GmbH, Weinheim, Germany, 2000.
[2] Hou, D; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1911–1940.
[3] Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527–548.
[4] a) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni–Argirusi, G.; Kirschning, A. *Angew. Chem; Int. Ed.* **2003**, *42*, 1166–1170; b) Schene, H.; Waldmann, H. J. *Chem. Soc; Chem. Commun*. **1998**, 2759–2769; c) Bielawska, H.; Michalska, M. *Tetrahedron Lett.* **1998**, *39*, 9761–9764; d) Li, H.; Chan, M.; Zhao, K. *Tetrahedron Lett.* **1997**, *38*, 6143–6144.
[5] a) Yadav, J. S.; Subba Reddy, B. V.; Vijaya Bhasker, E.; Raghavendra, S.; Narsaiah, A. V. *Tetrahedron Lett.* **2007**, *48*, 677–680; b) Sherry, B. D.; Loy, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4510–4511; c) Colinas, P.; Bravo, R. D. *Org. Lett.* **2003**, *5*, 4509–4511.

deoxyglycoside linkage and Ferrier by-products tend to minimize the efficiency of this approach.



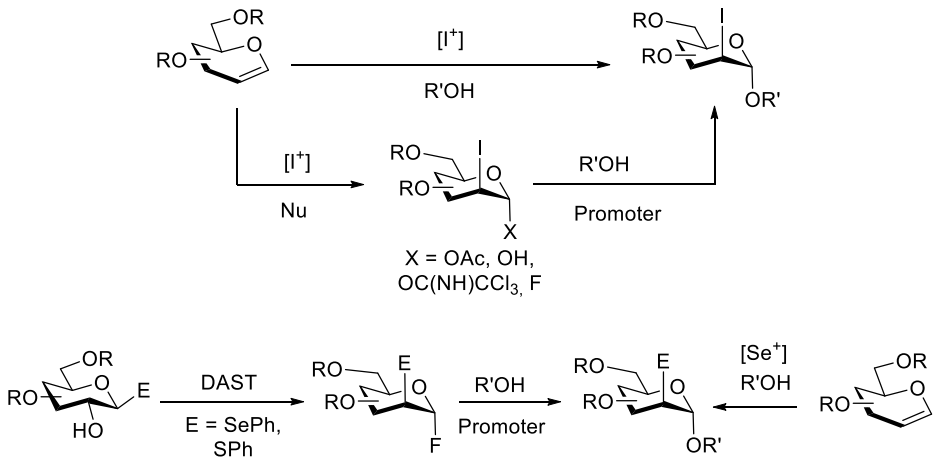
Scheme 6.1. Left: Common approaches for the synthesis of 2-deoxyglycosides; Right: Explanation of the anomeric effect.

Another strategy involves the use of temporary substituents at C–2 (halogen[6] and chalcogen[7] motifs) to control the stereoselectivity. These substituents are usually introduced by 1,2-migration or electrophilic addition to the more electronegative upper face of the enol ether moiety, Scheme 6.2. Hence, the new *axial* substituent forces the nucleophile to approach from the opposite face, resulting in the formation of 1,2-*trans* α-glycoside. In this regard, halonium, episulfonium, and selenonium cations have been proposed as intermediates to explain the stereoselectivity. Nonetheless, this issue generates controversy since computational studies demonstrated that the real intermediate is an oxonium cation, and the stereoselectively is governed by the steric hindrance of the neighboring substituent.[8]

[6] a) Battina, S. K; Kashyap, S. *Tetrahedron Lett.* **2016**, *57*, 811–814; b) Kimura, T; Takahashi, D; Toshima, K. *J. Org. Chem.* **2015**, *80*, 9552–9562; c) Sirion, U.; Purintawarrakun, S.; Sahakitpichan, P.; Saeeng, R. *Carbohydr. Res.* **2009**, *345*, 2401–2407; d) Friesen, R. W; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656–6660.

[7] a) Sau, A; Misra, A. K. *Carbohydr. Res.* **2012**, *361*, 41–48; b) Nicolaou, K. C; Mitchell, H. J; Fylaktakidou, K. C.; Suzuki, H. and Rodríguez, R. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1089–1093; c) Nicolaou, K. C; Fylaktakidou, K. C; Mitchell, H. J; van Delft, F. L; Rodríguez, R. M; Conley, S. R. and Jin, Z. *Chem. Eur. J.* ***2000***, *6,* 3166–3185; d) Nicolaou, K. C; Ladduwahetty, T; Randall, J. L; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466–2467.

[8] Bravo, F.; Viso, A.; Alcázar, E.; Molas, P.; Bo, C.; Castillón S. *J. Org. Chem.* **2003**, *68*, 686–691.



Scheme 6.2. Stereoselective synthesis of 2-deoxy-α–glycosides using temporary directing groups.

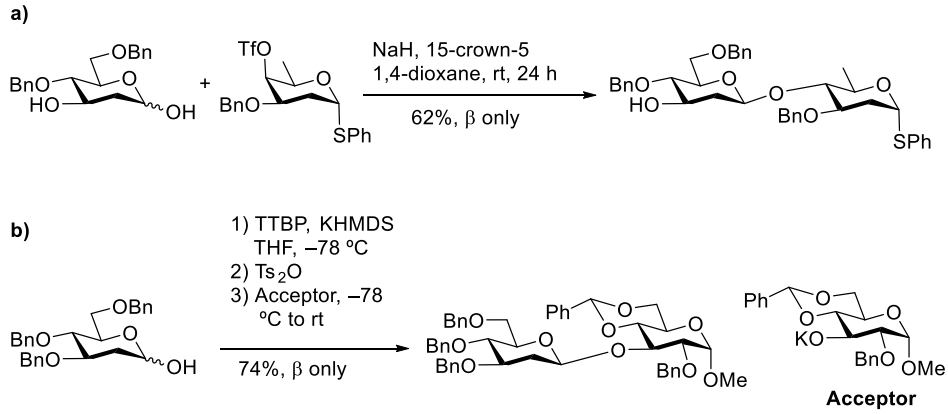
6.1.2. 2-Deoxy-β-glycosides

Stereoselective synthesis of 2-deoxy-β-glycosides is challenging because, in the absence of anchimeric assistance, the anomeric effect favors the formation of thermodynamic α–glycosides and the 2-deoxyanomeric linkage is prone to anomerize from the β-glycoside to the more stable α-epimer. Some reports highlight the use of 2-deoxyglycosyl donors and activation of glycals as approaches to access to β-glycosides although they lack from general applicability.[9]

Given the difficulties to stereoselectively obtain β-glycosides under conventional glycosylation conditions, more elaborated strategies have been described. Recently, β-glycosides have been prepared by *O*-alkylation of primary[10] and secondary[11] triflates owing to the enhanced

[9] a) Borovika, A; Nagorny, P. *J. Carbohydr. Chem.* **2012**, *31*, 255–283; b) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 2505–2507; c) Jaunzems, J.; Kashin, D.; Schönberger, A.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3435–3446; d) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979–3981; e) Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 3523–3525.
[10] Morris, W. J.; Shair, M. D. *Org. Lett.* **2009**, *11*, 9–12.
[11] Zhu, D; Baryal, K. N; Adhikari, S; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 3172–3175.

nucleophilicity of β-alkoxides (Scheme 6.3a). Bennet and Issa described the preparation of β-glycosides stereospecifically *via* a S_N2 displacement of a tosylate (formed *in situ*) by an alkoxide (Scheme 6.3b).[12]



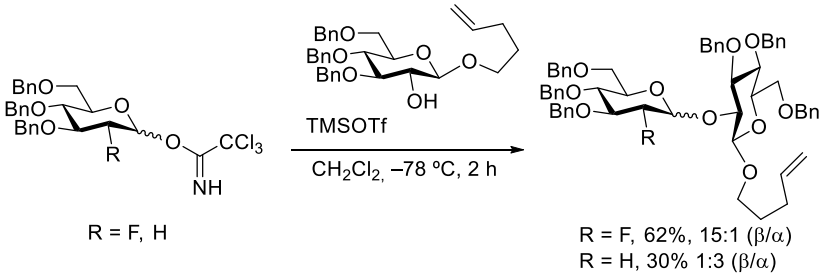
Scheme 6.3. Selected methods for the synthesis of 2-deoxy-β-glycosides.

The previously commented strategy based on the use of temporary groups at C–2 has also been applied to the preparation of 2-deoxy-β-glycosides. Halogen and chalcogen substituents serve as *β*-directing groups when positioned in *equatorial*.[13] However, this strategy is not general for β-glycosides since electrophilic addition to glycals generally introduces the substituent in axial position. Nevertheless, glycosyl donors bearing directing groups in equatorial positions have been successfully prepared starting from glycals protected with bulky silyl ether groups,[14] by acid-catalyzed ring-opening of 1,6-anhidro-2-

[12] Issa, J. P; Bennett, C. S. *J. Am. Chem. Soc.* **2014**, *136*, 5740−5744.
[13] a) Durham, T. B; Roush, W. R. *Org. Lett.* **2003**, *5*, 1875–1878; b) Guo, Y; Sulikowski, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 1392–1397; c) Roush, W. R; Lin, X.–F. *J. Am. Chem. Soc.* **1995**, *117*, 2236–2250; d) Sebesta, D. P; Roush, W. R. *J. Org. Chem.* **1992**, *57*, 4802–4809; e) Hashimoto, S; Yanagiya, Y; Honda, T; Ikegami, S. *Chem. Lett.* **1992**, *21*, 1511–1514.
[14] Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267–2274.

iodo-*gluco* derivatives,[15] or by iodination of 3,4-*O*-carbonate-protected glycals.[16]

The group of Ryan Gilmour has exploited the effect of fluorine on locking certain conformational intermediates by virtue of its high electronegativity and the occurrence of the *gauche* effect to achieve stereoselective transformations.[17] In 2010, this group reported a fluorine-directed glycosylation addressed by 2-deoxy-2-fluoroglycosyl trichloroacetimidates (Scheme 6.4).[18] High β-stereoselectivities were obtained for perbenzylated glucopyranoses whereas mannopyranoses bearing acetyl and pivaloyl protecting groups gave mainly α-anomers. According to the Anh–Eisenstein 1,2-induction model, fluorine adopts a pseudo-axial position, thus forcing the nucleophile to approach by alignment with the σ^*_{C-F} orbital. This strategy was also adapted for the glycosylation of galactopyranoses,[19] and rare sugars.[20]

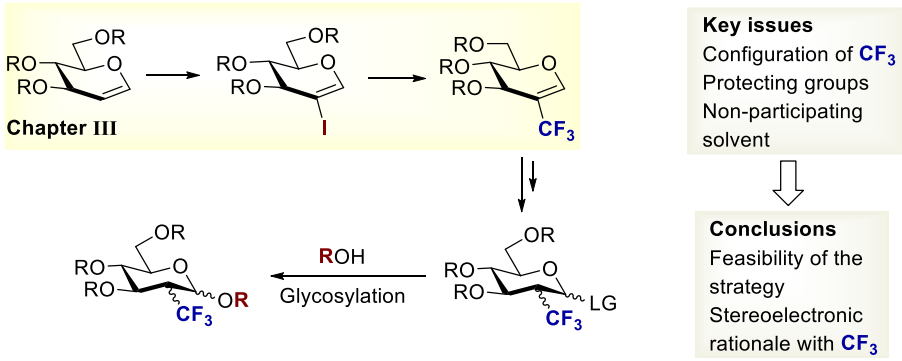


Scheme 6.4. Fluorine-directed glycosylation.

[15] Leteux, C.; Veyrières, A.; Robert, F. *Carbohydr. Res.* **1993**, *242*, 119–130.
[16] Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871–1874.
[17] a) Tanzer, E.–M.; Gilmour, R. *Chem. Eur. J.* **2012**, *18*, 2006–2013; b) Sparr, C.; Schweizer, W. B.; Senn, H. M.; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065–3068; c) Sparr, C.; Tanzer, E.–M.; Bachmann, J.; Gilmour, R. *Synthesis* **2010**, 1394–1397; d) Sparr, C.; Gilmour, R. *Angew. Chem.* **2010**, *122*, 6670; *Angew. Chem. Int. Ed.* **2010**, *49*, 6520–6523.
[18] Bucher, C., Gilmour, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 8724–8728.
[19] Durantie, E.; Bucher, C.; Gilmour, R. *Chem. Eur. J.* **2012**, *18*, 8208–8215.
[20] Aiguabella, N.; Holland, M. C.; Gilmour, R. *Org. Biomol. Chem.* **2016**, *14,* 5534–5538.

6.2. Objectives

This chapter deals with the derivatization of the trifluoromethyl glycals synthetized in Chapter III and their application for the preparation of trifluoromethyl-containing glycosides. The trifluoromethylation step can be performed using the CF_3H-derived $CuCF_3$ used in Chapter III or with the $TMSCF_3$/CuBr/KF system described in Chapter IV. Anticipating a high stereoelectronic effect imparted by the CF_3 group we sought to investigate the stereoselectivity in the glycosylation step depending on the configuration of the trifluoromethyl (*manno*- and *gluco*-) with both armed and disarmed glycosyl donors (Scheme 6.5). We also plan to compare the stereoselectivity of 2-trifluoromethylpyranoses with the corresponding 2-fluoroderivatives to gain insight on the stereoelectronic properties of both elements.



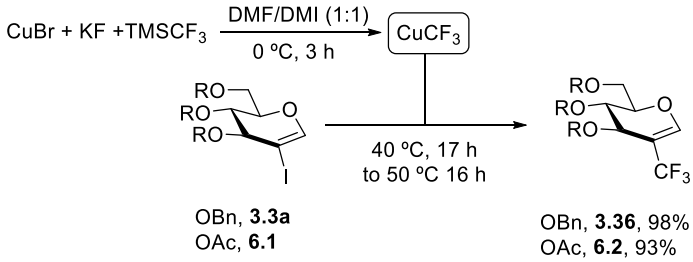
Scheme 6.5. Preparation of 2-trifluoromethylated glycosyl donors.

6.3. Results and discussion

6.3.1. Preparation of glycosyl donors

Preparative synthesis of trifluoromethyl glycals **3.36** and **6.2** was performed by the two-step iodination/trifluoromethylation sequence. Preparation of 2-iodoglycals was achieved following protocols described in Chapter III but the second stage was performed using $TMSCF_3$-derived

$CuCF_3$. This reagent was prepared in 89% in *ca*. 50 mmol scale and applied to the trifluoromethylation of **3.3a** and **6.1** in 98% and 93% yield, respectively (Scheme 6.6).



Scheme 6.6. Gram-scale preparation of **3.36** and **6.2**.

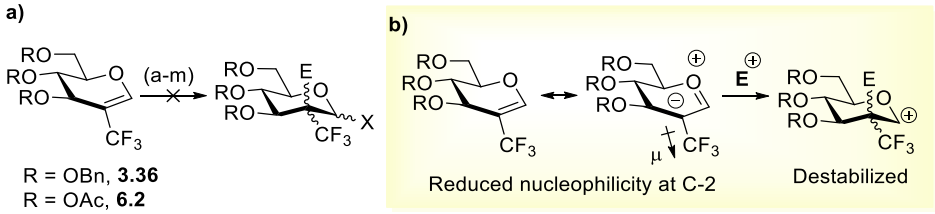
With trifluoromethylglycals **3.36** and **6.2** in hand, we tested various typical reactions applied to common glycals. The CF_3-containing vinyl moiety was reluctant to undergo general transformations including electrophilic halogenation, hydration and hydroboration (Scheme 6.7a). It is well known that polyfluorinated alkenes and aromatic compounds show reversed polarity, making them prone to nucleophilic attack under certain conditions.[21] Structural analysis of **3.36** and **6.2**, however, suggests a mismatch effect between the activating oxygen that increases the electron-density on the alkene through conjugation and the CF_3, which removes electron density by inductive effect, and at the same time, destabilizes the formation of a cationic intermediate upon electrophilic addition (Scheme 6.7b).[22]

After numerous failed reactions (Scheme 6.7), complete conversion of **6.1a** was obtained under hydroxymercuration conditions

[21] a) Sun, Y.; Sun, H.; Jia, J.; Du, A.; Li, X. *Organometallics,* **2014**, *33*, 1079−1081; b) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev*. **2015**, *115*, 931−972; c) Chambers, R. D.; Vaughan, J. F. S. *Top. Curr. Chem.* **1997**, *192*, 1–38.

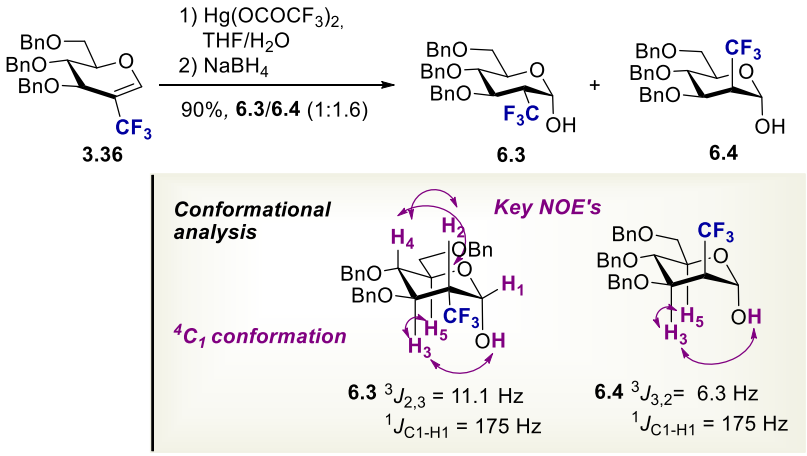
[22] a) Mercadante, M. A.; Kelly, C. B.; Hamlin, T. A.; Delle Chiaie, K. R.; Drago, M. D.; Duffy, K. K.; *et al. Chem. Sci*. **2014**, *5*, 3983–3994; b) Van Alem, K.; Belder, G.; Lodder, G.; Zuilhof, H. *J. Org. Chem*. **2005**, *70*, 179–190; c) Allen, A. D.; Fujio, M.; Mohammed, N.; Tidwell, T. T.; Tsuji, Y. *J. Org. Chem*. **1997**, *62*, 246–252; d) Paddon–Row, M. N.; Houk, K. N.; Tidwell, T. T. *Tetrahedron Lett*. **1982**, *23*, 383–386.

using $Hg(OCOCF_3)_2$ which gave a hydroxylated (1.6:1) mixture of *gluco*- and *manno*- pyranoses **6.3** and **6.4** (Scheme 6.8). NMR studies including NOESY, proton-coupled-HSQC and ^1H-^1H coupling constants where consistent with a $^4C_1$ conformation. Surprisingly only α-anomers were obtained and no epimerization was observed during the course of our studies.

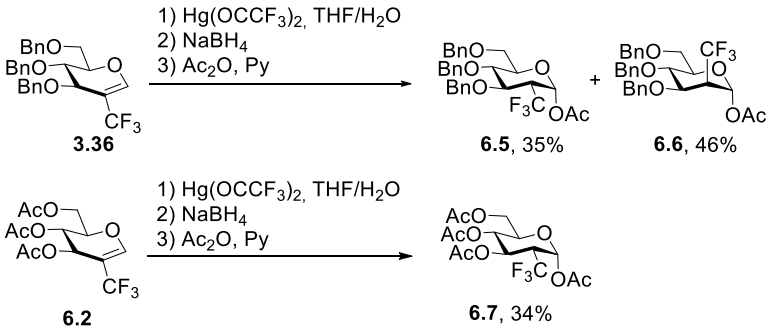


Scheme 6.7 a) Attempted reactions with **3.36** and **6.2**; a) Oxone, $NaHCO_3$, acetone in CH_2Cl_2/H_2O; b) MCPBA in MeOH; c) NaOCl in H_2O; d) PhIO in MeOH; e) Oxone, $NaHCO_3$, CF_3COCH_3 in CH_2Cl_2/H_2O f) DMDO in acetone; g) H_2O_2, NaOH, CH_2Cl_2; h) NIS, CH_3CN/H_2O, rt to 80 ºC; i) IDCP, CH_3CN/H_2O, rt to 80 ºC, j) NIS/TfOH, CH_3CN/ H_2O; k) NBS, $CH_3CN/H2O$, rt to 80 ºC; l) H_2SO_4, THF, rt to 85 ºC; m) BH_3·THF, THF, 0 ºC to rt; b) mismatched electronic effect in 2-trifluoromethylglycals.

The same strategy was applied to peracetylated glucal **6.2**. The hydroxymercuration step was very sluggish and acceptable conversion was only reached after increasing the concentration and the reaction time. The selectivity was rather poor and the crude showed Ferrier and other unidentified byproducts. Treatment of the reaction crude with Ac_2O/Py and purification by column chromatography afforded only the *gluco*- derivative **6.7** albeit in a low 34% yield.



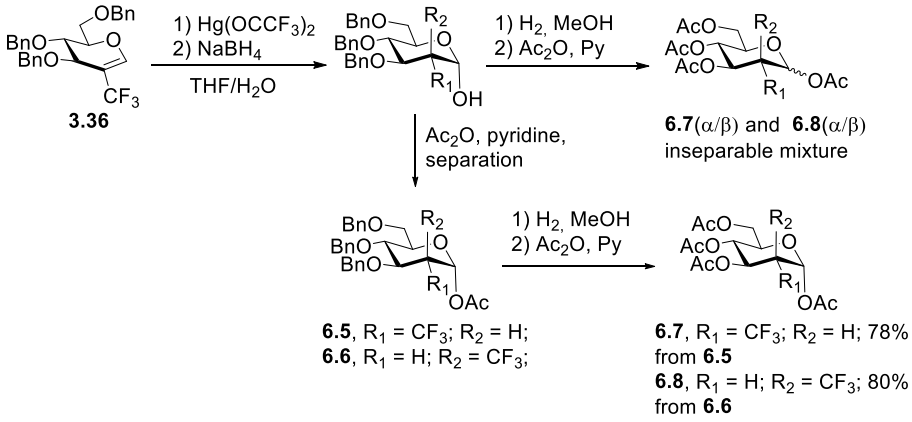
Scheme 6.8 Hydroxymercuration of **3.36** and conformational analysis of the products.



Scheme 6.9 Hydroxymercuration/acetylation sequence applied to **3.36** and **6.2**.

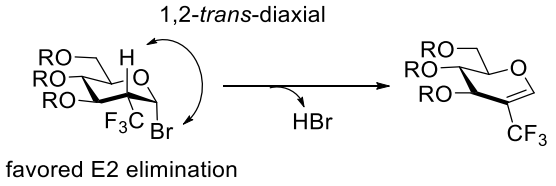
For accessing the *manno*-configured analog of **6.7** and improve the overall yield a different strategy was followed. Hydroxymercuration of **3.36** and sequential hydrogenolysis/acetylation afforded an inseparable mixture of four products consisting of an α/β mixture of both *manno*- and *gluco*-sugars **6.7** and **6.8**. Alternatively, the hydroxymercuration/acetylation sequence was applied to isolated **6.5**

and **6.6** and only α-anomers of **6.7** and **6.8** were obtained in 78% and 80% yield.



Scheme 6.10 Preparation of peracetylated pyranosides **6.7** and **6.8**.

Conversion of acetyl pyranosides **6.5**-**6.8** to the corresponding bromides was assayed using HBr in AcOH. Reaction control by TLC was essential for obtaining good yields, especially for armed pyranosides **6.5** and **6.6**, since the C–Br bond is easily activated under the reaction conditions. Bromination of *gluco* derivatives **6.5** and **6.7** was slower compared to the *manno* counterparts, probably as a result of the steric hindrance imparted by the neighboring CF_3. Moreover, formation of glycal **3.36** from **6.5** was favored due to the 1,2-transdiaxial disposition of the eliminating atoms. Considering these difficulties and the purification issues associated with benzylated-1-bromopyranosides we decided to perform the bromination and glycosylation in a stepwise manner, without isolation of bromide intermediates.



Scheme 6.11 Side-reaction during bromination of 1-acetoxy-2-trifluoromethylpyranosides.

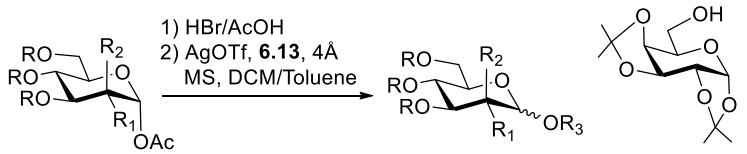
6.3.2. Glycosylation of 2-deoxy-2-trifluoromethylpyranoses

The glycosyl donors produced after treatment of **6.5**–**6.8** with HBr/AcOH were readily activated using AgOTf in DCM/toluene at –80 ºC in the presence of acceptor **6.13**. Reactions were completed within 3 h (TLC monitoring) and the α/β ratio, determined by ^{19}F NMR, and isolated yield are summarized in Table 6.1. As we anticipated, the selectivity was highly dependent on the configuration of the CF_3 and the protecting groups employed. β-selectivities were higher using *gluco* configured donors, whereas the *manno* epimers favored α-anomers. The stereoselectivity was also affected by the protecting groups. In this regard, the presence of benzyl ethers improved the β-selectivity compared to acetylated analogs within the same configuration. Thus, extreme situations are found using perbenzylated gluco-derivative **6.5a** (β-product favored, Table 6.1, entry 1) and peracetylated *manno*-derivative **6.6b** (α-product favored, Table 6.1, entry 4). Delightfully, anomers were separable by chromatographic techniques and pure diastereoisomers were isolated in good yields.

The configuration and conformation of the products were confirmed by ^{1}H, ^{13}C, HSQC, ^{1}H–coupled HSQC, HMBC, NOESY and COSY. $^{1}J_{C1,H1}$ values of 160–170 Hz are diagnostic of an axial anomeric proton that is associated with a β-glycoside adopting a $^{4}C_{1}$ conformation whereas $^{1}J_{C1,H1}$ > 170 Hz indicates an α-glycoside for the same conformation. The vicinal coupling constants and NOE contacts

suggested that all glycosylated products display the "normal" $^4C_1$ conformation (Figure 6.1).

Table 6.1 Bromination/glycosylation sequence of 1-acetoxy-pyranosides.



Entry	Donor	R	R_1	R_2	α/β [c]	% Yield (isomer)[d]
1	**6.5**	Bn	CF_3^{Gluco}	H	6:94	70 (**6.9β**)
2	**6.6**	Bn	H	CF_3^{Manno}	80:20	60 (**6.10α**), 16 (**6.10β**)
3	**6.7**	Ac	CF_3^{Gluco}	H	8:92	86 (**6.11β**)
4	**6.8**	Ac	H	CF_3^{Manno}	94:6	80 (**6.12α**)

[a]General condition for bromination (see experimental section for details); [b]General contionfs for ycosylation: Glycosyl donor (1 equiv), acceptor (3 equiv), AgOTf (2 equiv), in DCM/Toluene (1:1), –80 ºC, 3 h; [c]Determined by ^{19}F NMR; [d]Isolated yield after column chromatography.

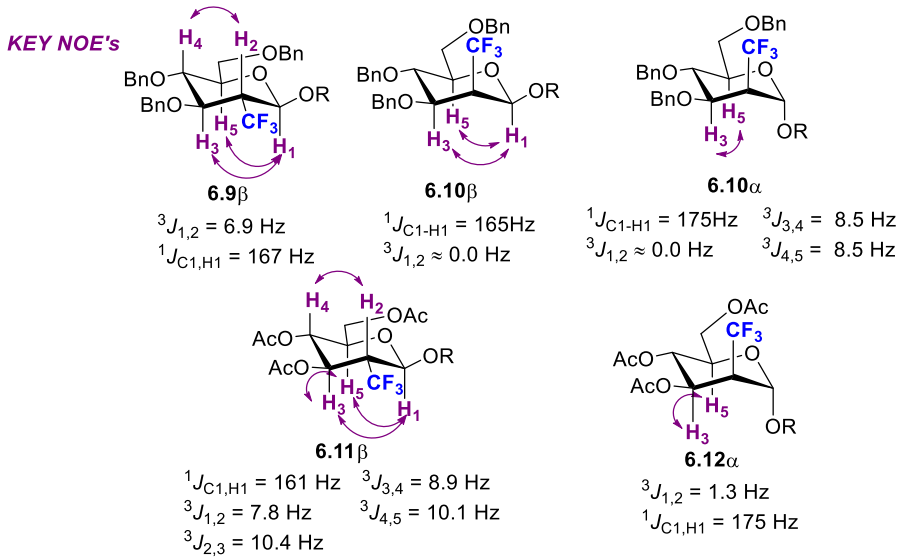


Figure 6.1. Structural analysis of glycosylated products.

Our findings are in agreement with the observations of Gilmour and coworkers in the glycosylation of 2-fluoroglycosyl donors.[23] Although they used trichloroacetimidates as leaving groups, the conditions employed were similar to the present study (triflate salt as Lewis Acid, non-participating solvent, glycosylation conducted at low temperature). Initially, we started our study also using trichloroacetimidate donors, however, their preparation from *gluco* derivatives was challenging, yet glycosylation of 3,4,6-tri-*O*-benzyl-2-trifluoromethyl-manno trichloroacetimidate gave similar selectivity, 68:32 (α/β), compared to that using bromide counterpart, 80:20 (α/β). Gilmour proposed a stereoselectivity model (Figure 6.2, left) based on the following considerations: after activation of the leaving group, the presence of benzyl ethers tends to stabilize the $^3H_4$ conformation due to electrostatic interactions between the partially charged oxygen on the ether and the cationic oxocarbenium.[24] On the other hand, acetoxy groups presumably prefer pseudo-equatorial positions on a $^4H_3$ conformation to avoid steric repulsions. According to the Anh–Eisenstein 1,2-induction model,[25] strong electron-withdrawing groups (*e.g.* F or CF_3) prefer to be antiperiplanar to the $\pi_{C=O}$ orbital (parallel to the $\pi^*_{C=O}$), to favor the approach of the entering nucleophile.

We compared the stereoselectivity depending on the group (F or CF_3) at C–2, Table 6.2. The extreme cases previously mentioned show comparable results with both CF_3 and F as substituents (Table 6.2, entries 1 and 4). However, differences are observed for intermediate situations. Glycosylation with a 2-deoxy-2-fluoromannose scaffold bearing OBn as protecting groups gives a slight preference for the β-product, but the trifluoromethylated analog **6.6** affords mainly the α-glycoside (Table 6.2,

[23] Bucher, C., Gilmour, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 8724–8728.
[24] D. M. Smith, K. A. Woerpel, *Org. Biomol. Chem.* **2006**, *4*, 1195–1201; b) L. Ayala, C. G. Lucero, J. Antionette, C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528; c) J. Antoinette, C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2000**, *122*, 168–169
[25] N. T. Ahn, O. Eisenstein, *Nouv. J. Chim.* **1977**, *1*, 61–70

entry 2). Furthermore, peracetylated 2-fluoroglucose gives a poor 34:66 (α/β) selectivity whereas trifluoromethylated counterpart **6.7** improved the selectivity to 8:92 (α/β), Table 6.2, entry 3. We attributed this difference to the sterically demanding CF_3 group, which increases the face differentiation of the nucleophile and thus, the selectivity not only results from electronic but also from steric effects.

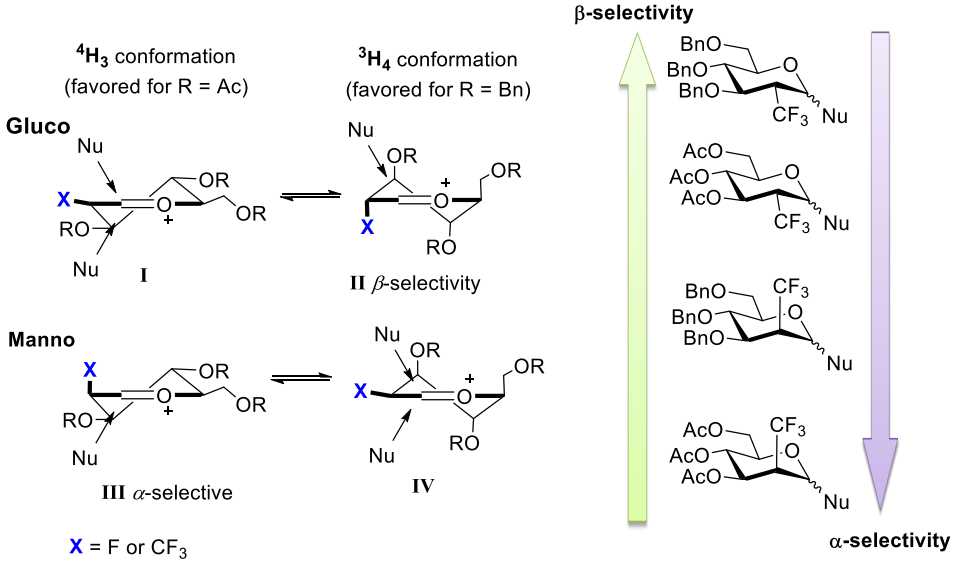
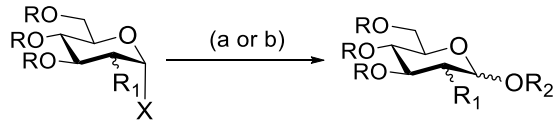


Figure 6.2 Left: Seteoselectivity model proposed by Ryan Gilmour and coworkers; Right: Stereoselectivity found in 2-CF_3 glycosides.

These observations suggest that the configuration of the CF_3 is more relevant that the effect imparted by the protecting groups, but the directing value of fluorine is not broadly predominant over that of substituents. This feature may be explained in terms of steric hindrance of CF_3, which largely amplifies the difference in energy of the transition states derived from the conformational intermediates $^4H_3$ and $^3H_4$. Hence, the major product results from the lowest TS (Curtin–Hammett principle) in which the glycosydic bond is always *trans* to the CF_3, regardless of the protecting groups. When the influence of the substituents matches with

the stereoelectronic effect of CF_3, the stereoselectivity is reinforced. On the other hand, fluorine control is mainly explained by electronic properties, making stereoselectivity more reliant on substituents. Hence, due to the lack of steric component of fluorine atom, the energy difference on the TS from configurational intermediates in the mismatched scenarios is lower for 2-fluorosugars.

Table 6.2. Comparison of the stereoselectivities using 2-fluoro or 2-trifluoromethyl glycosyl donors.



Entry	R	R_1, [**This work**]	α/β [a]	R_1, **[Gilmour]**	α/β [b]
1	Bn	CF_3^{Gluco}	6:94	F^{Gluco}	5:95
2	Bn	CF_3^{Manno}	80:20	F^{Manno}	24:76
3	Ac	CF_3^{Gluco}	8:92	F^{Gluco}	34:66
4	Ac	CF_3^{Manno}	94:6	F^{Manno}	α only

[a]Conditions a: Glycosyl bromide (1 equiv), acceptor (3 equiv), AgOTf (2 equiv), in DCM/Toluene (1:1), –80 ºC, 3 h; [b]Conditions b: glycosyl trichloroacetimidate (1 equiv), iPrOH (1.2 equiv), TMSOTf (0.1 equiv), DCM, –50 or –30 ºC, 2 h

6.4. Conclusions

In this chapter we have successfully implemented a strategy to functionalize poorly reactive 2-trifluoromethylglycals into suitable glycosyl donors for the preparation of CF_3-containg glycosides. The stereoselectivity of the hydroxymercuration step was rather poor but, far from entailing a disadvantage for the main objective of this project, it enabled access to pyranoses bearing both equatorial and axial CF_3. The availability of different trifluoromethyl configurations with both armed and disarmed pyranoses permitted the study of the stereoelectronic properties of the CF_3 under classical glycosylation conditions involving formation of an oxocarbenium intermediate. The results obtained were in

line with the findings of Ryan Gilmour and others, evidencing that fluorinated motif at C–2 have a strong influence in directing the glycosylation. However, the higher impact of CF_3 on the stereoselectivity compared to F might be explained by the combination of both electronic and steric factors.

6.5. Experimental section

6.5.1. General considerations

All reagents were purchased from Sigma Aldrich, Alfa Aesar and Carbosynth chemical companies. Dichloromethane (CH_2Cl_2) and tetrahydrofurane (THF) were dried using standard methods, acetonitrile was dried using activated 3 Å molecular sieves. CuBr was stirred overnight under argon in an excess of glacial acetic acid, and after filtration, the solid was washed with absolute ethanol, dry diethyl ether (Et_2O) and the white CuBr was dried under vacuum at 60 ºC. KF was dried under vacuum at 120 ºC overnight. ^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or on a Varian® NMR System 400 (400 MHz and 100.6 MHz respectively) spectrometer. NMR Spectra were fully assigned using COSY, HSQC and HMBC. Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, bt = broad triplet, bq = broad quadruplet and app = apparent. Infrared (IR) spectra were recorded on a JASCO FTIR–600 plus Fourier Transform Infrared Spectrophotometer. ESI-MS were run on an Agilent® 1100 Series LC/MSD instrument. Melting points (m.p.) were recorded with a Reichert apparatus. Optical rotations were measured on a Perkin–Elmer® 241 polarimeter in a 1 dm cell at 20ºC. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck® aluminium backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λmax = 254 nm) and/or by heating plates that were dipped in a H_2SO_4/ethanol (1:15). Flash chromatography was carried

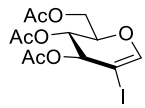
out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230–400 mesh).

Preparation of $CuCF_3$ reagent

DMF (25 mL) and DMI (25 mL) were added to a flask containing KF (3.56 g, 61.3 mol) and CuBr (8.79 g, 61.3 mol) under argon. The suspension was vigorously stirred at 0 ºC. $TMSCF_3$ (8.8 mL, 59.5 mmol) was slowly added and the mixture stirred for 3 h at 0 ºC. An aliquot (0.6 mL) was transferred to an NMR tube under argon and BTB (20 µL, 0.129 mmol) was added and the tube caped with a rubber septum. The $CuCF_3$ was produced in 89% yield as determined by quantitative ^{19}F NMR analysis. The batch solution was transferred to a schlenk under argon and kept at –30 ºC.

6.5.2. Synthetic procedures and characterization of compounds

3,4,6-Tri-*O*-acetyl-2-iodo-D-glucal (6.1)

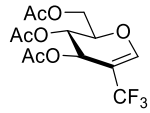


NIS (4.95 g, 22 mmol) and $AgNO_3$ (0.62 g, 3.65 mmol) were added under argon atmosphere to a solution of 3,4,6-Tri-*O*-acetyl-D-glucal (5.0 g, 18.36 mmol) in dry CH_3CN (50 mL) at room temperature. The reaction mixture was warmed up to 80 ºC and stirred for 4 h. The crude was filtered through a short path of Celite® 545 and the solvent evaporated. The residue was purified by column chromatography using (2:8 EtOAc/hexanes) to afford **6.1** (4.3 g, 59%) as a colorless syrup.

R_f (2:3 EtOAc/hexanes): 0.46; ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.69 (d, $J_{1,3}$ = 1.1 Hz, 1H, H–1), 5.36 (d, $J_{3,4}$ = 5.1 Hz, 1H, H–3), 5.10 (appt, J = 6.4 Hz, 1H, H–4), 4.35–4.23 (m, 2H, H–6a and H–5), 4.07 (dd, $J_{6b,a}$ = 14.6 Hz, $J_{6b,5}$ = 5.6 Hz, 1H, H–6b), 2.00, 1.96, 1.96 (s, 9H, $3CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.1, 169.6, 169.1 (3C=O), 149.1 (C–1), 73.7 (C–5),

70.3 (C–3), 67.30 (C–4), 66.2 (C–2), 60.7 (C–6), 20.7, 20.6, 20.5 ($3CH_3$, Ac). Spectroscopic data are in agreement with that reported.[26]

3,4,6-Tri-*O*-acetyl-2-trifluoromethyl-D-glucal (6.2)

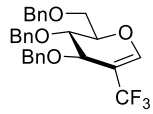


A round-bottom flask containing **6.1** (3.3 g, 8.29 mmol) was evacuated and backfilled with argon 4 times. DMI (20 mL) and $CuCF_3$ solution (20 mL, 16.6 mmol) were succesevely added and the mixture was shaken to complete homogeneity. The reaction was heated without stirring at 40 ºC for 17 h and then the temperature raised to 50 ºC for additional 16 h. Saturated aqueous NH_4Cl was slowly added at 0 ºC and the crude extracted with Et_2O dried over Na_2SO_4 and the solvent evaporated. Purification by column chromatography (3:7 EtOAc/hexanes) gave **6.2** (2.62 g, 93%) as a colorless syrup.

R_f (2:3 EtOAc/hexanes): 0.47; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.17 (q, $J_{1,F}$ = 1.5 Hz, 1H, H–1), 5.57 (d, $J_{3,4}$ = 3.4 Hz, 1H, H–3), 5.16 (t, $J_{4,5}$ = $J_{4,3}$ = 3.5 Hz, 1H, H–4), 4.54–4.49 (m, 1H, H–5), 4.45 (dd, $J_{6a,b}$ = 12.0 Hz, $J_{6a,5}$ = 7.6 Hz, 1H, H–6a), 4.20 (dd, $J_{6b,a}$ = 12.0 Hz, $J_{6b,5}$ = 4.2 Hz, 1H, H–6b), 2.10, 2.10, 2.08 (s, 9H, $3CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.5, 169.4, 169.4 (3C=O), 149.4 (q, J = 6.8 Hz, C–1), 123.9 (q, J = 270.1 Hz, CF_3), 102.1 (q, J = 32.0 Hz, C–2), 74.4 (C–5), 65.8 (C–4), 61.3 (C–3), 60.8 (C–6), 20.9, 20.8, 20.8 ($3CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –63.6 (s, 3F). Spectroscopic data were in agreement with those reported.[27]

[26] Dharuman, S. Vankar, Y.D. *Org. Lett.*, **2014**, 16, 1172–1175.
[27] Wang, B., Xiong, D.–C., Ye, X.–S. *Org. Lett.* **2015**, *17*, 5698–5701.

3,4,6-Tri-*O*-benzyl-2-trifluoromethy-D-glucal (3.36)

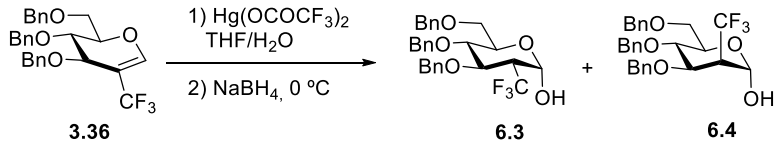


A round-bottom flask containing **3.3a**[28] (4.1 g, 7.55 mmol) was evacuated and backfilled with argon 4 times. DMI (18 mL) and $CuCF_3$ solution (18.2 mL, 15.1 mmol) were succesevely added and the mixture was shaken to complete homogeneity. The reaction was heated without stirring at 40 ºC for 17 h and then the temperature raised to 50 ºC for additional 16 h. Saturated aqueous NH_4Cl was slowly added at 0 ºC and the crude extracted with Et_2O dried over Na_2SO_4 and the solvent evaporated. Purification by column chromatography (1:15 EtOAc/hexanes) gave **3.36** (3.61 g, 98%) as a colorless syrup.

R_f (1:4 EtOAc/hexanes): 0.43; ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.21 (m, 15H, ArH), 7.07 (bq, $J_{1,F}$ = 1.5 Hz, 1H, H–1), 4.59–4.44 (m, 7H, 3CH_2Ph, H–5), 4.10 (bs, 1H, H–3), 3.90 (appt, $J_{3,4}$ = $J_{4,5}$ = 3.2 Hz, 1H, H–4), 3.78 (dd, $J_{6a,b}$ = 10.5 Hz, $J_{5,6a}$ = 6.9 Hz, 1H, H–6a), 3.67 (dd, $J_{6a,b}$ = 10.5 Hz, $J_{5,6b}$ = 5.1 Hz, 1H, H–6b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 148.1 (q, $J_{1,F}$ = 7.2 Hz, C–1), 137.8, 137.6, 137.4 (C, Ar), 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0 127.9, 127.8 (CH, Ar), 125.0 (q, $J_{C,F}$ = 269.9 Hz, CF_3), 103.6 (q, $J_{2,F}$ = 30.7 Hz, C–2), 76.5 (C–5), 73.4, 72.4, 72.2 (3CH_2Ph), 71.2 (C–4), 68.9 (C–3), 71.2 (C–4), 68.9 (C–3), 67.7 (C–6); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.6 (s, CF_3); Spectroscopic data were in agreement with those reported.[27]

[28] Preparation of **3.3a** is described in Chapter III.

Oxymercuration of 3.36



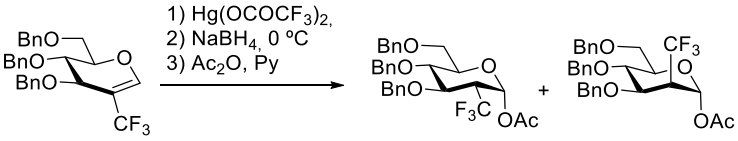
To a stirred solution of **3.36** (32 mg, 0.066 mmol) in THF (1 mL) was added a solution of $Hg(OCOCF_3)_2$ (42.3 mg, 0.099 mmol) in water (0.3 mL) at 0 ºC. The mixture was stirred 36 h at room temperature. H_2O (0.2 mL) was then added followed by portionwise addition of $NaBH_4$ (16 mg, 0.416 mmol) at 0 ºC and the mixture stirred at this temperature for 20 min. The crude was concentrated under vacuum and diluted with 1:1 (v/v) EtOAc/H_2O (10 mL) and the aqueous phase extracted successively with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and the solvent evaporated. The crude was purified using column chromatography (1:4 EtOAc/hexanes) to give a chromatographically inseparable **6.3**/**6.4** (1:1.6) mixture (30 mg, 90%) as a white solid. The solid was dissolved in hot hexanes and cooled to 4 ºC until precipitation ceased. The precipitate was separated and washed with cold hexanes to afford **6.3** as a white solid. The washings were combined with the previous mother liquor hexanes solution, the solvent evaporated and the whole process was repeated 5 times to afford additional **6.3** and pure fraction of **6.4** as a colorless syrup. The purification afforded **6.3** (9.9 mg, 30%) and **6.4** (12.9 mg, 39%).

(6.3): R_f (3:7 EtOAc/hexanes): 0.31; m.p: 151–153 ºC; $[\alpha]_D^{25}$: +18.1 (0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.37 (m, 15H, ArH), 5.52 (appt, $J_{1,OH}$= 3.5 Hz, $J_{1,2}$= 3.5 Hz, 1H, H–1), 4.85–4.48 (m, 6H, 3CH_2Ph), 4.23 (dd, $J_{2,3}$= 11.1 Hz , $J_{3,4}$= 9.0 Hz, 1H, H–3), 4.11 (ddd, $J_{4,5}$= 10.0 Hz, $J_{5,6a}$= 4.4 Hz, $J_{5,6b}$= 2.3 Hz, 1H, H–5), 3.70 (dd, $J_{6a,b}$ = 10.6 Hz, $J_{5,6a}$ = 4.4 Hz, 1H, H–6a), 3.67–3.58 (m, 2H, H–6b, H–4), 2,83 (dd, $J_{1,OH}$= 3.5 Hz, 1H, OH), 2.67 (m, 1H, H–2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.0, 137.9, 137.8 (C, Ar), 128.6, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9 (CH, Ar), 125.2 (q, $^1J_{C,F}$ = 280.1 Hz, CF_3), 90.3 (q, $^3J_{C,F}$ = 4.1 Hz, C–1), 79.1 (C–4), 77.4 (CH_2Ph), 76.2 (C–3), 75.3, 73.7 (2CH_2Ph), 71.1 (C–5), 68.7 (C–6), 50.2 (q, $^2J_{C,F}$ = 24.9

Hz, C–2); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –63.8 (d, $J_{F,2}$= 8.2 Hz, 3F); FT–IR (neat) *v* in cm^{-1}: 3353, 2944, 2867, 1463, 1190, 1103, 881; HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{28}H_{29}F_3NaO_5^+$ (*m/z*): calc. 525.1859; found 525.1857.

(6.4): R_f (3:7 EtOAc/hexanes): 0.31; $[\alpha]_D^{25}$: +14.3 (0.24, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38–7.11 (m, 15H, ArH), 5.58 (appt, $J_{1,OH}$= 3.4 Hz, 1H, H–1), 4.79–4.36 (m, 6H, $3CH_2Ph$), 4.20 (appt, $J_{3,2}$ = $J_{3,4}$ = 7.4 Hz, 1H, H–3), 4.07 (ddd, $J_{4,5}$ = 7.8 Hz, $J_{5,6a}$ = 5.7 Hz, $J_{5,6a}$ = 3.0 Hz, 1H, H–5), 3.74 (appt, $J_{3,4}$ = $J_{4,5}$ = 7.8 Hz, 1H, H–4), 3.65 (dd, $J_{6a,b}$= 10.2 Hz, $J_{5,6a}$ = 3.0 Hz, 1H, H–6a), 3.62 (dd, $J_{6a,b}$ = 10.2 Hz, $J_{5,6b}$ = 5.7 Hz, 1H, H–6b), 3.03 (d, $J_{1,OH}$= 3.4 Hz, 1H, OH), 2.95 (m, 1H, H–2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1, 138.0, 137.6 (3 X C–Ar), 128.6, 128.5, 128.2, 128.1, 128.8, 128.0, 127.9, 127.8 (CH–Ar), 125.7 (q, $^1J_{C,F}$ = 281.3 Hz, CF_3), 90.4 (q, $^3J_{C,F}$ = 4.6 Hz, C–1), 75.9 (C–3), 74.6 (C–4), 74.5, 73.5, 72.3 (3 X CH_2Ph), 71.5 (C–5), 69.6 (C–6), 46.3 (q, $^2J_{C,F}$ = 24.2 Hz, C–2); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.3 (d, $J_{F,2}$= 10.5 Hz, 3F); FT–IR (neat) *v* in cm^{-1}: 3385, 3031, 2924, 1454, 1365, 1263, 1158, 1097; HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{28}H_{29}F_3NaO_5^+$ (*m/z*): calc. 525.1859; found 525.1864.

Oxymercuration/acetylation sequence of 3.36



3.36 **6.5** **6.6**

To a stirred solution of **3.36** (3.23 g, 6.66 mmol) in THF (40 mL) was added a solution of $Hg(OCOCF_3)_2$ (4.26 g, 10 mmol) in H_2O (20 mL) at 0 ºC. The mixture was stirred 36 h at room temperature. H_2O (0.2 mL) was then added followed by portionwise addition of $NaBH_4$ (1.5 g, 40 mmol) at 0 ºC and the mixture stirred at this temperature for 20 min. The crude was concentrated under vacuum and diluted with 1:1 (v/v) EtOAc/H_2O (60 mL) and the aqueous phase extracted successively with EtOAc. The

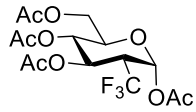
combined organic layers were dried with Na_2SO_4, filtered and the solvent evaporated. The crude was dissolved in pyridine (22.9 mL) and Ac_2O (2.26 mL) was added and the reaction mixture stirred at room temperature for 15 h. The solvent was then evaporated under vacuum and the residue dissolved in EtOAc and washed with saturated aqueous $CuSO_4$, NH_4Cl and NaCl. The organic phase was dried with Na_2SO_4, filtered, the solvent evaporated and the crude purified using column chromatography (1:9 EtOAc/hexanes) to give pure fractions of **6.5** (1.26 g, 35%) and **6.6** (1.67 g, 46%).

6.5: White solid. R_f (1:4 EtOAc/hexanes): 0.44; m.p: 114–116 ºC; $[\alpha]_D^{25}$: +74.9 (0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.15 (m, 15H, ArH), 6.44 (d, $J_{1,2}$ = 3.2 Hz, 1H, H–1), 4.89–4.81 (m, 2H, 2CHPh), 4.77 (d, $J_{a,b}$ = 10.2 Hz, 1H, CHPh), 4.63 (d, $J_{a,b}$ = 12.0 Hz, 1H, CHPh), 4.58 (d, $J_{a,b}$ = 10.7 Hz, 1H, CHPh), 4.50 (d, $J_{a,b}$ = 12.0 Hz, 1H, CHPh), 4.22 (m, 1H, H–3), 3.90–3.78 (m, 3H, H–4, H–5 and H–6a), 3.67 (bd, $J_{6b,a}$ = 10.9 Hz, H–6b), 2.85 (m, 1H, H–2), 2.13 (s, 3H, CH_3, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 168.5 (C=O, Ac), 137.9, 137.8, 137.7 (C, Ar), 128.6, 128.6, 128.5, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9 (CH, Ar), 124.7 (q, $J_{C,F}$ = 281.0 Hz, CF_3), 88.7 (q, $J_{C,F}$ = 4.7 Hz, C–1), 78.1 (C–4), 76.5 (C–3), 75.5, 75.4, 73.7 ($3CH_2Ph$), 73.3 (C–5), 67.9 (C–6), 49.11 (q, $J_{C,F}$ = 25.0 Hz, C–2), 20.9 (CH_3, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –63.9 (d, $J_{F,H2}$ = 8.25 Hz, 3F, CF_3); FT–IR (neat) *v* in cm^{-1}: 3063, 3032, 2870, 2361, 2331, 1757, 1455, 1367, 1221, 1156, 1116, 954, 738; HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{30}H_{31}F_3NaO_6^+$ (*m/z*): calc. 567.1965; found 567.1964.

6.6: Colorless syrup. R_f (1:4 EtOAc/hexanes): 0.35; $[\alpha]_D^{25}$: +41.4 (1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.45–7.15 (m, 15H, ArH), 6.53 (d, $J_{1,2}$ = 3.3 Hz, 1H, H–1), 4.75 (d, $J_{a,b}$ = 11.0 Hz, 1H, CHPh), 4.74 (d, $J_{a,b}$ = 11.1 Hz, 1H, CHPh), 4.63 (d, $J_{a,b}$ = 12.0 Hz, 1H, CHPh), 4.59 (d, $J_{a,b}$ = 11.1 Hz, 1H, CHPh), 4.53 (d, $J_{a,b}$ = 12.0 Hz, 1H, CHPh), 4.47 (d, $J_{a,b}$ = 11.0 Hz, 1H, CHPh), 4.17 (appt, $J_{2,3}$ = $J_{3,4}$ = 5.6 Hz, 1H, H–3), 4.01–3.90 (m, 2H, H–4 and H–5), 3.75 (dd, $J_{6a,b}$ = 11.0 Hz, $J_{6a,5}$ = 4.2 Hz, 1H, H–6a), 3.69 (dd, $J_{6b,a}$ = 11.1 Hz, $J_{6b,5}$ = 2.3 Hz, 1H, H–6b), 2.99 (m, 1H, H–2), 2.10 (s, 3H, CH_3, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 168.8 (C=O, Ac), 138.2, 137.8,

137.3 (C, Ar), 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 127.8, 127.7 (C, Ar), 125.2 (q, $J_{C,F}$ = 281.2 Hz, CF_3), 89.6 (q, $J_{C,F}$ = 4.4 Hz, C–1), 75.5 (C–3), 74.5 (CH_2Ph), 73.9 (C–5), 73.8 (C–4), 73.5, 72.4 ($2CH_2Ph$), 68.9 (C–6), 45.12 (q, $J_{C,F}$ = 24.7 Hz, C–2), 21.0 (CH_3, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –69.6 (bs, 3F, CF_3); FT–IR (neat) *v* in cm^{-1}: 3032, 2870,2361, 1758, 1222, 1173, 1118, 1010, 954, 740, 698; HRMS (TOF ES^+) for $(M+Na)^+$ $C_{30}H_{31}F_3NaO_6^+$ (*m/z*): calc. 567.1965; found 567.1964.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-trifluoromethyl-D-glucopyranose (6.7)

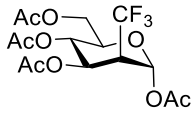


10% Pd/C (33 mg, 0.03 mmol Pd) was added to a solution of **6.5** (180 mg, 0.33 mmol) in dry and deoxygenated methanol (4 mL) at room temperature. The mixture was stirred under H_2 (1 atm) at the same temperature for 16 h, filtered through a short path of Celite® 545, and concentrated under reduced pressure. The crude was dissolved in pyridine (1 mL) and Ac_2O (0.23 mL) was added and the reaction stirred at room temperature overnight. Pyridine was then evaporated under vacuum and the residue dissolved in EtOAc and washed with saturated aqueous $CuSO_4$, NH_4Cl and NaCl. The organic phase was dried with Na_2SO_4, filtered, the solvent evaporated and the crude purified using column chromatography (3:7 EtOAc/hexanes) to give **6.7** (103 mg, 78%) as a white solid.

R_f (3:7 EtOAc/hexanes): 0.35; m.p: 94–96; $[\alpha]_D^{25}$: +111.2 (0.24, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.45 (d, $J_{1,2}$ = 3.4 Hz, 1H, H–1), 5.70 (dd, $J_{3,2}$ = 11.4 Hz, $J_{3,4}$ = 9.3 Hz 1H, H–3), 5.11 (appt, $J_{4,5}$ = $J_{4,3}$ = 9.5 Hz, 1H, H–4), 4.31 (dd, $J_{6a,b}$ = 12.3 Hz, $J_{6a,5}$ = 3.8 Hz, 1H, H–6a), 4.12–4.01 (m, 2H, H–5 and H–6b), 3.04–2.92 (m, 1H, H–2), 2.16, 2.08, 2.05, 2.04 (s, 12H, $4CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.7, 169.7, 169.7, 168.1 (4C=O, Ac), 123.7 (q, $J_{C,F}$ = 281.1 Hz, CF_3), 87.7 (q, $J_{C,F}$ = 4.3 Hz, C–1), 69.7 (C–5),

68.3 (C–4), 66.7 (bq, $J_{C,F}$ = 2.0 Hz, C–3), 61.5 (C–6), 47.7 (q, $J_{C,F}$ = 26.2 Hz, C–2), 20.8, 20.7, 20.7 ($4CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –65.3 (d, $J_{2,F}$ = 7.5 Hz, 3F, CF_3); FT–IR (neat) *v* in cm^{-1}: 2970, 1759, 1370, 1221, 1178, 1014, 938; HRMS (TOF ES^+) for $(M+Na)^+$ $C_{15}H_{19}F_3NaO_9^+$ (*m/z*): calc. 423.0873; found 423.0880.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-trifluoromethyl-D-mannopyranose (6.8)

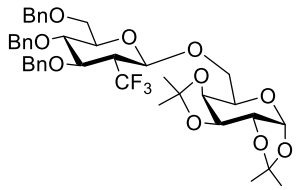


10% Pd/C (124 mg, 0.11 mmol Pd) was added to a solution of **6.6** (680 mg, 1.24 mmol) in dry and deoxygenated methanol (12 mL) at room temperature. The mixture was stirred under H_2 (1 atm) at the same temperature for 16 h, filtered through a short path of Celite® 545, and concentrated under reduced pressure. The crude was dissolved in pyridine (4.20 mL) and Ac_2O (0.9 mL) was added and the reaction stirred at room temperature overnight. Pyridine was then evaporated under vacuum and the residue dissolved in EtOAc and washed with saturated aqueous $CuSO_4$, NH_4Cl and NaCl. The organic phase was dried with Na_2SO_4, filtered, the solvent evaporated and the crude purified using column chromatography (3:7 EtOAc/hexanes) to give **6.8** (400mg, 80%) as a colorless syrup.

R_f (3:7 EtOAc/hexanes): 0.26; $[\alpha]_D^{25}$: +58.2 (0.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 6.45 (d, $J_{1,2}$ = 2.0 Hz, 1H, H–1), 5.47–5.31 (m, 2H, H–3, H–4), 4.20–4.10 (m, 2H, H–6a, H–6b), 4.03 (m, 1H, H–5), 3.14 (m, 1H, H–2), 2.16, 2.06, 2.06 (s, 12H, $4CH_3$, Ac); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.7, 170.2, 169.4, 168.2 ((4C=O, Ac), 124.4 (q, $J_{C,F}$ = 281.3 Hz, CF_3), 88.9 (q, $J_{C,F}$ = 4.5 Hz, C–1), 70.5 (C–5), 67.4 (C–3), 65.4 (C–4), 62.0 (C–6), 45.2 (q, $J_{C,F}$ = 25.5 Hz, C–2), 20.9, 20.8, 20.7 ($4CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.8 (d, $J_{2,F}$ = 9.3 Hz, 3F); FT–IR (neat) *v* in cm^{-1}: 2969, 1749,

1371, 1220, 1159, 1125; HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{15}H_{19}F_3NaO_9^+$ (*m/z*): calc. 423.0873; found 423.0872.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trifluoromethyl-β-D-glucopyranosyl-(1→6)-[1:2,3:4]-di-*O*-isopropylidene-α-D-galactopyranoside (6.9β)

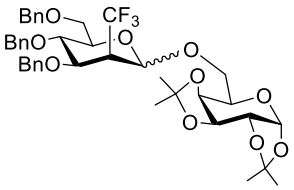


To a solution of **6.5** (26 mg, 0.0477 mmol) in CH_2Cl_2 (1.4 mL) was added 33% HBr in AcOH (83 µL) at 0 °C. The reaction was stirred at room temperature for 3 h. The crude was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$ was added at 0 °C. The two phases were separated and the aqueous layer successively extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated. The resulting crude was azeotropically dried with toluene, maintained under high vacuum for 3 h, dissolved in CH_2Cl_2 (0.5 mL) and transferred under argon to a Schlenk containing acceptor **6.13** (37 mg, 0.142 mmol) and activated 4Å MS. The solution was stirred at –80 °C for 30 minutes and azeotropically dried AgOTf (24 mg, 0.095 mmol) was dissolved in dry toluene (0.5 mL) and the solution transferred to the Schlenk *via* cannula under argon. The reaction was stirred at –80 °C for 2 h, diluted with CH_2Cl_2, filtered through a short path of silica and the solvent evaporated. An α/β (6:94) ratio was determined by ^{19}F NMR. The crude was purified by column chromatography (1:4 EtOAc/hexanes) to give **6.9β** (25 mg, 70%) as a colorless syrup.

R_f (1:4 EtOAc/hexanes): 0.29; $[\alpha]_D^{25}$: +44.5 (1.76, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.36–7.15 (m, 15H, ArH), 5.52 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H–1'), 4.81 (d, $J_{1,2}$ = 6.9 Hz, 1H, H–1), 4.81–4.52 (m, 7H, $3CH_2Ph$ and H–3'), 4.30 (dd, $J_{1',2}$ = 4.9 Hz, $J_{2',3'}$ = 2.4 Hz, 1H, H–2'), 4.12 (dd, $J_{3',4'}$ = 8.0 Hz, $J_{4',5'}$ = 1.7 Hz, 1H, H–4'), 4.03 (dd, $J_{6a,b}$ = 11.0 Hz, $J_{5,6a}$ = 4.7 Hz, 1H, H–6a), 3.96

(m, 1H, H–5'), 3.89–3.80 (m, 2H, H–3 and H–4), 3.77–3.68 (m, 3H, H–6b, H–6a' and H–6b'), 3.56 (m, 1H, H–5), 2.68 (m, 1H, H–2), 1.52, 1.43, 1.33, 1.31 (s, 12H, $4CH_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.2, 138.1, 137.9 (C, Ar), 128.6, 128.5, 128.5, 128.0, 127.9, 127.9, 127.8, (CH, Ar), 125.6 (q, $J_{C,F}$ = 281.7 Hz, CF_3), 109.4, 108.8 ($2C_{ketal}$), 98.2 (q, J = 2.7 Hz, C–1), 96.4 (C–1'), 78.3 (C–3), 78.2 (C–4), 75.0 (C–5), 74.8, 74.5, 73.6 ($3CH_2Ph$), 71.3 (C–4'), 70.8 (C–3'), 70.6 (C–2'), 69.1 (C–6), 68.1 (C–6'), 67.6 (C–5'), 51.3 (q, $J_{C,F}$ = 23.6 Hz, C–2), 26.1, 26.0, 25.2, 24.5 ($4CH_3$'); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –61.2 (d, $J_{F,2}$ = 8.49 Hz, 3F); HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{30}H_{31}F_3NaO_6^+$ (*m/z*): calc. 767.3014; found 767.3008.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-trifluoromethyl-α/β-D-mannopyranosyl-(1→6)-[1:2,3:4]-di-*O*-isopropylidene-α-D-galactopyranoside (6.10)



To a solution of **6.6** (89 mg, 0.163 mmol) in CH_2Cl_2 (4.8 mL) was added 33% HBr in AcOH (260 μL) at 0 ºC. The reaction was stirred at room temperature for 30 minutes. The crude was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$ was added at 0 ºC. The two phases were separated and the aqueous layer successively extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated. The resulting crude was azeotropically dried with toluene, maintained under high vacuum for 3 h, dissolved in CH_2Cl_2 (1.6 mL) and transferred under argon to a schlenk containing acceptor **6.13** (127 mg, 0.489 mmol) and activated 4Å MS. The solution was stirred at –80 ºC for 30 minutes and azeotropically dried AgOTf (83.7 mg, 0.33 mmol) was dissolved in dry toluene (1.6 mL) and the solution transferred to the schlenk *via* cannula under argon. The reaction was stirred at –80 ºC for 2 h, diluted with CH_2Cl_2, filtered through a short path of silica and the

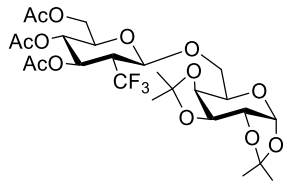
solvent evaporated. An α/β (80:20) ratio was determined by ^{19}F NMR. The crude was purified by column chromatography (1:19 EtOAc/hexanes) to give **6.10β** (19 mg, 16%) and **6.10α** (73 mg, 60%) as colorless syrups.

6.10α: R_f (2:3 EtOAc/hexanes): 0.27; $[\alpha]_D^{25}$: +15.2 (1.21, $CHCl_3$);^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.42–7.02 (m, 15H, ArH), 5.53 (d, $J_{1',2'}$ = 4.99 Hz, 1H, H–1'), 5.28 (bs, 1H, H–1), 4.78–4.35 (m, 7H, 3CH_2Ph and H–3'), 4.32 (dd, $J_{1',2}$ = 5.0 Hz, $J_{2',3'}$ = 2.4 Hz, 1H, H–2'), 4.21–4.13 (m, 2H, H–4' and H–3), 3.98 (appt, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H–5'), 3.92 (appt, $J_{3,4}$ = $J_{4,5}$ = 8.5 Hz, 1H, H–4), 3.88–3.76 (m, 2H, H–6a' and H–5), 3.75–3.62 (m, 3H, H–6b', H–6a and H–6b), 3.03 (m, 1H, H–2), 1.52, 1.44, 1.33 (s, 12H, 4CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.4, 138.2, 137.8 (C, Ar), 128.5, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.8, 127.6 (CH, Ar), 125.6 (q, $J_{C,F}$ = 281.0 Hz, CF_3), 109.5, 108.7 (2C_{ketal}), 97.4 (C–1'), 95.3 (q, $J_{C,F}$ = 4.5 Hz, C–1), 76.4 (C–3), 74.6 (CH_2Ph), 74.4 (C–4), 73.4, 72.3 (2CH_2Ph), 71.5 (C–5), 71.0 (C–4'), 70.7 (C–3'), 70.7 (C–2'), 69.0 (C–6), 65.8 (C–6'), 65.4 (C–5'), 43.9 (q, $J_{C,F}$ = 24.0 Hz, C–2), 26.1, 26.1, 25.0, 24.5 (4CH_3'); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.2 (bd, $J_{2,F}$ = 7.7 Hz, 3F, CF_3); HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{30}H_{31}F_3NaO_6^+$ (*m/z*): calc. 767.3014; found 767.3024.

6.10β: R_f (2:3 EtOAc/hexanes): 0.27; $[\alpha]_D^{25}$: –60.2 (0.49, $CHCl_3$);^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.38–7.14 (m, 15H, ArH), 5.52 (d, $J_{1',2'}$ = 4.9 Hz, 1H, H–1'), 4.88 (bs, 1H, H–1), 4.70 (d, $J_{a,b}$ = 11.2 Hz, 1H, CHPh), 4.66 (d, $J_{a,b}$ = 11.6 Hz, 1H, CHPh), 4.57 (dd, $J_{3',4'}$ = 8.0 Hz, $J_{2',3'}$ = 2.4 Hz, 1H, H–3'), 4.55–4.45 (m, 4H, 2CH_2Ph), 4.30 (dd, $J_{1',2'}$ = 4.9 Hz, $J_{2',3'}$ = 2.3 Hz, 1H, H–2'), 4.19 (bd, $J_{3',4'}$ = 8.0 Hz, 1H, H–4'), 4.07–4.01 (m, 2H, H–5' and H–6a'), 3.95–3.84 (m, 3H, H–6a, H–3 and H–4), 380–3.72 (m, 2H, H–6b and H–5), 3.66 (dd, $J_{6a',b'}$ = 11.9 Hz, $J_{5',6'}$ = 8.2 Hz, 1H, H–6b'), 3.17 (m, 1H, H–2), 1.53, 1.43, 1.34, 1.28 (s, 12H, 4CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.5, 138.0, 137.5 (C, Ar), 128.2, 128.4, 128.1, 128.1, 128.0, 127.9, 127.7, 127.6 (CH, Ar), 125.6 (q, $J_{C,F}$ = 282.1 Hz, CF_3), 109.5, 109.0 (2C_{ketal}), 97.9 (C–1), 96.4 (C–1'), 76.4 (C–3), 75.1 (C–5), 73.8, 73.3 (2CH_2Ph), 72.7 (C–4), 72.0 (CH_2Ph), 71.5 (C–4'), 70.8 (C–3'), 70.7 (C–2'), 69.8 (C–6), 69.1 (C–6'), 68.3 (C–5'), 43.9 (q, $J_{C,F}$ = 24.4 Hz, C–2), 26.1, 26.0, 25.2, 24.5 (4CH_3'); ^{19}F NMR

($CDCl_3$, 376.5 MHz) δ in ppm: –60.6 (bs, 3F); HRMS (TOF ES^+) for $(M+Na)^+$ $C_{30}H_{31}F_3NaO_6^+$ (*m/z*): calc. 767.3014; found 767.3014.

3,4,6–Tri-*O*-acetyl-2-deoxy-2-trifluoromethyl-β-D-glucopyranosyl-(1→6)-[1:2,3:4]-di-*O*-sopropylidene-α-D-galactopyranoside (6.11β)

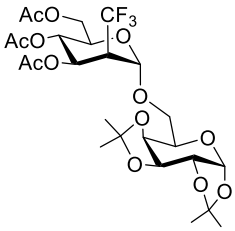


To a solution of **6.7** (97 mg, 0.242 mmol) in CH_2Cl_2 (1 mL) was added 33% HBr in AcOH (1 mL) at 0 ºC. The reaction was stirred at room temperature for 3 h. The crude was diluted with CH_2Cl_2DCM and saturated aqueous $NaHCO_3$ was added at 0 ºC. The two phases were separated and the aqueous layer successively extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated. The resulting crude was azeotropically dried with toluene, maintained under high vacuum for 3 h, dissolved in CH_2Cl_2 (2.5 mL) and transferred under argon to a schlenk containing acceptor **6.13** (126 mg, 0.484 mmol) and activated 4Å MS. The solution was stirred at –80 ºC for 30 minutes and azeotropically dried AgOTf (125 mg, 0.484 mmol) was dissolved in dry toluene (0.5 mL) and the solution transferred to the schlenk *via* cannula under argon. The reaction was stirred at –80 ºC for 2 h, diluted with CH_2Cl_2, filtered through a short path of silica and the solvent evaporated. An α/β (8:92) ratio was determined by ^{19}F NMR. The crude was purified by column chromatography (1:4 EtOAc/hexanes) to give **6.11β** (124 mg, 86%) as a white solid.

R_f (2:3 EtOAc/hexanes): 0.41; m.p: 148–150 ºC; $[\alpha]_D^{25}$: –20.7 (1.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.49 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H–1'), 5.42 (dd, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 8.9 Hz, 1H, H–3), 5.04 (dd, $J_{4,5}$ = 10.1 Hz, $J_{3,4}$ = 8.9 Hz, 1H, H–4), 4.86 (d, $J_{1,2}$ = 7.8 Hz, 1H, H–1), 4.59 (dd, $J_{3',4'}$ = 7.9 Hz, $J_{2',3'}$ = 2.4 Hz, 1H, H–3'), 4.30 (dd, $J_{1',2'}$ = 5.0 Hz, $J_{2',3'}$ = 2.4 Hz, 1H, H–2'), 4.28 (dd, $J_{6a,b}$ = 12.3 Hz, $J_{5,6a}$ = 5.1 Hz, 1H, H–6a), 4.20 (dd, $J_{3',4'}$ = 7.9 Hz, $J_{4',5'}$ = 1.8

Hz, 1H, H–4′), 4.10 (dd, $J_{6a,b}$ = 12.3 Hz, $J_{5,6b}$ = 2.5 Hz, 1H, H–6b), 4.01–3.94 (m, 2H, H–6a′ and H–5′), 3.79 (dd, $J_{6a',b'}$ = 12.8 Hz, $J_{5',6b'}$ = 8.2 Hz, 1H, H–6b′), 3.71 (ddd, $J_{4,5}$ = 10.1 Hz, $J_{5,6a}$ = 5.1 Hz, $J_{5,6b}$ = 2.5 Hz, 1H, H–5), 2.68 (m, 1H, H–2), 2.07, 2.01, 2.01 (s, 9H, $3CH_3$, Ac), 1.50, 1.43, 1.32 (s, 12H, $4CH_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.8, 169.8, 169.7 (3C=O, Ac), 126.0 (q, $J_{C,F}$ = 282.0 Hz, CF_3), 109.5, 108.9 ($2C_{ketal}$), 98.5 (q, $J_{C,F}$ = 2.5 Hz, C–1), 96.4 (C–1′), 71.5 (C–5), 71.3 (C–4′), 70.7 (C–3′), 70.5 (C–2′), 69.0 (C–4), 68.6 (C–6′), 68.1 (q, $J_{C,F}$ = 1.6 Hz, C–3), 67.7 (C–5′), 62.3 (C–6), 49.8 (q, $J_{C,F}$ = 24.5 Hz, C–2), 26.1, 26.0, 25.1, 24.5 ($4CH_3$′), 20.9, 20.7 ($3CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –65.8 (d, $J_{2,F}$ = 7.7 Hz, 3F, CF_3); HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{28}H_{27}F_3NaO_4^+$ (*m/z*): calc. 623.1922; found 623.1916.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trifluoromethyl-α-D-mannopyranosyl-(1→6)-[1:2,3:4]-di-*O*-isopropylidene-α-D-galactopyranoside (6.12)



To a solution of **6.8** (47 mg, 0.117 mmol) in CH_2Cl_2 (0.47 mL) was added 33% HBr in AcOH (0.47 mL) at 0 ºC. The reaction was stirred at room temperature for 1.5 h. The crude was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$ was added at 0 ºC. The two phases were separated and the aqueous layer successively extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated. The resulting crude was azeotropically dried with toluene, maintained under high vacuum for 3 h, dissolved in CH_2Cl_2 (1.7 mL) and transferred under argon to a schlenk containing acceptor **6.13** (91.7 mg, 0.35 mmol) and activated 4Å MS. The solution was stirred at –80 ºC for 30 minutes and azeotropically dried AgOTf (60 mg, 0.235 mmol) was dissolved in dry toluene (1.1 mL) and the solution transferred to the

schlenk *via* cannula under argon. The reaction was stirred at –80 ºC for 2 h, diluted with CH_2Cl_2, filtered through a short path of silica and the solvent evaporated. An α/β (94:6) ratio was determined by ^{19}F NMR. The crude was purified by column chromatography (1:7 EtOAc/hexanes) to give **6.12α** (56 mg, 80%) as a colorless syrup.

R_f (2:3 EtOAc/hexanes): 0.41; $[\alpha]_D^{25}$: +7.4 (0.59, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.51 (d, $J_{1',2'}$ = 5.0 Hz, 1H, H–1'), 5.42–5.32 (m, 2H, H–4 and H–3), 5.23 (d, $J_{1,2}$ = 1.3 Hz, 1H, H–1), 4.62 (dd, $J_{3',4'}$ = 7.9 Hz, $J_{2',3'}$ = 2.5 Hz, 1H, H–3'), 4.33 (dd, $J_{1',2'}$ = 5.0 Hz, $J_{2',3'}$ = 2.5 Hz, 1H, H–2'), 4.24–4.13 (m, 3H, H–4', H–6a and H–6b), 4.07 (ddd, $J_{4,5}$ = 9.1 Hz, $J_{5,6a}$ = 4.5 Hz, $J_{5,6b}$ = 2.4 Hz, 1H, H–5), 3.98 (td, $J_{5',6a'}$ = $J_{5',6b'}$ = 6.4 Hz, $J_{4',5'}$ = 1.8 Hz, 1H, H–5'), 3.81 (dd, $J_{6a',b'}$ = 10.6 Hz, $J_{5',6a'}$ = 6.4 Hz, 1H, H–6a'), 3.72 (dd, $J_{6a',b'}$ = 10.6 Hz, $J_{5',6b'}$ = 6.4 Hz, 1H, H–6b'), 3.19 (m, 1H, H–2), 2.09, 2.06, 2.05 (s, 9H, $3CH_3$, Ac), 1.54 (s, 3H, CH_3'), 1.43 (s, 3H, CH_3'), 1.33 (s, 3H, CH_3'), 1.33 (s, 3H, CH_3'); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 170.9, 170.3, 169.6 (3C=O, Ac), 124.8 (q, $J_{C,F}$ = 281.0 Hz, CF_3), 109.6, 108.8 ($2C_{ketal}$), 96.4 (C–1'), 95.5 (q, $J_{C,F}$ = 4.5 Hz, C–1), 71.0 (C–4'), 70.7 (C–3'), 70.6 (C–2'), 68.5 (C–5), 68.0 (C–3), 67.1 (C–6'), 66.1 (C–5'), 65.8 (C–4), 62.4 (C–6), 46.2 (q, $J_{C,F}$ = 24.9 Hz, C–2), 26.2, 26.1, 25.1, 24.5 ($4CH_3$'), 20.9, 20.8 ($3CH_3$, Ac); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ in ppm: –62.6 (d, $J_{2,F}$ = 9.7 Hz, 3F, CF_3); HRMS (TOF ES$^+$) for $(M+Na)^+$ $C_{28}H_{27}F_3NaO_4^+$ (*m/z*): calc. 623.1922; found 623.1923.

UNIVERSITAT ROVIRA I VIRGILI
COPPER-MEDIATED VINYLIC AND BENZYLIC FLUOROALKYLATIONS AND STEREOSELECTIVE SYNTHESIS OF 2-TRIFLUOROMETHYLGLYCOSIDES
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CHAPTER VII

Stereoselective Synthesis of 2-Deoxyglycosides. Chemical Access to Cardenolide N-1

UNIVERSITAT ROVIRA I VIRGILI
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7.1. Introduction

Cardiac glycosides are biologically active compounds containing a glycosidic moiety and a steroidal aglicone and are classified either as cardenolides *e.g.* oleandrine, digital and digoxine or bufanolides *e.g.* bufaline (Figure 7.1).[1] The structural difference on the lactone ring determines its nature as cardenolide (5 membered-ring) or bufanolide (6 membered-ring). They are applied in medicine for the treatment of congestive cardiac insufficiency and as antiarrhythmic drugs. These compounds started to become important in medicine since a physicist, William Withering, observed that a patient with congestive cardiac insufficiency improved after being treated with an extract containing digital (*Digitalis purpurea L.).*

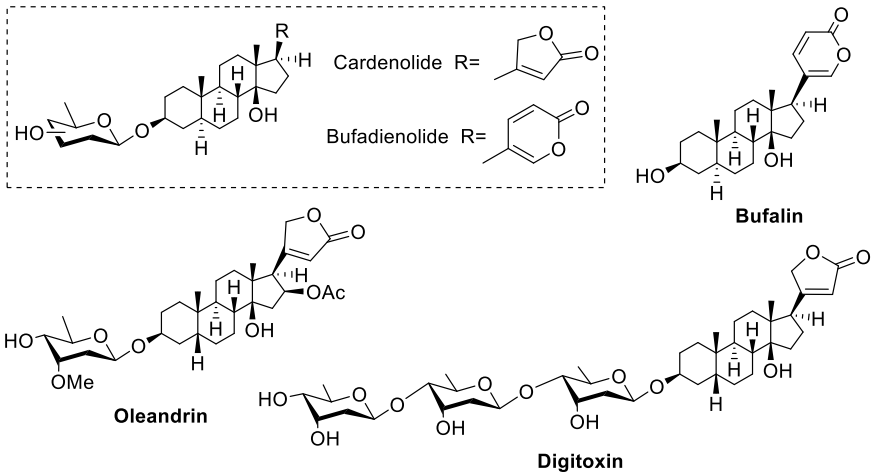


Figure 7.1. Examples of cardiac glycosides.

7.1.1. Physiological activity of cardiac glycosides

The mode of action of cardiac glycosides is associated with the inhibition of Na^+/K^+-ATPase enzyme. Since a transient increase of the intracellular concentration of Ca^{2+} reinforces the contraction of heart

[1] For key reviews see: a) Ziff, O. J.; Kotecha, D. *Trends. Cardiovasc Med.* **2016**, *26*, 585–595; b) Kumar, A.; De, T.; Mishra, A.; Mishra, A. *Pharmacogn Rev.* **2013**, *7*, 131–139; c) Schoner, W.; Scheiner–Bobis, G. *Am. J. Cardiovasc. Drugs* **2007**, *7*, 173–189.

muscle, accumulation of such ions in the sarcoplasmic reticle produced by inhibition of Na^+/K^+-ATPase enzyme improves the strength of the cardiac muscle (Figure 7.2A).[2] Other research groups discovered that treatment with cardiac glycosides enhance calcium intake of the sarcoplasmic reticle, thus increasing the activity of a ryanodine receptor channels (Figure 7.2B).[3] On the other hand Santana and coworkers reported a mechanism on which the Ca^{2+} transference inside the cell occurs after the opening of sodium channels induced by cardiac glycosides (Figure 7.2C).[4]

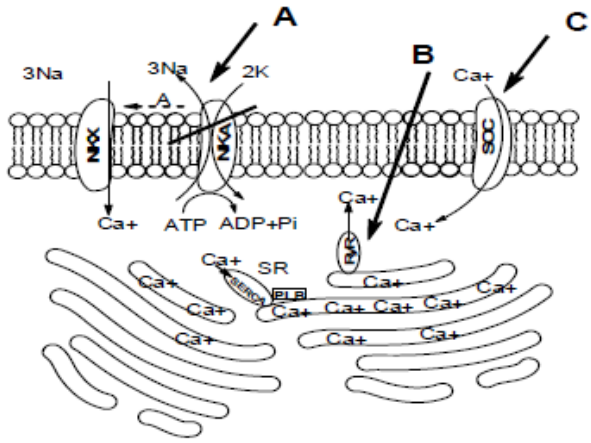


Figure 7.2. Modes of action of cardiac glycosides.[5]

7.1.2. Stereoselective synthesis of 2-deoxyglycosides

Even though the therapeutic effect is attributed to the aglicone motif of cardiotonic drugs, removal of the glycosidic part can cause the loss of efficiency and/or specificity as it is involved in the

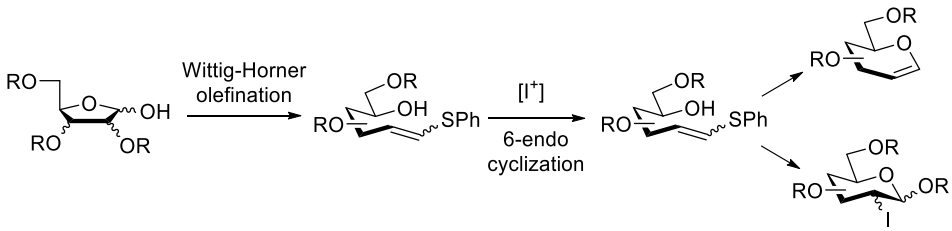
[2] Lee, C. O.; Abete, P.; Pecker, M.; Sonn, J. K.; Vassalle, M. *J. Mol. Cell. Cardiol.* **1985**, *17*, 1043–1053.
[3] Sagawa, T.; Sagawa, K.; Kelly, J. E.; Tsushima, R. G.; Wasserstrom, J. A. *Am. J. Physiol. Heart Circ. Physiol.* **2002**, *282*, H1118– H1126.
[4] Santana, L. F.; Gomez, A. M.; Lederer, W. *J. Science* **1998**, *279*, 1027–1033.
[5] Adapted from: Schwinger, R. H. G.; Bundgaard, H.; Müller–Ehmsen, J.; Kjeldsen, K. *Cardiovasc. Res.* **2003**, *57*, 913–920.

pharmacokinetic properties of the drug.[6] Deoxyglycosides are ubiquitous in nature and they are present in lipopolysacharides, glycoproteins and glycolipids that play important roles as cell-cell interaction ligands, serve as targets for toxins, antibodies or microorganism, are also involved in biochemical and bioorganic processes such as active transport through the cell membrane and enzymatic inhibition.[7] They are also present in the structure of antitumoural drugs, antibacterials, aureolic acids, calicheamicin, spiramycin and in some appetite suppressor compounds.

The biological importance of deoxyglycosides has attracted the attention of medicine, organic synthesis and bioorganic chemistry for its efficient synthesis. Last but not least, since some 2-deoxysacharides have not been isolated and extracted in enough amounts from natural sources, their chemical synthesis is important. Despite recent efforts in the preparation of 2-deoxy and 2,6-dideoxyglycosides,[8] elaboration of "rare" deoxypyranosyl configurations (*e.g.*, D-sarmentose) still remains a laborious task.[9] In this context, our group developed a general strategy for the synthesis of 2-deoxyglycosides of all configurations, being particularly effective for those with β-D-*ribo* and -*xylo*.[10–14] This process

[6] Kren, V.; Martínková, L. *Curr. Med. Chem.* **2001**, *8*, 1303–1328.
[7] a) Albrecht, H. P. In Naturally Ocurring Glycosides, Ikan, R.; Ed.; Wiley, Chichester, 1999; b) Weymouth–Wilson, A.C. *Nat. Prod. Rep.* **1997**, *14*, 99–110; c) Kirschning, A.; Bechtold, A. F.–W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1–84; d) Allen, H. J.; Kisailus, E. C. Eds.; Glycoconjugates: Composition, Structure and Function, Marcel Dekker, New York, 1992.
[8] a) Palo–Nieto, C.; Sau, A.; Williams, R.; Galan, M. C. *J. Org. Chem.* **2017**, *82*, 407–414 and references cited therein; b) Nogueira, J. M. Bylsma, M.; Bright, D. K.; Bennett, C. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 10088–10092 and references cited therein; c) Balmond, E. I.; Benito–Alifonso, D.; Coe, D. M.; AldeVr, R. W.; McGarrigle, E. M.; Galan, M. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 8190–8194; d) Zhu, D.; Baryal, K. N.; Adhikari, S.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 3172−3175.
[9] a) Beattie, R. J.; Hornsby, T. W.; Craig, G.; Galan, M. C.; Willis, C. L. *Chem. Sci.* **2016**, *7*, 2743–2747; b) Brasholz, M.; Reißig, H.–U. *Eur. J. Org. Chem.* **2009**, 3595–3604; c) Herczegh, P.; Kovács, I.; Sztaricskai, F. J. *Tetrahedron* **1991**, *47*, 1541–1546.
[10] Rodríguez, M. A.; Boutureira, O.; Arnés, X.; Díaz, Y.; Matheu, M. I.; Castillón, S. *J. Org. Chem.* **2005**, *70*, 10297–10310.
[11] a) Kövér, A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *J. Org. Chem.* **2014**, *79,* 3060–3068; b) Boutureira, O.; Rodríguez, M. A.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Org. Lett.* **2006**, *8*, 673–675.
[12] a) Boutureira, O.; Rodríguez, M. A.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Carbohydr. Res.* **2010**, *345*, 1041–1045; b) Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, M. I.; Díaz,

involves three steps: a) Wittig-Horner olefination of a pentose to afford a sulfanyl alkene, b) iodonium induced cyclization giving 2-deoxy-2-iodothioglycosides, and c) glycosylation to produce the desired 2-deoxy-2-iodoglycoside (Scheme 7.1).[10,11a,14] Thus, the stereoselectivity is controlled by a temporary I group which can be removed in the last step of the synthesis. Glycals of different configurations, which are difficult to obtain by other procedures, can also be obtained from the 2-deoxy-2-iodothioglycoside intermediates.[11b]



Scheme 7.1. Strategy to access to 2-deoxypyranosides from furanoses.

General trends of this three-step process are the following:

a) The olefination is performed under Wittig-Horner (WH) conditions which proved to be optimal for this transformation.[15] WH olefination using lithiated bases is described as a two-step process. First, the reaction of the ylide and a carbonyl produce a β-hydroxyphosphine followed by elimination promoted by KH or NaH to afford the

Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 3564–3572; c) Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S.; Seeberger, P. H. *J. Org. Chem.* **2007**, *72*, 8998–9001.

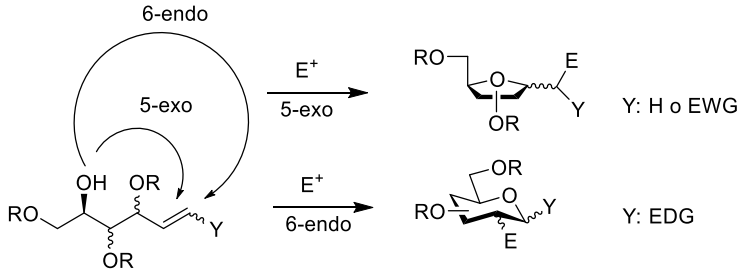
[13] a) Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *RSC Adv.* **2014**, *4*, 19794–19799; b) Cobo, I.; Matheu, M. I.; Castillón, S.; Boutureira, O.; Davis, B. G. *Org. Lett.* **2012**, *14*, 1728–1731; c) Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Carbohydr. Res.* **2007**, *342*, 736–743.

[14] Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 2470–2476.

[15] Boutureira, O. Ph.D. Thesis, URV, Tarragona, 2007.

corresponding alkene. However, with semistabilized phosphine oxides, the formation of the alkene occurs in a single step.[16]

b) The iodonium-induced cyclization involves the activation of the double bond with an electrophilic iodine species, which promotes the intramolecular nucleophilic addition of the free hydroxyl. The regioselectivity of this process is determinaded by the nature of the alkene substituent. Thus, 6-*endo* products are mainly obtained in the presence of electron donatig substituents, whereas EWG favor the formation of 5-*exo* products (Scheme 7.2).[17]



Scheme 7.2. Cyclization products depending on the Y substituent.

The stereoselectivity of the product is controlled by the *inside alkoxy effect* (Figure 7.3).[18] Conformation B, with the alkoxide *outside* the plane of the alkene, has its σ^*_{C-O} orbital parallel to the π-system of the double bond leading to the existence of hyperconjugation interactions. This effect lowers the electronic density of the double bond reducing its nucleophilicity and, as a consequence, the reactivity of the conformer. In contrast, since hyperconjugation cannot occur in conformation A (σ^*_{C-O} is perpendicular to the π-system), the resulting TS is the more reactive and

[16] Buss, A. D.; Warren, S. *J. Chem. Soc.; Perkin Trans. 1*, **1985**, 2307–2325.
[17] a) Freeman, F.; Robarge, K. D. *J. Org. Chem.* **1989**, *54*, 346–359; b) Guindon, Y.; Soucy, F.; Yoakim, C.; Ogilvie, W. W.; Plamondon, L. *J. Org. Chem.* **2001**, *66*, 8992–8996; c) Jung, M. E.; Lew, W. *J. Org. Chem.* **1991**, *56*, 1347–1349; d) Faivre, V.; Lila, C.; Saroli, A.; Doutheau, A. *Tetrahedron Lett.* **1989**, *45*, 7765–7782.
[18] a) Halter, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031–8034; b) Houk, K.N.; Moses, S.R.; Wu, Y.–D.; Rondan, N.G.; Jäger, V.; Schohe, R.; Fronczek, F.R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882; c) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951–3954.

the product afforded has the alkoxy and the iodine in a *cis* disposition. The same scenario occurs with the *Z* alkene but steric interactions between the thiophenyl and the alkoxide slows the cyclization process.

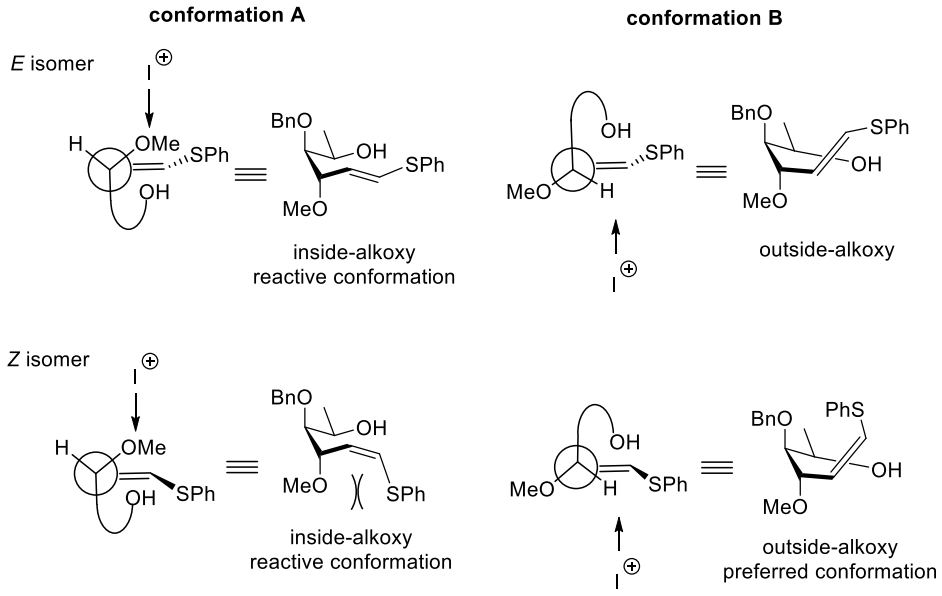


Figure 7.3. *Inside alkoxy effect* in the iodonium-induced cyclization.

c) Glycosylation: After the activation of a thiophenyl donor using NIS/TfOH system, an oxocarbenium intermediate is produced. Among all the possible conformational intermediates, the discussion is restricted to the most prevalent half-chair conformations $^{3}H_4$ and $^{4}H_3$, Figure 7.4. When the iodine is positioned in *axial* (*manno* configuration) the lowest transition state is derived from the $^{4}H_3$ conformation in which the nucleophile approaches from the bottom face, thus avoiding steric repulsion with the bulky I group. On the other hand, when I is in *equatorial* (*gluco* configuration), the favored TS is displayed with the nucleophile attacking from the top face to produce the β-glycosylated product. This model also explains why the major products, displaying a 1,2-*trans* relative configuration, are not produced stereospecifically as it

should be expected by the occurrence of usually proposed cyclic iodonium intermediates.

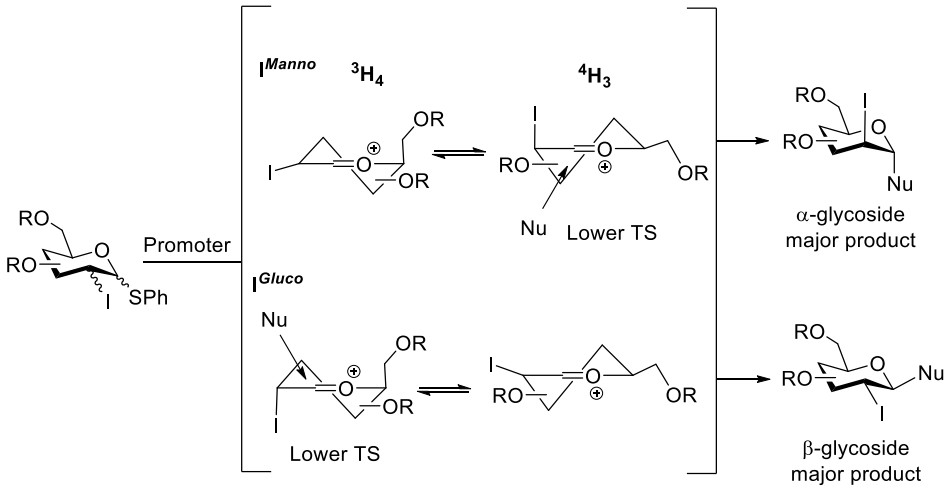
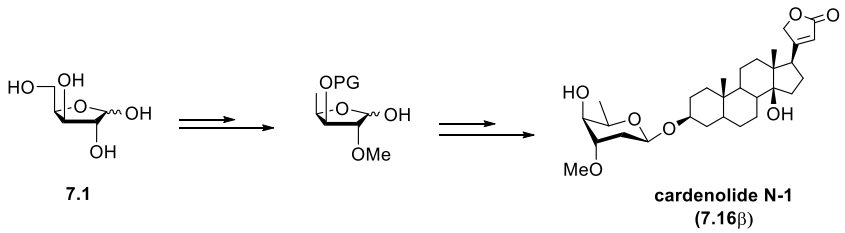


Figure 7.4. Proposed model to explain the stereoselectivity in the glycosylation of 2-deoxy-2-iodoglycosyl donors.

7.2. Objectives

The main objective of this chapter is to perform the first total synthesis of cardenolide N-1 (**7.16**β). This product was extracted from *Nerium Oleander* twigs and its structure was first elucidated with the aid of NMR techniques.[19] The glycosyl unit contains an hexo-monosaccharide of D-*xylo* configuration. Hence, the proposed synthetic plan highlights the utility of the methodology reported in our research group for the stereoselective preparation of "rare" 2-deoxyglycosides. Moreover, the proposed characterization using spectroscopic data from the plants extract will be verified.

[19] Zhao, M.; Bai, L.; Wang, L.; Toki, A.; Hasegawa, T.; Kikuchi, M.; Abe, M.; Sakai, J.; Hasegawa, R.; Bai, Y.; Mitsui, T.; Ogura, H.; Kataoka, T.; Oka, S.; Tsushima, H.; Kiuchi, M.; Hirose, K.; Tomida, A.; Tsuruo, T.; Ando, M. *J. Nat. Prod.* **2007**, *70,* 1098–1103.



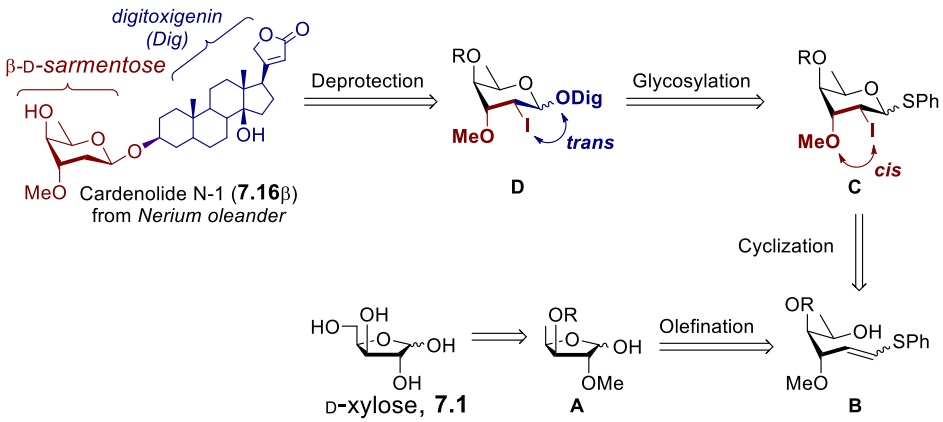
Scheme 7.3. Synthetic approach to cardenolide N-1.

The major issue to overcome in the design of the synthetic plan involve the preparation of a 2,6-deoxyglycosyl donor able to promote a high β-selectivity during the glycosylation step. Such donor can be prepared from a key intermediate furanose applying the aforementioned strategy, which in turn can be accessed from commercially available, inexpensive D-xylose, **7.1** (Scheme 7.3).

7.3. Results and discussion

7.3.1. Retrosynthetic analysis

Configurational analysis of the C–3 and C–1 stereogenic centers reveals a relative *trans* configuration (Scheme 7.4). This design enables the application of the strategy implemented in our group for the stereoselective synthesis of 2-deoxyglycosides. We anticipated that a β-glycosylation would conceivably be orchestrated by the presence of an ancillary *equatorial* I at C–2 in **C**. The position of I is in turn potentially controlled by the *inside alkoxy effect*[18] during the iodonium-induced cyclization of **B**, rendering the halogen *cis* to the substituent at C–3. Structure **A**, precursor of this methodology, can be prepared from **7.1** by a reaction sequence involving 1,2-acetal formation, C–6 deoxygenation, protection of 3–OH, deprotection, and selective methylation.

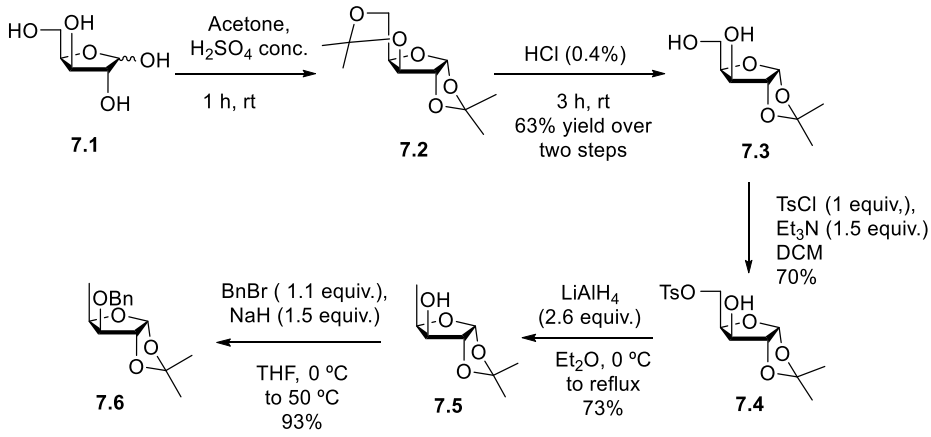


Scheme 7.4. Retrosynthetic analysis of cardenolide N-1.

7.3.2. Preparation of furanose precursor

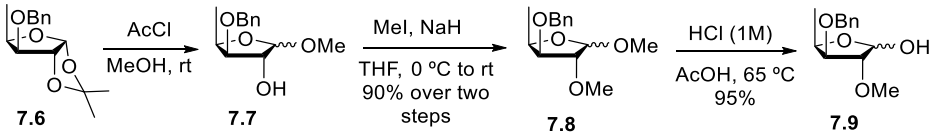
Compound **7.6** is a suitable intermediate for the preparation of furanose precursor **A** and its synthesis has been previously described (Scheme 7.5).[20] Following reported protocols, **7.3** is accessed from D-xylose **7.1** by protection of the 4 hydroxyl groups with acetone/H_2SO_4 to give **7.2** followed by selective hydrolysis of the more labile acetal at C–3 and C–5.[21] The preparation of the 5-deoxyderivative **7.5** was accomplished by selective sulfonation of the primary alcohol in **7.3** with bulky tosyl chloride affording **7.4**[22] followed by S_N2 displacement with $LiAlH_4$[23] to afford the desired product in good 73% yield. Finally, conventional benzylation afforded compound **7.6** in excellent 93% yield.

[20] Sharma, G.V.M.; Damera, K. *Tetrahedron Asymmetry*. **2008**, *19*, 2092–2095.
[21] Chang, J. European Patent EP 2177527, 2010.
[22] Sharma, G. V.; Gopinath, T. *Tetrahedron*, **2003**, *59*, 6521–6530.
[23] Hildebrandt, B.; Nakamura, Y.; Ogawa, S. *Carbohydr. Res.* **1991**, *214*, 87–93.



Scheme 7.5. Synthesis of 1,2-*O*-isopropylidene-D-xylose **7.6**.

Although preparation of **7.9** is unknown, it can be constructed from **7.6** using classical carbohydrate transformations. Thus, cleavage of isopropylidene acetal in **7.6** using AcCl/MeOH and subsequent methylation of the free hydroxyl at C-2 furnished **7.8** in 90% yield over two steps (Scheme 7.5). Standard methylation using MeI and NaH furnished **7.8** in excellent yield over two steps, which after hydrolysis of the anomeric bond smoothly produced the desired furanose precursor **7.9** (95%).



Scheme 7.6. Synthesis of sarmentosyl precursor **7.9**.

7.3.3. Olefination, iodonium-induced cyclization, and glycosylation

The olefination was carried out under Wittig-Horner (WH) conditions, which have previously been proved to be optimal for this

transformation.[24] Firstly, olefination of **7.9** with $Ph_2P(O)CH_2SPh$ and high excess of *n*-BuLi produced a mixture of products, presumably due to base-promoted elimination reactions (Table 7.1, entry 1). The use of 2.2 equiv of phosphine oxide derivative and *n*-BuLi produced **7.10** after 3 h with an *E*/*Z* ratio of 8:1, although in very low yield (Table 7.1, entry 2). Extending the reaction time improved the yield to 41% while the *Z*/*E* ratio decreased to 1:2.9 (Table 7.1, entry 3). Surprisingly, when the amount of phosphine oxide/*n*-BuLi was increased to 4 equivalents the reaction became sluggish and low conversion of **7.9** was observed even after 3 days (Table 7.1, entry 4). Using 2.5 equiv of phosphine oxide and *n*-BuLi, **7.10** was isolated after 48 h in a very good 83% yield and a 1.5:1 *E*/*Z* ratio (Table 7.1, entry 5). Quenching the reaction after 24 h afforded the sulfanyl alkene in 52% yield and 5.3:1 *E*/*Z* selectivity (Table 7.1, entry 6). When the reaction was quenched after 24 h, two fractions were obtained (Table 1, entry 6). The first consisted of **7.10** in 52% yield and 1:5.3 *Z*/*E* ratio and the second contained a β-hydroxyphosphine oxide intermediate, which was subsequent treated with NaH to afford an additional fraction of **7.10** in 29% yield and 20:1 *Z*/*E* ratio. Generally, the selection of reaction conditions leading to diastereomerically enriched *E*-isomers is desirable because cyclization of *Z*-sulfanyl alkenes occurs slower than that of *E*-isomers, thus compromising the efficiency of the overall process.[10,11a] However, in the following cyclization optimization we observed that both *Z*- and *E*-isomers of **7.10** were completely consumed (Table 7.2) and thus, optimal conditions were those affording the highest yield (Table 7.1, entry 5).

The similarity in yield and stereoselectivity of entry 5 with the combined fractions of entry 6, suggests that the same reaction outcome can be obtained following either the one-step or the stepwise protocol. The only advantage of the two-step process is the possibility to separate enriched fractions with both isomers. Given that the only difference between the two protocols is the reaction time, a rationalization was attained considering the WH olefination mechanism. After 24 h, a **7.10*E***

[24] Boutureira, O. Ph.D. Thesis, URV, Tarragona, 2007.

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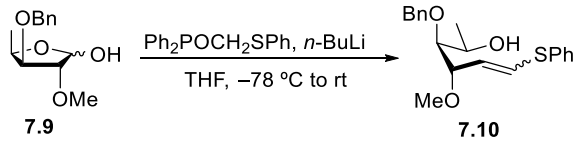
COPPER-MEDIATED VINYLIC AND BENZYLIC FLUOROALKYLATIONS AND STEREOSELECTIVE
SYNTHESIS OF 2-TRIFLUOROMETHYLGLYCOSIDES
Jordi Mestre Ventura

enriched mixture is obtained along with an additional fraction containing intermediate **7.9*Z′***. This suggests that the TS to produce **7.10*Z*** from **7.9*Z′*** is higher in energy than that to produce **7.10*E*** from **7.9*E′*** (Scheme 7.7). This difference was attributed the higher steric repulsion between the thiophenyl and the sugar skeleton in the geometry required to permit the nucleophilic attack of the oxygen to form the oxaphosphetane from **7.9*Z′***.

Table 7.1. Optimization of olefination of **7.9**.

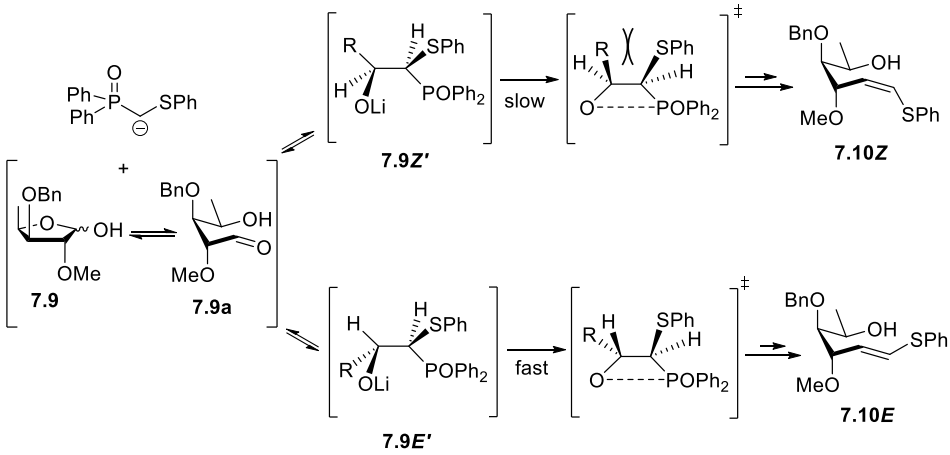


7.9 **7.10**

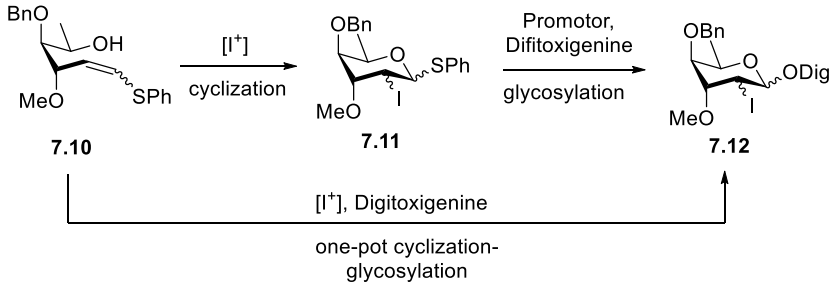
Entry	**5** (equiv)	*n*-BuLi (equiv)	time (h)	yield (%)[b]	*Z*/*E* ratio[c]
1	2	3.5	16	–[d]	ND
2	2.2	2.2	3.5	22	1:8
3	2.2	2.2	15	41	1:2.9
4	4	4	72	–[e]	1:1.2
5	2.5	2.5	48	83	1:1.5
6[f]	3.2	3.2	24	52	1:5.3

[a]*General conditions*: phosphine oxide, *n*-BuLi, and D-xylofuranose **7.9** in dry THF unless otherwise indicated. [b]Isolated yield after purification by column chromatography. [c]Determined by integration of the olefinic proton signals in the ^{1}H NMR spectrum of the crude reaction mixture. [d]Degradation. [e]Incomplete conversion. [f]The fraction containing β-hydroxyphosphine oxide intermediate was treated with 60% NaH (1 mg mg^{-1} crude) in dry THF to afford additional **7.10** in 29% yield and 20:1 *Z*/*E* ratio. ND=not determined.

The following step in the synthetic strategy was the cyclization of **7.10** to thioglycoside donor **7.11** to be used as a glycosyl donor (Scheme 7.8). Moreover, it is also possible to prepare **7.12** by consecutive cyclization/glycosylation strategy, which proved to perform better in terms of yield although with slight loss of stereoselectivity.[14]



Scheme 7.7. Mechanism of WH olefination and reactivity difference.

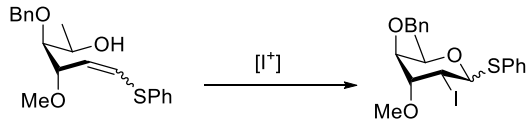


Scheme 7.8. Stepwise and one pot cyclization/glycosylation reaction of **7.10**.

After optimizing the olefination of **4**, [I$^+$]-induced *6-endo* cyclization of **6** was further examined. First attempts to cyclize **7.10** with NIS produced a mixture of products, which apart from the corresponding thioglycoside **7.11**, by-products from elimination reactions, and glycosylations with succinimide or traces of water were also obtained (Table 7.2, entry 1). When iodonium di-*sym*-collidine perchlorate (IDCP) was used, **7.11** was isolated in a good 63% yield and 1:2.7 α/β ratio (Table 7.2, entry 2). While addition of 4Å MS caused decomposition of the product (Table 7.2, entry 3), lower temperature and shorter reaction

times (meticulous control on the reaction progress by TLC) beneficed the reaction yield (Table 7.2, entries 4–6).

Table 7.2. Optimization of cyclization of **7.10**.



7.10 **7.11**

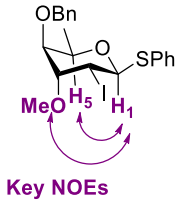
entry	[I$^+$] (equiv)	additive (equiv)	*T* (ºC)	time (h)	yield (%)[b]
1	NIS (1.5)	$NaHCO_3$ (1.5)	–40	1	–[d]
2	IDCP (3)	–	–30 to –10	1	63
3	IDCP (3)	4Å MS	–30 to –10	1	–[d]
4	IDCP (3)	–	–40 to –30	3.5	63
5	IDCP (3)	–	–45 to –42	3.5	70
6	IDCP (3)	–	–45 to –42	1	84

[a] *General conditions*: Iodonium reagent and **6** (1:1.5 *Z*/*E*) in dry CH_3CN unless otherwise indicated. [b]Isolated yield after purification by column chromatography. [c]Determined by integration of H_1 (**7**α) and H_2 (**7**β) in the ^{1}H NMR spectrum of the crude reaction mixture. [d]Degradation. ND=not determined, MS=molecular sieves.

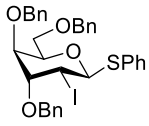
Since product **7.11** is highly unstable, in the latest entries the α/β ratio was not determined and, after purification using column chromatography, the product was immediately used in the following reaction. Although full characterization of **7.11** was not possible, spectroscopic data collected were compared with *gulo*-configured sugar **7.20**.[25] As shown in Table 7.3, the ^{1}H-^{1}H coupling and ^{1}H chemical shifts were very similar and additional NOE and HSQC-coupled experiments suggested a $^4C_1$ conformation. This result is in line with similar transformations using donors of D-*gulo* configuration.[10]

[25] Data extracted from: Rodríguez, M. A. Ph.D. Thesis, URV, Tarragona, 2007

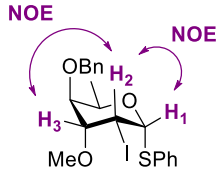
Table 7.3. Comparison of ^{1}H NMR data of thioglycosides within the same configuration.



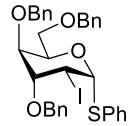
7.11β



7.20β



7.11α

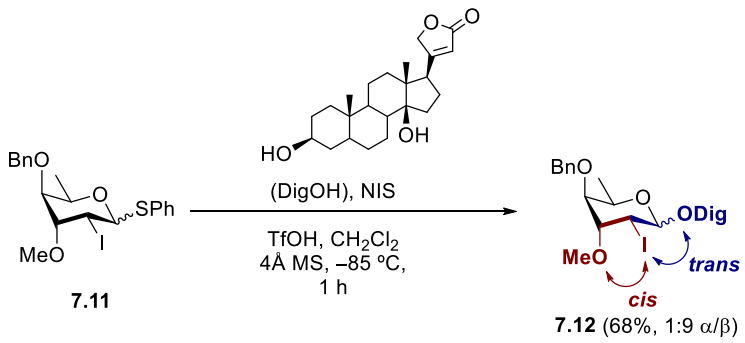


7.20α

^{1}H NMR data	**7.11**β	**7.20**β	**7.11**α	**7.20**α
$J_{1,2}$	11.1 Hz	11.2 Hz	4.89 Hz	5.2 Hz
$J_{2,3}$	3.1 Hz	2.8 Hz	2.93 Hz	2.8 Hz
$J_{3,4}$	3.5 Hz	3.4 Hz	bs	bs
$J_{4,6}$	1.3 Hz	1.2 Hz	1.0	bs
H–1	5.00 (d)	5.13 (d)	5.35 (d)	5.41 (d)
H–2	4.41 (dd)	4.44 (dd)	5.02 (dd)	5.06 (dd)
H–4	3.22 (dd)	3.37 (dd)	3.37 (bs)	3.46 bs
J_{H1-C1}	161 Hz	–	168 Hz	–

Spectroscopic data of **7.20** (α/β) was extracted from literature.[10]

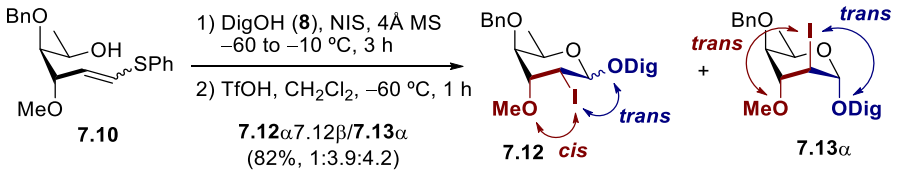
We next explored the stereoselective preparation of 2,6-dideoxy-2-iodohexopyranosyl glycosides and their subsequent elaboration to final cardenolide N-1 (**16**β) and its α-anomer (**16**α) (Scheme 7.9). Glycosylation of digitoxigenin with 1-thioglycosyl donor **7.11** was first performed at –85 ºC using NIS/TfOH as the promoter system. Under these mild conditions, **7.12** was obtained in 68% yield and 1:9 α/β ratio, which is in line with the results obtained with similar D-*gulo* donors and cholesterol as an acceptor (66%, 1:8 α/β).[10] Unfortunately, the anomeric products were chromatographically inseparable and the mixture obtained was used in the following reaction.



Scheme 7.9. Glycosylation of **7.11** with digitoxigenin.

Alternatively, the straightforward *"one-pot"* version was attempted directly from **7.10**. The reaction was started at −60 °C and then allowed to warm until cyclization was completed (*ca.* −10 °C); moment in which the reaction mixture was re-cooled to −60 °C and TfOH was added to promote glycosylation. However, together with expected **7.12**α/β, a substantial amount of 2-I-epimer **7.13**α (D-*ido*) was also obtained (Scheme 7.10). The lower product selectivity could be explained by the fact that higher temperatures are required in the *"one-pot"* protocol compared to those of the sequential method and the high reactivity of transient **7.11**, which was consumed before addition of TfOH. The formation of **7.13**α could be rationalized, as already described in our previous studies, by either the *in situ* formation of the corresponding glycal byproduct[11a,26] and its subsequent [I$^+$]-induced glycosylation or the alternative *outside-alkoxy* cyclization.[14] Thus, stereoselective control in the stepwise approach seems more favorable for accessing cardenolide N-1 precursor **7.12**β, whereas the improved selectivity towards **7.12**α and **7.13**α (both precursors of **7.16**α) resulting from the *"one-pot"* method gives the opportunity to ultimately access the α-anomer (**7.16**α) of Cardenolide N-1.

[26] a); b) Boutureira, O.; Rodríguez, M. A.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Carbohydr. Res.* **2010**, *345*, 1041–1045; c) Boutureira, O.; Rodríguez, M. A.; Benito, D.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2007**, 3564–3572; d) Rodríguez, M. A.; Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S.; Seeberger, P. H. *J. Org. Chem.* **2007**, *72*, 8998–9001.



Scheme 7.10. Consecutive "one-pot" cyclization/glycosilation of **7.10**.

The structures were confirmed by NMR experiments including ^{1}H, ^{13}C, HSQC, ^{1}H-coupled HSQC, HMBC, NOESY, and COSY (Figure 7.5). The high value of vicinal coupling constants of **7.12**β ($J_{1,2}$ = 9.2 Hz) and **7.13**α ($J_{1,2}$ = 8.4 Hz) and the heteronuclear coupling constant value J_{C1-H1} *ca*. 160 Hz of both products indicate a relative *trans-diaxial* disposition between H-1 and H-2. On the other hand, key NOE contacts suggest a $^{4}C_1$ conformation for **7.12**β whereas **7.13**α apparently adopts a $^{1}C_4$ geometry, probably as a result of locating all substituent in *equatorial* positions. NMR data collection from **7.12**α was challenging owing to the low concentration and the presence of overlapping signals. Nevertheless, **7.12**α showed characteristic features of α-glycosides including a slight downfield shift of H-1 compared to the β-glycosides (4.64 and 4.74 ppm for **7.12**β and **7.12**α, respectively), and the values of coupling constants J_{C1-H1} = 171 Hz and $J_{1,2}$ = 3.9 Hz suggest a *cis* relative configuration between H-1 and H-2.

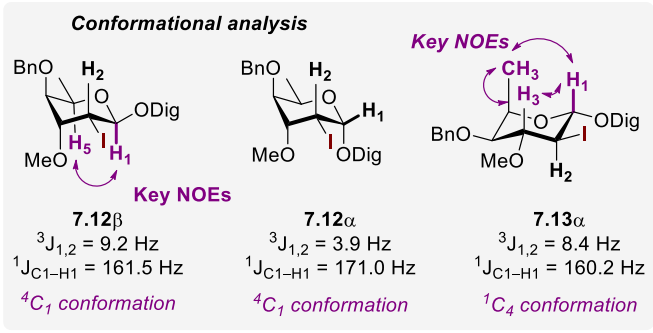
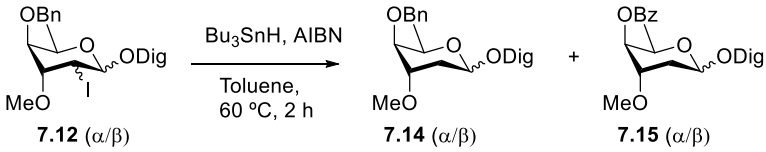


Figure 7.5. Selected NMR data of glycosylation products.

7.3.4. Deprotection steps

With the glycosylated mixture in hand, deprotection of iodine and benzyl group was attempted under different reaction conditions. First, hydrogenation in basic media was assayed but unfortunately, no conversion was observed (Table 7.4, entries 1–2). When hydrogenation was performed in the absence of a base, a mixture of products was observed presumably promoted by HI, which is coproduced during reduction of the C–I bond (Table 7.4, entry 3). Radical deiodination using Bu_3SnH/Et_3B gave deiodinated product **7.14** along with unidentified products, but problems on reproducibility were observed (Table 7.4, entry 4). More reliable results were obtained replacing Et_3B by AIBN (Table 7.4, entry 5). Experiments using the latter set up produced variable ammounts of the same unknown byproducts. ^1H NMR spectrocopic analysis showed some aromatic protons abnormally deshielded, resembling to that of benzoate groups and the presence of **7.15** was further confirmed by ESI–MS. Although **7.15** and tin contaminants could be easily removed after flash chromathography, anomeric products **7.14** (α/β) proved inseparable and hydrogenation was performed directly from the mixture.

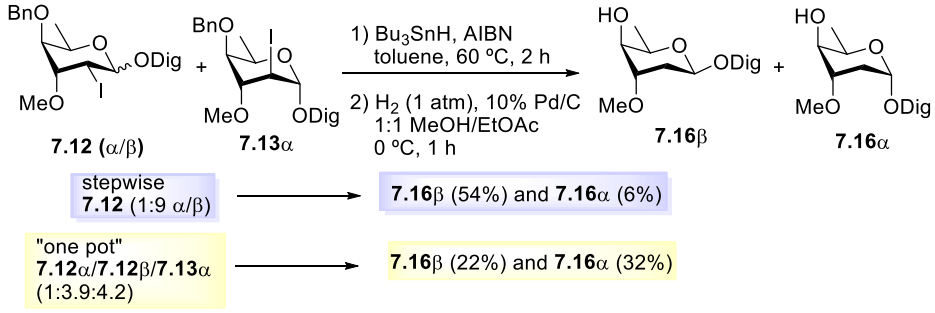
Table 7.4. Optimization of deiodination of **7.12.**



7.12 (α/β) **7.14** (α/β) **7.15** (α/β)

Entry	T (ºC)	t (h)	Conditions	Observations
1	rt	24	H_2, $NaHCO_3$, MeOH	Conv. <5%
2	rt	8	H_2, Et_3N, MeOH	Conv. <5%
3	rt	3	H_2, MeOH	Complex mixture
4	rt	16	Bu_3SnH, Et_3B, Toluene	Deiodination quant (problems on reproducibility)
5	60	2	Bu_3SnH, AIBN, Toluene	Deiodination quant.

Removal of 4-OBn using 10% Pd/C at 0 ºC resulted in final cardenolide N-1 (**1**β) and its α-anomer (**1**α) in 54% yield from **9**α/β (stepwise) and 32% yield from **9**α/**9**β/**10**α "one-pot", respectively (Scheme 3). Then, **7.14**(α/β) was treated under H_2 (1 atm) in the presence of 10% Pd/C at room temperature. Unexpectedly,[27] hydrogenation of the lactone moiety was observed under these conditions. Benzyl ether could be selectively cleaved driving the reaction at 0 ºC for 1 h, and to our delight, products resulted nicely separable by chromatographic techniques and pure fractions of **7.16**β and **7.16**α were obtained in 54% and 6% yield, respectively from **9**α/β (stepwise) (Scheme 7.11). The reaction sequence was then applied to the mixture obtained from the "one-pot" cyclization/glycosylation protocol and **7.16**β and **7.16**α were obtained in 22% and 32% yield, respectively (Scheme 7.11).



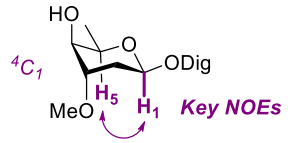
Scheme 7.11. Deprotection sequence and product distribution from a) stepwise protocol and b) "one-pot" protocol.

The ^{1}H and ^{13}C NMR data collected from **7.16**β was identical to that reported for the natural product (Table 7.5) and the structure was further confirmed by ESI–MS, FTIR, and optical rotation $[\alpha]_D^{20}$: –3.5 (*c* 0.23, $CHCl_3$) [lit. –1.3 (*c* 0.231, $CHCl_3$)].[19] Key NOE peaks H_1–H_5 and $^1J_{C1-H1}$ = 162

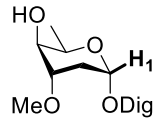
[27] a) Zhang, J.; Ponomareva, L. V.; Nandurkar, N. S.; Yuan, Y.; Fang, L.; Zhan, C.–G.; Thorson, J. S. *ACS Med. Chem. Lett.* **2015**, *6*, 1053–1058; b) Heasley, B. *Chem. Eur. J.* **2010**, *18*, 3092–3120; c) Qazzaz, H. M. A. M.; EL–MASRI, M. A.; Valdes R. Jr. *Endocrinology* **2000**, *141*, 3200–3209; d) Wiesner, K.; Tsai, T. Y. R.; Kumar, R.; Sivaramakrishnan, H. *Helv. Chim. Acta* **1984**, *67*, 1128–1135.

Hz indicates a $^4C_1$ conformation for **7.16**β. The conformational evaluation of **7.16**α proved more challenging. The small values of vicinal coupling constants, the presence of only vicinal contacts in the NOESY experiment, and the ambiguous $^1J_{C1-H1}$ value of 165 Hz was not conclusive. Fortunately, X-ray diffraction (XRD) definitely confirmed the $^4C_1$ conformation in **7.16**$\underline{\alpha}$. Notably, the analysis of the stereoselectivity of final products also provides an indirect evidence of the relative disposition of the I atom in precursors **7.12** and **7.13**α.

Table 7.5. Selected characterization data of **7.16**β and **7.16**α.

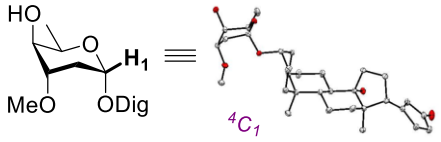


$^1J_{C1-H1}$ = 162 Hz



$^1J_{C1-H1}$ = 165 Hz

position	natural (**7.16**β)[b]	this work (**7.16**β)	this work (**7.16**α)
H-1	4.71 (dd, *J* = 9.5, 2.6)	4.71 (dd, *J* = 9.5, 2.6)	4.85 (dd, *J* = 3.3)
H-2	1.84–1.76 (m)	1.84–1.76 (m)	1.95–1.75 (m)
H-3	3.58 (q, *J* = 2.9)	3.58 (q, *J* = 3.2)	3.53 (q, *J* = 4.0)
H-4	3.39 (m)	3.41–3.35 (m)	3.47 (m)
H-5	3.91 (q, *J* = 6.6)	3.91 (qd, *J* = 6.6, 1.1)	4.33 (qd, *J* = 6.8, 1.6)
5-Me	1.23 (d, *J* = 6.6)	1.24 (d, *J* = 6.6)	1.17 (d, *J* = 6.8)
3-OMe	3.38 (s)	3.38 (s)	3.39 (s)



$^1J_{C1-H1}$ = 165 Hz

[a] Coupling constants reported in Hz. [b] See ref 19.

7.4. Conclusions

The first total synthesis of cardenolide N-1 (**7.16**β) and its α-anomer (**1**α) has been successfully accomplished starting from the very common D-xylose. Key steps involved Wittig–Horner olefination, [I^+]-

induced *6-endo* cyclization, and 1,2-*trans* stereoselective glycosylation. This synthesis illustrates the flexibility of our method for accessing 2-deoxyglycosides of "rare" configurations. Indeed, their ready preparation will afford sufficient material to perform robust evaluations of benefit for the medicinal and biological chemistry fields.

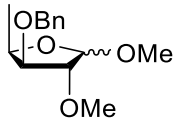
7.5. Experimental section

7.5.1. General considerations

All reagents were purchased from Sigma Aldrich, Alfa Aesar and Carbosynth chemical companies. Dichloromethane (CH_2Cl_2) and tetrahydrofurane (THF) were dried using standard methods, acetonitrile was dried using activated 3 Å molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or on a Varian® NMR System 400 (400 MHz and 100.6 MHz respectively) spectrometer. NMR Spectra were fully assigned using COSY, HSQC and HMBC. Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, bt = broad triplet, bq = broad quadruplet and app = apparent. Infrared (IR) spectra were recorded on a JASCO FTIR-600 plus Fourier Transform Infrared Spectrophotometer. ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Melting points (m.p.) were recorded with a Reichert apparatus. Optical rotations were measured on a Perkin–Elmer® 241 polarimeter in a 1 dm cell at 20ºC. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck® aluminium backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λmax = 254 nm) and/or by heating plates that were dipped in a H_2SO_4/ethanol (1:15). Flash chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230–400 mesh).

7.5.2. Synthetic procedures and characterization of compounds

Methyl 3-*O*-benzyl-5-deoxy-2-*O*-methyl-α-β-D-xylofuranoside (7.8)

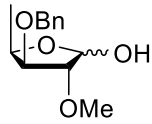


To a flask containing AcCl (4.5 mL, 63.30 mmol), dry MeOH (15 mL) was added slowly under argon at 0 ºC followed by a solution of **7.6**[20] (3.9 g, 14.75 mmol) in MeOH (15 mL). After stirring at room temperature for 5 h, the reaction mixture was neutralized by addition of NH_3 and the solvent was evaporated. The product was extracted with EtOAc and the combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed and the crude was concentrated under reduced pressure. The mixture was then dissolved in THF (35 mL), cooled to 0 ºC and NaH (0.9 g, 22.50 mmol) was added portion wise under argon. After 15 minutes MeI (1.8 mL, 28.90 mmol) was added and the reaction mixture stirred at room temperature. After 3 h, another portion of MeI (0.72 mL, 11.56 mmol) was added and the mixture stirred overnight. The reaction mixture was then quenched with a saturated solution of NH_4Cl and the solvent evaporated. The residue was redissolved with EtOAc and washed with water, brine and the organic phase dried with Na_2SO_4. After filtration and removal of the solvent under vaccum, the crude was purified using column chromatography (1:4 EtOAc/hexane) to afford **7.8** (3.35 g, 90% over two steps) as a 1.2:1 α/β mixture as a colorless syrup.

Data obtained from the mixture. FT–IR (neat) *v* in cm^{-1}: 3064, 3031, 2982, 2931, 2907, 2829, 1497, 1454, 1065, 1046, 1191, 1118, 738, 698; HRMS (TOF ES+) for $(M+Na)^+$ $C_{14}H_{20}NaO_4^+$(*m/z*): calc. 275.1254; found 275.1256. α-anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H, ArH), 4.93 (d, $J_{1,2}$ = 4.4 Hz, 1H, H-1), 4.65 (d, $J_{a,b}$ = 11.8 Hz, 1H, CH_aPh), 4.55 (d, $J_{a,b}$ = 11.8 Hz, 1H, CH_bPh), 4.36 (p, $J_{3,4}$ = $J_{4,Me}$ = 6.6 Hz, 1H, H-4), 4.08 (dd, $J_{3,4}$ = 6.6 Hz, $J_{2,3}$ = 5.3 Hz, 1H, H-3), 3.84 (m, 1H, H-2), 3.44 (s, 3H, OMe), 3.43 (s, 3H, OMe), 1.27 (d, $J_{4,Me}$ = 6.6 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.1 (C, Ar), 128.4,

127.8, 127.6 (CH, Ar), 100.3 (C-1), 86.7 (C-2), 82.2 (C-3), 73.8 (C-4), 72.3 (CH_2Ph), 58.5 (OMe), 55.2 (OMe), 15.7 (Me). β-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.39–7.27 (m, 5H, ArH), 4.79 (d, $J_{1,2}$ = 1.7 Hz, 1H, H-1), 4.66 (d, $J_{a,b}$ = 12.2 Hz, 1H, CH_aPh), 4.53 (d, $J_{a,b}$ = 12.2 Hz, 1H, CH_bPh), 4.31 (p, $J_{3,4}$ = $J_{4,Me}$ = 6.3 Hz, 1H, H-4), 3.84 (m, 1H, H-3), 3.79 (m, 1H, H-2), 3.42 (s, 3H, OMe), 3.36 (s, 3H, OMe), 1.32 (d, $J_{4,Me}$ = 6.6 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm:138.3 (C, Ar), 128.5, 127.9, 127.8 (CH, Ar), 107.9 (C-1), 89.5 (C-2), 82.2 (C-3), 77.0 (C-4), 72.1 (CH_2Ph), 57.9 (OMe), 55.2 (OMe), 16.2 (Me).

3-*O*-Benzyl-5-deoxy-2-*O*-methyl- α-β-D-xylofuranose (7.9)

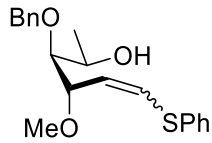


To a solution of **7.8** (3.35 g, 13.24 mmol) in 15 mL of AcOH was added HCl 1M (1 mL) at rt. The reaction mixture was stirred at 65 ºC and after 3 h, TLC showed full conversion. The reaction flask was cooled to 0 ºC and neutralized with saturated $NaHCO_3$. The product was extracted with EtOAc, the combined organic layers washed with brine and dried with Na_2SO_4. After filtration and solvent under vacuum, the crude was purified by column cromatographyeluting with EtOAc/ Hexane (1:1) to afford **7.9** (3.00 g, 95%) as a (1:1.3) α/β mixture as a colorless syrup.

Data obtained from the mixture. R_f EtOAc/Hexane (1:1): 0.3; FT–IR (neat) *v* in cm^{-1}: 3421, 3031, 2979, 2932, 2830, 1454, 1117, 1062, 739, 698; HRMS (TOF ES+) for $(M+Na)^+$ $C_{13}H_{18}NaO_4^+$ (*m/z*): calc. 261.1097; found 261.1100. α-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.28 (m, 5H, ArH), 5.46 (dd, $J_{1,OH}$ = 8.6 Hz, $J_{1,2}$ = 4.4 Hz, 1H, H-1), 4.65 (d, $J_{a,b}$ = 12.1 Hz, 1H, CH_aPh), 4.57 (d, $J_{a,b}$ = 12.1 Hz, 1H, CH_bPh), 4.33–4.25 (m, 1H, H-4), 3.85–3.81 (m, 1H, OH), 3.81 (dd, $J_{3,4}$ = 4.3 Hz, $J_{2,3}$ = 2.1 Hz, 1H, H-3), 3.74 (dd, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 2.1 Hz, 1H, H-2), 3.43 (s, 3H, OMe), 1.28 (d, $J_{4,Me}$ = 6.5 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.8 (C, Ar), 128.4, 128.1, 127.8 (CH, Ar), 95.23 (C-1), 84.60 (C-2), 81.7 (C-3), 74.4 (C-4),

72.0 (CH_2Ph), 58.6 (OMe), 14.6 (Me). β-anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.28 (m, 5H, ArH), 5.17 (d, $J_{1,OH}$ = 11.1 Hz, 1H, H-1), 4.69 (d, $J_{a,b}$ = 11.8 Hz, 1H, CH_aPh), 4.57 (d, $J_{a,b}$ = 11.8 Hz, 1H, CH_bPh), 4.33–4.25 (m, 1H, H-4), 3.79 (bs, 1H, H-2), 3.77 (m, 1H, H-3), 3.39 (s, 3H, OMe), 3.36–3.31 (m, 1H, OH), 1.38 (d, $J_{4,Me}$ = 6.6 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 137.3 (C, Ar), 128.5, 127.8, 127.6 (CH, Ar), 100.6 (C-1), 87.6 (C-2), 81.1 (C-3), 74.6 (C-4), 72.3 (CH_2Ph), 57.5 (OMe), 15.4 (Me).

(*Z*/*E*)-4-*O*-Benzyl-3-*O*-methyl-1,2,6-trideoxy-1-phenylsulfanyl-*D*-*xylo*-hex-1-enitol (7.10)

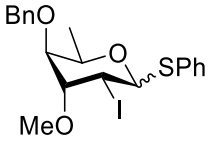


*n*BuLi (1.6 M, 1.91 mL, 4.77 mmol) was added to a solution of diphenyl (phenylsulfanylmethyl)phosphine oxide (1.58 g, 4.87 mmol) in THF (33 mL) at -78ºC and the mixture stirred at this temperature for 45 minutes. A solution of **7.9** (455 mg, 1.91 mmol) in THF (33 mL) was added to the orange solution at -78 ºC over a period of 30 minutes. After stirring at rt for 48 h, the reaction mixture was quenched by addition of a saturated solution of NH_4Cl, the product wa extracted with Et_2O, the combined organic layers were dried with Na_2SO_4, filtered and the solvent evaporated under vacuum. The product was purified by column cromatography eluting with EtOAc/Hexane (2:8) to afford **7.10** (546 mg, 83%) as an inseparable *E*/*Z* (1.5:1) mixture as a colorless syrup.

Data obtained from the mixture. R_f EtOAc/Hexane (3:7): 0.38; FT–IR (neat) *v* in cm^{-1}: 3464, 3060, 3030, 2974, 2927, 2891, 2820, 1606, 1584, 1479, 1440, 1067, 736, 690; HRMS (TOF ES+) for $(M+Na)^+$ $C_{20}H_{24}NaO_3S^+$ (*m*/*z*): calc. 367.1338; found 367.1353. *E*-isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.43–7.23 (m, 10H, ArH), 6.50 (dd, $J_{1,2}$ = 15.2 Hz, $J_{1,3}$ = 0.8 Hz, 1H, H-1), 5.72 (dd, $J_{1,2}$ = 15.2 Hz, $J_{2,3}$ = 7.9 Hz, 1H, H-2), 4.83 (d, $J_{a,b}$ = 11.2 Hz, 1H, CH_aPh), 4.59 (d, J = 11.2 Hz, 1H, CH_bPh), 3.91 (ddd, $J_{2,3}$ = 7.9 Hz, $J_{3,4}$ = 5.5 Hz, $J_{1,3}$ = 0.8 Hz, 1H, H-3), 3.98–3.84 (m, 1H, H-5), 3.34 (s, 3H,

OMe), 3.21 (dd, $J_{3,4}$ = 5.5 Hz, $J_{4,5}$ = 4.1 Hz, 1H, H-4), 2.27 (d, $J_{5,OH}$ = 6.2 Hz, 1H, OH), 1.20 (d, $J_{5,Me}$ = 6.4 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3, 134.4 (C, Ar), 130.5, 129.4, 128.6 (CH, Ar), 128.4 (C-1), 128.3 (CH, Ar), 128.3 (C-2), 128.0, 127.4 (CH, Ar), 85.3 (C-4), 83.8 (C-3), 75.5 (CH_2Ph), 67.6 (C-5), 57.1 (OMe), 20.3 (Me). *Z*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.43–7.23 (m, 10H, ArH), 6.55 (dd, $J_{1,2}$ = 9.6 Hz, $J_{1,3}$ = 0.9 Hz, 1H, H-1), 5.82 (dd, $J_{1,2}$ = 9.6 Hz, $J_{2,3}$ = 9.0 Hz, 1H, H-2), 4.91 (d, $J_{a,b}$ = 11.3 Hz, 1H, CH_aPh), 4.63 (d, $J_{a,b}$ = 11.3 Hz, 1H, CH_bPh), 4.45 (ddd, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 4.9 Hz, $J_{1,3}$ = 0.9 Hz, 1H, H-3), 3.98–3.84 (m, 1H, H-5), 3.39 (s, 3H, OMe), 3.35-3.31 (m, 1H, H-4), 2.41 (d, $J_{5,OH}$ = 5.5 Hz, 1H, OH), 1.23 (d, $J_{5,Me}$ = 6.4 Hz, 3H, Me); ^{113}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 138.3, 135.7 (C, Ar), 129.6, 129.3 (CH, Ar) 129.3 (C-1), 128.9 (C-2), 128.6, 128.3, 128.0, 127.0 (CH, Ar), 84.8 (C-4), 79.3 (C-3), 75.4 (CH_2Ph), 67.7 (C-5), 57.1 (OMe), 20.2 (Me).

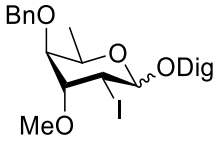
Phenyl 4-*O*-benzyl-2,6-dideoxy-2-iodo-3-*O*-methyl-1-thio-α/β-D-gulopyranoside (7.11)



Note: The isolated product decomposed in solution (light/temperature-sensitive) and was therefore quickly subjected to the next reaction. Sulfanyl alkene **7.10** (33 mg, 0.096 mmol) was dissolved in CH_3CN and cooled to -45 ºC. IDCP (135 mg, 0.287 mmol) was then added and the reaction mixture stirred at -40 ºC and monitored by TLC. After 1 h, the reaction was diluted with DCM and a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ was added at low temperature and gradually warmed to rt. The product was extracted with CH_2Cl_2, the organic phase dried with Na_2SO_4, filtered and the solvent evaporated. The product was purified using flash chromatography eluting with EtOAc/Hexane (1:9) to afford **7.11** (37.7 mg, 84%) in a α/β (1:2.4) ratio as a colorless syrup.

Data obtained from the mixture. R_f EtOAc/Hexane (1:9): 0.27; FT–IR (neat) ν in cm^{-1}: 3060, 3029, 2982, 2929, 2891, 2827, 1625, 1584, 1455, 1356, 1069, 1014, 740, 693; HRMS (TOF ES+) for $(M+Na)^+$ $C_{20}H_{23}INaO_3S^+$ (*m/z*): calc. 493.0305; found 493.0313. β-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.64-7.25 (m, 10H, ArH), 5.00 (d, $J_{1,2}$ = 11.1 Hz, 1H, H-1), 4.71-4.57 (m, 2H, CH_aPh and CH_bPh), 4.41 (dd, $J_{1,2}$ = 11.1 Hz, $J_{2,3}$ = 3.3 Hz, 1H, H-2), 4.05 (qd, $J_{5,Me}$ = 6.5 Hz, $J_{4,5}$ = 1.3 Hz, 1H, H-5), 3.54 (t, $J_{2,3}$ = $J_{3,4}$ = 3.3 Hz, 1H, H-3), 3.40 (s, 3H, OMe), 3.22 (dd, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 1.4 Hz, 1H, H-4), 1.23 (d, $J_{5,Me}$ = 6.5 Hz, 3H, Me). α-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ in ppm: 7.64-7.25 (m, 10H, ArH), 5.35 (bd, $J_{1,2}$ = 4.9 Hz, 1H, H-1), 5.02 (dd, $J_{1,2}$ = 4.9 Hz, $J_{2,3}$ = 3.0 Hz, 1H, H-2), 4.71-4.57 (m, 3H, CH_aPh, CH_bPh and H-5), 3.48-3.43 (m, 4H, OMe, H-3), 3.37 (bs, 1H, H-4), 1.20 (d, $J_{5,Me}$ = 6.6 Hz, 3H, Me).

Digitoxigenyl 2,6-dideoxy-4-*O*-benzyl-2-iodo-3-*O*-methyl-α,β-D-gulopyranoside (7.12)



To a Schlenk flask containing activated 4Å MS and digitoxigenin (21.7 mg, 0.058 mmol) azeotropically dried with toluene, was transferred *via* cannula **7.11** (13 mg, 0.028 mmol) dissolved in CH_2Cl_2 (1 mL). After stirring for 30 minutes at -60 ºC, NIS (18.6 mg, 0.083 mmol) azeotropically dried with toluene and TfOH (1 μL, 0.011 mmol) were successively added. After 1 h at -60 ºC, the reaction was quenched by addition of a saturated solution of $NaHCO_3$ and $Na_2S_2O_3$. The product was extracted with CH_2Cl_2, dried with Na_2SO_4, filtered and the solvent evaporated. The crude was purified using flash chromatography EtOAc/Hexane (1:9 to 1:1) to afford **7.12** (14 mg, 68%) as an inseparable 1:9 α/β mixture as a colorless syrup.

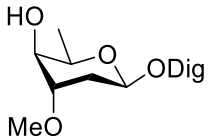
Data obtained from the mixture. R_f EtOAc/Hexane (1:1): 0.33; FT–IR (neat) ν in cm^{-1}: 3482, 2931, 1742, 1621, 1453, 1130, 1068, 1026, 1002, 738; HRMS (TOF ES+) for $(M+Na)^+$ $C_{37}H_{51}INaO_7^+$ (*m/z*): calc. 757.2572; found 757.2576. **7.12**β ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.27 (m, 5H, ArH), 5.86 (bt, 1H, $J_{21a,22Dig}$ = $J_{21b,22Dig}$ = 1.7 Hz, 1H, H-22_{Dig}), 4.99 (dd, $J_{21a,bDig}$ = 18.1 Hz, $J_{21a,22Dig}$ = 1.7 Hz, 1H, H-$21a_{Dig}$), 4.80 (dd, $J_{21a,bDig}$ = 18.1 Hz, $J_{21b,22Dig}$ = 1.7 Hz, 1H, H-$21a_{Dig}$), 4.64 (d, $J_{1,2}$ = 9.2 Hz, 1H, H-1), 4.63 (d, $J_{a,b}$ = 12.1 Hz, 1H, CH_aPh), 4.58 (d, $J_{a,b}$ = 12.1 Hz, 1H, CH_bPh), 4.32 (dd, $J_{1,2}$ = 9.2 Hz, $J_{2,3}$ = 3.3 Hz, 1H, H-2), 4.01-3.91 (m, 2H, H-3_{Dig}, and H-5), 3.50 (t, $J_{2,3}$ = $J_{3,4}$ = 3.3 Hz, 1H, H-3), 3.35 (s, 3H, OMe), 3.18 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.3 Hz, 1H, H_4), 2.77 (m, 1H, OH_{Dig}), 2.17-1.20 (m, 22H, H_{Dig}), 1.18 (d, 3H, $J_{5,Me}$ = 6.6 Hz, Me), 0.92 (s, 3H, Me_{Dig}), 0.86 (s, 3H, Me_{Dig}); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 174.8 ($C=O_{Dig}$), 174.7 (C-20_{Dig}), 137.7 (C, Ar), 128.6, 128.5, 128.3 (CH, Ar), 117.8 (C-22_{Dig}), 97.6 (C-1), 85.8 (C-14_{Dig}), 81.2 (C-3), 75.3 (C-4), 73.6 (C-21_{Dig}), 73.1 (C-3_{Dig}), 73.0 (CH_2Ph), 69.4 (C-5), 59.4 (OMe), 51.1, 49.7, 42.0, 40.2, 36.1, 36.0, 35.3 ($7C_{Dig}$), 33.5 (C-2), 33.3, 30.1, 29.0, 27.0, 26.6, 26,6 23.7, 21.5, 21.3, ($8C_{Dig}$), 16.7 (C-6), 15.9 (Me_{Dig}). Selected signals for **7.12**α ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.27 (m, 5H, ArH), 4.74 (d, $J_{1,2}$ = 3.9 Hz, 1H, H-1), 4.68-4.52 (m, 2H, CH_aPh and CH_bPh), 4.26 (qd, $J_{5,Me}$ = 6.9 Hz, $J_{4,5}$ = 1.2Hz, 1H, H-5), 3.81-3.73 (m, 1H, H-2), 3.37-3.35 (m, 3H, H-3 and OMe), 3.29 (m, 1H, H-4), 1.10 (d, $J_{5,Me}$ = 6.7 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 97.1 (C-1), 79.0 (C-3), 76.1 (C-4), 61.7 (C-5), 59.4 (OMe), 33.1 (C-2), 16.5 (C-6).

Consecutive "One-pot" Cyclization and Glycosylation. To a Schlenk flask containing activated 4Å MS and digitoxigenin (110 mg, 0.29 mmol) azeotropically dried with toluene, was transferred *via* cannula **7.10** (60 mg, 0.174 mmol) in CH_2Cl_2 (4.35 mL). After stirring for 30 minutes at –60 ºC, NIS (117.3 mg, 0.52 mmol) was then added and the reaction gradually warmed up to –10 ºC. After 3 h, the reaction mixture was cooled again to –60 ºC and TfOH (7.5 μL, 0.035 mmol) was added. After 1 h at –60 ºC, the reaction mixture was quenched by addition of a saturated solution of $NaHCO_3$ and $Na_2S_2O_3$. The product was extracted with CH_2Cl_2, dried over

Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (1:1 EtOAc/hexane) to afford **7.12**α/**7.12**β/**7.13**α (105 mg, 82%) as an inseparable 1:3.9:4.2 mixture as a yellowish syrup.

Data obtained from the mixture. R_f (1:1 EtOAc/hexane): 0.33; FTIR–ATR (neat, ν_{max}) 3480, 2931, 1741, 1620, 1453, 1131, 1066, 1026, 1002, 735; HRMS (TOF ES$^+$) (*m*/*z*) [M+Na]$^+$ Calcd for $C_{37}H_{51}INaO_7^+$ 757.2572; Found 757.2575. Selected signals for **7.13**α ($CDCl_3$, 400 MHz) δ in ppm: 7.40–7.27 (m, 5H, ArH), 4.85 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 4.70 (d, $J_{a,b}$ = 11.7 Hz, 1H, CH_aPh), 4.57 (d, $J_{a,b}$ = 11.7 Hz, 1H, CH_bPh), 4.22-4.14 (m, 1H, H-5), 3.93 (bs, 1H, H-3b$_{Dig}$), 3.81-3.73 (m, 1H, H-2), 3.63 (s, 3H, OMe), 3.58-3.54 (m, 1H, H-3 and H-4), 1.26 (d, 3H, $J_{5,Me}$ = 7.0 Hz, Me); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 97.0 (C-1), 83.0 (C-3), 80.7 (C-4), 73.8 (C-3$_{Dig}$), 73.1 (CH_2Ph), 68.7 (C-5), 60.7 (OMe), 33.2 (C-2), 13.4 (C-6). Spectroscopic data for **7.12** α/β were identical to those reported above.

Digitoxigenyl 2,6-dideoxy-3-*O*-methyl-β-D-gulopyranoside (7.16β)

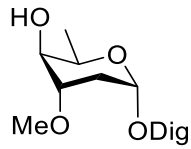


To a solution of **7.12** (1:9 α/β) (11.7 mg, 0.016 mmol) in degassed toluene (0.7 mL) were successively added Bu_3SnH (12 µL, 0.045 mmol) and AIBN (1 mg, 0.006 mmol) and the mixture was heated at 60 ºC for 2 h. After cooling, the reaction mixture was diluted with EtOAc, the organic layer washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude was subjected to a short column chromatography eluting with EtOAc/Hexane (1:1) containing 5% of Et_3N to separate tin contaminants from inseparable glycosylated products. The eluted fraction was dissolved in 1 mL of 1:1 (v/v) EtOAc/MeOH and 10% Pd/C Degussa type (24 mg) was added. The mixture was stirred at 0 ºC under H_2 (1 atm) and, after 1 h, the reaction was diluted with EtOAc and

filtered through a short path of Celite®. The crude was purified using flash chromatography eluting with EtOAc/Hexane (1:9 to 6:4) to afford pure **7.16**β (4.5 mg, 54% over two steps yield, 61% based on starting β isomer) and **7.16**α (0.5 mg, 6% over two steps yield, 60% based on starting α isomers) as white powders.

R_f EtOAc/Hexane (6:4): 0.35; $[\alpha]_D^{20}$: -3.50 (0.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.87 (bt, $J_{21a,22Dig}$ = $J_{21b,22Dig}$ = 1.5 Hz, 1H, H-22_{Dig}), 4.99 (dd, $J_{21a,bDig}$ = 18.2 Hz, $J_{21a,22Dig}$ = 1.5 Hz, 1H, H-$21a_{Dig}$), 4.80 (dd, $J_{21a,bDig}$ = 18.2 Hz, $J_{21b,22Dig}$ = 1.5 Hz, 1H, H-$21b_{Dig}$), 4.71 (dd, $J_{1,2a}$ = 9.5 Hz, $J_{1,2b}$ = 2.6 Hz, 1H, H-1), 4.03 (bs, 1H, H-$3b_{Dig}$), 3.91 (qd, $J_{5,Me}$ = 6.6 Hz, $J_{4,5}$ = 1.1 Hz, 1H, H-5), 3.58 (q, $J_{2a,3}$ = $J_{2b,3}$ = $J_{3,4}$ = 3.2, 1H, H-3), 3.41-3.35 (m, 4H, H-4, OMe), 2.78 (m, 1H, $OH14_{Dig}$), 2.23-1.20 (m, 24H, H-2a, H-2b, H_{Dig}), 1.24 (d, 3H, $J_{5,Me}$ = 6.6 Hz, Me), 0.93 (s, 3H, Me_{Dig}), 0.87 (s, 3H, Me_{Dig}); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 174.7 ($C{=}O_{Dig}$), 174.7 (C-20_{Dig}), 117.8 (C-22_{Dig}), 96.6 (C-1), 85.8 (C-14_{Dig}), 78.6 (C-3), 73.6 (C-21_{Dig}), 72.8 (C-3_{Dig}), 69.2 (C-5), 68.0 (C-4), 57.3 (OMe), 51.0, 49.7, 42.0, 40.2, 36.4, 35.9, 35.3, 33.3 ($8C_{Dig}$), 31.6 (C-2), 30.3, 30.0, 27.0, 26.8, 26.8, 23.8, 21.5, 21.3 ($8C_{Dig}$), 16.7 (C-6), 15.9 (Me_{Dig}); FT–IR (neat) *v* in cm^{-1}: 3450, 2855, 1781, 1742, 1666, 1619, 14228, 1362, 1260, 1171, 1096, 1026, 800; HRMS (TOF ES+) for $(M+Na)^+$ $C_{30}H_{46}NaO_7^+$ (*m/z*): calc. 541.3136; found 541.3129.

Digitoxigenyl 2,6-dideoxy-3-*O*-methyl-α-D-gulopyranoside (7.16α)



To a solution of **7.12**α/**7.12**β/**7.13**α (1:3.9:4.2 ratio) (17 mg, 0.023 mmol) in degassed toluene (1 mL) were successively added Bu_3SnH (16 µL, 0.059 mmol) and AIBN (1.9 mg, 0.011 mmol) and the mixture was heated at 60 ºC for 2 h. After cooling, the reaction mixture was diluted with EtOAc, the organic layer washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude was subjected to a short

column chromatography eluting with EtOAc/Hexane (1:1) containing 5% of Et_3N to separate tin salts from inseparable glycosylated products. The eluted fraction was dissolved in 1.3 mL of 1:1 (v/v) EtOAc/MeOH and 10% Pd/C Degussa type (35 mg) was added. The mixture was stirred at 0 ºC under H_2 (1 atm) and, after 1 h, the reaction was diluted with EtOAc and filtered through a short path of Celite®. The crude was purified using flash chromatography eluting with EtOAc/Hexane (1:9 to 6:4) to afford pure **7.16**β (2.6 mg, 22% over two steps yield, 51% based on starting β isomer) and **7.16**α (3.8 mg, 32% over two steps, 57% based on starting α isomers) as white powders.

R_f EtOAc/Hexane (6:4): 0.24; $[\alpha]_D^{20}$: +23.30 (0.33, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ in ppm: 5.87 (bt, $J_{21a,22Dig}$ = $J_{21b,22Dig}$ = 1.6 Hz, 1H, H-22_{Dig}), 4.99 (dd, $J_{21a,bDig}$ = 18.3 Hz, $J_{21a,22Dig}$ = 1.6 Hz, 1H, H-$21a_{Dig}$), 4.85 (bt, $J_{1,2a}$ = $J_{1,2b}$ = 3.3 Hz, 1H, H-1), 4.81 (dd, $J_{21a,bDig}$ = 18.3 Hz, $J_{21b,22Dig}$ = 1.6 Hz, 1H, H-$21b_{Dig}$), 4.33 (qd, $J_{5,Me}$ = 6.8 Hz, $J_{4,5}$ = 1.6 Hz, 1H, H-5), 3.87 (bs, 1H, H-$3b_{Dig}$), 3.53 (q, $J_{2a,3}$ = $J_{2b,3}$ = $J_{3,4}$ = 4.0, 1H, H-3), 3.47 (m, 1H, H-4), 3.39 (s, 3H, OMe), 2.78 (m, 1H, OH_{Dig}), 2.23-1.20 (m, 24H, H-2a, H-2b, $22H_{Dig}$), 1.17 (d, $J_{5,6}$ = 6.8 Hz, 3H, H-6), 0.93 (s, 3H, Me_{Dig}), 0.87 (s, 3H, Me_{Dig}); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ in ppm: 174.7 ($C{=}O_{Dig}$), 174.7 (C-20_{Dig}), 117.8 (C-22_{Dig}), 95.5 (C-1), 85.8 (C-14_{Dig}), 76.3 (C-3), 73.6 (C-21_{Dig}), 72.7 (C-3_{Dig}), 70.3 (C-4), 63.2 (C-5), 56.0 (OMe), 51.1, 49.7, 42.1, 40.2, 36.9, 35.8, 35.4, 33.3, 32.4, 30.4, 22.7, 27.0 ($12C_{Dig}$), 26.9 (C-2), 25.2, 24.0, 21.5, 21.4 ($4C_{Dig}$), 16.2 (C-6), 15.9 (Me); FT–IR (neat) *v* in cm^{-1}: 3456, 2926, 1738, 1620, 1447, 1127, 1109, 1026, 984; HRMS (TOF ES+) for $(M+Na)^+$ $C_{30}H_{46}NaO_7^+$ (*m/z*): calc. 541.3136; found 541.3140.

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CHAPTER VIII

General Conclusions

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8.1. General conlusions

The main objectives proposed for the two major blocks of this PhD thesis have been reached.

1) Copper-mediated perfluoroalkylation of $C(sp^2)$– and $C(sp^3)$–bonds.

Chapter III

- A wide range of different haloglycals, mainly iodoglycals, have been prepared. Two different strategies were followed for the preparation of the precursors and, the one-pot methodology developed by Kumar and Vankar proved more general and effective.
- Iodoglycals proved suitable precursors for trifluoromethylation, however, bromo derivatives proved inefficient in this reaction owing to the higher $C(sp^2)$–Br bond strength. The strategy was applicable to other iodinated heterocycles and benzoderivatives with yields ranging from 70% up to 95%.
- The introduction of CF_3 into positions with different electronic properties was accomplished by previous regioselective introduction of iodine.
- The functional group tolerance was demonstrated with OAc, OPiv, OTIPS, OBn, isopropilidene, F, N-Me, NBoc, and CO_2Me.
- While iodine substituted glycals, nucleosides and nitrogenated bases required excess of HF and heating, indoles (especially unprotected *N*-H indoles) were found to be more reactive.
- A common hydrodehalogenation reaction was observed with indoles but, fortunately, milder reaction conditions greatly diminished this detrimental side-reaction. Mechanistic investigations suggested this process may be governed by a radical mechanism mechanism.

Chapter IV

The results included in this chapter are protected due to the possibility of generation patents.

Chapter V

The results included in this chapter are protected due to the possibility of generation patents.

Chapter VI

- Different reactions were applied to trifluoromethylglycals prepared in chapter VI but only hydroxymercuration was successful. The low reactivity found in this substrates is attributed to both electronic and steric effects imparted by CF_3.
- Peracetylated and perbenzylated 2-CF_3-*manno*- and *gluco*-bromopyranosides were prepared as glycosyl donors.
- Good stereoselectivities were found in the glycosylations and the new glycosydic bond was formed preferentially *trans* to CF_3.
- Comparison of our results with the stereoselectivities found by Prof. Ryan Gilmour in the glycosylation 2-deoxy-2-fluoroglycosides was performed. The stereoselectivities obtained using 2-trifluoromethylglycosides can be explained incorporating a steric component to the model proposed by Gilmour.

Chapter VII

- The first total synthesis of Cardenolide N-1 has been accomplished.
- Key steps of the synthesis included a Wittig-Horner olefination of a pentose to afford a sulfanyl alkene followrd by iodonium-induced cyclization producing a 2-deoxy-2-iodothioglycosides, and glycosylation affording the desired 2-deoxy-2-iodoglycoside.
- Spectroscopic data obtained perfectly matched that collected from the extracted natural product, thus confirming the original structural proposal.

- Enough material of previously unreported α-epimer of cardenolide N-1 was also obtained and characterized for the first time.

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