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COMMUNICATION

Exploring F/CF₃ substituted oxocarbenium ions for the diastereoselective assembly of highly substituted tetrahydrofurans

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Understanding the influence of emerging fluorinated motifs is of a crucial importance in the context of the exponentially growing exploitation of fluorine in many fields. Herein, we report on the dramatic effect of a local partial charge inversion by replacing a CHCH₃ group by a CFCF₃. This strategy allows the diastereoselective reduction of 5-membered ring oxocarbenium ions to access highly substituted tetrahydrofurans.

Tetrahydrofurans (THFs), as well as their analogues in higher oxidation states, are important structural motifs found in both natural and unnatural bioactive products.¹ Examples include highly substituted natural products (+)-fragransin A2,² jiadifenin,³ (-)-talaumidin,⁴ sofosbuvir,⁵ a polymerase NSSB inhibitor employed in curative treatments of hepatitis C virus or bicyclic pyridinone **16** used in neurological disorders treatment. All exhibit an aryl group in position 2 and/or a methyl group in position 3 (Figure 1). Owing to their inherent biological properties, the construction of highly substituted THFs in an efficient way is therefore a significant task in synthetic chemistry. With more than 25% of FDA-approved drugs containing fluorine atoms,⁷ the development of synthetic strategies towards fluorinated functionalized small molecules exploded over the past years,⁸ and generating emergent fluorinated motifs with unprecedented physicochemical properties is needed.⁹ We thus embarked in the development of a robust synthetic route to highly substituted 2-aryl THFs exhibiting CF₃ and F groups in position 3 with a CF₃^{δ-}/F^{δ-} complete charge inversion versus CH₃^{δ+}/H^{δ+} analogues. These original analogues of C3-methylated THFs exhibit local partial charge inversion, a strategy recently elegantly applied to phenethylamine pharmacophore¹⁰ and saccharides,¹¹ foreshadowing unique properties and further developments in this direction.¹² A rapid retrosynthetic analysis confirmed the

accessibility of these structures after arylation and reduction of a key structural unit **2** (Scheme 1) that could be generated in a two-step procedure from the hexafluoropropene–diethylamine adduct and allylic alcohol after Claisen rearrangement followed by iodolactonization (see SI).¹³

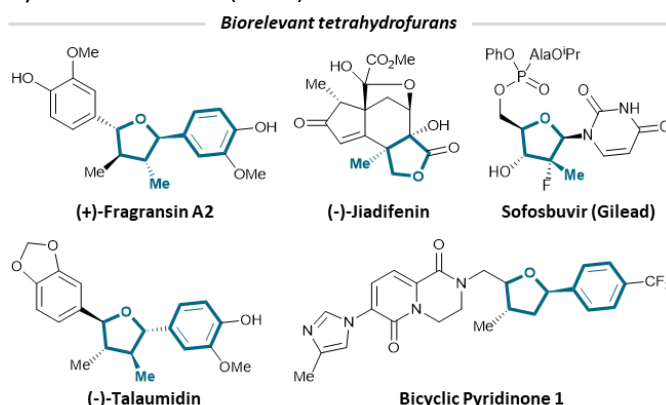


Figure 1 Biologically important highly substituted THFs exhibiting C2-aryl and/or C3-methyl substituents.

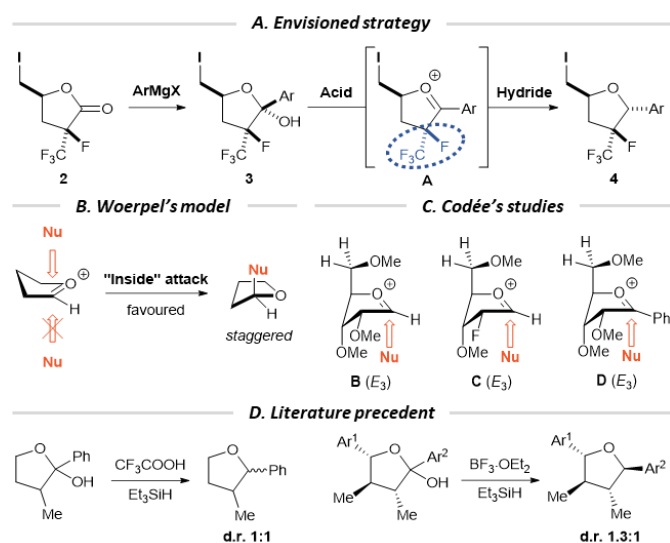
One question also arises behind this strategy: how could the CF₃^{δ-}/F^{δ-} complete charge inversion (versus CH₃^{δ+}/H^{δ+}) influence the stereochemical outcome of the nucleophilic trapping of a postulated phenyl-substituted oxocarbenium ion **A**, generated after hemiketal activation (Scheme 1A)?^{14,15} Stereoelectronic models have been nicely recommended by Woerpel to explain the highly stereoselective reaction of five-membered ring oxocarbenium ions with nucleophiles (Scheme 1B).¹⁶ The “inside” attack model, based on the stereoelectronically controlled inside attack of the nucleophile on the lower energy conformer, allows for predicting Lewis acid-promoted substitution to form the product in the lowest energy conformation. A complete survey developed by Codée also reinforces the fact that the stereochemical outcome of the acid-catalysed reduction of furanosyl oxocarbenium ions **B** is directly dependent on the inside attack of the nucleophile on the most stable conformer (Scheme 1C).¹⁷ A 2-fluoro ribofuranosyl oxocarbenium ion **C** has also been studied by calculation and interestingly, the preferred *E*₃ conformation exhibiting a pseudo-equatorial orientation of the fluorine atom is favoured.

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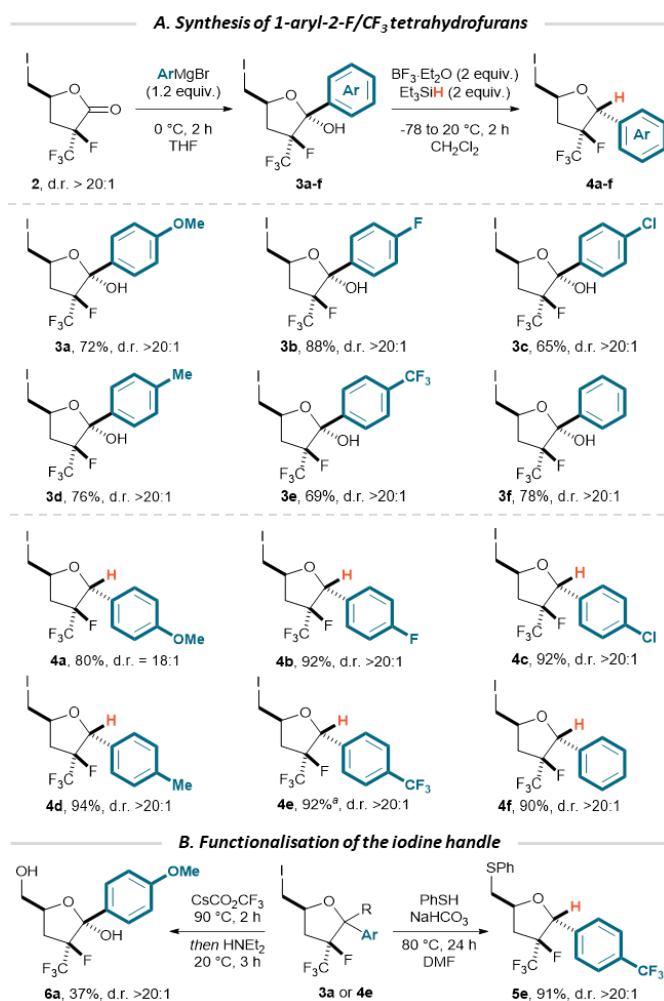
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Here, this conformation must favour the stabilization of the oxocarbenium ion by hyperconjugation with the geminal C–H bond.¹⁸ Interestingly, the same E_3 conformation is estimated to be adopted by the phenyl-substituted ribofuranosyl oxocarbenium ion **D**, even though the energy difference with the 3E conformer is smaller when the cation is substituted by a phenyl group.^{19,20} The attack model also serves to predict and analyse systematically the impact of substituents located in different positions of the phenyl-substituted oxocarbenium ion.²¹ In addition, and noteworthily, the acid-catalysed reduction of 3-methyl-2-phenyl-tetrahydrofuran hemiketals is reported to be poorly diastereoselective (Scheme 1D).²² This needs to be taken into consideration when exploring the reactivity of the highly substituted furanosyl oxocarbenium ion **A** that is supposed to be involved in this study.



Scheme 1 A. Proposed strategy for the synthesis of F/CF₃ substituted aryl-THFs and impact of the F/CF₃ substitution on the reactivity of oxocarbenium ion **A**. B. "Inside" attack model developed by Woerpel. C. Calculated preferred conformations and reactivity of furanosyl oxocarbeniums. D. Reported Lewis acid-promoted reductions of 2-aryl-3-methyl-THF hemiketals.

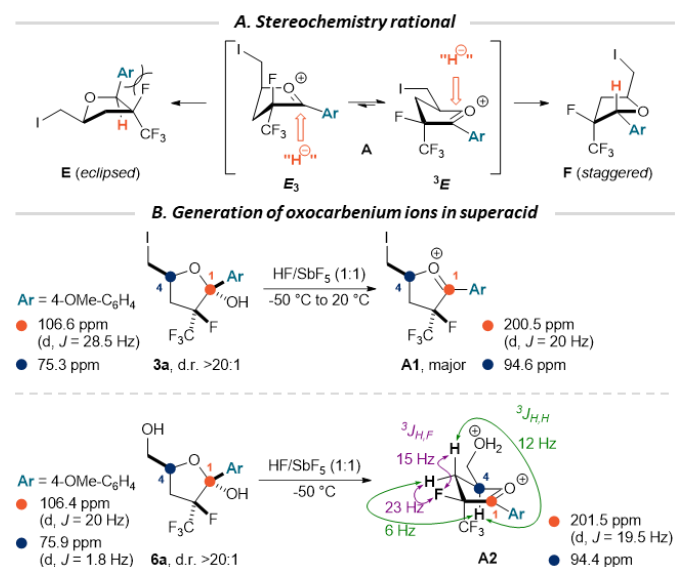
To test our strategy, first, the reaction of lactone **2**²³ in the presence of various aryl Grignard reagents was tested in THF at 0 °C.²⁴ Satisfyingly, the reaction of 4-methoxyphenylmagnesium bromide with **2** afforded the desired hemiketal in 72% yield with a good diastereoselectivity in favour of the diastereomer **3a** exhibiting OH and F groups in *anti* relationship, whose structure was confirmed by X-ray analysis.²⁵ The reaction was shown to be very versatile allowing to generate products **3b–f** in good yield with excellent diastereoselectivity (Scheme 2A). This confirmed the ability to use this strategy toward the synthesis of halogen-, methyl- or trifluoromethyl-substituted arylated hemiketals. At this stage, it was also interesting to note the impact of the F/CF₃ vicinal substituted C3 carbon atom on the reaction, as only one diastereomer could be observed in the reaction crude, suggesting a very favoured approach of the Grignard reagent away from the face that is stereoelectronically hindered by the CF₃ group.



Scheme 2 A. Synthesis of arylated hemiketals **3a–f** and their reduction to 2-aryl-3-F/CF₃ tetrahydrofurans **4a–f**. B. Synthesis of hydroxylated **6a** and thiophenylated **5e** tetrahydrofurans. ^a Et₃SiH (3 eq.), BF₃·Et₂O (3 eq.), 14 h.

Hemiketals **3** were then subjected to a Lewis acid-mediated reduction protocol using triethylsilane as reducing agent and boron trifluoride diethyl etherate as Lewis acid in dichloromethane. A first attempt with 4-methoxyphenyl-substituted substrate **3a** gratifyingly afforded the desired corresponding product **4a** in 80% yield with a good 18:1 d.r. (Scheme 2A). The reaction also proceeded very well with halogen- or methyl-substituted substrates **3b–d** with excellent diastereoselectivity (d.r. >20:1). To verify whether a decrease of electron density on the aromatic ring could be prejudicial to the efficiency of the reaction, trifluoromethylated substrate **3e** was tested. The reaction was slower in this case but using an excess of Lewis acid and reducing agent allowed to overcome this difficulty and the desired product **4e** could be generated in 92% yield with a complete diastereocontrol. The reaction was also efficient when phenyl-substituted cyclic hemiketal **3f** was employed. Interestingly, the ability to access to original fluorinated analogues of C-furanosides was shown by generating thiophenyl analogue **5e** and alcohol **6a** in reasonable yields opening further application perspectives (Scheme 2B).²⁶

Interestingly, despite the presence of the F/CF₃-substituted vicinal carbon, the acid-catalysed reduction proceeded well, and with an excellent diastereocontrol. The full polarity inversion close to the postulated oxocarbenium ion must strongly influence its conformational behaviour and reactivity. This aspect is supported by the dramatic difference of behaviour between substrates **3** studied here and analogous reactions with 2-phenyl-3-methyl THF hemiketals (Scheme 1D).²⁷ This reinforced our curiosity to understand the behaviour of the hypothetical oxocarbenium ion that is thought to be involved in this process. Considering precedent studies on furanosyl oxocarbenium ions, two hypothetical conformers could reasonably be postulated (Scheme 3A).



Scheme 3 A. Hypothetical fluorinated oxocarbeniums conformation and resulting product conformers. **B.** In situ NMR analysis of F/CF₃ substituted oxocarbeniums.

A first conformation of type *E*₃ features the C–F bond in a pseudo axial arrangement, the CF₃ being placed in equatorial position and the iodomethylene moiety axially oriented. An addition of the nucleophile to conformer *E*₃ would lead to a torsionally disfavoured transition state, precursor of **E**. On the other hand, the attack to the second conformation ³*E* generates a torsionally favoured transition state leading to **F** with the C–CF₃ bond adopting an axial arrangement while the C–F and C–CH₂I bonds being placed in equatorial positions. Woerpel's model suggests the oxocarbenium ion adopts a privileged ³*E* conformation, which is approached by its inside face by the nucleophile, delivering one diastereomer **4**. Interestingly, the erosion of the diastereoselectivity in the case of product **4a** could be attributed to the partial inside attack of a minor *E*₃ conformation that could exist, as stabilized through resonance effect of the 4-methoxyphenyl ring. To further reinforce this hypothesis, we embarked in scrutinizing the hypothetical formation of oxocarbenium **A** in superacid solutions. The ability to use superacid solutions²⁸ to generate, stabilize and study carbocations using low-temperature *in situ* NMR has been elegantly developed and exploited by Olah.²⁹ Recently, we demonstrated that this strategy can be applied to study

superelectrophilic polycations,³⁰ including glycosyl oxocarbenium ions.³¹ Here, the challenge was especially associated with the proximity of the electron-withdrawing F/CF₃ moiety that must enhance the electrophilic character of oxocarbenium ions of type **A**, shifting these species from electrophiles to superelectrophiles.³² Substrate **3a** was thus submitted to a HF/SbF₅ solution, furnishing a cationic species whose ¹³C NMR spectrum fits well with cation **A1** (Scheme 3B). The signal for the C1 carbon is a clean doublet with a highly deshielded chemical shift at 200.5 ppm and a *J*_{C-F} coupling constant of 20 Hz. The C4 carbon atom is also deshielded by 19.3 ppm compared to the starting material. Unfortunately, the resolution of the ¹H NMR spectrum disallowed any accurate determination of the conformation of this ion **A1** in solution. We thus moved to study the behaviour of the hydroxylated analogue **6a** under similar conditions. The higher resolution of the corresponding NMR spectra enabled access to the conformation of ion **A2**. Evidence for a flattening of the oxocarbenium was provided by *J* coupling analysis, whose values were perfectly in line with a ³*E* conformation. The ³*J*_{H-F} coupling constants between F_{C2} and H₃_{eq} of 23 Hz and F_{C2} and H₃_{ax} of 15 Hz are in accordance with an equatorial orientation of the C–F bond and the ³*J*_{H3-H4} coupling constant, consistent with the proposed envelope conformation. Although the weakly nucleophilic conditions used to observe **A2** are different from those in the reduction reaction conducted in CH₂Cl₂, the observation of stable oxocarbenium ions **A1** and **A2** in a ³*E* conformation suggests that a similar conformation is likely involved in the reduction reaction.

To conclude, a very robust diastereocontrolled synthetic route to highly substituted phenyl THFs endowed with an original F/CF₃ substituted carbon has been developed from easily accessible lactone **2**. These species can be considered as valuable analogues of 2-methylfuranoside derivatives with a complete electronic inversion in position 2. Furthermore, this study reveals a pronounced beneficial effect of substituting a CHCH₃ by a CFCF₃ group for the stereochemical control of the nucleophilic trapping of the furanosyl oxocarbenium ion, reinforcing the necessity to expand fluorinated architectures in the molecular field.

Conflicts of interest

There are no conflicts to declare.

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