CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201302070

Addition of Electrophilic Radicals to 2-Benzyloxyglycals: Synthesis and Functionalization of Fluorinated α-*C*-Glycosides and Derivatives

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Abstract: A new method for the synthesis of fluorinated α-*C*-glycosides is described. The reactions between highly electrophilic radicals (fluorinated or unfluorinated) and a 2-benzyloxyglucal or galactal provide 2-keto-D-arabino- or 2-keto-D-lyxo-hexopyranosides through an addition/fragmentation process. Sodium borohydride mediated or Meerwein–Ponndorf–Verley (MPV) reduction of these compounds provides α-*C*-glycosides that feature appropriate anchoring groups for further synthetic elaboration. The presence of CF_2CO_2iPr or CF_2Br groups at the pseudo-anomeric position allows efficient reduction/olefination or Br/Li-exchange/nucleophilic-addition sequences. These transformations open the way for the synthesis of fluorinated *C*-glycosidic analogues of glycoconjugates.

Keywords: fluorine · glycomimetics · olefination · radicals · reduction

Introduction

Among the various biomolecules, carbohydrates and their derivatives, such as glycopeptides and glycolipids, have received careful attention in recent years for the purpose of drug research.[1] Indeed, such structures often play a crucial role in various biological processes, in particular in protein structure modulation or cell–cell recognition. Therefore, their use as drugs would be promising if their efficiency were not undermined by their low metabolic stability, owing to the in vivo cleavage of the anomeric bond by glycosidases. As such, the resulting low bioavailability of carbohydrate-based drugs is a severe drawback that could be overcome by the creation of analogues with similar bioactivity and increased in vivo stability. *C*-glycosides, in which the anomeric oxygen atom is replaced by a CH_2 group, were the first structures to be developed for this purpose.[2] Surprisingly, their synthesis has been intensively investigated but scarcely applied to the preparation of analogues of bioactive glycoconjugates. One striking exception is the preparation of *C*-glycosidic analogues of immunoregulative α-galactosylceramides by the Franck group. These molecules exhibited a 100-to-1000-fold increase in activity against malaria or melanoma cells compared to their parent *O*-glycolipid.[3] Although isolated, this example demonstrates the relevance of preparing *C*-glycosidic surrogates of biologically active *O*-glycoconjugates. A further step in the development of *C*-glycosides as glycomimetics was to replace the anomeric oxygen atom by a CHF or CF_2 group instead of a nonpolar CH_2 group.[4] Thanks to the physical and electronic properties of fluorine and fluoroalkyl groups (atom size, electronegativity, bond energy, length, etc.), this replacement was expected to provide compounds with better mimicking abilities.[5–7] Of course, this hypothesis remains to be challenged, but first requires the development of efficient and stereoselective methods that allow the preparation of analogues of complex *O*-glycoconjugates. However, despite the work that has been performed by our group and others since the seminal publications of Motherwell and co-workers, the chemist's toolbox is far less complete than that for the synthesis of classical CH_2-glycosides.[4,8,9] Therefore, we wanted to develop strategies that afford selective access to CF_2-glycosidic building blocks for a given carbohydrate series and a given configuration of the pseudo-anomeric center. Moreover, these intermediates should feature a functional group that would allow the introduction of an aglycon chain, for an efficient synthesis of glycoconjugate analogues. In two previous communications, we described a new method based on the addition of difluoromethyl radicals to 2-benzyloxyglycals.[10] In addition to these preliminary results, herein, we report a full study on this topic, including the extension of the addition reaction to other electrophilic radicals, as well as additional results for the reduction step and for the functionalization reactions.

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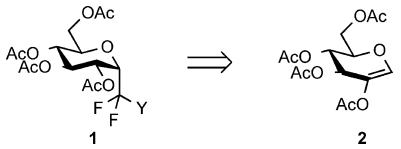
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302070.

Results and Discussion

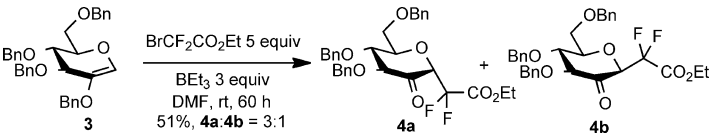
The addition of perfluoroalkyl or difluoromethyl radicals to double bonds is a well-known and efficient method for the synthesis of fluorine-containing molecules.[11] The addition of difluoromethyl and other electrophilic radicals to standard glycals has also been studied.[12,13] This addition reaction was regioselective and exclusively took place at the C2 carbon atom, although the introduction of an alkoxy substituent at this position was expected to direct the addition to the less-hindered C1 carbon atom (Scheme 1). This assumption was confirmed by the group of Miethchen, who reported the sodium dithionite mediated addition of bromochlorodifluoromethane to compound **2** during the early stages of our study.[9e] The corresponding α-CF_2-glucoside analogue (**1**, Y = Cl) was obtained with good selectivity, but with low conversion (Scheme 1).



Scheme 1. Synthesis of CF_2-glycosides through radical addition to 2-alkoxyglycals.

We were interested in the introduction of fluorinated synthons that were more suitable for further synthetic elaboration than the moderately reactive CF_2Cl group.[9f] As such, ethyl bromodifluoroacetate, a commercially available and easy-to-handle fluorinated synthon, or dibromodifluoromethane seemed more appropriate for such a purpose. The addition of the CF_2CO_2Et radical to double bonds generally involves the use of the less-common iodide or requires the painstaking synthesis of the corresponding selenide.[14] Indeed, the use of ethyl bromodifluoroacetate has scarcely been reported; nonetheless, the reaction was tested by using this reagent[15] with acetylated or benzylated D-glucal (**2** or **3**) as the starting material.[16]

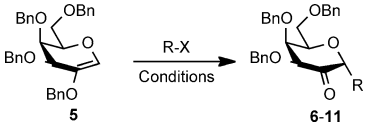
A short survey of various initiators and conditions led to a first positive result: 2-Ketohexopyranoside **4** was isolated, although in trace amounts, by using benzylated D-glucal **3** as the substrate and triethylborane as the initiator under non-reductive conditions in CH_2Cl_2. Pleasingly, polar solvents greatly promoted the reaction and the yield was increased to 21% in a 2:1 THF/water mixture and to 51% in DMF, by using an excess of the reagents. These latter two sets of conditions led to the isolation of two diastereomers in the crude mixture, that is, compounds **4a** and **4b**, in a 3:1 ratio (by ^{19}F NMR spectroscopy), which were readily separated by column chromatography on silica gel (Scheme 2). Then,



Scheme 2. Addition of ethyl bromodifluoroacetate to 2-benzyloxy-D-glucal **3**.

these optimized conditions were tested on benzylated D-galactal **5** and the appreciable α selectivity for compound **3** improved to complete selectivity. Indeed, 2-ketohexopyranoside **6** was present as a single diastereomer in the crude mixture (^{19}F NMR spectroscopy) and could be isolated in 58% yield (Table 1, entry 1). Thus, this method appeared to be a good route to α-*C*-galactosides and, hence, the scope of alkyl radicals that could undergo an addition to compound **5** was explored next. As anticipated, the addition of R–X to this electron-rich double bond only occurred efficiently with electrophilic radicals. Dibromodifluoromethane underwent a clean and fast addition, because 2-oxogalactoside **7** was the sole reaction product, according to TLC and NMR analysis of the crude mixture. However, the moderate stability of compound **7** on silica gel led to a disappointing 41% yield after chromatography (entry 2). The addition of fluorotribromomethane was less efficient, because compound **8** was isolated in poor yield from a complex reaction mixture (entry 3). The xanthate that was derived from ethyl bromofluoroacetate underwent a dilauroyl peroxide (DLP)-promoted addition to afford compound **9** in 59% yield and as a 1:1 mixture of C1′ epimers (entry 4).[17,18] The same reaction conditions allowed the addition of diethyl bromomalonate to occur (entry 5). It remains unclear why the DLP-mediat-

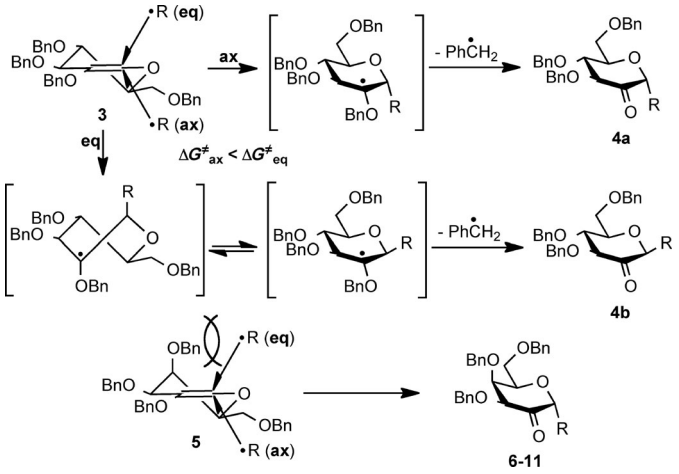
Table 1. Addition of electrophilic radicals to 2-benzyloxy-D-galactal **5**.



Entry	R–X (equiv)	Initiator (equiv)	Conditions	Product	Yield [%]
1	EtO_2CCF_2–Br (5)	BEt_3 (2.5)	DMF, air, RT	**6**	58
2	$BrCF_2$–Br (10)	BEt_3 (2)	DMF, air, RT	**7**	41
3	Br_2CF–Br (5)	BEt_3 (1)	DMF, air, RT	**8**	16
4		DLP (1)	DCE/*t*BuOH (1:1), 95 °C	**9**	59
5		DLP (1)	DCE/*t*BuOH (1:1), 95 °C	**10**	54
6		$Mn(OAc)_3$ (3)	MeCN, 85 °C	**10**	52
7	$PhSO_2CF_2$–Br (3)	BEt_3 (3)	DMF, air, RT	**11**	38

ed conditions were better suited to these last two examples, for which lower yields were obtained with BEt_3. Thus, both sets of conditions were examined for each substrate to determine the appropriate procedure.[19] Compound **10** could also be obtained in similar yield directly from diethyl malonate by using Mn^{III}-mediated oxidative conditions (entry 6).[13,20] Finally, bromodifluoromethyl phenyl sulfone was also examined and the reaction afforded compound **11** in modest yield (entry 7).[21] In all cases, only the α diastereomer was detected and isolated.

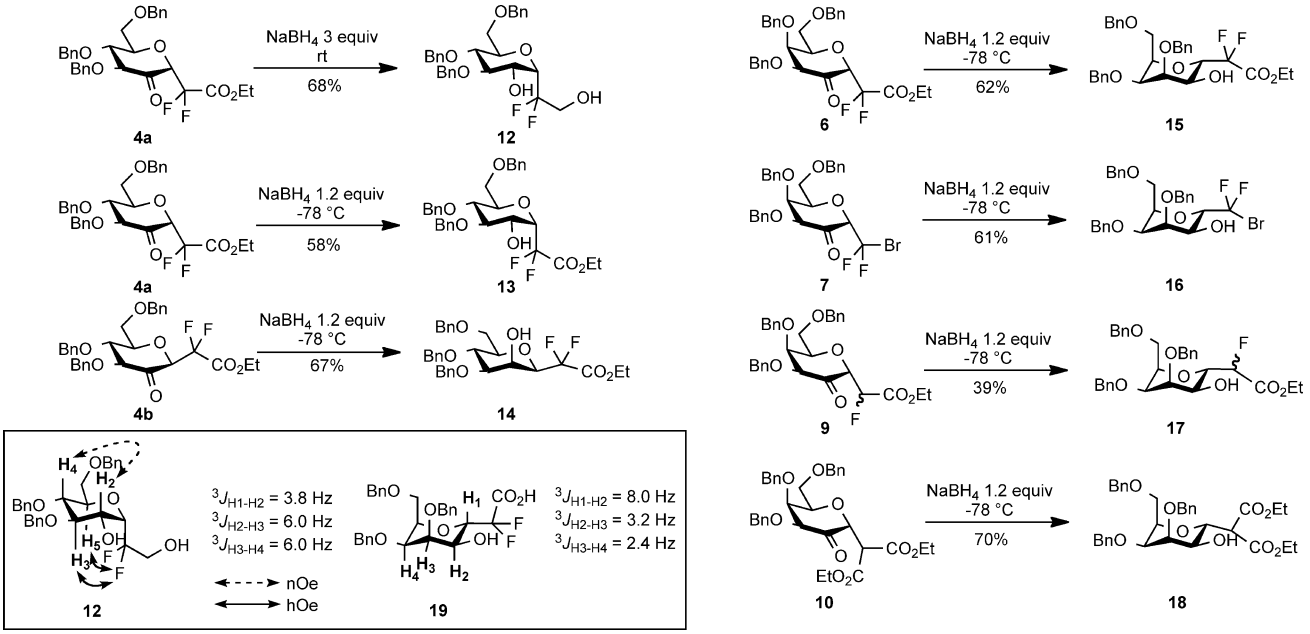
To our disappointment, no reactions occurred with dibromomethane, ethyl bromoacetate, di-isopropyl bromomethylphosphonate, or bromomethyl phenyl sulfone, under any conditions. We first suspected that the electrophilicity of the corresponding radicals was too low. However, this explanation was surprising and unsatisfactory for explaining the results that were obtained with dibromodifluoromethane. Indeed, the electrophilicity of simple trifluoromethyl or difluoromethyl radicals is often overemphasized, as demonstrated by several experimental and theoretical studies.[22,23] For example, the trifluoromethyl radical has recently been classified as less electrophilic than the *tert*-butoxycarbonylmethyl radical and ranked as a weak nucleophile.[23] Although no data are available for the $^{\bullet}CF_2Br$ radical, its behavior should be close to that of $^{\bullet}CF_3$ and, thus, it should hardly be considered as more electrophilic than $^{\bullet}CH_2CO_2Et$. However, the generally higher reactivity of fluoro- and difluoromethyl radicals relative to their hydrogenated counterparts should certainly account for these results.[11a] The positive effect of a polar solvent on BEt_3-mediated reactions is also in agreement with the general behavior of fluoroalkyl radicals. Indeed, the addition reactions of such radicals to electron-rich double bonds generally gives rise to polar transition states, which are stabilized in polar media.[11a] The formation of 2-ketohexopyranosides in these reactions results from a fragmentation of the radical that is obtained after the addition of $^{\bullet}CF_2CO_2Et$. The driving force for this fragmentation process was probably the departure of a stabilized tolyl radical, even if no byproducts that could account for the formation of this radical (benzyl bromide, 1,2-diphenylethane, etc.) were isolated (Scheme 3).[24] In addition, monitoring of these reactions by ^{19}F NMR spectroscopy never showed the presence of other addition products than compounds **6**–**11**, thus ruling out a putative bromohydrin-type intermediate that would collapse upon hydrolysis of the crude reaction mixture. Finally, the rationale for the strong α selectivity that is observed in these reactions relies on the same line of reasoning as the interpretation of Le Bel et al. and Beckwith regarding the addition of sulfuryl radicals to cyclohexene.[25] The attack on the pro-equatorial face of glucal **3** is indeed disfavored because it would lead to a twist intermediate through a high-energy transition state. If the same explanation also stands for galactal **5**, then the attack on the pro-equatorial face would be even more disfavored, owing to steric repulsion between the axial C4 substituent and the incoming radical.



Scheme 3. Rationale for the stereoselectivity of the radical addition.

Next, the reduction of 2-ketohexopyranosides **4** and **6**–**10** into their corresponding *C*-glycosides was explored. First, the simple sodium borohydride mediated reductions of glucose derivatives **4a** and **4b** were examined and afforded the desired *C*-glycosides. Notably, low temperatures were required to avoid the simultaneous reduction of the difluoroester group: This undesired transformation occurred at room temperature and compound **12** could be obtained in 68% yield if a three-fold excess of sodium borohydride was used (Scheme 4). The selective reduction of the ketone group was achieved by performing the reduction at −78°C. Then, α-D-glucoside **13** and β-D-mannoside **14** were obtained from compounds **4a** and **4b**, respectively, in fair yields. Moreover, in each case, only one diastereomer could be detected from the ^{19}F NMR spectrum of the crude mixtures (Scheme 4). As described in a preliminary communication, the configurations of compounds **12**, **13**, and **14** were confirmed by careful NMR spectroscopic experiments and an X-ray diffraction study on crystalline compound **13**.[10a] As reported in the study of Jiménez-Barbero, Vogel, and coworkers on CF_2 analogues of an α-galactoside, compound **13** adopted a classical $^4C_1$ chair conformation in the solid state, whereas the vicinal proton–proton coupling constants clearly indicated that this conformation was not the only one in solution.[9k] The observed stereoselectivities were in agreement with the numerous reports on the reduction of α- and β-2-keto-D-arabino-hexopyranosides.[26]

A similar reduction of galactose derivatives **6**–**10** provided CF_2-glycosides **15**–**18** in good yields and with complete diastereoselectivity (Scheme 4). In contrast to the glucose derivatives, the determination of the relative configuration of these compounds was not straightforward. HOESY $^{19}F/^1H$ NMR spectroscopic experiments showed no significant correlations and the coupling constants that were extracted from the ^1H NMR spectra of compounds **15** and **16** were not compatible with a $^4C_1$ conformation. Moreover, the ^1H NMR spectrum of carboxylic acid **19**, which was derived from compound **15**, revealed that the $J(H_1,H_2)$, $J(H_2,H_3)$, and $J(H_3,H_4)$ coupling constants were consistent

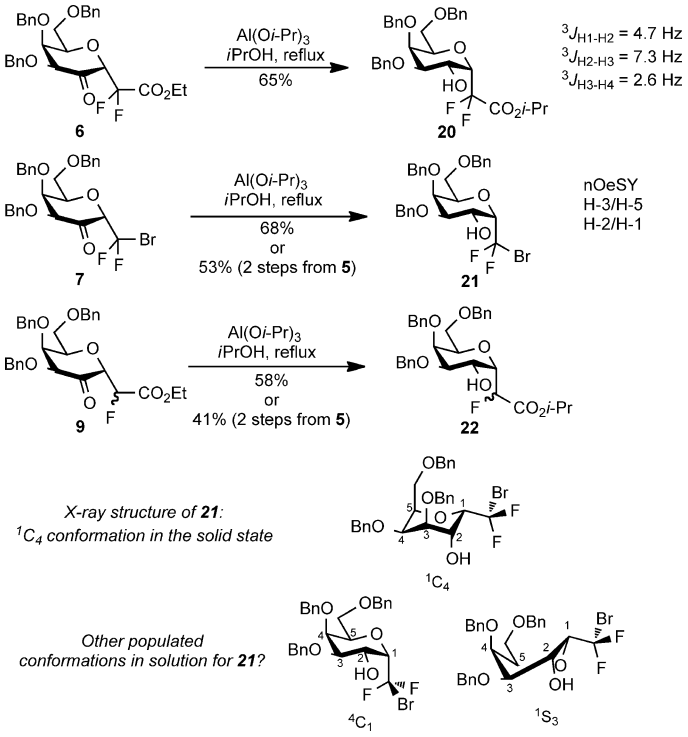


Scheme 4. Reduction of 2-ketohexopyranosides **4** and **6**–**10** with sodium borohydride.

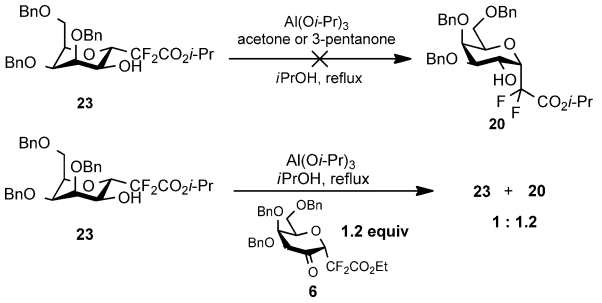
with an axial–axial–equatorial disposition of atoms $H_1/H_2/H_3$. Thus, compounds **15**–**18** were assigned to have an α-D-taloside configuration, with a $^1C_4$ conformation for the most-populated conformer in each case (Scheme 4). Although disappointing, this stereochemical outcome has previously been reported for other 2-oxogalactosides.[27] Other hydride-mediated reductions were tested (diisobutylaluminum hydride (DIBAH), L-selectride, Et_3BHLi, etc.), but led to the same stereoselectivity. Substitution reactions with inversion of configuration at the C2-position were also attempted from compound **15**, but met with failure. For instance, the Mitsunobu-type reactions only afforded unreacted starting material and substitution reactions of the triflate that was derived from compound **15** did not afford the desired α-D-galactoside, but rather yielded an elimination product.

To overcome the issue of diastereoselectivity in the metal hydride mediated reduction of 2-oxogalactosides **6**–**10**, we followed a very simple line of reasoning: Because these reactions are presumably under kinetic control, that is, they proceed through an attack of the hydride on the least-hindered face, the use of a thermodynamically controlled reduction reaction might reverse the selectivity. As a matter of fact, compound **15** was not expected to be the most-stable diastereomer because of its presumably strong 1,3-diaxial interaction between the substituents at the C3 and C5-positions. Thus, the Meerwein–Ponndorf–Verley (MPV) reaction, a well-known hydride-transfer and reversible reduction reaction, was considered.[28] By using standard conditions (aluminum isopropoxide at reflux in isopropanol), CF_2-glycosides **20**–**22** were obtained from compounds **6**, **7**,and **9**, respectively, in good yields, each time as a single diastereomer. In contrast to the use of sodium borohydride, a direct reduction of the crude compound that was obtained from the radical addition was even possible under the MPV conditions. A two-step/single-purification procedure for the radical-addition/reduction sequence allowed us to significantly improve the global yields (Scheme 5). The case of compound **7** is notable because avoiding the purification of this sensitive compound led to an appreciable 53% global yield of compound **21** from galactal **5**. However, this statement should be tempered by the slight decrease in yield that was observed when up-scaling the reaction (41% starting from 2 g of compound **5**).

Because the NMR spectroscopic data of compounds **16** and **21** were clearly different, we concluded that they were diastereomers and, therefore, that compound **21** was the desired α-CF_2-D-galactoside. Ethyl esters were converted into isopropyl esters during the MPV reduction but the saponification of compounds **15** and **20** led to carboxylic acids with different NMR spectroscopic data, thus leading to the same conclusion. The saponification of monofluoroesters **17** and **22** also led to different sets of diastereomers. The coupling constants between atoms H1, H2, and H3 in compound **20** were now within the same range as for α-*C*-glucose derivatives **12** and **13**, thus indicating that, once again, the $^4C_1$ conformation did not seem to be the most-populated one in solution. However, the H1/H2, H3/H5 and H1/H6 NOESY correlations could fit with an α-D-galactoside configuration and with contributions from the $^1S_3$ skew-boat and $^1C_4$ chair conformations.[10k] Finally, an X-ray diffraction study of compound **21** confirmed the configuration at the C2 position. However, crystallization of this benzyl-protected compound occurred in a $^1C_4$ chair conformation, in contrast with the results that were obtained by Jiménez-Barbero, Vogel, and coworkers. Indeed, their fully deprotected α-CF_2-galactoside adopted a $^4C_1$ conformation in the solid state. However, this time in agreement with the above-mentioned study, our compound appeared to be flexible in solution. For example,



Scheme 5. MPV reduction of compounds **6**–**9**.



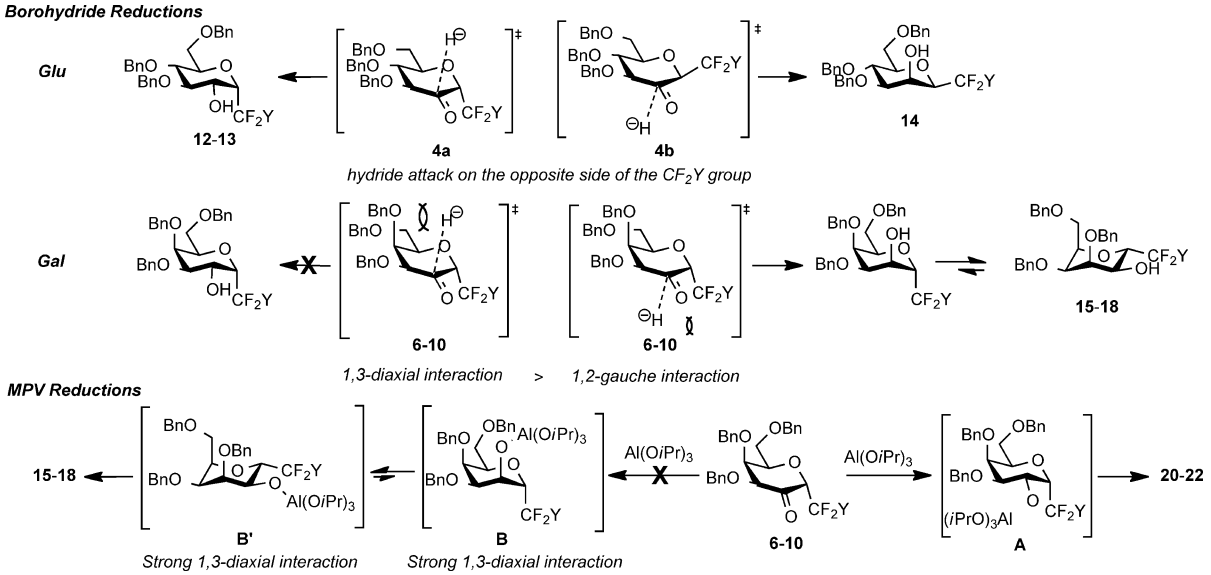
Scheme 6. Experiments to challenge the reversibility of the reaction.

a significant H3/H5 NOESY correlation, which was only compatible with $^1S_3$ skew-boat or $^4C_1$ chair conformations, was observed, thus demonstrating that the $^1C_4$ chair conformation, if populated, was not exclusive.

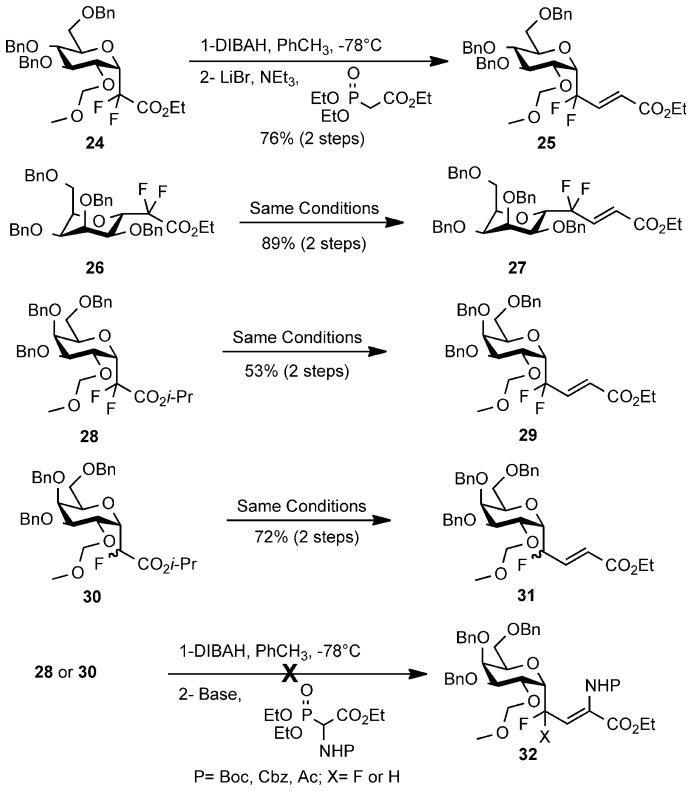
To gain deeper insight into the mechanism of the MPV reaction, the reversibility of the reaction was tested though several experiments. Compound **15** (the "kinetic diastereomer") was converted into its isopropyl ester (**23**) and placed under the MPV reduction conditions by using acetone or 3-pentanone as a co-oxidant. No equilibration towards the "thermodynamic diastereomer" (**20**) occurred under these conditions. Initially, we thought that the oxidation potentials of acetone and 3-pentanone were too low to reverse the reaction. Thus, these co-solvents were replaced with 1.2 equivalents of starting 2-ketopyranoside **6** to mimic the exact reaction conditions (Scheme 6). A 1:1.2 mixture of compounds **23** and **20**, was obtained, with the latter product arising from the reduction of compound **6**. Clearly, no equilibration took place during the process and, therefore, the MPV reduction of compound **20** was not reversible. However, as demonstrated by Burke et al., irreversible MPV reductions are characterized by a late transition state. Consequently, they typically afford the thermodynamically more-stable product, even if the reaction is not reversible.[29] A possible rationale for the stereoselectivity of the different reduction reactions is described in Scheme 7. The sodium borohydride mediated reduction of glucose derivatives **4a** and **4b** follows the literature reports, that is, an attack of the hydride on the opposite side of the CF_2Y group to avoid 1,2-*gauche* interactions. The inversion of selectivity for galactose derivatives **6**–**10** probably arises from a 1,3-diaxial interaction between the C4 benzyloxy group and the incoming hydride, which would be stronger than the 1,2-*gauche* interaction. As suggested in our first communication, a different conformational behavior between compounds **4a** and **6**–**10** might also favor this orientation.[10a] Finally, if the relative energies of the two possible diastereomers are responsible of the observed selectivity in the MPV reduction of compounds **6**–**10**, the strong 1,3-diaxial interactions in structures **B** and **B′** would certainly account for the preferential formation of structure **A** and compounds **20**–**22**. However, given the observed conformational flexibility of compounds **15**–**22**, these transition states should be merely considered as a working hypothesis.

Thanks to this radical-addition/reduction process, we had several functionalized fluorinated α-*C*-glycosides in hand and we wanted to explore their further synthetic elaboration. Our goal was to develop a method that could allow us to convert these advanced intermediates into their glycoconjugate analogues. The $CFXCO_2R$ and CF_2Br groups in derivatives **13**, **15**, and **20**–**22** appeared to be appropriate anchoring groups for introducing aglycon moieties through olefination reactions or Br/Li exchange, followed by nucleophilic addition. Thus, the reduction/olefination sequence that was reported in the preliminary communication for compound **24** was also applied to tallose and galactose derivatives **26**, **28**, and **30**, thereby affording the corresponding products in satisfactory yields (Scheme 8). As reported in the earlier communication, the double bond in compounds **25** and **27** was successfully hydrogenated in the presence of the benzyl ether protecting groups by using Wilkinson's catalyst.[10a] If successful, such a reaction sequence with α-aminophosphonoacetates as Horner–Wadsworth–Emmons (HWE) reagents would have provided compounds **32**, which featured the required functional groups for a synthesis of α-*C*-galactosylserine or α-*C*-galactosylceramide. Disappointingly, despite our numerous attempts, the HWE reactions only met with failure. The hemiketal nature of the intermediate might explain this lack of reactivity, even though similar reactions have been reported on less functionalized fluorinated substrates.[30]

An alternative to this HWE strategy was to explore the derivatization of the CF_2Br group of compound **21**. Bromine/lithium exchange, followed by addition onto an appropriate electrophile, would provide an interesting route to

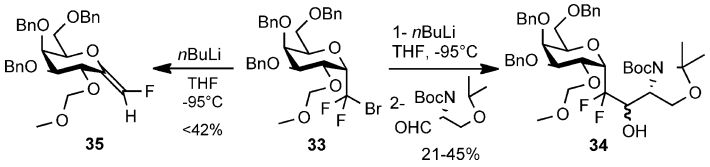


Scheme 7. Rationale for the diastereoselectivities that were observed in the reduction reactions.



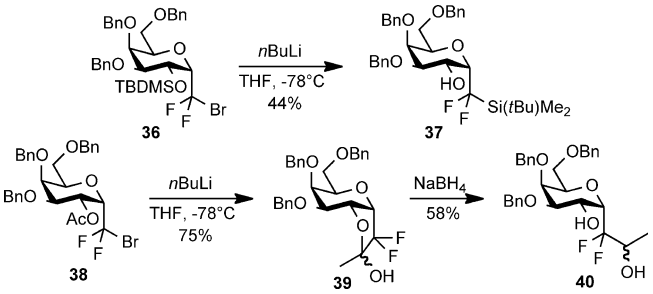
Scheme 8. Side chain elongation by HWE olefination. Boc = *tert*-butoxycarbonyl; Cbz = carbobenzyloxy.

glycoconjugate analogues. However, the carbenoid nature of the corresponding RCF_2Li species was worrisome because it would probably compromise its thermal stability.[31] Our first attempts at generating this lithium compound confirmed this prediction because performing a Br/Li exchange on compound **33**, followed by trapping with Garner's aldehyde, led to poor and irreproducible results. The addition product (**34**) was obtained in 21–45% yield, if at all, along with various amounts of compound **35**, which resulted from a Fritsch–Buttenberg–Wiechell rearrangement (Scheme 9).[31,32] Of course, this typical carbenoid rearrangement also occurs in the absence of an electrophile, but the yield of compound **35** remained, at best, moderate.



Scheme 9. Br/Li exchange and intermolecular addition to electrophiles.

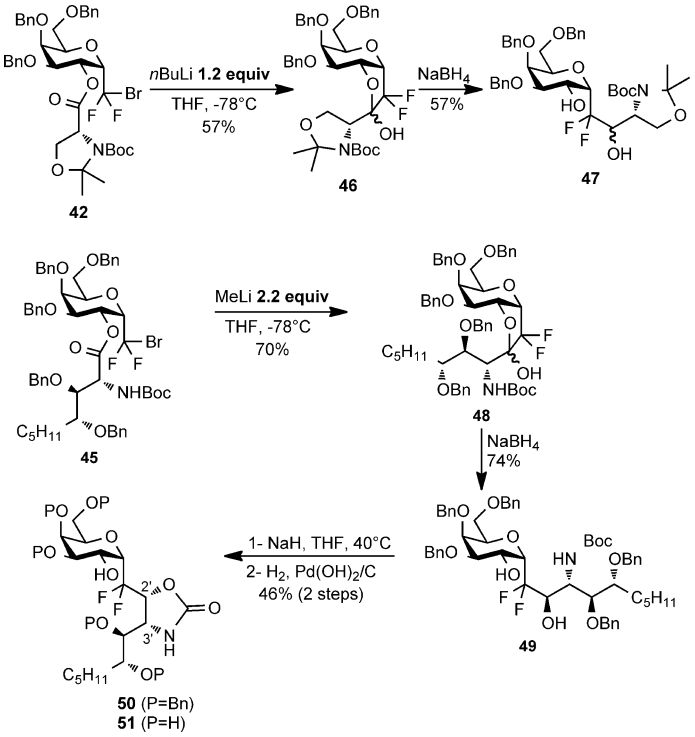
Thus, this strategy appeared to be compromised until a Br/Li exchange on OTBS-derivative **36** (TBS = *tert*-butyldimethylsilyl) was performed, which resulted in a migration of the TBS group from the O2 to C1′ atoms to provide the corresponding CF_2TBS derivative (**37**) in a nonoptimized 44% yield (Scheme 10). Despite this moderate yield, the reaction seemed to proceed cleanly and no degradation product was detected. Thus, intramolecular trapping of the lithium species emerged as the method of choice to circumvent the potential problem of stability. As a matter of fact, Br/Li exchange on compound **38** resulted in the immediate trapping of the lithium species by the neighboring acetate.[33] Stable hemiketal species **39** was isolated in 75% yield as an inseparable mixture of diasteromers. Reduction of this intermediate provided alcohol **40** in 68% yield. Therefore, the global transformation can be considered to be a formal addition of the lithiated anion of compound **21** to acetaldehyde. The two diastereomers of compound **40** were only partially separated and their ratio could only be estimated to be approximately 2:1.



Scheme 10. Br/Li exchange and intramolecular addition to electrophiles. DMAP = 4-dimethylaminopyridine.

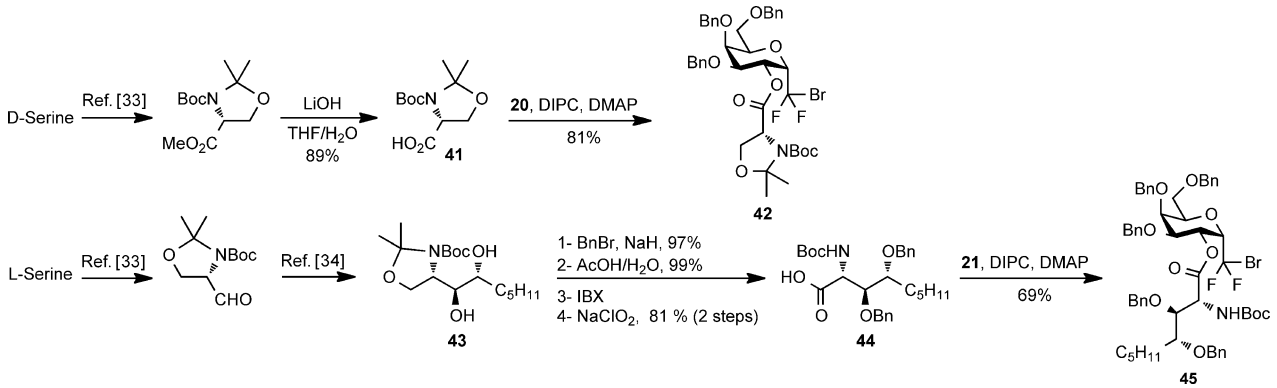
This reductive migration of an ester from the O2 to C1′-positions appeared as a nice entry to *O*-glycoconjugate analogues, provided that a highly functionalized ester was placed at the 2-position of compound **21**. Thus, two carboxylic acids of increasing complexity were prepared and coupled with compound **21** (Scheme 11). The acetonide that was derived from *N*-Boc-D-serine methyl ester, a precursor of Garner's aldehyde,[34b] was converted into acid **41** and then into ester **42** through a *N*,*N*′-diisopropylcarbodiimide (DIPC)-mediated coupling reaction with compound **21**. A more complex substrate was prepared by using phytosphingosine-derived carboxylic acid **44**. Savage's procedure was used to prepare compound **43** from Garner's aldehyde.[35] Benzylation, acetonide hydrolysis, and a two-step procedure that involved a 2-iodoxybenzoic acid (IBX)-mediated Pinnick oxidation yielded **44**. The same esterification method as described above was used to prepare compound **45** from **21** and **44**. With two functionalized substrates (**42** and **45**) in hand, the reductive migration sequence was attempted next.

Starting from compound **42**, the sequence was uneventful: Br/Li exchange with 1.2 equivalents of *n*BuLi at −78 °C provided the corresponding hemiketal (**46**) in 57 % yield as a mixture of diastereomers (Scheme 12). Reduction of the latter compound afforded the desired functionalized α-*C*-galactoside (**47**) in 57 % yield, once again as an inseparable mixture of diastereomers; however, the evaluation of the diastereomeric ratio was impossible, owing to the presence of rotamers. In contrast, the reaction with phytosphingosine-derived substrate **45** required some optimization. The use of



Scheme 12. Reductive acyl chain migration sequence with functionalized substrates.

1.2 equivalents of *n*BuLi afforded the expected hemiketal (**48**) in low yield (< 15 %), along with recovery of large amounts of the starting material (50 %) and of its reduced CF_2H derivative (35 %). Performing the reaction with 2.2 equivalents of *n*BuLi allowed us to obtain complete conversion, but the results were rather irreproducible and a maximum yield of 50 % was only obtained once. Whereas, *t*BuLi only led to degradation, MeLi was a much better mediator because the addition of 2.2 equivalents of this reagent yielded compound **48** in a reproducible 70 % yield. The reduction of this hemiketal was performed as above and compound **49** was obtained in 74 % yield. Surprisingly, this compound was isolated as a single diastereomer. The conversion of this compound into oxazolidinone **50** under basic conditions was an opportunity to determine the configuration at



Scheme 11. Synthesis of functionalized carboxylic acids.

the C3′-position; however, the ^{1}H NMR spectrum of compound **50** was crowded with the signals of the benzyl groups and, thus, useless for NOESY experiments or for the extraction of coupling constants. Importantly, a standard hydrogenolysis reaction provided compound **51** and a solution to this problem, because, this time, the ^{1}H NMR spectrum of this compound was much clearer. The strong NOESY correlation and the 7.4 Hz scalar coupling constant between the H2′ and H3′ atoms were, beyond doubt, diagnostic of a *cis* relationship between these two protons.[36] Thus, this O2-to-C1′ acyl-transfer sequence was extremely efficient, even on highly functionalized substrates. Provided that a simple solution can be found to remove the hydroxy group at the 2′-position, this method could allow us to prepare CF_2-glycosidic analogues of galactosylaminoacids or galactosylceramides.

Conclusion

Overall, the different strategies that have been described in this article provide efficient access to fluorinated α-*C*-glycosides. The core of the method involves an addition of difluoromethyl radicals to 2-benzyloxyglycals, which can be extended to other electrophilic radicals. Reduction of the resulting 2-ketohexopyranosides afforded the desired α-*C*-glycosides in satisfactory overall yields with complete diastereoselectivity for each step. The synthetic elaboration of these compounds has also been studied and useful methods have been disclosed. In particular, the reactions that involved a Br/Li exchange on derivatives of bromide **21** appeared to be a method of choice for the future synthesis of *O*-glycoconjugate analogues. Indeed, the intramolecular addition of the lithiated species to a neighboring ester group allows the introduction of various aglycon moieties at the pseudo-anomeric position through a simple and mild process. We are currently investigating the synthesis of a whole family of difluorinated α-*C*-galactosylceramides, as well as the biological evaluation of these compounds.

Experimental Section

For the sake of brevity, only the most important procedures are described in the Experimental Section. For full experimental details, see the Supporting Information.

Bromodifluoro-(3,4,6-tri-*O*-benzyl-α-D-lyxo-hexopyranosid-2-ulosyl)methane (7): Dibromodifluoromethane (0.229 mL, 2.5 mmol, 5 equiv) and triethylborane (1 M in THF, 0.500 mL, 0.5 mmol, 1 equiv) were added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-galactal (**5**, 0.260 g, 0.5 mmol) in aerated DMF (4 mL). The mixture was stirred at RT for 3 h and the conversion was checked by TLC (cyclohexane/EtOAc, 8:2). The addition of CF_2Br_2 (5 equiv) and BEt_3 (1 equiv) and stirring for a further 3 h were typically required to reach completion. Then, a saturated aqueous solution of NH_4Cl (50 mL) was added and the mixture was extracted with Et_2O (3×30 mL). The organic layer was washed with water (5×30 mL), dried over $MgSO_4$, and evaporated. Purification by column chromatography on silica gel (cyclohexane/EtOAc, 97:3) afforded **7** as a colorless oil (0.115 g, 41% yield). Analytical TLC (silica gel 60; EtOAc/cyclohexane, 20%): R_f=0.50; $[\alpha]_D^{20}$=+311.5 $cm^3 g^{-1} dm^{-1}$ (c=0.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.20 (m, 15H), 5.00 (d, J=11.8 Hz, 1H), 4.91 (d, J=11.4 Hz, 1H), 4.59 (d, J=10.3 Hz, 1H), 4.55 (d, J=9.7 Hz, 1H), 4.53–4.42 (m, 5H), 4.30 (app t, J(app)=2.4 Hz, 1H), 3.68–3.59 ppm (m, 2H); ^{19}F NMR (282.5 MHz; $CDCl_3$): δ=−52.4 (dd, J(F,F)=168.8, J(F,H)=8.0 Hz, 1F), −54.4 ppm (dd, J(F,F)=168.8, J(F,H)=14.0 Hz, 1F); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ=199.4, 137.8, 137.7, 137.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 119.4 (t, J=313.1 Hz), 83.5 (t, J=23.6 Hz), 83.5, 77.5, 77.0, 75.0, 74.0, 73.6, 68.0 ppm; IR: $\tilde{\nu}$=3090, 3064, 3031 ($\nu_{CH\,Ar}$), 2925, 2858 ($\nu_{CH\,Aliph}$), 1760 cm^{-1} ($\nu_{C=O}$); MS (ESI$^+$): m/z: 585.1, 583.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{28}H_{27}BrF_2O_5$: C 59.24, H 4.60; found: C 59.27, H 4.58.

Ethyl fluoro-2-(3,4,6-tri-*O*-benzyl-α-D-lyxo-hexopyranosid-2-ulosyl)acetate (9): A degassed solution of 2,3,4,6-tetra-*O*-benzyl-D-galactal (**5**, 0.783 g, 1.5 mmol) and ethyl bromodifluoroacetate derived xanthate (0.679 g, 3.0 mmol) in 1,2-dichloroethane (3 mL) and *t*BuOH (3 mL) was heated at reflux (95 °C). A degassed solution of dilauroyl peroxide (0.598 g, 1.5 mmol) in 1,2-dichloroethane (9 mL) and *t*BuOH (9 mL) was added to the refluxing solution over 6 h with a syringe pump. The mixture was heated at reflux for a further 6 h (conversion was checked by TLC; cyclohexane/EtOAc, 8:2) and evaporated. Purification by chromatography on a flash purification systemflash column chromatography on silica gel (EtOAc/cyclohexane, 2–20%) afforded compound **9** (mixture of diastereomers) as a colorless oil (0.115 g, 59% yield). Analytical TLC (silica gel 60; EtOAc/cyclohexane, 20%): R_f=0.28; ^{1}H NMR (300 MHz; $CDCl_3$): δ=7.38–7.17 (m, 15H and 15H′), 5.36 (dd, J=46.7, J=1.9 Hz, 1H), 5.33 (dd, J=47.1, J=1.8 Hz, 1H′), 5.02 (d, J=11.8 Hz, 1H′), 5.01 (d, J=11.9 Hz, 1H), 4.92 (d, J=11.9 Hz, 1H), 4.91 (d, J=11.8 Hz, 1H′), 4.74–4.48 (m, 5H and 5H′), 4.46–4.33 (m, 2H and 2H′), 4.32–4.18 (m, 3H and 3H′), 3.68–3.52 (m, 2H and 2H′), 1.25 ppm (t, J=7.2 Hz, 3H and 3H′); ^{19}F NMR (282.5 MHz; $CDCl_3$): δ=−200.9 (dd, J=47.4, J=21.7 Hz, 1F′), −204.2 ppm (dd, J=46.4, J=33.0 Hz, 1F); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ=204.7, 204.4 (d, J=6.0 Hz), 166.6 (d, J=24.2 Hz), 166.4 (d, J=24.2 Hz), 137.9, 137.8, 137.5, 137.2, 128.7, 128.6, 128.5, 128.45, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 88.9 (d, J=194.8 Hz), 88.1 (d, J=192.5 Hz), 83.4, 83.1 (d, J=3.0 Hz), 79.6 (d, J=20.4 Hz), 79.5 (d, J=20.4 Hz), 76.9, 76.5, 76.1, 76.0, 74.7, 74.5, 73.6, 73.5, 73.3, 73.1, 67.5, 67.3, 62.2, 62.1, 14.2, 14.1 ppm; IR: $\tilde{\nu}$=3031.4 ($\nu_{CH\,Ar}$), 2918, 2850 ($\nu_{CH\,Aliph}$), 1755 cm^{-1} ($\nu_{C=O}$); MS (ESI$^+$): m/z: 554.1 $[M+H_2O]^+$; elemental analysis calcd (%) for $C_{31}H_{33}FO_7$: C 69.39, H 6.20; found: C 69.41, H 6.13.

Bromodifluoro-(3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)methane (21): $Al(OiPr)_3$ (0.286 g, 1.4 mmol) was added to a solution of bromodifluoro-(3,4,6-tri-*O*-benzyl-α-D-lyxo-hexopyranosid-2-ulosyl)methane (**7**, 0.310 g, 0.56 mmol) in isopropanol. The resulting suspension was heated at reflux and the reaction was complete within 4–6 h, as monitored by TLC (cyclohexane/EtOAc, 8:2). Then, the mixture was neutralized with a 1 M aqueous solution of HCl (5 mL) and extracted with EtOAc (4×10 mL). The combined organic extracts were washed with water (2×10 mL), a saturated aqueous solution of $NaHCO_3$ (2×10 mL), and brine (10 mL), dried over Na_2SO_4, and evaporated. Purification by chromatography on a flash purification system (EtOAc/cyclohexane, 5–40%) afforded compound **21** as a white crystalline solid (0.212 g, 68% yield). The application of this procedure directly from crude bromodifluoro-(3,4,6-tri-*O*-benzyl-α-D-lyxo-hexopyranosid-2-ulosyl)methane (**7**) afforded compound **21** in 55% overall yield from compound **5**. Analytical TLC (silica gel 60; EtOAc/cyclohexane, 20%): R_f=0.17; $[\alpha]_D^{20}$=+37.4 $cm^3 g^{-1} dm^{-1}$ (c=0.76, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD): δ=7.34–7.25 (m, 15H), 4.68 (d, J=11.9 Hz, 1H), 4.61 (d, J=11.9 Hz, 1H), 4.60 (d, J=11.7 Hz, 1H), 4.55 (app s, 2H), 4.54 (d, J=11.7 Hz, 1H), 4.35 (ddd, J=8.5, J=6.0, J=2.8 Hz, 1H), 4.24 (ddd, J=13.6, J=8.5, J=2.3 Hz, 1H), 4.21–4.17 (m, 1H), 4.13 (dd, J=6.0, J=2.9 Hz, 1H), 4.00 (dd, J=11.8, J=8.5 Hz, 1H), 3.83 (dd, J=4.9, J=2.9 Hz, 1H), 3.74 ppm (dd, J=11.8, J=2.8 Hz, 1H); ^{19}F NMR (282.5 MHz; CD_3OD): δ=−53.0 (dd, J=164.0, J=14.2 Hz, 1F), −55.3 ppm (d, J=164.0 Hz, 1F); ^{13}C NMR (75.5 MHz; CD_3OD): δ=139.6, 139.5, 139.4, 129.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.6, 123.3 (dd, J=312.6 Hz, J=308.8 Hz), 78.2, 77.0, 75.3 (dd, J=25.0 Hz, J=20.2 Hz), 74.3, 74.0, 73.9, 73.0, 68.2, 66.7 ppm; IR: $\tilde{\nu}$=3410 (ν_{OH}), 3031 ($\nu_{CH\,Ar}$), 2877 cm^{-1} ($\nu_{CH\,Aliph}$); MS (ESI$^+$): m/z: 582.0, 580.0 $[M+H_2O]^+$; elemental analysis calcd (%) for $C_{28}H_{29}BrF_2O_5$: C 59.69, H 5.19; found: C 59.94, H 5.15.

Ethyl 2-fluoro-2-(3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)acetate (22): The same procedure as for the synthesis of compound **21** was applied to 2-fluoro-2-(3,4,6-tri-*O*-benzyl-α-D-lyxo-hexopyranosid-2-ulosyl)acetate (**9**, 0.500 g, 0.93 mmol). The reaction was complete within 4–6 h, as monitored by TLC (cyclohexane/EtOAc, 8:2). Purification by chromatography on a flash purification system (EtOAc/cyclohexane, 3–30%) afforded compound **22** as a colorless oil (0.298 g, 58% yield). Careful purification allowed us to obtain fractions that contained each diastereomer as the major compound. The application of this procedure directly from crude 2-fluoro-2-(3,4,6-tri-*O*-benzyl-α-D-lyxo-hexopyranosid-2-ulosyl)acetate (**9**) afforded compound **22** in 41% overall yield from compound **5**.

Diastereomer 1: Analytical TLC (silica gel 60; EtOAc/cyclohexane, 20%): $R_f = 0.18$; ^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 7.36$–7.23 (m, 15H), 5.38 (dd, $J = 47.9$, $J = 1.7$ Hz, 1H), 5.13 (hept, $J = 6.2$ Hz, 1H), 4.82 (d, $J = 11.5$ Hz, 1H), 4.74 (d, $J = 11.5$ Hz, 1H), 4.60–4.39 (m, 6H), 4.25 (app t, $J = 6.5$ Hz, 1H), 4.08 (br s, 1H), 3.99–3.93 (m, 1H), 2.50 (br s, 1H), 1.23 ppm (d, $J = 6.2$ Hz, 6H); ^{19}F NMR (282.5 MHz; $CDCl_3$): $\delta = -196.7$ ppm (app t, $J = 41.7$ Hz, 1F); ^{13}C NMR (75.5 MHz; $CDCl_3$): $\delta =$ 167.7 (d, $J = 25.3$ Hz), 138.5, 138.1, 137.9, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 91.0 (d, $J = 192.7$ Hz), 80.3 (d, $J =$ 25.3 Hz), 74.7, 74.6, 74.4 (d, $J = 9.9$ Hz), 73.4, 73.0, 72.0, 69.7, 68.7, 68.5, 21.8 ppm.

Diastereomer 2: Analytical TLC (silica gel 60; EtOAc/cyclohexane, 20%): $R_f = 0.14$; ^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 7.38$–7.23 (m, 15H), 5.17 (dd, $J = 48.9$, $J = 2.9$ Hz, 1H), 5.12 (hept, $J = 6.2$ Hz, 1H), 4.73 (d, $J =$ 11.7 Hz, 1H), 4.72 (d, $J = 11.5$ Hz, 1H), 4.62–4.44 (m, 5H), 4.32–4.22 (m, 2H), 4.06 (app t, $J = 2.8$ Hz, 1H), 3.94 (dd, $J = 7.7$, $J = 2.3$ Hz, 1H), 3.80 (dd, $J = 10.2$, $J = 7.0$ Hz, 1H), 3.64 (dd, $J = 10.2$, $J = 7.0$ Hz, 1H), 1.25 ppm (d, $J = 6.2$ Hz, 6H); ^{19}F NMR (282.5 MHz; $CDCl_3$): $\delta = -196.2$ (dd, $J =$ 47.4, $J = 30.9$ Hz, 1F); ^{13}C NMR (75.5 MHz; $CDCl_3$): $\delta = 167.5$ (d, $J =$ 23.1 Hz), 138.3, 138.1, 138.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.75, 127.7, 127.6, 91.5 (d, $J = 191.1$ Hz), 79.0, 74.9 (d, $J =$ 2.2 Hz), 73.5, 73.4, 73.0, 72.5, 69.8, 67.9, 67.8, 21.6 ppm; IR: $\tilde{\nu} = 3480$ (ν_{OH}), 3028 ($\nu_{CH\,Ar}$), 2928 ($\nu_{CH\,Aliph}$), 1758 cm^{-1} ($\nu_{C=O}$); MS (ESI$^+$): *m*/*z*: 575.2 $[M+Na]^+$; 570.1 $[M+H_2O]^+$; 553.1 $[M+H]^+$; elemental analysis calcd (%) for $C_{32}H_{37}F0_7$: C 69.55, H 6.75; found: C 69.51, H 6.76.

1,1-Difluoro-1-(3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)propan-2-ol (40): *n*BuLi (1.53 M in hexanes, 0.337 mL, 0.52 mmol) was added to a solution of acetate **38** (0.260 g, 0.43 mmol), which was obtained by the acetylation of compound **21** by using Ac_2O, NEt_3, and DMAP (cat.), in THF (5 mL) at −78 °C under an argon atmosphere. The mixture was stirred for 1 h at −78 °C (TLC analysis showed complete conversion) and then quenched with 1 M HCl (5 mL) and extracted with EtOAc (3×10 mL). The combined organic compounds were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and evaporated. Purification by chromatography on a flash purification system (EtOAc/cyclohexane, 3–30%) afforded intermediate **39** as a colorless oil (0.171 g, 75% yield) and as a mixture of diastereomers. Analytical TLC (silica gel 60; EtOAc/cyclohexane, 15%): $R_f = 0.16$; ^{1}H NMR (300 MHz; CD_3OD): $\delta = 7.42$–7.20 (m, 15H), 4.84–4.64 (m, 4H), 4.57–4.17 (m, 5H), 4.10–3.94 (m, 2H), 3.68–3.54 (m, 3H), 1.47–1.37 ppm (m, 3H); ^{19}F NMR (282.5 MHz; CD_3OD): $\delta = -117.0$ (dd, J(F,F) = 243.4, J(F,H) = 13.4 Hz, 1F), −127.6 (dd, J(F,F) = 232.0, J(F,H) = 19.1 Hz, 1F′), −129.6 (dd, J(F,F) = 232.0, J(F,H) = 8.3 Hz, 1F′), −130.3 ppm (dd, J(F,F) = 243.4, J(F,H) = 3.1 Hz, 1F); ^{13}C NMR (75.5 MHz; CD_3OD): $\delta =$ 139.9, 139.8, 139.7, 139.4, 139.3, 129.5, 129.4, 129.3, 129.3, 129.2, 129.1, 129.05, 129.0, 128.9, 128.85, 128.8, 128.75, 128.7, 128.6, 124.5 (dd, $J = 262.5$, $J = 255.9$ Hz), 101.9 (dd, $J = 31.8$, $J = 23.1$ Hz), 100.3 (dd, $J = 29.7$, $J = 23.6$ Hz), 81.5, 81.4, 77.1, 76.9 (d, $J = 2.7$ Hz), 75.4, 75.3, 75.2, 75.1, 74.8 (t, $J = 25.3$ Hz), 74.5 (t, $J = 16.5$ Hz), 74.3, 74.2, 73.9, 73.3, 72.7, 69.6, 68.8, 20.6, 20.55 ppm; MS (ESI$^+$): *m*/*z*: 544.1 $[M+H_2O]^+$.

$NaBH_4$ (0.019 g, 0.50 mmol) was added to a solution of compound **39** (0.171 g, 0.32 mmol) in MeOH (5 mL) at 0 °C. The mixture was stirred for 3 h at 0 °C, at which point TLC analysis (cyclohexane/EtOAc, 70:30) showed the complete conversion of compound **39**. The mixture was warmed to RT, quenched with a saturated aqueous solution of NH_4Cl, and extracted with EtOAc (3×10 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Purification by chromatography on a flash purification system (EtOAc/cyclohexane, 7–60%) afforded compound **40** as a colorless oil (0.098 g, 58% yield). Each diastereomer could be obtained in its almost pure form, with only a slight amount of the other diastereomer.

Diastereomer 1: Analytical TLC (silica gel 60; 30% EtOAc in cyclohexane): $R_f = 0.22$; ^{1}H NMR (300 MHz; CD_3OD): $\delta = 7.34$–7.23 (m, 15H), 4.70–4.45 (m, 6H), 4.41–4.25 (m, 2H), 4.22–4.02 (m, 4H), 3.87 (dd, $J =$ 4.6, $J = 2.9$ Hz, 1H), 3.71 (dd, $J = 11.7$, $J = 2.5$ Hz, 1H), 1.22 ppm (d, $J =$ 6.8 Hz, 3H); ^{19}F NMR (282.5 MHz; CD_3OD): $\delta = -120.7$ (dd, J(F,F) = 259.9, J(F,H) = 20.6 Hz, 1F), −127.0 ppm (dd, J(F,F) = 261.0, J(F,H) = 20.6 Hz, 1F); ^{13}C NMR (75.5 MHz; CD_3OD): $\delta = 139.8$, 139.7, 139.4, 129.5, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 123.6 (dd, $J = 253.7$, $J = 247.1$ Hz), 78.0, 76.3, 74.3, 74.2, 74.1, 72.9, 67.6 (dd, $J = 24.7$, $J =$ 8.2 Hz), 67.5, 67.0 (dd, $J = 22.0$, $J = 12.1$ Hz), 66.9, 15.0 ppm.

Diastereomer 2: Analytical TLC (silica gel 60; 30% EtOAc in cyclohexane): $R_f = 0.16$; ^{1}H NMR (300 MHz; CD_3OD): $\delta = 7.32$–7.22 (m, 15H), 4.65 (d, $J = 11.7$ Hz, 1H), 4.60 (d, $J = 11.7$ Hz, 1H), 4.57 (d, $J = 11.7$ Hz, 1H), 4.55–4.43 (m, 3H), 4.37–4.20 (m, 2H), 4.19–4.02 (m, 4H), 3.86 (dd, $J = 4.4$ Hz, $J = 3.1$ Hz, 1H), 3.71 (dd, $J = 11.9$ Hz, $J = 2.3$ Hz, 1H), 1.25 ppm (d, $J = 6.2$ Hz, 3H); ^{19}F NMR (282.5 MHz; CD_3OD): $\delta = -114.5$ (app dt, J(F,F) = 260.9, J(F,H) = 8.2 Hz, 1F), −124.0 ppm (app dt, J(F,F) = 260.9, J(F,H) = 13.4 Hz, 1F); ^{13}C NMR (75.5 MHz; CD_3OD): $\delta = 139.8$, 139.7, 139.6, 129.5, 129.45, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 123.1 (dd, $J = 252.0$, $J = 247.6$ Hz), 77.6, 76.8, 74.2, 74.1, 72.8, 65.6 (app t, $J = 27.2$ Hz), 67.7, 67.6 (app t, $J = 26.4$ Hz), 66.7, 16.0 ppm; IR: $\tilde{\nu} = 3339$ (ν_{OH}), 3028 ($\nu_{CH\,Ar}$), 2925 cm^{-1} ($\nu_{CH\,Aliph}$); MS (ESI$^+$): *m*/*z*: 1079.0 $[2M+Na]^+$, 551.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{30}H_{34}F_20_6$: C 68.17, H 6.48; found: C 68.28, H 6.44.

Acknowledgements

This work was supported by the INSA-ROUEN, University of Rouen, Région Haute-Normandie, Centre National de la Recherche Scientifique (CNRS), European Fund for Research Development (EFRD), Agence Nationale de la Recherche (ANR), and LABEX SynOrg. The ANR is gratefully acknowledged for a doctoral fellowship to S.C. The EFRD (FEDER 43209) is gratefully acknowledged for a postdoctoral fellowship to N.V.H. We also thank Dr. P. Lameiras and Prof. H. Oulyadi for performing the NOESY and HOESY experiments.

[1] *Carbohydrate-Based Drug Discovery* (Ed.: C.-H. Wong), Wiley-VCH, Weinheim, **2003**.

[2] For reviews on *C*-glycoside synthesis, see: a) T. Nishikawa, M. Adachi, M. Isobe in *Glycoscience: Chemistry and Chemical Biology, Vol. 3*, 2nd ed. (Eds.: B. Fraser Reid, K. Tatstuta, J. Thiem, G. L. Coté, S. Flitsch, Y. Ito, H. Kondo, S. Nishimura, B. Yu), Springer, Heidelberg, **2008**, pp. 755–811; b) B. Vauzeilles, D. Urban, G. Doisneau, J. M. Beau in *Glycoscience: Chemistry and Chemical Biology, Vol. 9, 2nd ed.* (Eds.: B. Fraser Reid, K. Tatstuta, J. Thiem, G. L. Coté, S. Flitsch, Y. Ito, H. Kondo, S. Nishimura, B. Yu), Springer, Heidelberg, **2008**, pp. 2021–2077, and the references therein.

[3] a) G. Chen, M. Chien, M. Tsuji, R. W. Franck, *ChemBioChem* **2006**, *7*, 1017–1022; b) R. W. Franck, M. Tsuji, *Acc. Chem. Res.* **2006**, *39*, 692–701; c) G. Yang, J. Schmieg, M. Tsuji, R. W. Franck, *Angew. Chem.* **2004**, *116*, 3906–3910; *Angew. Chem. Int. Ed.* **2004**, *43*, 3818–3822.

[4] For a review on nonhydrolyzable fluorinated glycomimetics, see: E. Leclerc, X. Pannecoucke, M. Ethève-Quelquejeu, M. Sollogoub, *Chem. Soc. Rev.* **2013**, *42*, 4270–4283.

[5] a) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**; b) H. J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; c) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, **2008**; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[6] a) A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441–451; b) J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem* **2004**, *5*, 622–627, and references therein; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[7] For potent nonhydrolyzable CF_2 analogues of bioactive molecules, see: a) T. R. Burke, Jr, K. Lee, *Acc. Chem. Res.* **2003**, *36*, 426–433; b) T. R. Burke, Jr, M. S. Smyth, A. Otaka, M. Nomizu, P. P. Roller, G. Wolf, R. Case, S. E. Shoelson, *Biochemistry* **1994**, *33*, 6490–6494; c) G. M. Blackburn, D. L. Jakeman, A. J. Ivory, M. P. Williamson, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2573–2578; d) T. Nakano, M. Makino, Y. Morizawa, Y. Matsumura, *Angew. Chem.* **1996**, *108*, 1082–1084; *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 1019–1021, and the references therein.

[8] For an account of our work, see: E. Leclerc, X. Pannecoucke, *C. R. Chim.* **2012**, *15*, 57–67.

[9] a) J. S. Houlton, W. B. Motherwell, B. C. Ross, M. J. Tozer, D. J. Williams, A. M. Z. Slawin, *Tetrahedron* **1993**, *49*, 8087–8106; b) T. Brigaud, O. Lefebvre, R. Plantier-Royon, C. Portella, *Tetrahedron Lett.* **1996**, *37*, 6115–6116; c) T. F. Herpin, W. B. Motherwell, J.-M. Weibel, *Chem. Commun.* **1997**, 923–924; d) H. Berber, T. Brigaud, O. Lefebvre, R. Plantier-Royon, C. Portella, *Chem. Eur. J.* **2001**, *7*, 903–909; e) A. Wegert, R. Miethchen, M. Hein, H. Reinke, *Synthesis* **2005**, 1850–1858; f) A. Wegert, M. Hein, H. Reinke, N. Hoffmann, R. Miethchen, *Carbohydr. Res.* **2006**, *341*, 2641–2652; g) J. Picard, N. Lubin-Germain, J. Uziel, J. Augé, *Synthesis* **2006**, 979–982; h) G. Hirai, T. Watanabe, K. Yamaguchi, T. Miyagi, M. Sodeoka, *J. Am. Chem. Soc.* **2007**, *129*, 15420–15421; i) K. A. Tony, R. W. Denton, A. Dilhas, J. Jiménez-Barbero, D. R. Mootoo, *Org. Lett.* **2007**, *9*, 1441–1444; j) R. W. Denton, K. A. Tony, J. J. Hernandez-Gay, F. J. Canada, J. Jiménez-Barbero, D. R. Mootoo, *Carbohydr. Res.* **2007**, *342*, 1624–1635; k) M. Kolympadi, M. Fontanella, C. Venturi, S. André, H.-J. Gabius, J. Jimenez-Barbero, P. Vogel, *Chem. Eur. J.* **2009**, *15*, 2861–2873; l) J. L. Chaytor, R. N. Ben, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5251–5254.

[10] a) B. Moreno, C. Quehen, M. Rose-Hélène, E. Leclerc, J.-C. Quirion, *Org. Lett.* **2007**, *9*, 2477–2480; b) S. Colombel, M. Sanselme, E. Leclerc, J.-C. Quirion, X. Pannecoucke, *Chem. Eur. J.* **2011**, *17*, 5238–5241.

[11] a) W. R. Dolbier, Jr, *Chem. Rev.* **1996**, *96*, 1557–1584; b) P. Kirsch in *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**, pp. 91–101 c) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465–7478.

[12] a) R. Miethchen, M. Hein, H. Reinke, *Eur. J. Org. Chem.* **1998**, 919–923; b) A. Wegert, H. Reinke, R. Miethchen, *Carbohydr. Res.* **2004**, *339*, 1833–1837.

[13] a) T. Linker, T. Sommermann, F. Kahlenberg, *J. Am. Chem. Soc.* **1997**, *119*, 9377–9384; b) T. Linker, D. Schanzenbach, E. Elamparuthi, T. Sommermann, W. Fudickar, V. Gyóllai, L. Somsák, W. Demuth, M. Schmittel, *J. Am. Chem. Soc.* **2008**, *130*, 16003–16010.

[14] a) Z.-Y. Yang, D. J. Burton, *J. Org. Chem.* **1991**, *56*, 5125–5132; b) K. Iseki, D. Asada, M. Takahashi, T. Nagai, Y. Kobayashi, *Tetrahedron Lett.* **1994**, *35*, 7399–7400; c) F. Xiao, F. Wu, Y. Shen, L. Zhou, *J. Fluorine Chem.* **2005**, *126*, 63–67; d) S. Murakami, H. Ishii, T. Tajima, T. Fuchigami, *Tetrahedron* **2006**, *62*, 3761–3769; e) H. Nagura, S. Murakami, T. Fuchigami, *Tetrahedron* **2007**, *63*, 10237–10245; f) L. Leung, B. Linclau, *J. Fluorine Chem.* **2008**, *129*, 986–990.

[15] For other radical additions of $BrCF_2CO_2Et$, see: a) D. Morel, F. Dawans, *Tetrahedron* **1977**, *33*, 1445–1447; b) K. Sato, M. Omote, A. Ando, I. Kumadaki, *J. Fluorine Chem.* **2004**, *125*, 509–515; c) E. Godineau, C. Schäfer, Y. Landais, *Org. Lett.* **2006**, *8*, 4871–4874; d) X. Yang, W. Yuan, S. Gu, X. Yang, F. Xiao, Q. Shen, F. Wu, *J. Fluorine Chem.* **2007**, *128*, 540–544; e) E. Godineau, K. Schenk, Y. Landais, *J. Org. Chem.* **2008**, *73*, 6983–6993.

[16] Glycals **2**, **3**, and **5** were prepared according to a very efficient literature procedure; see: D. J. Chambers, G. R. Evans, A. J. Fairbanks, *Tetrahedron* **2004**, *60*, 8411–8419.

[17] L. Jean-Baptiste, S. Yemets, R. Legay, T. Lequeux, *J. Org. Chem.* **2006**, *71*, 2352–2359.

[18] B. Quiclet-Sire, S. Z. Zard, *Chem. Eur. J.* **2006**, *12*, 6002–6016.

[19] The use of DLP at reflux in DCE/*t*BuOH was not possible with $BrCF_2CO_2Et$ and CF_2Br_2 because of their volatility.

[20] B. B. Snider, *Chem. Rev.* **1996**, *96*, 339–363.

[21] a) D. J. Burton, D. M. Wiemers, *J. Fluorine Chem.* **1981**, *18*, 573–582; b) G. K. Surya Prakash, J. Hu, G. A. Olah, *J. Org. Chem.* **2003**, *68*, 4457–4463; c) Y. Li, H. Li, J. Hu, *Tetrahedron* **2009**, *65*, 478–483.

[22] L. A. Buttle, W. B. Motherwell, *Tetrahedron Lett.* **1994**, *35*, 3995–3998.

[23] a) F. De Vleeschouwer, V. Van Speybroeck, M. Waroquier, P. Geerlings, F. De Proft, *Org. Lett.* **2007**, *9*, 1441–1444; b) F. De Vleeschouwer, V. Van Speybroeck, M. Waroquier, P. Geerlings, F. De Proft, *J. Org. Chem.* **2008**, *73*, 9109–9120.

[24] M. G. Roepel, *Tetrahedron Lett.* **2002**, *43*, 1973–1976.

[25] a) N. A. LeBel, R. F. Czaja, A. DeBoer, *J. Org. Chem.* **1969**, *34*, 3112–3126; b) A. L. J. Beckwith, *Tetrahedron* **1981**, *37*, 3073–3100.

[26] a) F. W. Lichtenthaler, M. Lergenmüller, S. Peters, Z. Varga, *Tetrahedron: Asymmetry* **2003**, *14*, 727–736; b) F. W. Lichtenthaler, M. Lergenmüller, S. Schwidetzky, *Eur. J. Org. Chem.* **2003**, 3094–3103.

[27] L. Cipolla, B. La Ferla, L. Lay, F. Peri, F. Nicotra, *Tetrahedron: Asymmetry* **2000**, *11*, 295–303.

[28] C. F. de Graauw, J. A. Peters, H. van Bekkum, J. Huskens, *Synthesis* **1994**, 1007–1017.

[29] A. K. Dilger, V. Gopalsamuthiram, S. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 16273–16277.

[30] a) J. Lamar, J. Hu, A. B. Bueno, H.-C. Yang, D. Guo, J. D. Copp, J. McGee, B. Gitter, D. Timm, P. May, J. McCarthy, S.-H. Chen, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 239–243; b) Z. Hu, W. Han, *Tetrahedron Lett.* **2008**, *49*, 901–902.

[31] For a recent review on lithium carbenoids, see: V. Capriati, S. Florio, *Chem. Eur. J.* **2010**, *16*, 4152–4162.

[32] This widely described and useful rearrangement for sp^2 carbenoids is much less common in the sp^3 series; see: a) M. Braun in *The Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, pp. 829–900; b) E. Jahnke, R. R. Tykwinski, *Chem. Commun.* **2010**, *46*, 3235–3249.

[33] For a related cyclization of a difluoromethyllithium species, see: a) R. S. Timofte, B. Linclau, *Org. Lett.* **2008**, *10*, 3673–3676; b) B. Linclau, A. J. Boydell, R. S. Timofte, K. J. Brown, V. Vinader, A. C. Weymouth-Wilson, *Org. Biomol. Chem.* **2009**, *7*, 803–814.

[34] a) P. Garner, J. M. Park, *Org. Synth.* **1992**, *70*, 18–24; b) A. Dondoni, D. Perrone, *Org. Synth.* **2000**, *77*, 64–77.

[35] R. Goff, Y. Gao, J. Mattner, D. Zhou, N. Yin, C. Cantu, L. Teyton, A. Bendelac, P. B. Savage, *J. Am. Chem. Soc.* **2004**, *126*, 13602–13603.

[36] For the relationship between the coupling constant and the relative configuration of fluoroalkyl-substituted oxazolidinone, see: M. Omote, Y. Eto, A. Tarui, K. Sato, A. Ando, *Tetrahedron: Asymmetry* **2007**, *18*, 2768–2772.

Received: May 30, 2013
Published online: August 16, 2013

