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Stereocontrolled Synthesis of 2-Fluorinated *C*-Glycosides

Anna Sadurní,[a] and Ryan Gilmour*[a,b]

Abstract: A systematic study of the addition of *C*-based nucleophiles to fluorinated lactones based on 2-deoxy-2-fluoro-D-pyranoses is disclosed. This high yielding, *α*-selective process was found to be independent on the nature or configuration [(*R*)-C(sp^3)-F, (*S*)-C(sp^3)-F] of the substituent at *C2*. Representative, fluorinated analogues of Trehalose, Carminic acid, and the spirocyclic cores of Tofogliflozin and Papulacandin D are also reported. These glycomimics constitute a valuable series of ^{19}F NMR active probes for application in structural biology.

The diversity of mammalian and bacterial "*glycospace*" provides a rich platform from which to design tailored glycomimetics for applications in medicine.[1] Through relatively modest structural modifications, the natural role of complex carbohydrates in molecular recognition events can be harnessed for therapeutic purposes.[2] Subtle, often single site, alterations are sufficient to markedly enhance a biological response[3] or even to engage pathways that elude the native sugars.[4] Of the plethora of structural modifications employed in glycomimic design, formation of *C*-glycosides is arguably one of the most common (Figure 1). These scaffolds mitigate the intrinsic risk of enzymatic degradation by replacing the C(sp^3)-O bond of the glycosidic link with a more robust C(sp^3)-C(sp^3/sp^2/sp) bond. A number of successful pharmaceuticals contain this structural feature, including a series of SGLT-2 inhibitors such as Dapagliflozin (**1**).[5] It is also important to note that the aryl *C*-glycoside motif is found in numerous natural products,[6] including Carminic acid (**2**) and Papulacandin D (**3**). Whilst this approach is logical, the intrinsic challenges associated with the generation of crowded, often quaternary,[7] stereocentres must be considered.

A second strategy in devising metabolically robust glycomimics is the strategic OH → F substitution at *C2* of pyranoside glycosyl donors.[8] This seemingly subtle modification introduces several notable features that include enhanced hydrolytic stability,[9] retention of the electronegativity intrinsic to the native structure, and the ability to direct glycosylation selectivity.[3,4,8,10] A classic bioisostere of the hydroxyl group,[11] fluorine also functions as a valuable ^{19}F NMR probe[12] (Figure 2, upper) and allows various physicochemical parameters to be modulated such as lipophilicity, metabolic stability, and the pK_a values of neighbouring groups.[13] Despite the rich body of literature describing fluoro-*C*-glycosides and fluoro-carbasugars,[14] strategies that simultaneously exploit *C*-glycoside formation and fluorine installation at *C2* appear conspicuously absent from the glycosylation repertoire. To address this, a systematic study of the addition of various *C*-based nucleophiles to fluorinated lactones based on 2-deoxy-2-fluoro-D-pyranoses is disclosed.

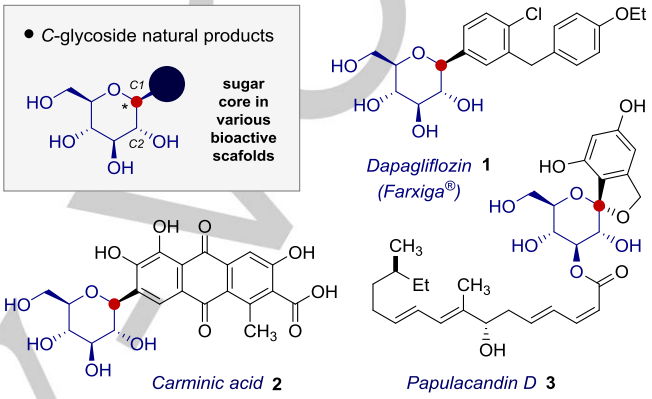

Figure 1. Selected examples of *C*-glycosides.

Specifically, benzylated lactones based on D-glucose and D-galactose were investigated in which the substituent at *C2* was varied (X = F, OBn and H). In the case of the fluorinated electrophiles, both the gluco- and manno-configured systems were studied to assess any possible influence of the configuration on reaction efficiency. The nucleophile series was composed of simple organometallic species that were either commercially available or could be easily prepared by simple halogen-metal exchange (Figure 2, lower).

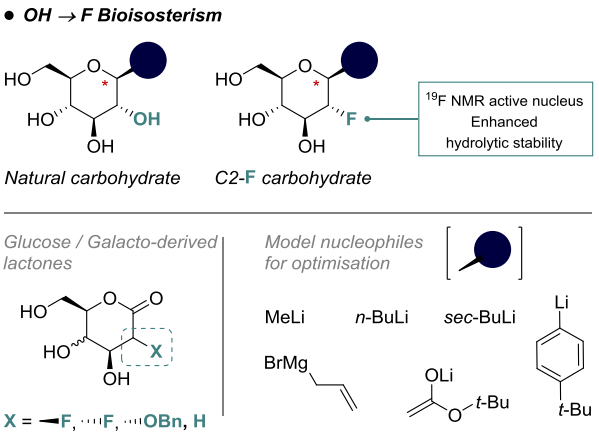

Figure 2. An overview of the scope of this study.

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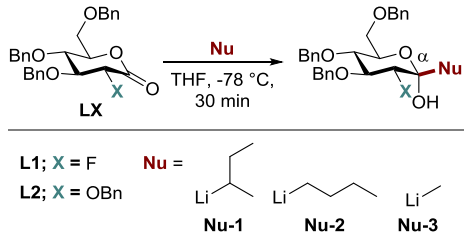
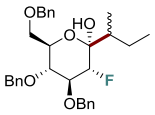
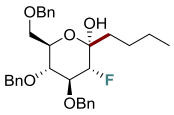
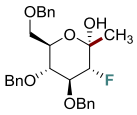
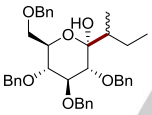
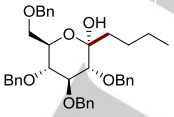
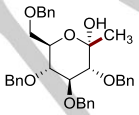
Preliminary studies to assess the comparative efficiency and selectivity of additions were performed with lactones **L1**[15] and **L2** (X = F and OBn, respectively. Table 1). For this purpose, commercially available organo-lithium reagents were employed (**Nu-1** = *sec*-BuLi, **Nu-2** = *n*-BuLi and **Nu-3** = MeLi).

Table 1. Exploring the effect of *C2*-substituent and nucleophile on *C*-glycosylation.[a]



Entry	Nucleophile (Nu)	Product	Yield (%)	Anomeric *α*:*β* ratio[b]
1	**Nu-1**		60	>20:1[C]
2	**Nu-2**		70	>20:1
3	**Nu-3**		88	>20:1
4	**Nu-1**		85	>20:1[C]
5	**Nu-2**		92	>20:1
6	**Nu-3**		94	>20:1

[a] Reactions were performed with the specified lactone (**LX**) (0.1 mmol, 1.0 eq.) and the specified nucleophile (0.11 mmol, 1.1 eq) in 0.58 mL of THF. The lithium enolate **Nu-5** was obtained from *tert*-butyl acetate and LHMDS. [b] Selectivity determined by ^{19}F NMR analysis of the crude reaction mixture; [c] 1:1 mixture of diastereomers with respect to the *sec*-butyl moiety.

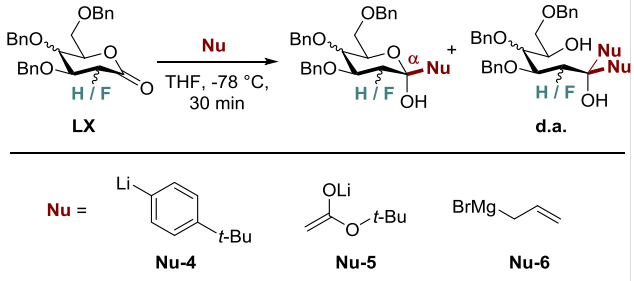
Reactions were performed in THF at -78 °C for 0.5 h prior to being quenched, and the *α*:*β* ratio of the product was determined by ^{19}F NMR spectroscopy and NOE experiments of the crude mixture.[4] Importantly, care must be exercised during the work-up to prevent epimerisation at *C2*. This was observed when utilising MeOH and furnished an inseparable mixture of gluco- and manno-configured analogues. This issue could be easily circumvented by performing an aqueous work up (Full details in the SI).

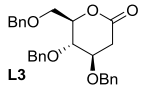
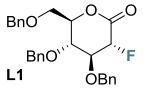
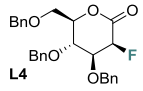
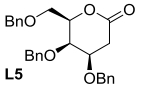
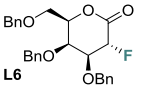
As is immediately evident from Table 1, the addition of nucleophiles **Nu-1**, **Nu-2** and **Nu-3** to the fluorinated lactone **L1** proceeded smoothly to deliver the corresponding products exclusively as the *α*-anomer (>20:1, up to 88% yield, entries 1, 2 and 3) irrespective of the substituent at *C2*. This clear manifestation of the anomeric effect[16] would prove useful in subsequent transformations (*vide infra*). Comparable behaviour was also observed with the 2-OBn derivative **L2** (entries 4, 5 and 6) where the *α*-anomer predominated and synthetically useful yields were observed (up to 94%).

Encouraged by these preliminary results, the nucleophile scope was extended to include aryl lithium (**Nu-4**), lithium enolate (**Nu-5**) and allyl magnesium species (**Nu-6**) (Table 2). Moreover, since **L1** and **L2** displayed closely similar behaviour in the initial investigation, 2-deoxy lactones (**L3**) were evaluated. Since hydrogen is often substituted by fluorine in molecular editing processes, this transformation may provide facile access to another class of bioisosteres.[11] For completeness, the manno-configured lactone **L4** was included in this comparison to assess the effect of the configuration at *C2* on the reaction outcome. Initially, the independent additions of **Nu-4**, **Nu-5** and **Nu-6** to the 2-deoxy lactone **L3** were performed (entries 1, 2 and 3).

Whilst employing **Nu-5** and **Nu-6** delivered the expected products (α:β>20:1, entries 2 and 3, respectively), double addition was observed with the aryl lithium **Nu-4** (entry 1). In contrast, the gluco-configured lactone **L-1** was smoothly converted to the expected *α*-product, irrespective of the nucleophile employed (entries 4, 5 and 6; 97%, 96% and 90% yield, respectively). Inverting the configuration of the *C2* fluorine had no effect on selectivity, and again furnished the product glycosides in good yields (99%, 95%, 91% yield; entries 7, 8 and 9, respectively). The 2-deoxy-galactose derived lactone **L-5** proved troublesome under the general condition of the study. Double addition was observed with **Nu-4** (entry 10), where with **Nu-5** and **Nu-6**, a significant reduction in yield was noted (45% and 53%, entries 11 and 12, respectively). Reintroducing the fluorine substituent at *C2* was found to significantly enhanced the reaction efficiency (89%, quant., 94% yield, entries 13, 14 and 15, respectively.)

Table 2. Exploring the effect of the lactone on *C*-glycosylation.[a]

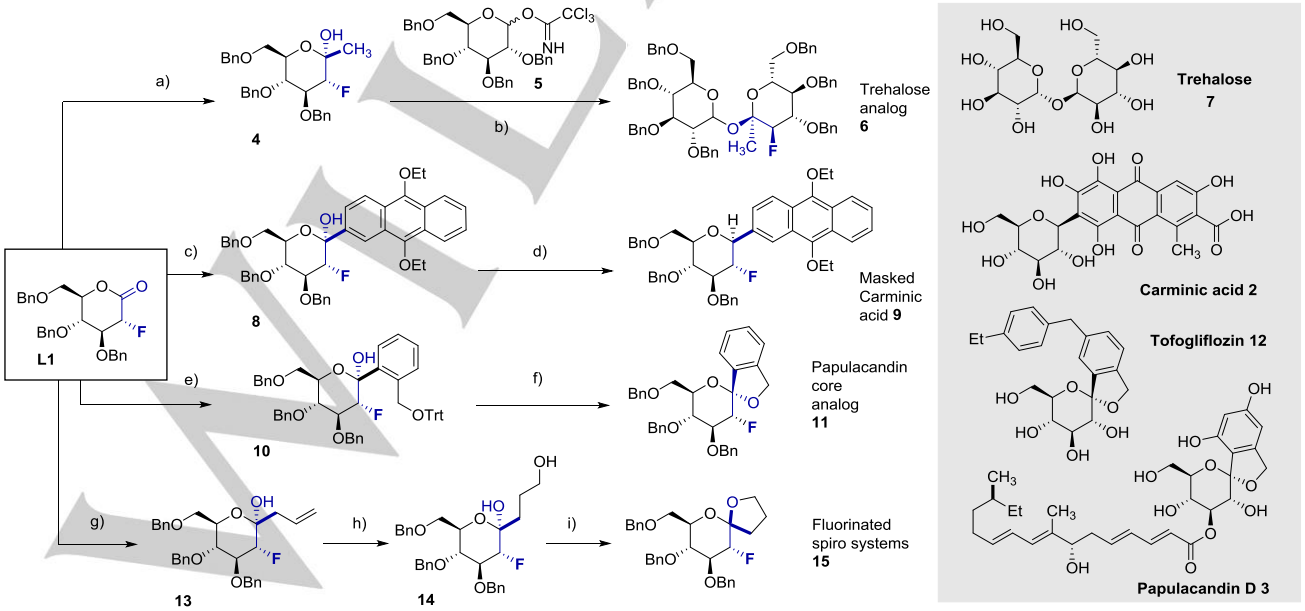


Entry	Lactone	Nucleophile (Nu)	Yield (%)	Anomeric α:β ratio[d]
1	 L3	**Nu-4**	62[b]	3(d.a.):1:1
2		**Nu-5**	99	>20:1
3		**Nu-6**	62	>20:1
4	 L1	**Nu-4**	97	>20:1
5		**Nu-5**	90	>20:1
6		**Nu-6**	96	>20:1
7	 L4	**Nu-4**	99	>20:1
8		**Nu-5**	95	>20:1
9		**Nu-6**	91	>20:1
10	 L5	**Nu-4**	d.a.	-
11		**Nu-5**	45	>20:1
12		**Nu-6**	53[c]	>20:1
13	 L6	**Nu-4**	89	>20:1
14		**Nu-5**	quant.	>20:1
15		**Nu-6**	94	>20:1

[a] Reactions were performed with the specified lactone (LX) (0.1 mmol, 1.0 eq.) and the specified nucleophile (0.11 mmol, 1.1 eq) in toluene:THF (2:1) or THF. [b] Mixture of product and double addition (d.a.); [c] Mixture of product and opened form of the product [d] Selectivity determined by ^{19}F NMR analysis of the crude reaction mixture.

Having validated this class of fluorinated lactones as competent electrophiles *en route* to *C*-glycosides, a series of natural and non-natural products were prepared employing **L1** as a common foundation (Scheme 1). In the preparation of a fluorinated analogue of trehalose (**6**), **L1** was smoothly converted to **4** by the addition of MeLi at -78 °C in THF. The expected, *α*-configured product was isolated in quantitative yield, before being processed to the disaccharide core. This was achieved by standard glycosylation conditions employing the TCA donor **5** (TMSOTf, CH_2Cl_2) to furnish the fluorinated glycomimetic **6** (30%) as a mixture of diastereoisomers (α:*β* 1.8:1). Next, a masked analogue of Carminic acid (**9**) was prepared by exposure to the appropriate aryl lithium reagent with concomitant reduction with Et_3SiH and BF_3•Et_2O. This first fluorinated analogue of Carminic acid **9** was isolated in 80% yield, again with exclusive *β* selectivity. By extension, an addition / deprotection / cyclisation sequence provided an efficient and α-selective route to compound **11**, which is a structural analogue of the cores of Tofogliflozin (**12**) and Papulacandin D (**3**). Finally, the addition of allyl magnesium bromide, followed by hydroboration / oxidation generated the alcohol **14**. When exposed to CSA, this material readily cyclised to furnish the fluorinated spiro-systems **15** further underscoring the versatility of **L1** as a starting material.

Scheme 1. a) MeLi, THF, -78 °C, 30 min. quant. *α*:*β* 1:0; b) **4**, **5**, TMSOTf, CH_2Cl_2, -78 °C to r.t. overnight, 30%, α*α*:α*β* 1.8:1; c) *n*-BuLi, ArBr (see SI), THF, -78 °C, 1 h, 73%, *α*:*β* 1:0; d) Et_3SiH, BF_3•Et_2O, CH_2Cl_2:MeCN, -10 °C to r.t., 3h, 80%, *α*:*β* 0:1; e) *n*-BuLi, ArBr (see SI), THF:toluene (1:2), -78 °C, 1 h, 73%, *α*:*β* 1:0; f) Et_3SiH, BF_3•Et_2O, MeCN, -40 °C to 0 °C, 2h, 69%, *α*:*β* 1:0; g) Allyl magnesium bromide, THF, -78 °C, 30 min., 96%, *α*:*β* 1:0; h) 9-BBN, H_2O_2 (30% in H_2O), NaOH (3 M aq.), overnight, r.t., 50%; i) CSA, dioxane, 80 °C, 8 h, 53%, *α*:*β* 1:1.



Motivated by rapid advances in glycobiology, a series of glycomimetics have been prepared that exploit the stability advantages of *C*-glycosides and 2-fluorosugars over the native systems. This study demonstrates that whilst the OBn → F substitution at *C2* is extremely well tolerated, the fluorinated lactones more robust towards the addition of organometallic reagents than the corresponding 2-deoxy lactones. The *α*-selectivity observed for the 2-OBn and 2-F sugars can be exploited in subsequent transformations. In this study, a series of natural and non-natural product analogues have been prepared in a stereoselective manner. Exploiting these systems in the context of chemical biology will be the focus of future efforts from this laboratory.

Experimental Section

Full experimental details are provided in the supporting information.

Acknowledgements

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Keywords: carbohydrate • fluorine • glycosides • bioisostere • natural products

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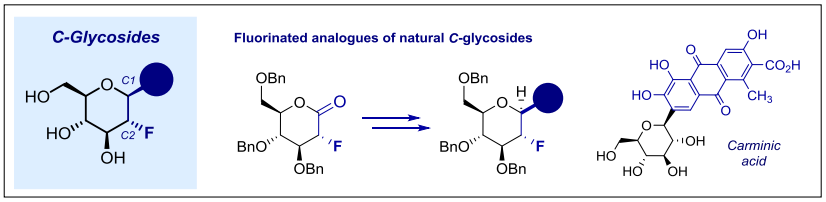

Organofluorine chemistry

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A study of the addition of *C*-based nucleophiles to fluorinated lactones based on 2-deoxy-2-fluoro-D-pyranoses is disclosed. This high yielding, *α*-selective process was found to be independent on the nature or configuration of the substituent at *C2*. Representative, fluorinated analogues of Trehalose, Carminic acid, and the spirocyclic cores of Tofogliflozin and Papulacandin D are also reported.