Fluoro Sugars

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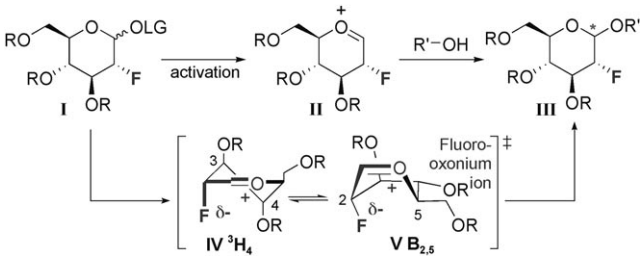
Fluorine-Directed Glycosylation**

*Christoph Bucher and Ryan Gilmour**

Dedicated to Professor Peter H. Seeberger

Carbohydrates are ubiquitous in nature, ranging from cellular energy sources to modulators of surface-based molecular recognition.[1] Unsurprisingly, these functional biomolecules have been the subject of intense synthesis campaigns culminating in a vast arsenal of glycosylation methods that are amenable to the stereocontrolled synthesis of complex oligosaccharides.[2] Central to virtually all of these strategies is an intermediary oxonium ion, the conformation of which is decisive in determining the configuration of the newly formed anomeric center.[3] However, controlling oxonium ion conformation in a predictable manner is challenging,[4] especially for 2-deoxy sugars where the protecting group regime at C2 cannot be modulated to govern stereoselectivity.[5] Cognisant of the tendency of organofluorine compounds to adopt conformations that allow for stabilizing hyperconjugative and attractive electrostatic interactions,[6] we envisaged that the transient oxonium ions derived from 2-fluoropyranoses (**I**→**II**) would be intriguing candidates for investigation (Scheme 1).

Consistent with Synder and Lankin's observation of a {NH-FC} dipole effect in 3-fluoropiperidine derivatives,[7] together with O'Hagan's findings pertaining to the conformational dynamics of protonated β-fluoroazetidinium and ethylpyridinium cations,[8] we postulated that in a *gluco*-configured 2-fluoro-oxonium ion the polarized C–F bond would orient towards the electropositive center;[9] in essence, conformational rigidification would be induced by perturbations in charge distribution around the anomeric center. Consequently, the $^3H_4$ and/or $B_{2,5}$ oxonium ion conformers (**IV** and **V**, respectively) would be favored, conceivably leading to a highly β-selective glycosylation event, complementary to the often α-selective processes associated with 2-deoxy sugars.[5,10] Whilst the overall oxonium ion topology would be responsive to electronic and steric modifications around the ring periphery, we envisaged that the fluorine atom would exert a controlling influence over the conformation that would ultimately be manifested in the selectivity of the subsequent glycosylation (**II**→**III**) (Scheme 1). Herein we present a preliminary validation of the C–F bond as design feature to control oxonium ion conformation in 2-fluoropyranose derivatives. The consequence of inverting the configuration at C2 (*gluco*-F→*manno*-F) is described together with the influence of weakly versus strongly inductive protecting groups. Implicit is the realization that fluorine's low steric demand, high bond strength to carbon, and consequent reactive inertness render the starting monosaccharides excellent bioisosteres of 2-deoxy sugars.[11] Moreover, fluorinated glycostructures continue to play an important role in medicine and pharmaceutical development[12] making this investigation, and the products described herein, timely.



Scheme 1. Conformational control in 2-fluoro-oxonium ions.

Initially, we elected to study a series of perbenzylated glycosyl trichloroacetimidates (Table 1) owing to the popularity of these systems in preparative glycochemistry,[13] and the mild conditions required to generate the transitory oxonium species. Employing isopropyl alcohol as the glycosyl acceptor facilitated reaction analysis by ^{1}H NMR spectroscopy, whilst CH_2Cl_2 was strategically chosen as the reaction medium to minimize the risk of solvent–oxonium ion complex formation that may bias the selectivity. To our delight, we observed that the C2 *gluco*-configured fluoride (entry 1, Table 1) furnished the desired isopropyl glycoside in excellent yield and with an impressive level of diastereocontrol (β/α 57:1). Conversely, the 2-deoxy glycosyl donor (entry 4, Table 1) gave markedly reduced selectivities (β/α 6:1), presumably due to the lack of structural control imparted by the fluorine. Moreover, by simple configurational inversion at C2 (*gluco*→*manno*), the diastereocontrol was once again substantially eroded giving results comparable to the 2-deoxy system. Intriguingly, under the conditions of this comparative study, the commonly used, perbenzylated glucose derivative (Table 1, entry 5, C2-OBn) gave levels of induction that again were lower than with the inital *gluco*-configured fluoro-glycoside (entry 1, Table 1). Interestingly, the C2 *gem*-difluoride derivative was recalci-

[*] C. Bucher, Prof. Dr. R. Gilmour
Swiss Federal Institute of Technology (ETH) Zurich
Laboratory for Organic Chemistry
Department of Chemistry and Applied Biosciences
Wolfgang-Pauli-Strasse 10, 8093 Zurich (Switzerland)
E-mail: ryan.gilmour@org.chem.ethz.ch
Homepage: http://www.gilmour.ethz.ch

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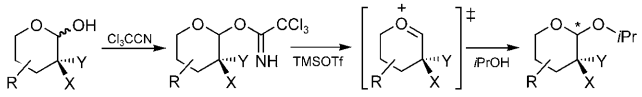
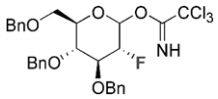
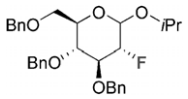
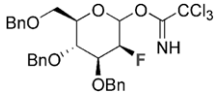
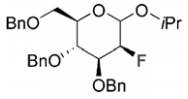
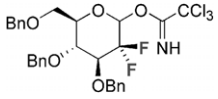
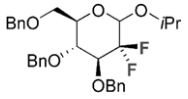
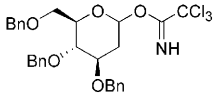
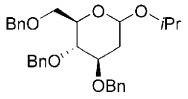
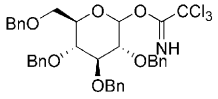
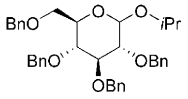
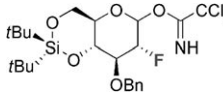
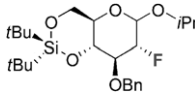
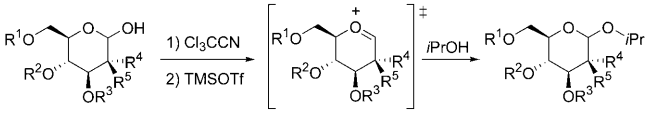
Table 1: Glycosylation reactions of 2-fluoro sugars.[a]



Entry	Substrate	Product	Yield [%][b]	β/α[c]
1			71	57:1
2			71	3.2:1
3			n.r.[d]	–
4			82	6:1
5			55	7:1
6			70[e]	1:1

[a] TMSOTf (0.1 equiv) was added to the trichloroacetimidate (1 equiv) and *i*PrOH (1.2 equiv) in CH_2Cl_2 at −78 °C. Entries 2 and 6 were performed at −50 °C and 0 °C, respectively. [b] The yields refer to the two-step activation/glycosylation sequence from the starting lactol (see the Supporting Information). [c] Ratios were determined by ^{1}H and ^{19}F NMR spectroscopy. [d] The reaction mixture was heated at reflux for 48 h. [e] The reaction was performed with an inseparable mixture of *manno*- and *gluco*-configured substrates. The combined yield is given, whilst the β/α ratio refers only to the *gluco*-configured system as determined by ^{1}H and ^{19}F NMR studies.

Table 2: Screening reactions of 2-fluoro sugars.[a]



Entry	R^1	R^2	R^3	R^4	R^5	Yield	β/α[e]
1[b]	Bn	Bn	Bn	F^{Gluc}	H	85	21:1
2[b]	Bn	Bn	Bn	H	F^{Mann}	71	3.2:1
3[b]	Bn	Bn	Bn	H	H	78	2.7:1
4[b]	allyl	allyl	allyl	F^{Gluc}	H	90	12:1
5[b]	allyl	allyl	allyl	H	F^{Mann}	76	2.5:1
6[b]	allyl	allyl	allyl	H	H	78	2.1:1
7[b]	Me	Me	Me	F^{Gluc}	H	83	8:1
8[b]	Me	Me	Me	H	F^{Mann}	81	2.2:1
9[b]	Me	Me	Me	H	H	71	2:1
10[c]	Ac	Ac	Ac	F^{Gluc}	H	62	1.9:1
11[c]	Ac	Ac	Ac	H	F^{Mann}	81	α only
12[c]	Ac	Ac	Ac	H	H	91	1:2
13[d]	Piv	Piv	Piv	F^{Gluc}	H	69	1:3
14[c]	Piv	Piv	Piv	H	F^{Mann}	83	α only
15[c]	Piv	Piv	Piv	H	H	69	1:1.7

[a] A solution of the trichloroacetimidate (1 equiv) and *i*PrOH (1.2 equiv) in CH_2Cl_2 was treated with TMSOTf (0.1 equiv) at the specified temperature for 2 h. The yields refer to the two-step activation/glycosylation sequence from the starting lactol (see the Supporting Information). [b] Reaction was performed at −50 °C. [c] Reaction was performed at −30 °C. [d] Reaction was performed at 0 °C. At −30 °C the reaction did not proceed to completion. [e] Determined by ^{1}H/^{19}F NMR spectroscopy.

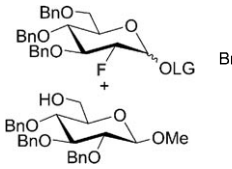
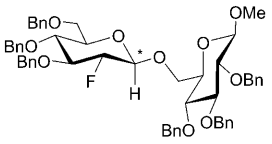
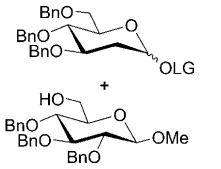
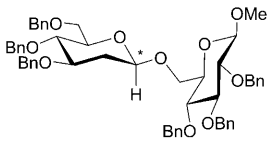
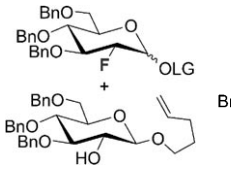
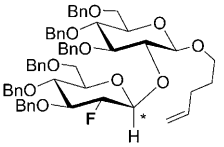
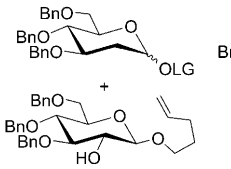
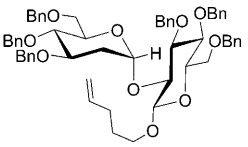
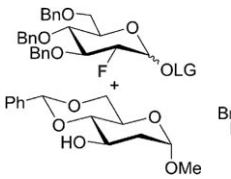
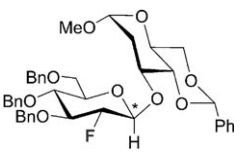
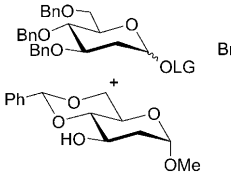
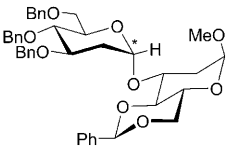
trant to glycosylation and proved to be extremely thermally stable, even when heated at reflux for 48 h (entry 3, Table 1). As an additional control substrate the structurally rigidified, bicyclic derivative (entry 6, Table 1) was prepared and subjected to our standard conditions, mindful that the conformational lability had been constricted.[14] This species proved to be a nonselective glycosyl donor (β/α 1:1).

Having probed the effect of the substitution and configuration at C2, the influence of the ancillary protecting groups on selectivity was investigated by comparing weakly and strongly inductive systems (benzyl/methyl/allyl and acetyl/pivaloyl. respectively). Initially, the benzyl derivatives (F^{Gluc}, F^{Mann}, deoxy) were re-investigated as glycosyl donors at −50 °C (Table 2, entries 1, 2, and 3, respectively). Even at this elevated temperature, the *gluco*-configured system conferred the highest levels of diastereocontrol (β/α 21:1), with the F^{Mann} and deoxy counterparts giving more modest selectivities (β/α ≈3:1). This remarkable trend was once again observed with the allyl series (F^{Gluc} > F^{Mann} > deoxy; β/α 12:1, 2.5:1, and 2.1:1, respectively; entries 4–6, Table 2). Finally, investigation of the methoxy derivatives (entries 7–9, Table 2) confirmed the previous results, again showing a clear diastereoselectivity trend from the *gluco*-configured (F^{Gluc}) donor and the corresponding *manno* (F^{Mann}) and deoxy derivatives (β:α 8:1 versus 2.2:1 and 2:1, respectively).

To our surprise, inversion of configuration at C2 and substitution of the weakly inductive protecting groups by more powerful acetyl and pivaloyl moieties culminated in a glycosyl donor complementary to the previous system. Whereas glycosylation of the peracetylated *gluco* substrate (F^{Gluc}, entry 10, Table 2) furnished the desired isopropyl glycoside with only marginal β-selectivity (β/α 1.9:1), the epimeric F^{Manno} system[15] furnished the α-glycoside exclusively (entry 11, Table 2). Dehalogenation at C2 furnished a slightly α-selective glycosyl donor (α/β 2.0:1, entry 12, Table 2), analogous to the F^{Gluc} system (entry 10, Table 2). Increasing the steric demand of the protecting group from acetyl to pivaloyl on the mannose-derived system (F^{Mann}) retained the high α-selectivity of the glycosylation (entry 14, Table 2). Intriguingly, the F^{Glu} and deoxy systems showed a marginal α-selectivity (α/β 3:1 and 1.7:1, respectively, F^{Mann} > F^{Gluc} ≈ deoxy) in contrast to their acetyl counterparts (entries 10 and 12, Table 2).

Finally, our attention was focused on showcasing the applicability of the perbenzylated F^{Gluc} donor (Table 1, entry 1) to the synthesis of 2-deoxy-containing disaccharide isosteres (Table 3). Initially, we examined coupling to the 6-position of a benzylated β-methyl glycoside acceptor (entry 1, Table 3). Gratifyingly, the activation/glycosylation sequence furnished the desired β(1→6)-linked analogue of cellobiose in excellent yield (76%, two steps) and diastereoselectivity (β/α 74:1). Importantly, the control reaction using the 2-deoxy

Table 3: Glycosylation reactions of 2-fluoro versus 2-deoxy sugars.[a]

Entry	Glycosyl donor/ glycosyl acceptor combination	Product disaccharide (major product)	Yield [%]	β/ α[b]
1			80	74:1
2			64	2:1
3			62	15:1
4			30[c]	1:3
5			73	24:1
6			68	1:5[d]

[a] Typical procedure: A solution of the glycosyl donor (1 equiv) and the glycosyl acceptor (1.2 equiv) in CH_2Cl_2 was treated with TMSOTf (0.1 equiv) at −78 °C for 2 h (see the Supporting Information). The yields refer to the two-step activation/glycosylation sequence from the starting lactol (see the Supporting Information). [b] Determined by $^1H/^{19}F$ NMR spectroscopy. LG = leaving group (trichloroacetimidate). [c] Incomplete conversion (45% yield by ^1H NMR analysis prior to isolation). The product was prone to decomposition during purification by flash chromatography on silica gel. [d] Determined after separation.

surrogate (entry 2, Table 3) proceeded with significantly diminished levels of induction (β/α 2:1).

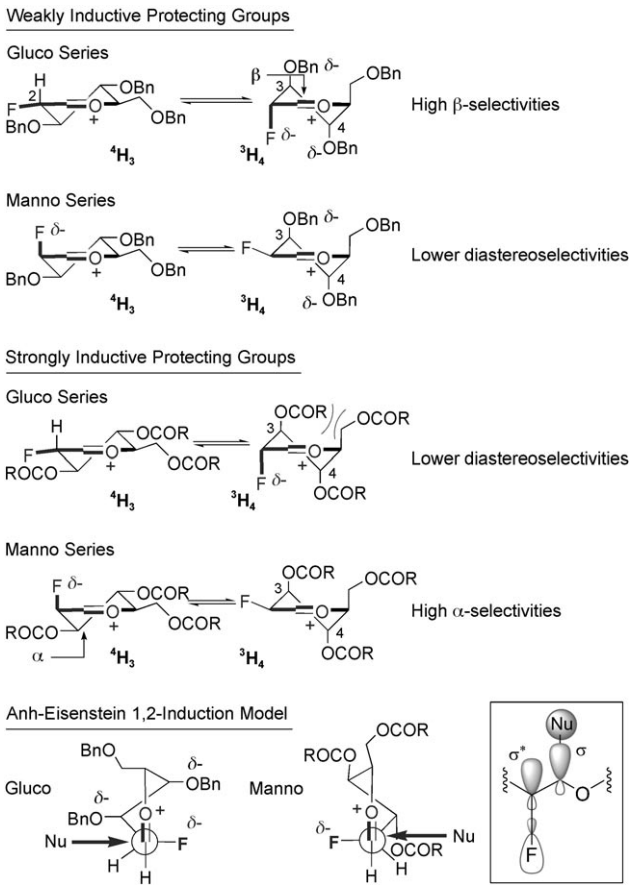
Next, the more challenging coupling to the C2 position of an *n*-pentenyl glycoside[16] (entry 3, Table 3) was performed. Once again, the glycosylation proved to be highly β-selective (β/α 15:1), furnishing the expected β(1→2) disaccharide as the major product in excellent yield (62%, two steps from the lactol). By comparison, the related 2-deoxy glycosyl donor was found to reverse the stereoselectivity albeit with lower levels of control, favoring the α-anomer (entry 4, Table 3).

To conclude this study, coupling of the 2-F^{Gluco} donor to a conformationally restricted acceptor was investigated (entry 5, Table 3). Despite the considerable steric hindrance, the reaction proceeded in excellent yield (73%, two steps) favoring the β-anomer (β/α 24:1). The selective formation of this β(1→3)-linked disaccharide is complementary to the analogous reaction using the 2-deoxy donor, a process that favors formation of the α(1→3)-linked disaccharide (α/β 5:1) with similar yields (entry 6, Table 3). The consistently high β-selectivity observed with the fluorinated donor renders it an important reagent for the stereoselective synthesis of fluorinated glycostructures.

The remarkable diastereoselectivities observed in the glycosylation of *gluco*-configured 2-fluoro sugars bearing nonparticipating protecting groups (Table 1) warrant some discussion of the possible oxonium ion conformations implicit in the glycosylation event. Due to the conformational fluidity of pyranose-derived oxonium ions, this analysis is restricted to the two half-chair intermediates ($^4\mathbf{H}_3$ and $^3\mathbf{H}_4$), necessarily excluding the infinite number of intermediate conformers. Contingent on our empirical findings, it seems credible that the transient oxonium ions likely resemble the $^3\mathbf{H}_4$ half-chair conformation based on the facial selectivity of nucleophilic addition and the findings of Woerpel who has described the axial preference of electronegative substituents at the C4 position.[5b,17] Furthermore, theoretical studies by Woods and co-workers suggest that hydroxy substituents at C3 and C4 of pyranose-derived oxonium ions prefer axial configurations arising from enhanced electrostatic stabilization.[18] However, it is important to note that by substituting fluorine by OBn at C2, the stereoinduction is eroded (Table 1, entry 5): these findings support the notion that the fluorine center is decisive in orchestrating the transfer of chiral information. In addition, the stereoselectivity is massively diminished by simply inverting the configuration of C2 to give the *manno* series (Scheme 2).

Conversely, the high α-selectivity observed in the *manno*-configured 2-fluoro sugars bearing strongly inductive protecting groups cannot be explained by the same model and is probably due to a flip in oxonium ion conformation. It is also likely that the sterically demanding protecting groups will adopt a pseudo-equatorial orientation, such that a conformation reminiscent of $^4\mathbf{H}_3$ is a likely contender (Scheme 2, lower). The influence of the fluorine atom ($\chi \approx 4$) on the electrophilicity of the oxonium ion, and the trajectory of an incoming nucleophile in the transition state, must also be considered.[19] The inductive effect will likely amplify the electrophilicity of the oxonium ion rendering the stabilizing contributions of the diaxial OBn groups at C3 and C4 important thus favoring the $^3H_4$ conformation (Scheme 2, upper). Conversely, such stabilizing interactions are not possible with strongly inductive protecting groups leading to the $^4H_3$ conformer (Scheme 2, middle). It is envisaged that the nucleophile will approach the oxonium ion in a manner consistent with the Anh–Eisenstein model for 1,2-induction such that transition-state stabilization is achieved by alignment with the σ^*_{C-F} orbital.[20]

In summary, we disclose a complementary set of highly diastereoselective glycosyl donors based upon the 2-fluoro-



Scheme 2. A possible stereoselectivity model.

pyranose scaffold. A reinforcing combination of the C2 fluorine configuration together with the inductive nature of the protecting-group pattern leads to highly selective glycosylation events [2-F^{Gluc}/Bn→β; 2-F^{Manno}/Piv→α]. Application of the method in the synthesis of 2-deoxy disaccharide isosteres led to fluoro-glycostructures/2-deoxy sugar bioisosteres with excellent control over the anomeric configuration. Efforts to refine the selectivity model by both spectroscopic and theoretical methods are currently ongoing in our laboratory and will be reported in due course.

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