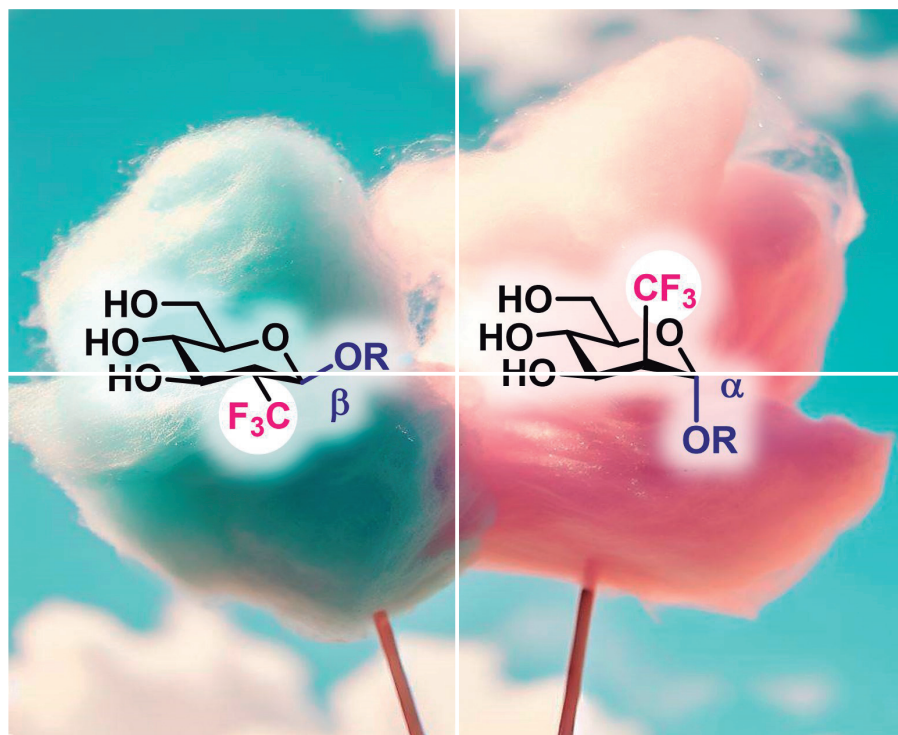


10
YEARS
ANNIVERSARY



ORGANIC CHEMISTRY

FRONTIERS



CHINESE
CHEMICAL
SOCIETY



ROYAL SOCIETY
OF CHEMISTRY

rsc.li/frontiers-organic

RESEARCH ARTICLE

View Article Online

View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2023, 10, 2405Stereoselective access to 2-deoxy-2-trifluoromethyl sugar mimetics by trifluoromethyl-directed 1,2-*trans* glycosylation†

Jordi Mestre, , Isabel Bascuas, , Miguel Bernús, , Sergio Castellón and Omar Boutureira *

Fluorinated carbohydrate mimetics are valuable molecular fragments in contemporary *Glycoscience*. Available synthetic protocols are mainly restricted to the preparation of 'standard' monofluorinated derivatives, whereas their more complex C(sp³)-CF₃ congeners remain virtually underdeveloped. A protocol for accessing a series of previously uncharted 2-deoxy-2-trifluoromethyl-*D*-hexopyranosides from *D*-glycals is disclosed. The stereoselectivity of the glycosylation step, which is mainly governed by a combination of electronic and more dominant steric factors, revealed a pronounced substrate control rendering 1,2-*trans* glycosides as a result of the configuration of the CF₃ moiety at C-2. The synthetic utility of this approach was demonstrated in the preparation of 2-CF₃-glycoconjugates of natural origin, including disaccharides, cholesterol analogs, amino acids, and sphingosine/phytosphingosine derivatives.

Received 22nd February 2023,

Accepted 25th March 2023

DOI: 10.1039/d3qo00274h

rsc.li/frontiers-organic

Introduction

There is growing interest in the preparation of carbohydrate mimetics that overcome some of the limitations, such as short lifetimes and low absorption properties (reduced hydrophobicity), typically associated with drugs based on natural carbohydrates.¹ Among them, F-glycomimetics,² resulting from the bioisosteric replacement of H and OH by F,³ and particularly those featuring polyfluoroalkyl groups (R_F),⁴ such as CF₃,⁵ (CH₃ isoster) and C₂F₅,⁶ have recently attracted considerable interest (Fig. 1A).⁷ However, although the preparation of CF₃-containing active principal ingredients (APIs) has been long appreciated in *MedChem* due to the beneficial properties such polyfluorinated groups impart (e.g., enhanced lipophilicity and metabolic/oxidative stability),⁸ CF₃-glycosides remain largely underrepresented^{9,10} in *Glycoscience* compared to their monofluorinated congeners. Interestingly, the latter are widely used as inhibitors of glycosidases,¹¹ lectin ligands,¹² building blocks to construct synthetic (glyco)peptides/proteins^{13–15} for carbohydrate vaccine design,¹⁶ as well as radiotracers for imaging applications (e.g., [¹⁸F]FDG).¹⁷

We hypothesise the unique properties³ of the CF₃ group, with similar polarity but larger steric constraints compared to those of the F atom; will likely influence metabolism, distribution, uptake, and therapeutic potential in CF₃-monosaccharides (Fig. 1B, *top*). This trend is also supported by calculations of electrostatic potential surface (EPS), van der Waals volume, and dipole moment (magnitude and vector) for 2-CF₃^{manno,gluco} vs. 2-F^{manno,gluco} hexopyranoses (Fig. 1B, *bottom* and Figs. S1–S4, ESI†).^{18,19} Moreover, CF₃ moieties may confer conformational constraints and enzymatic stability as well as privileged imaging potential (increased sensitivity in ¹⁹F-MRI and possibility to access [¹⁸F]-derivatives for PET imaging).^{17,20} Readily available trifluoroacetamides (NHC(O)CF₃) and trifluoroacetoxy (OC(O)CF₃) groups are the closest-art and the most frequent motifs among C(sp²)(O)CF₃-containing glycosides.^{9,21} Unfortunately, other CF₃-sugars are only limited to α-C(sp³)-CF₃ alcohols resulting from 1,2-nucleophilic addition of TMSCF₃ to carbonyls²² and, more recently, C(sp²)-CF₃-glycals produced by photoredox²³/electrochemical²⁴ radical additions or *via* cross-couplings of CuCF₃ with 2-iodoglycals.⁵ Besides its remarkable biophysical properties, F has also proven an efficient steering group for the stereoselective preparation of 2-deoxy-2-fluoroglycosides.²⁵ In this case, the high 1,2-*anti* selectivity results from the preferred conformation of the oxocarbenium ion in the transition state reminiscent to half-chair geometries that are favoured by the high electronegativity of F. The energy of the transition state is minimized when the nucleophile trajectory is aligned with the σ_{C–F}^{*} orbital, consistent with the Felkin–Anh–Eisenstein model for

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo 1, 43007 Tarragona, Spain. E-mail: omar.boutureira@urv.cat

†Electronic supplementary information (ESI) available. CCDC 2128831 (7b) and 2128832 (4c). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3qo00274h>

*Equal contribution.



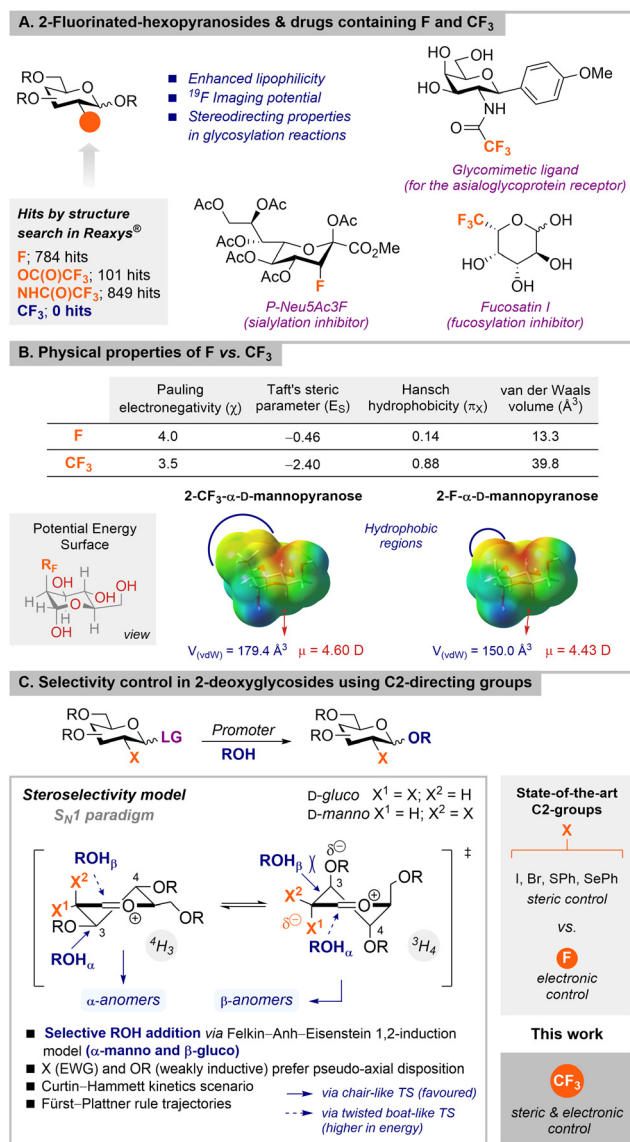


Fig. 1 (A) 2-Fluorinated-hexopyranosides and selected drugs containing F and CF₃ groups. Hits obtained with the Reaxys database. (B) Physical properties of F vs. CF₃ groups (top). Calculated Electrostatic potential surfaces (EPS), van der Waals volume (blue), and dipole moment (magnitude and vector, red) (bottom) (see the ESI† for details). (C) Selectivity control in 2-deoxyglycosides bearing temporary (X = I, Br, SPh, SePh) and permanent (X = F, CF₃) C2-directing groups.

1,2-stereoinduction.²⁵ This contrasts with the stereoselectivity observed in similar examples using larger temporary C-2-directing groups such as halogens²⁶ and chalcogens²⁷ in which the 1,2-*trans* stereoselectivity is mainly governed by steric (Pauli) factors (Fig. 1C).²⁸ Removal of these groups affords the corresponding 2-deoxyglycosides.²⁹

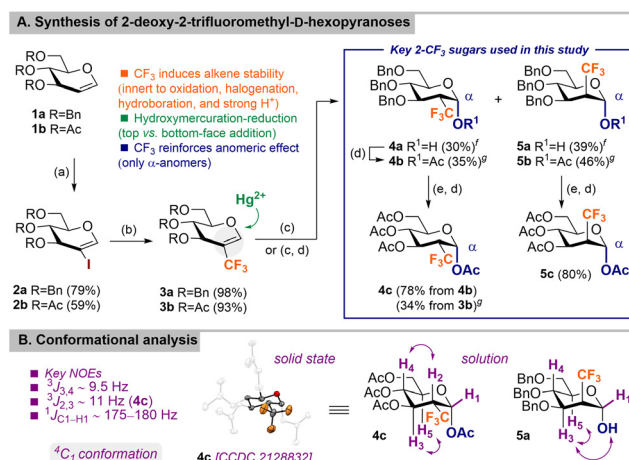
In this context, we were intrigued on the behaviour of the CF₃ group when placed at the C-2 position of a glycosyl donor, and whether the presence of such an electron-withdrawing and bulky unit may impart stabilizing/destabilizing interactions at the nearby oxocarbenium ion (e.g., nF \rightarrow 2pC inter-

actions),³⁰ affecting the stereochemical outcome of the glycosylation reaction. Thus, here we report the development of a synthetic route (including a detailed study of the glycosylation reaction) to access new C(sp³)-CF₃-(glyco)architectures. In particular, it would be interesting to comparatively determine if the electronic factors that govern the stereochemical outcome of the glycosylation of 2-deoxy-2-fluoro-glycosides are also operating in the case of 2-deoxy-2-CF₃-derivatives (Fig. 1C, X = CF₃). We anticipate the development of synthetic methods such as the one described in this study will establish the basis for successfully approaching further studies in complex fluorinated glycomimetics.

Results and discussion

Synthesis of glycosyl donors

In light of this, a strategy for the preparation of 2-CF₃-glycosyl donors was envisaged from commercially available D-glucals as precursors (Scheme 1A). In our previous work, we reported the synthesis of **3a** by iodination of D-glucal **1a** to **2a** (64% *via* dehydrative elimination)³¹ followed by selective trifluoromethylation using CF₃H-derived CuCF₃ (80%).⁵ This trifluoromethylation process required the use of a glovebox and



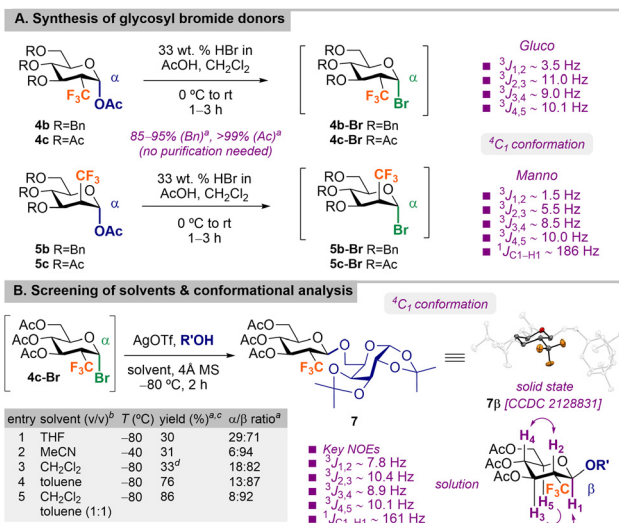
Scheme 1 (A) Synthesis of 2-deoxy-2-trifluoromethyl-D-hexopyranoses of *gluco* and *manno* configurations and (B) conformational analysis. Reagents and conditions: (a) **1a,b** (1 equiv.), AgNO₃ (0.2 equiv.), dry MeCN, reflux, 1 h (for **1a**) up to 4 h (for **1b**). (b) **2a,b** (1 equiv.), CuCF₃ (2 equiv.), 1 : 1 (v/v) DMF/DMI, 40 °C, 17 h and 50 °C, 16 h. (c) (i) **3a,b** (1 equiv.), Hg(OTFA)₂ (1.5 equiv.), 3 : 1 THF/H₂O, 0 °C to rt, 36 h; (ii) NaBH₄ (6.3 equiv.), H₂O, 0 °C, 20 min. (d) Ac₂O (3.6 equiv.), pyridine, rt, 15 h. (e) H₂ (1 atm), 10% Pd/C, MeOH, rt, 16 h. ^fThis yield corresponds to a pure analytical sample obtained after a tedious fractional crystallization process. Prior column chromatography of the crude reaction afforded an inseparable mixture of 1 : 1.6 **4a/5a** in 90% yield. ^gYield over three steps from **3a** (for **4b**, **5b**) and **3b** (for **4c**). Isolated yields given for all compounds unless otherwise indicated (see the ESI† for details). DMF = *N,N*-dimethylformamide, DMI = 1,3-dimethyl-2-imidazolidinone, TFA = trifluoroacetic acid, THF = tetrahydrofuran. ORTEP drawing of **4c** with thermal ellipsoids drawn at the 50% probability level (H atoms omitted for clarity).



manipulation of gaseous reagents. Herein, the overall synthetic sequence was improved by using first a more efficient iodination protocol (79% for **2a**; 59% for **2b**)³² and second, the use of a trifluoromethylation system (TMSCF₃/KF/CuBr) that permits readily scalable synthesis and employs simpler reaction setup to access valuable 2-CF₃-glycals (98% for **3a**; 93% for **3b**). Next, functionalization of the double bond was attempted, but the 2-CF₃-alkene proved reluctant to undergo electrophilic additions, including halogenation, H⁺-mediated hydration, hydroboration, and epoxidation (Scheme S2, ESI†). Polyfluorinated alkenes and aromatic compounds are likely to reverse the natural polarity of such π -systems, making them prone to nucleophilic attacks.³³ Nonetheless, structural examination of **3a,b** advises a push-pull effect between the electron-donating oxygen of the enol ether and the electron-withdrawal of the CF₃ group that in combination with its steric bulkiness, renders this double bond considerable unreactive (Scheme S2, ESI†). To our delight, hydroxymercuration of **3a** using Hg(OTFA)₂ followed by reductive demercuration with NaBH₄ afforded a 1 : 1.6 mixture of *gluco* **4a** and *manno* **5a** pyranoses in 90% yield that after acetylation yielded chromatographically separable **4b** (35%) and **5b** (46%) (Scheme S3, ESI†). Collectively, the detection of only α -anomers indicates that similarly to 2-F, 2-CF₃ reinforces the anomeric effect.³⁴ O-Benzyl protecting groups in 1-O-acetyl-pyranoses **4b** and **5b** were removed under hydrogenolysis conditions and subsequent acetylation afforded products **4c** and **5c** in good overall yields (up to 80%). Same reaction sequence starting from parent 1-OH-pyranoses **4a** and **5a** resulted in detrimental anomerization to afford inseparable α/β mixtures of *gluco* **4c** and *manno* **5c** pyranoses. Direct hydroxymercuration-reduction of 2-CF₃-tri-O-acetyl-D-glucal **3b** proved inefficient and **4b** was obtained in a poor 34% yield along with unidentified rearrangement byproducts. Analysis of **4c** by X-ray diffraction† indicated that typical ⁴C₁ conformation is adopted in the *solid state* despite the presence of the sterically demanding CF₃ group. ¹H and ¹³C NMR data showed that the same geometry is also conserved in *solution* for both *gluco* and *manno* derivatives as determined by diagnostic ¹J_{C1-H1} and ³J_{H,H} coupling constants and key NOE contacts (Scheme 1B and Fig. S141, ESI†).

After optimizing the preparation of 2-CF₃-pyranoses, the synthesis of suitable glycosyl donors was further examined (Scheme 2A and Scheme S4, ESI†). We first explored the preparation of trichloroacetimidate **5a-OTCA** by reacting **5a** with DBU and Cl₃CN, but the poor yields obtained (48%) and the need of purification reduced its synthetic utility.

Reacting **5b** with BF₃·OEt₂ and thiophenol in CH₂Cl₂ afforded thioglycoside donor **5b-SPh** in a very low 23% isolated yield (Scheme S4, ESI†). Notably, reaction of pyranoses **4-5b,c** with HBr in AcOH delivered glycosyl bromides (**4-5b,c**)-Br in almost quantitative yields (Scheme 2A). Glycosyl bromides proved to be stable, and they were directly used as glycosyl donors in subsequent glycosylation reactions without further purification.



Scheme 2 (A) Synthesis of glycosyl bromide donors and (B) screening of glycosylation solvents and conformational analysis. Reagents and conditions: ^aYield and selectivity determined by ¹⁹F NMR of the crude reaction mixture using 1,4-difluorobenzene as internal standard unless otherwise indicated. ^bReactions performed at 0.1 M concentration. ^cYield over two steps from **4c**. ^dPoor solubility of AgOTf observed (see the ESI† for details). MS = molecular sieves, THF = tetrahydrofuran, NR = no reaction. ORTEP drawing of **7b** with thermal ellipsoids drawn at the 50% probability level (H atoms omitted for clarity).

Glycosylation reaction

Next, preliminary glycosylation reactions were attempted using anomeric acetates **4b**, **5b**, trichloroacetimidate **5a-OTCA**, and thioglycoside **5b-SPh** as donors (Scheme S5, ESI†). While the reaction of anomeric acetates showed no conversion using common promoters (0.1–4 equiv. TMSOTf or 3 equiv. BF₃·OEt₂ up to 72 h at room temperature) for both *manno* and *gluco* configurations (Scheme S5, entries 1–3, ESI†), trichloroacetimidate **5a-OTCA** afforded expected product **6a** in a good combined 69% yield and 38 : 62 α/β ratio (Scheme S5, entry 4, ESI†). In contrast, activation of **5b-SPh** with the NIS/TfOH³⁵ system only started when temperatures above –35 °C were reached, affording **6a** (73%) in a 58 : 42 α/β ratio along with hydrolysis byproducts (~27%) (Scheme S5, entry 5, ESI†). In summary, the preparation of thioglycoside and trichloroacetimidates resulted problematic, delivering low isolated yields of **5a-OTCA** and **5b-SPh**, required additional purification steps, and are not applicable to *gluco* configurations. Moreover, glycosylation of these donors offered substantial hydrolysis, poor 1,2-*trans* control of the CF₃ group (**5a-OTCA**), required higher activation temperatures (**5b-SPh**) that compromise good stereoselectivities for general application of this protocol or showed no reactivity (**4b** and **5b**). Next, we focused our attention towards the glycosylation of easily accessible glycosyl bromides (Scheme 2B),³⁶ which showed smooth activation at very low temperatures. Thus, CF₃^{gluco} **4c-Br** was selected as a model substrate and 1,2 : 3,4-di-O-isopropylidene- α -D-galactopyranose as the acceptor with 4 Å MS and silver triflate (AgOTf) as the promoter (Scheme 2B). Preliminary tests showed the importance



of conducting the reaction at very low temperature (*ca.* -80°C), in particular for *gluco* configuration, due to the propensity of 2- CF_3 -glucosyl bromides to undergo elimination processes to the parent 2- CF_3 -D-glucal (5–20%). Solvent screening showed that reactions in THF afforded low yields and the selectivity was poor (Scheme 2B, entry 1). When using acetonitrile at -40°C , excellent β -selectivities were obtained, albeit with lower yield (Scheme 2B, entry 2). Using either CH_2Cl_2 or toluene, the selectivity was similar, affording **7b** as the major isomer, yet in CH_2Cl_2 , the yield was eroded, probably due to solubility issues with AgOTf (Scheme 2B, entries 3 vs. 4). In this case, no surface effects on selectivity were detected. Finally, best yield and selectivities were obtained in a 1 : 1 (v/v) CH_2Cl_2 /toluene mixture (Scheme 2B, entry 5). Treatment of **7b** under these optimized glycosylation conditions discarded anomerization of final 2- CF_3 -glycosides during the reaction. Similarly to their hexopyranose precursors and the resulting glycosyl donors (Schemes 1B and 2A), glycosylation products also maintain the same $^4\text{C}_1$ conformation both in the *solid state* (X-ray for **7b**)[†] and *in solution* (Scheme 2B and Fig. S5 and S142, ESI[†]). This observation suggests that *a priori*, 2-deoxy-2- CF_3 -glycoside analogs of natural products could be designed to maintain molecular recognition events (unless key specific interactions are operative at C-2) by biological entities, validating our starting hypothesis ($\text{F}^{\delta-} \rightarrow \text{CF}_3^{\delta-}$).

Aiming to analyze the directing effect of the CF_3 on the stereoselectivity of the glycosylation reaction, donors with different 2- CF_3 -configuration and electronically different protecting groups were examined (Table 1). To facilitate direct comparison of the stereodirecting value of CF_3 vs. F, isopropanol was chosen as nucleophile following seminal reports by Gilmour.²⁵ *Gluc*- CF_3 glycosyl donors favoured formation of β -products, whereas α -glycosides were preferred in *manno*- CF_3 donors (Table 1, entries 1–4). The best selectivities obtained resulted from the combination of OAc-protecting groups with $\text{CF}_3^{\text{manno}}$ **5c-Br** (95 : 5 α/β) and OBn groups with $\text{CF}_3^{\text{gluco}}$ **4b-Br** (3 : 97 α/β). We first evaluated the role of the concentration (0.05 vs. 0.1 M)³⁷ and stoichiometry (1 : 1, 1 : 2, and 1 : 15 donor/acceptor molar ratio),³⁸ which are critical parameters for the glycosylation outcome (Table S1, entries 1–4, ESI[†]).³⁹ Only little yield (except in the case of using 1 equiv. of acceptor where more byproducts are detected) and selectivity differences were found in reactions conducted at different reaction concentrations or with increased acceptor stoichiometry that suggests a more $\text{S}_{\text{N}}1$ -like dissociative mechanism. The use of promoters bearing non-nucleophilic counter ions such as AgBF_4 ⁴⁰ and AgSbF_6 (unable to provide OTf to the reaction medium) afforded similar selectivities that those with AgOTf, which strongly suggests that anomeric triflates are not likely responsible for the selectivity observed (Table S1, entries 1–4 vs. 5 and 6, ESI[†]). Our findings are in line with the results obtained in the glycosylation of 2-fluorosugars, yet in this case, trichloroacetimidates were used as glycosyl donors.²⁵ Remarkably, the role of the leaving group in the stereoselectivity seems important ($\text{CF}_3^{\text{manno}}$ **5a-OTCA**; 38 : 62 α/β ratio; Scheme S5, ESI[†]) vs. ($\text{CF}_3^{\text{manno}}$ **5b-SPh**; 58 : 42 α/β ratio;

Table 1 Effect of pyranose configuration, C-2 substituent, protecting groups, and acceptor nucleophilicity in the glycosylation reaction^a

Reaction scheme showing the glycosylation of 2-X-pyranoses (Gluco or Manno) with AgOTf and R'OH under conditions 1) HBr, 2) AgOTf, R'OH. The reaction yields a mixture of α and β anomers in a 10–20% yield. X = F, CF₃; R = Ac, Bn.

Entry	2-X-pyranose	R	R'	Product yield ^b (%)	α/β ratio ^b	
1	CF ₃ ^{gluco}	4c	Ac	iPr	10 , 61	33 : 67
2	CF ₃ ^{manno}	5c	Ac	iPr	11 , 91	95 : 5
3	CF ₃ ^{gluco}	4b	Bn	iPr	12 , 72	3 : 97
4	CF ₃ ^{manno}	5b	Bn	iPr	13 , 62	79 : 21
5	F ^{gluco}	8a	Ac	iPr	14 , 95	24 : 76
6	F ^{manno}	9a	Ac	iPr	15 , 84	95 : 5
7	F ^{gluco}	8b	Bn	iPr	16 , 78	4 : 96
8	F ^{manno}	9b	Bn	iPr	17 , 65	20 : 80
9	CF ₃ ^{gluco}	4c	Ac	Et	18 , 78	22 : 78
10	CF ₃ ^{gluco}	4c	Ac	tBu	19 , 58	42 : 58
11	CF ₃ ^{gluco}	4c	Ac	CH ₂ CF ₃	20 , 62	72 : 28

^a General conditions: (1) 2-X-pyranose (1 equiv.), 33 wt% HBr in AcOH, 0°C to rt, 1–3 h; (2) glycosyl bromide donor (1 equiv.), R'OH (2 equiv.), and AgOTf (2 equiv.) in 1 : 1 (v/v) CH_2Cl_2 /toluene (0.05 M), -80°C , 3 h unless otherwise indicated. Variable amounts of elimination side-reactions to the parent 2- CF_3 -D-glucal were detected by ^{19}F NMR (9–32% in *Glc* and <10% in *Man*). ^b Determined by ^{19}F NMR analysis of the crude reaction mixture using 1,4-difluorobenzene as internal standard (see the ESI[†] for details).

Scheme S5, ESI[†]) vs. ($\text{CF}_3^{\text{manno}}$ **5b-Br**, 79 : 21 α/β ; Table 1, entry 4).³⁹ Reactions using α -Br/Sph as leaving groups seem to be placed closer to the $\text{S}_{\text{N}}1$ end of the glycosylation mechanistic continuum, proceeding *via* a common oxocarbenium ion/solvent-separated ion pair (SSIP) species. Small differences in selectivity may be attributed to slightly different activation temperatures (-80°C for Br vs. -35°C for Sph).⁴¹ Attempts to shed light on putative reactive intermediates were performed by ^{19}F and ^1H variable temperature (VT)-NMR experiments⁴² with bromide **4c-Br** using our optimized reaction conditions but no intermediates were detected under preactivation conditions (preferred to detect transient intermediates). Subsequent addition of the nucleophile (iPrOH) delivered a complex mixture of signals from which only traces of final glycosylation product **10** could be observed. This result is in line with that using only 1 equiv. of acceptor in which increased amounts of byproducts are detected (Table S1, entry 3, ESI[†]). On the other hand, as expected,^{42,43} a more biased $\text{S}_{\text{N}}2$ -like scenario with a larger contribution of α -contact ion pair (CIP) species or even α -anomeric triflates from **5a-OTCA** to tentatively rationalize the increased β -selectivity is invoked.⁴⁴ Thus, for the sake of a more accurate comparison (F vs. CF_3), 2-deoxy-2-fluoroglycosyl bromides **8–9a,b-Br**¹⁴ were synthesized from **8–9a,b** and submitted to the same reaction conditions of the present study. Stereoselectivities in 2-deoxy-2-fluoro derivatives **14–16** were similar to those of trifluoromethylated



analogs **10–12** (Table 1, entries 1–3 vs. 5–7). However, inversion of the selectivity was observed in the OBn-*manno*-sugars **13** and **17** (Table 1, entry 4 vs. 8). Limited stereoselective control was also detected for OBn-*manno* derivatives in previous works,²⁵ due to mismatched effects between protecting groups and the 2-fluoro substituent. Stereoselectivity in 2-deoxy-2-fluorosugars is rationalized by the Felkin-Anh-Eisenstein 1,2-induction model (Fig. 1C, X = F) in which stereoselective control is reinforced or diminished depending on the electronic nature of protecting groups (due to electrostatic and hyperconjugative interactions).⁴⁵ The higher α -stereoselectivity observed in CF₃^{manno} vs. F^{manno} OBn-derivatives may arise from a higher contribution of the steric control, which is reminiscent to that observed with methyl groups in substitution reactions of acyclic α -methyl- β -alkoxy acetals *via* electrostatically stabilized oxocarbenium ion intermediates.⁴⁶ Next, the effect of the acceptor nucleophilicity was examined with donor CF₃^{gluco} **4c-Br**. No remarkable differences were observed when isopropanol and ethanol were used as acceptors and high 1,2-*trans* stereoselectivities were again obtained (Table 1, entry 1 vs. 9). On the other hand, lower or even inverted (1,2-*cis*) stereoselectivities were found when larger/weaker nucleophilic *tert*-butyl alcohol and trifluoroethanol were used as acceptors as they require donors with substantial oxocarbenium ion character and are engaged in dissociative S_N1-like reactions (Table 1, entries 10 and 11).⁴⁷ The increased steric hindrance of the acceptor may disfavour its approach by the top face due

to steric (Pauli) repulsions with protecting groups (Fig. 2, *middle*). Results are compatible with a Curtin-Hammett scenario, where $\Delta G^{\ddagger II}$ increases energy more than $\Delta G^{\ddagger I}$ for bulky and/or weak nucleophiles (Fig. 2, *bottom*).

Glycosylation scope

Finally, reaction scope was further examined using a diversity of representative acceptors, including primary and secondary glycosides, amino acids, and lipid aglycones such as cholesterol and sphingosine/phytosphingosine derivatives (Scheme 3). Thus, sequential bromination of **4b**, **5b,c** and sub-

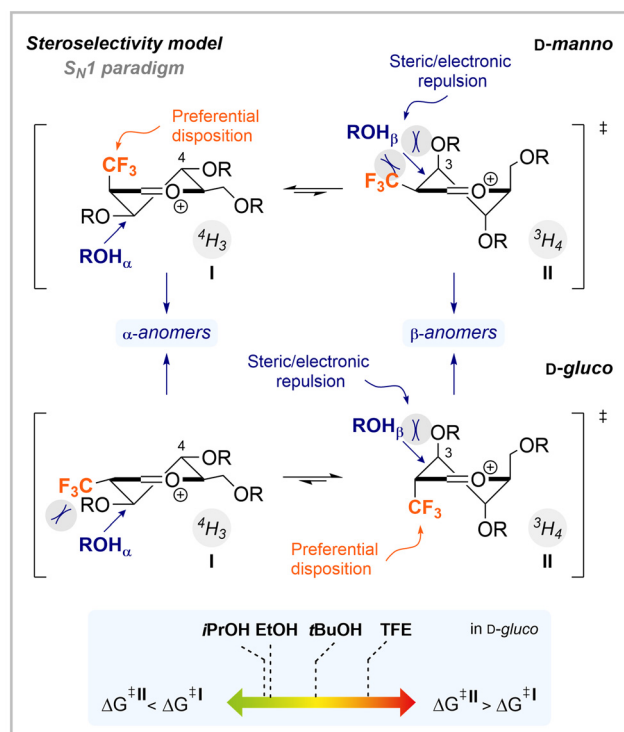
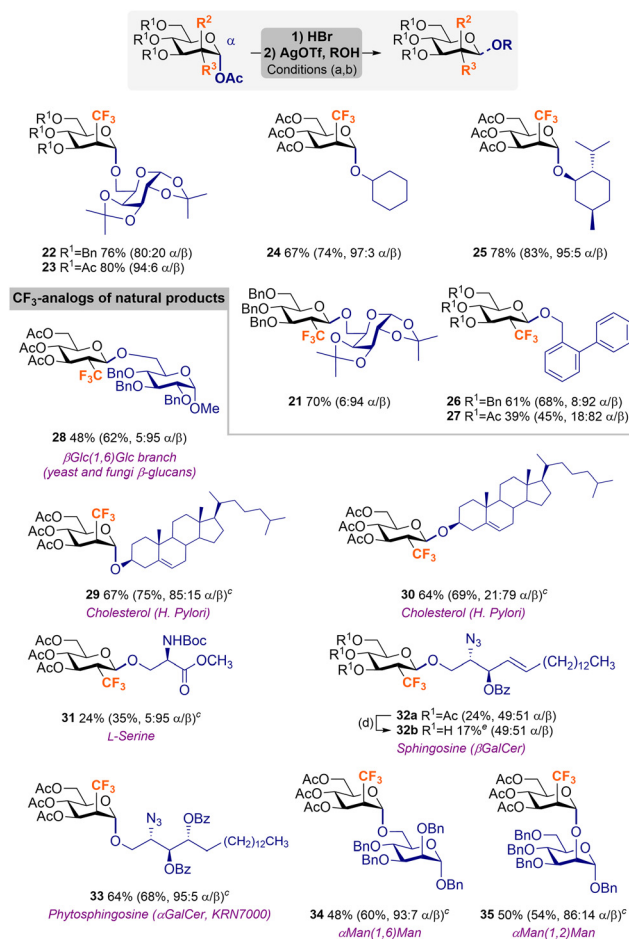


Fig. 2 Stereoselectivity rationalization of the glycosylation step in *D-manno* (top) and *D-gluco* series (middle). Analysis of the glycosylation of *D-gluco* donors with small alcohols possessing different stereoelectronic properties as acceptors (bottom).



Scheme 3 Glycosylation scope. Reagents and conditions: (a) **4–5b,c** (1 equiv.), 33 wt% HBr in AcOH, 0 °C to rt, 4 h. (b) Glycosyl donor (1 equiv.), ROH (2 equiv.), and AgOTf (2 equiv.) in 1:1 (v/v) CH₂Cl₂/toluene (0.05 M), –80 °C, 2 h. (c) To facilitate purification, the crude was subjected to acetylation; Ac₂O (6 equiv.), 1:1 (v/v) pyridine/CH₂Cl₂, rt, 16 h and the residue purified by flash column chromatography. (d) To facilitate purification, the crude was subjected to Zemplén deacetylation; NaOMe, MeOH, rt, 6 h and the residue purified by flash column chromatography. ^aYield over three steps from **4c**. Isolated yields given for all compounds unless otherwise indicated. In parenthesis yield and/or diastereomeric ratio calculated by ¹⁹F NMR of the crude reaction mixture using 1,4-difluorobenzene as internal standard (see the ESI† for details). Variable amounts of elimination side-reactions to the parent 2-CF₃-D-glucal were detected by ¹⁹F NMR (10–35% in Glc and <10% in Man). Boc = *tert*-butoxycarbonyl.

sequent glycosylation with the primary acceptor 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose afforded products **21–23** in good yields (up to 80%) with expected 1,2-*trans* stereoselectivities (up to 94 : 6 α/β in *manno*; 6 : 94 α/β in *gluco*). In most cases, the major anomer was obtained as a single product after chromatographic purification. When the minor isomer was produced to some extent, the epimers could be successfully separated and structurally characterized. Again, analysis of **8**, **21–23** by ^1H NMR showed $^4\text{C}_1$ conformations dominate in all cases (Fig. S5, ESI†). It should be noted that 2- CF_3 -D-glucal byproduct was obtained in variable amounts (10–35%) upon competing elimination process using $\text{CF}_3^{\text{gluco}}$ donors that resulted in reduced overall yields for certain glycosylations. As expected, $\text{CF}_3^{\text{manno}}$ afforded preferably α -glycosides **24** (67%) and **25** (78%) with excellent stereoselectivities (up to 97 : 3 α/β) and slightly better yields when reacted with these secondary alcohols, since elimination side-reactions are significantly less operative from *manno*-configured donors (<10%). Reaction with biphenyl-2-methanol occurred smoothly with *gluco* donors to afford β -glycosides and selectivity was slightly benefited using OBn groups (8 : 92 α/β in **26** vs. 18 : 82 α/β in **27**). In this case, the lower yield obtained for peracetylated biphenyl methyl **27** is caused by the higher amount of elimination (29%) in comparison to the perbenzylated counterpart (11%).

The presented protocol was applied to the stereoselective synthesis of 2- CF_3 -analogs of some relevant natural products. Despite the higher amount of side-elimination reactions using peracetylated glycosyl donors (typically in $\text{CF}_3^{\text{gluco}}$), these were chosen as reactants in the glycosylation scope, mainly due to their higher flexibility for accessing final unprotected derivatives (*via* Zemplén deacetylation) in comparison to the perbenzylated analogs. Fair yield, although excellent selectivity, was observed in the synthesis of **28** ($\beta\text{Glc}(1,6)\text{Glc}$ branch found in yeast and fungi β -glucans) from the mismatched donor **4c-Br** (48%, 5 : 95 α/β). Reaction of cholesterol with both *gluco* and *manno* epimers afforded **29** and **30** (mimetics of natural cholesteryl glucosides from *H. pylori*) with good isolated yields (up to 67%) and stereoselectivities (85 : 15 α/β in **29**; 21 : 79 α/β in **30**) and only minute elimination (10–15%). When using protected L-serine as acceptor, low yield of the desired product **31** (24%) was obtained due to competing elimination process (25%). However, excellent β -selectivity (5 : 95 α/β) was achieved by virtue of the equatorial CF_3 configuration. Unexpectedly, the stereoselective control was completely eroded using a protected azido-sphingosine analog⁴⁸ that reacted with $\text{CF}_3^{\text{gluco}}$ **4c-Br** producing an equimolar anomeric mixture of the desired product **32a** (24% by ^{19}F NMR). Moreover, its problematic purification required the hydrolysis of acetyl groups to obtain **32b** in pure form and a poor 17% isolated yield (over three steps from **4c**). In stark contrast, when protected azido-phytosphingosine acceptor was reacted with $\text{CF}_3^{\text{manno}}$ **5c-Br**, excellent α -selectivity was obtained (95 : 5 α/β) and **33** (KRN7000 precursor)⁴⁹ was isolated in 64% yield. The same glycosyl donor smoothly reacted with primary and secondary sugar acceptors to afford important $\alpha\text{Man}(1,6)\text{Man}$ and $\alpha\text{Man}(1,2)\text{Man}$ epi-

topes **34** (48%) and **35** (50%), respectively with preferred α -configuration (up to 93 : 7 α/β).

Conclusion

In summary, we have disclosed the unprecedented synthesis and glycosylation of 2-deoxy-2-trifluoromethylsugars that are in turn prepared from readily available D-glycals.

The study of the stereoelectronic properties of the CF_3 group highlighted the selectivity control of glycosylation affording 1,2-*trans* glycosides. Structural screening indicated that best stereoselectivities are reinforced by the effect of protecting groups (OBn/ $\text{CF}_3^{\text{gluco}}$ as β -selective; OAc/ $\text{CF}_3^{\text{manno}}$ as α -selective). Glycosylation proved successful for a range of different alcohols including primary and secondary aliphatic-OH, sugars, and complex aglycones. Interestingly, conformational analyses of resulting CF_3 -glycosides showed no perturbations in the molecular geometry, which may stimulate the development of new CF_3 -sugar mimetics with interesting physicochemical properties (*e.g.*, log *P* enhancement and/or increased ^{19}F NMR sensitivity) to complement the applications of traditional F-sugars. Indeed, reaction scope also proved successful for the preparation biologically relevant $\text{C}(\text{sp}^3)$ - CF_3 -glycosides including amino acids, cholesterol, and sphingosine/phytosphingosine analogs. Collectively, it has been demonstrated that the method is synthetically useful for accessing novel 2-deoxy-2- CF_3 -glycosides bearing aglycones of different structural nature in very high stereoselectivities even when a non-optimal combination of protecting groups and CF_3 configuration is used. We expect this report will help to flourish the field of polyfluoroalkyl sugar chemistry by establishing a new direction of development in glycomimetic design. Further synthetic developments and mechanistic investigations on the role of CF_3 in the stability of the glycosidic bond and the modulation of physicochemical and recognition/processing properties are subjects of ongoing studies in our laboratory.

Author contributions

J.M and I.B. performed all of the experiments. M.B. performed the computational calculations. O.B. supervised the project. O. B. and S.C. were responsible for funding acquisition. All authors contributed to the preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Spanish Government-MCIU/MCIN, the national agency of investigation-AEI/10.13039/501100011033, and the European Regional Development Fund-ERDF (projects;



CTQ2017-90088-R and PID2020-120584RB-I00 to O. B., CTQ2017-89750-R to S. C. FPI Fellowship; PRE2018-085730 to I. B. and FPU Fellowship; FPU19/01969 to M. B.) and the Universitat Rovira i Virgili (Martí i Franquès Research Fellowship Programme; 2012BPURV-67 to J. M.) for financial support. We also thank the ICIQ X-ray diffraction unit for the crystallographic studies and Aria Valaei for preliminary experiments. O. B. was a Ramón y Cajal Fellow (RYC-2015-17705).

References

- (a) R. Hevey, Strategies for the development of glycomimetic drug candidates, *Pharmaceuticals*, 2019, **12**, 55; (b) R. C. Saliba and N. L. B. Pohl, Designing sugar mimetics: non-natural pyranosides as innovative chemical tools, *Curr. Opin. Chem. Biol.*, 2016, **34**, 127–134.
- (a) R. Hevey, The role of fluorine in glycomimetic drug design, *Chem. – Eur. J.*, 2021, **27**, 2240–2253; (b) B. Linclau, A. Ardá, N. C. Reichardt, M. Sollogoub, L. Unione, S. P. Vincent and J. Jiménez-Barbero, Fluorinated carbohydrates as chemical probes for molecular recognition studies. Current status and perspective, *Chem. Soc. Rev.*, 2020, **49**, 3863–3888.
- (a) R. Hevey, Bioisosteres of carbohydrate functional groups in glycomimetic design, *Biomimetics*, 2019, **4**, 53; (b) N. A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, *J. Med. Chem.*, 2018, **61**, 5822–5880; (c) G. A. Patani and E. J. LaVoie, Bioisosterism: a rational approach in drug design, *Chem. Rev.*, 1996, **96**, 3147–3176.
- M. L. Uhrig, E. W. Mora Flores and A. Postigo, Approaches to the synthesis of perfluoroalkyl-modified carbohydrates and derivatives: thiosugars, iminosugars, and tetrahydro (thio)pyrans, *Chem. – Eur. J.*, 2021, **27**, 7813–7825.
- J. Mestre, A. Lishchynskyi, S. Castellón and O. Boutureira, Trifluoromethylation of electron-rich alkenyl iodides with fluoroform-derived “ligandless” CuCF₃, *J. Org. Chem.*, 2018, **83**, 8150–8160.
- J. Mestre, S. Castellón and O. Boutureira, “Ligandless” pentafluoroethylation of unactivated (hetero)aryl and alkenyl halides enabled by the controlled self-condensation of TMSCF₃-derived CuCF₃, *J. Org. Chem.*, 2019, **84**, 15087–15097.
- M. A. Miller and E. M. Sletten, Perfluorocarbons in chemical biology, *ChemBioChem*, 2020, **21**, 3451–3462.
- (a) D. Cahard and J.-A. Ma, *Emerging fluorinated motifs: synthesis, properties, and applications*, Wiley-VCH, Weinheim, 2020; (b) B. M. Johnson, Y.-Z. Shu, X. Zhuo and N. A. Meanwell, Metabolic and pharmaceutical aspects of fluorinated compounds, *J. Med. Chem.*, 2020, **63**, 6315–6386; (c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, Applications of fluorine in medicinal chemistry, *J. Med. Chem.*, 2015, **58**, 8315–8359.
- (a) C. Song, X.-J. Zheng, H. Guo, Y. Cao, F. Zhang, Q. Li, X.-S. Ye and Y. Zhou, Fluorine-modified sialyl-Tn-CRM₁₉₇ vaccine elicits a robust immune response, *Glycoconjugate J.*, 2019, **36**, 399–408; (b) C.-X. Huo, X.-J. Zheng, A. Xiao, C.-C. Liu, S. Sun, Z. Lv and X.-S. Ye, Synthetic and immunological studies of *N*-acyl modified *S*-linked STn derivatives as anticancer vaccine candidates, *Org. Biomol. Chem.*, 2015, **13**, 3677–3690; (c) H.-Y. Lee, C.-Y. Chen, T.-I. Tsai, S.-T. Li, K.-H. Lin, Y.-Y. Cheng, C.-T. Ren, T.-J. R. Cheng, C.-Y. Wu and C.-H. Wong, Immunogenicity study of Globo H analogues with modification at the reducing or nonreducing end of the tumor antigen, *J. Am. Chem. Soc.*, 2014, **136**, 16844–16853; (d) F. Yang, X.-J. Zheng, C.-X. Huo, Y. Wang, Y. Zhang and X.-S. Ye, Enhancement of the immunogenicity of synthetic carbohydrate vaccines by chemical modifications of STn antigen, *ACS Chem. Biol.*, 2011, **6**, 252–259; (e) L. Dafik, M. d'Alarcao and K. Kumar, Modulation of cellular adhesion by glycoengineering, *J. Med. Chem.*, 2010, **53**, 4277–4284.
- R. F. G. Fröhlich, E. Schrank and K. Zangger, 2,2,2-Trifluoroethyl 6-thio-β-D-glucopyranoside as a selective tag for cysteines in proteins, *Carbohydr. Res.*, 2012, **361**, 100–104.
- (a) L. Wu, Z. Armstrong, S. P. Schröder, C. de Boer, M. Artola, J. M. Aerts, H. S. Overkleeft and G. J. Davies, An overview of activity-based probes for glycosidases, *Curr. Opin. Chem. Biol.*, 2019, **53**, 25–36; (b) B. P. Rempel and S. G. Withers, Covalent inhibitors of glycosidases and their applications in biochemistry and biology, *Glycobiology*, 2008, **18**, 570–586; (c) S. J. Williams and S. G. Withers, Glycosyl fluorides in enzymatic reactions, *Carbohydr. Res.*, 2000, **327**, 27–46.
- (a) G. Fittolani, E. Shanina, M. Guberman, P. H. Seeberger, C. Rademacher and M. Delbianco, Automated glycan assembly of ¹⁹F-labeled glycan probes enables high-throughput NMR studies of protein–glycan interactions, *Angew. Chem., Int. Ed.*, 2021, **60**, 13302–13309; (b) J. D. Martínez, A. I. Manzano, E. Calviño, A. D. Diego, B. Rodríguez de Francisco, C. Romanò, S. Oscarson, O. Millet, H. J. Gabius, J. Jiménez-Barbero and F. J. Cañada, Fluorinated carbohydrates as lectin ligands: simultaneous screening of a monosaccharide library and chemical mapping by ¹⁹F NMR spectroscopy, *J. Org. Chem.*, 2020, **85**, 16072–16081; (c) J. D. Martínez, A. S. Infantino, P. Valverde, T. Diercks, S. Delgado, N.-C. Reichardt, A. Ardá, F. J. Cañada, S. Oscarson and J. Jiménez-Barbero, The interaction of fluorinated glycomimetics with DC-SIGN: multiple binding modes disentangled by the combination of NMR methods and MD simulations, *Pharmaceuticals*, 2020, **13**, 179; (d) J. D. Martínez, P. Valverde, S. Delgado, C. Romanò, B. Linclau, N.-C. Reichardt, S. Oscarson, A. Ardá, J. Jiménez-Barbero and F. J. Cañada, Unraveling sugar binding modes to DC-SIGN by employing fluorinated carbohydrates, *Molecules*, 2019, **24**, 2337; (e) T. Diercks, A. S. Infantino, L. Unione, J. Jiménez-Barbero, S. Oscarson and H. J. Gabius, Fluorinated carbohydrates as lectin



- ligands: synthesis of OH/F-substituted *N*-glycan core trimannoside and epitope mapping by 2D STD-TOCSYreF NMR spectroscopy, *Chem. – Eur. J.*, 2018, **24**, 15761–15765; (f) J. P. Ribeiro, T. Diercks, J. Jiménez-Barbero, S. André, H. J. Gabius and F. J. Cañada, Fluorinated carbohydrates as lectin Ligands: ^{19}F -based direct STD monitoring for detection of anomeric selectivity, *Biomolecules*, 2015, **5**, 3177–3192; (g) E. Matei, S. André, A. Glinschert, A. S. Infantino, S. Oscarson, H.-J. Gabius and A. M. Gronenborn, Fluorinated carbohydrates as lectin ligands: dissecting glycan–cyanovirin interactions by using ^{19}F NMR spectroscopy, *Chem. – Eur. J.*, 2013, **19**, 5364–5374; (h) S. André, F. J. Cañada, T. C. Shiao, L. Largartera, T. Diercks, M. Bergeron-Brlek, K. el Biari, A. Papadopoulos, J. P. Ribeiro, M. Touaibia, D. Solís, M. Menéndez, J. Jiménez-Barbero, R. Roy and H.-J. Gabius, Fluorinated carbohydrates as lectin ligands: biorelevant sensors with capacity to monitor anomer affinity in ^{19}F -NMR-based inhibitor screening, *Eur. J. Org. Chem.*, 2012, 4354–4364; (i) T. Diercks, J. P. Ribeiro, F. J. Cañada, S. André, J. Jiménez-Barbero and H. J. Gabius, Fluorinated carbohydrates as lectin ligands: versatile sensors in ^{19}F -detected saturation transfer difference NMR spectroscopy, *Chem. – Eur. J.*, 2009, **15**, 5666–5668.
- 13 (a) M. Johannes, M. Reindl, B. Gerlitzki, E. Schmitt and A. Hoffmann-Röder, Synthesis and biological evaluation of a novel MUC1 glycopeptide conjugate vaccine candidate comprising a 4'-deoxy-4'-fluoro-Thomsen–Friedenreich epitope, *Beilstein J. Org. Chem.*, 2015, **11**, 155–161; (b) S. Lamandé-Langle, C. Collet, R. Hensienne, C. Vala, F. Chrétien, Y. Chapleur, A. Mohamadi, P. Lacolley and V. Regnault, 'Click' glycosylation of peptides through cysteine propargylation and CuAAC, *Bioorg. Med. Chem.*, 2014, **22**, 6672–6683; (c) C. Vala, F. Chrétien, E. Balentova, S. Lamandé-Langle and Y. Chapleur, Neoglycopeptides through direct functionalization of cysteine, *Tetrahedron Lett.*, 2011, **52**, 17–20; (d) T. Oberbillig, C. Mersch, S. Wagner and A. Hoffmann-Röder, Antibody recognition of fluorinated MUC1 glycopeptide antigens, *Chem. Commun.*, 2012, **48**, 1487–1489; (e) S. Wagner, C. Mersch and A. Hoffmann-Röder, Fluorinated glycosyl amino acids for mucin-like glycopeptide antigen analogues, *Chem. – Eur. J.*, 2010, **16**, 7319–7330; (f) A. Hoffmann-Röder, A. Kaiser, S. Wagner, N. Gaidzik, D. Kowalczyk, U. Westerlind, B. Gerlitzki, E. Schmitt and H. Kunz, Synthetic antitumor vaccines from tetanus toxoid conjugates of MUC1 glycopeptides with the Thomsen–Friedenreich antigen and a fluorine-substituted analogue, *Angew. Chem., Int. Ed.*, 2010, **49**, 8498–8503.
 - 14 M. Salvadó, B. Amgarten, S. Castillón, G. J. L. Bernardes and O. Boutureira, Synthesis of fluorosugar reagents for the construction of well-defined fluoroglycoproteins, *Org. Lett.*, 2015, **17**, 2836–2839.
 - 15 (a) C.-C. Liu, C.-X. Huo, C. Zhai, X.-J. Zheng, D.-C. Xiong and X.-S. Ye, Synthesis and immunological evaluation of pentamannose-based HIV-1 vaccine candidates, *Bioconjugate Chem.*, 2022, **33**, 807–820; (b) P. M. S. D. Cal, G. J. L. Bernardes and O. Boutureira, Fluoroglycoproteins by Copper-Free Strain-Promoted Azide–Alkyne Cycloaddition in *Peptide and Protein Engineering*, ed. O. Iranzo and A. C. Roque, Springer Protocols Handbooks, Humana, New York, 2020, p. 53; (c) J. Orwenyo, W. Huang and L. X. Wang, Chemoenzymatic synthesis and lectin recognition of a selectively fluorinated glycoprotein, *Bioorg. Med. Chem.*, 2013, **21**, 4768–4777; (d) O. Boutureira, G. J. L. Bernardes, M. Fernández-González, D. C. Anthony and B. G. Davis, Selenenylsulfide–Linked Homogeneous Glycopeptides and Glycoproteins: Synthesis of Human "Hepatic Se Metabolite A", *Angew. Chem., Int. Ed.*, 2012, **51**, 1432–1436; (e) O. Boutureira, G. J. L. Bernardes, F. D'Hooze and B. G. Davis, Direct radiolabelling of proteins at cysteine using [^{18}F]-fluorosugars, *Chem. Commun.*, 2011, **47**, 10010–10012; (f) M. Fernández-González, O. Boutureira, G. J. L. Bernardes, J. M. Chalker, M. A. Young, J. C. Errey and B. G. Davis, Site-selective chemoenzymatic construction of synthetic glycoproteins using endoglycosidases, *Chem. Sci.*, 2010, **1**, 709–715; (g) O. Boutureira, F. D'Hooze, M. Fernández-González, G. J. L. Bernardes, M. Sánchez-Navarro, J. R. Koeppe and B. G. Davis, Fluoroglycoproteins: ready chemical site-selective incorporation of fluorosugars into proteins, *Chem. Commun.*, 2010, **46**, 8142–8144.
 - 16 (a) O. Boutureira, Site-Selective Conjugation Chemistry for Synthetic Glycoconjugate Vaccine Development in *Recent Trends in Carbohydrate Chemistry: Synthesis and Biomedical Applications of Glycans and Glycoconjugates*, ed. A. P. Rauter, B. E. Christensen, L. Somsák, P. Kosma and R. Adamo, Elsevier, 2020, vol. 2, p. 335; (b) R. Adamo, A. Nilo, B. Castagner, O. Boutureira, F. Berti and G. J. L. Bernardes, Synthetically defined glycoprotein vaccines: current status and future directions, *Chem. Sci.*, 2013, **4**, 2995–3008.
 - 17 (a) S. S. Shinde, S. Maschauer and O. Prante, Sweetening pharmaceutical radiochemistry by ^{18}F -fluoroglycosylation: recent progress and future prospects, *Pharmaceuticals*, 2021, **14**, 1175; (b) O. Jacobson, D. O. Kiesewetter and X. Chen, Fluorine-18 radiochemistry, labeling strategies and synthetic routes, *Bioconjugate Chem.*, 2015, **26**, 1–18; (c) I. Tirota, V. Dichiarante, C. Pigliacelli, G. Cavallo, G. Terraneo, F. B. Bombelli, P. Metrangolo and G. Resnati, ^{19}F Magnetic resonance imaging (MRI): from design of materials to clinical applications, *Chem. Rev.*, 2015, **115**, 1106–1129; (d) G. R. Morais, R. A. Falconer and I. Santos, Carbohydrate-based molecules for molecular imaging in nuclear medicine, *Eur. J. Org. Chem.*, 2013, 1401–1414.
 - 18 Electrostatic potential surfaces were calculated after geometry optimization at the CPCM (water) B3LYP/6–311+G(d,p) level of theory using Gaussian 09. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao,



- H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, revision D.01*, Gaussian, Inc., Wallingford, CT, 2013.
- 19 Y. Zhao, M. Abraham and A. Zissimos, Fast calculation of van der Waals volume as a sum of atomic and bond contributions and its application to drug compounds, *J. Org. Chem.*, 2003, **68**, 7368–7373.
- 20 (a) S. Preshlock, M. Tredwell and V. Gouverneur, Labeling of arenes and heteroarenes for applications in positron emission tomography, *Chem. Rev.*, 2016, **116**, 719–766; (b) D. Van der Born, C. Sewing, J. K. D. M. Herscheid, A. D. Windhorst, R. V. A. Orru and D. J. A. Vugts, Universal procedure for the [¹⁸F]trifluoromethylation of aryl iodides and aryl boronic acids with highly improved specific activity, *Angew. Chem., Int. Ed.*, 2014, **53**, 11046–11050.
- 21 L. Unione, M. Alcalá, B. Echeverria, S. Serna, A. Ardá, A. Franconetti, F. J. Cañada, T. Diercks, N. Reichardt and J. Jiménez-Barbero, Fluoroacetamide moieties as NMR spectroscopy probes for the molecular recognition of GlcNAc-containing sugars: modulation of the CH– π stacking interactions by different fluorination patterns, *Chem. – Eur. J.*, 2017, **23**, 3957–3965.
- 22 (a) A. R. Mandhapati, T. Kato, T. Matsushita, B. Ksebati, A. Vasella, E. C. Böttger and D. Crich, Fluorine-decoupled carbon spectroscopy for the determination of configuration at fully substituted, trifluoromethyl- and perfluoroalkyl-bearing carbons: comparison with ¹⁹F–¹H heteronuclear overhauser effect spectroscopy, *J. Org. Chem.*, 2015, **80**, 1754–1763; (b) D. Crich and O. Vinogradova, Synthesis and glycosylation of a series of 6-mono-, di-, and trifluoro S-phenyl 2,3,4-tri-O-benzyl-thiorhamnopyranosides. Effect of the fluorine substituents on glycosylation stereoselectivity, *J. Am. Chem. Soc.*, 2007, **129**, 11756–11765; (c) R. Plantier-Royon and C. Portella, Difluoromethylene-containing, C-trifluoromethyl and C-perfluoroalkyl carbohydrates. Synthesis by carbohydrate transformation or building block methods, *Carbohydr. Res.*, 2000, **327**, 119–146.
- 23 B. Wang, D.-C. Xiong and X.-S. Ye, Direct C–H trifluoromethylation of glycals by photoredox catalysis, *Org. Lett.*, 2015, **17**, 5698–5701.
- 24 M. Liu, Z.-X. Luo, T. Li, D.-C. Xiong and X.-S. Ye, Electrochemical trifluoromethylation of glycals, *J. Org. Chem.*, 2021, **86**, 16187–16194.
- 25 (a) C. S. Teschers and R. Gilmour, Fluorine-directed automated mannoside assembly, *Angew. Chem., Int. Ed.*, 2023, **62**, e202213304; (b) A. Axer, R. P. Jumde, S. Adam, A. Faust, M. Schäfers, M. Fobker, J. Koehnke, A. K. H. Hirsch and R. Gilmour, Enhancing glycan stability via site-selective fluorination: modulating substrate orientation by molecular design, *Chem. Sci.*, 2021, **12**, 1286–1294; (c) T. J. Kieser, N. Santschi, L. Nowack, A. Axer, G. Kehr, S. Albrecht and R. Gilmour, Total chemical syntheses of the GM3 and F-GM3 ganglioside epitopes and comparative pre-clinical evaluation for non-invasive imaging of oligodendrocyte differentiation, *ACS Chem. Neurosci.*, 2020, **11**, 2129–2136; (d) T. Hayashi, A. Axer, G. Kehr, K. Bergander and R. Gilmour, Halogen-directed chemical sialylation: pseudo-stereodivergent access to marine ganglioside epitopes, *Chem. Sci.*, 2020, **11**, 6527–6531; (e) T. Hayashi, G. Kehr, K. Bergander and R. Gilmour, Stereospecific α -Sialylation by site-selective fluorination, *Angew. Chem., Int. Ed.*, 2019, **58**, 3814–3818; (f) T. J. Kieser, N. Santschi, L. Nowack, G. Kehr, T. Kuhlmann, S. Albrecht and R. Gilmour, Single site fluorination of the GM4 ganglioside epitope upregulates oligodendrocyte differentiation, *ACS Chem. Neurosci.*, 2018, **9**, 1159–1165; (g) A. Sadurni, G. Kehr, M. Ahlqvist, J. Wernevik, H. Peilot-Sjögren, C. Kankkonen, L. Knerr and R. Gilmour, Fluorine-directed glycosylation enables the stereocontrolled synthesis of selective SGLT2 inhibitors for type II diabetes, *Chem. – Eur. J.*, 2018, **24**, 2832–2836; (h) A. Sadurni and R. Gilmour, Stereocontrolled synthesis of 2-fluorinated C-glycosides, *Eur. J. Org. Chem.*, 2018, 3684–3687; (i) N. Santschi and R. Gilmour, Comparative analysis of fluorine-directed glycosylation selectivity: interrogating C2 [OH \rightarrow F] Substitution in D-glucose and D-galactose, *Eur. J. Org. Chem.*, 2015, 6983–6987; (j) N. Aiguabella, M. C. Holland and R. Gilmour, Fluorine-directed 1,2-*trans* glycosylation of rare sugars, *Org. Biomol. Chem.*, 2016, **14**, 5534–5538; (k) E. Durantie, C. Bucher and R. Gilmour, Fluorine-Directed β -Galactosylation: chemical glycosylation development by molecular editing, *Chem. – Eur. J.*, 2012, **18**, 8208–8215; (l) C. Bucher and R. Gilmour, Fluorine-directed glycosylation, *Angew. Chem., Int. Ed.*, 2010, **49**, 8724–8728.
- 26 (a) J. Mestre, D. Collado, D. Benito-Alifonso, M. A. Rodríguez, M. I. Matheu, Y. Díaz, S. Castellón and O. Boutureira, Highly reactive 2-deoxy-2-iodo-d-allo and D-gulo pyranosyl sulfoxide donors ensure β -stereoselective glycosylations with steroidal aglycones, *RSC Adv.*, 2018, **8**, 30076–30079; (b) J. Mestre, M. I. Matheu, Y. Díaz, S. Castellón and O. Boutureira, Chemical access to D-Sarmentose units enables the total synthesis of cardenolide monoglycoside N-1 from Nerium oleander, *J. Org. Chem.*, 2017, **82**, 3327–3333; (c) T. Kimura, D. Takahashi and K. Toshima, Glycosylations of glycals using N-Iodosuccinimide (NIS) and phosphorus compounds for syntheses of 2-iodo- and 2-deoxyglycosides, *J. Org. Chem.*, 2015, **80**, 9552–9562; (d) A. Kövér, O. Boutureira, M. I. Matheu, Y. Díaz and S. Castellón, Tuning the stereo-electronic properties of 1-sulfanylhex-1-enitols for the sequential stereoselective synthesis of 2-deoxy-2-iodo- β -D-



- allopentofuranosides, *J. Org. Chem.*, 2014, **79**, 3060–3068; (e) M. A. Rodríguez, O. Boutureira, M. I. Matheu, Y. Díaz and S. Castellón, Stereoselective synthesis of 2-deoxyglycosides from sulfanyl alkenes by consecutive “one pot” cyclization and glycosylation reactions, *Eur. J. Org. Chem.*, 2007, 2470–2476; (f) M. A. Rodríguez, O. Boutureira, X. Arnés, Y. Díaz, M. I. Matheu and S. Castellón, Stereoselective synthesis of 2-deoxy-2-iodo-glycosides from furanoses. A new route to 2-deoxy-glycosides and 2-deoxy-oligosaccharides of *ribo* and *xylo* configuration, *J. Org. Chem.*, 2005, **70**, 10297–10310.
- 27 (a) O. Boutureira, M. A. Rodríguez, D. Benito, M. I. Matheu, Y. Díaz and S. Castellón, Stereoselective synthesis of 2-deoxy-2-phenylselenenyl glycosides from furanoses: implication of the phenylselenenyl group in the stereocontrolled preparation of 2-deoxy-*ribo*- and 2-deoxy-*xylo*-oligosaccharides, *Eur. J. Org. Chem.*, 2007, 3564–3572; (b) K. C. Nicolaou, H. J. Mitchell, K. C. Fylaktakidou, H. Suzuki and R. M. Rodríguez, 1,2-Seleno migrations in carbohydrate chemistry: solution and solid-phase synthesis of 2-deoxy glycosides, orthoesters, and allyl orthoesters, *Angew. Chem., Int. Ed.*, 2000, **39**, 1089–1093.
- 28 (a) K. M. Demkiw, W. A. Remmerswaal, T. Hansen, G. A. van der Marel, J. D. C. Codée and K. A. Woerpel, Halogen atom participation in guiding the stereochemical outcomes of acetal substitution reactions, *Angew. Chem., Int. Ed.*, 2022, **61**, e202209401; (b) A. Franconetti, A. Ardá, J. L. Asensio, Y. Blériot, S. Thibaudeau and J. Jiménez-Barbero, Glycosyl oxocarbenium ions: structure, conformation, reactivity, and interactions, *Acc. Chem. Res.*, 2021, **54**, 2552–2564; (c) L. Lebedel, A. Ardá, A. Martin, J. Désiré, A. Mingot, M. Aufiero, N. Aiguabella Font, R. Gilmour, J. Jiménez-Barbero, Y. Blériot and S. Thibaudeau, Structural and computational analysis of 2-halogeno-glycosyl cations in the presence of a superacid: an expansive platform, *Angew. Chem., Int. Ed.*, 2019, **58**, 13758–13762; (d) M. G. Beaver, S. B. Billings and K. A. Woerpel, Nucleophilic substitution reactions of 2-phenylthio-substituted carbohydrate acetals and related systems: episulfonium ions vs. oxocarbenium ions as reactive intermediates, *Eur. J. Org. Chem.*, 2008, 771–781; (e) F. Bravo, A. Viso, E. Alcázar, P. Molas, C. Bo and S. Castellón, Computational insight into the reaction intermediates in the glycosylation reaction assisted by donor heteroatoms, *J. Org. Chem.*, 2003, **68**, 686–691.
- 29 C. S. Bennett and M. C. Galan, Methods for 2-deoxyglycoside synthesis, *Chem. Rev.*, 2018, **118**, 7931–7985.
- 30 A. J. Fernandes, A. Panossian, B. Michelet, A. Martin-Mingot, F. R. Leroux and S. Thibaudeau, CF₃-substituted carbocations: underexploited intermediates with great potential in modern synthetic chemistry, *Beilstein J. Org. Chem.*, 2021, **17**, 343–378.
- 31 (a) I. Cobo, M. I. Matheu, S. Castellón, O. Boutureira and B. G. Davis, Phosphine-free Suzuki–Miyaura cross-coupling in aqueous media enables access to 2-C-aryl-glycosides, *Org. Lett.*, 2012, **14**, 1728–1731; (b) M. A. Rodríguez, O. Boutureira, Y. Díaz, M. I. Matheu, S. Castellón and P. H. Seeberger, Synthesis of 2-iodoglycals, glycals, and 1,1'-disaccharides from 2-deoxy-2-iodopyranoses under dehydrative glycosylation conditions, *J. Org. Chem.*, 2007, **72**, 8998–9001.
- 32 S. Dharuman and Y. D. Vankar, Halosuccinimide/AgNO₃-efficient reagent systems for one-step synthesis of 2-haloglycals from glycals: application in the synthesis of 2C-branched sugars via Heck coupling reactions, *Org. Lett.*, 2014, **16**, 1172–1175.
- 33 S. Rohrbach, A. J. Smith, J. H. Pang, D. L. Poole, T. Tuttle, S. Chiba and J. A. Murphy, Concerted nucleophilic aromatic substitution reactions, *Angew. Chem., Int. Ed.*, 2019, **58**, 16368–16388.
- 34 (a) I. V. Alabugin, L. Kuhn, N. V. Krivoshchapov, P. Mehaffy and M. G. Medvedev, Anomeric effect, hyperconjugation and electrostatics: Lessons from complexity in a classic stereoelectronic phenomenon, *Chem. Soc. Rev.*, 2021, **50**, 10212–10252; (b) T. M. Barbosa, R. V. Viesser, R. J. Abraham, R. Rittner and C. F. Tormeno, Experimental and theoretical evaluation of *trans*-3-halo-2-hydroxy-tetrahydropyran conformational preferences. Beyond anomeric interaction, *RSC Adv.*, 2015, **5**, 35412–35420.
- 35 G. Lian, X. Zhang and B. Yu, Thioglycosides in carbohydrate research, *Carbohydr. Res.*, 2015, **403**, 13–22.
- 36 Y. Singh, S. A. Geringer and A. V. Demchenko, Synthesis and glycosidation of anomeric halides: evolution from early studies to modern methods of the 21st century, *Chem. Rev.*, 2022, **122**, 11701–11758.
- 37 (a) L. O. Kononov, N. N. Malysheva, A. V. Orlova, A. I. Zinin, T. V. Laptinskaya, E. G. Kononova and N. G. Kolotyrkina, Concentration dependence of glycosylation outcome: a clue to reproducibility and understanding the reasons behind, *Eur. J. Org. Chem.*, 2012, 1926–1934; (b) C.-S. Chao, C.-W. Li, M.-C. Chen, S.-S. Chang and K.-K. T. Mong, Low-concentration 1,2-*trans*- β -selective glycosylation strategy and its applications in oligosaccharide synthesis, *Chem. – Eur. J.*, 2009, **15**, 10972–10982.
- 38 (a) P. O. Adero, T. Furukawa, M. Huang, D. Mukherjee, P. Retailleau, L. Bohé and D. Crich, Cation clock reactions for the determination of relative reaction kinetics in glycosylation reactions: Applications to gluco- and mannopyranosyl sulfoxide and trichloroacetimidate type donors, *J. Am. Chem. Soc.*, 2015, **137**, 10336–10345; (b) M. Huang, P. Retailleau, L. Bohé and D. Crich, Cation clock permits distinction between the mechanisms of α - and β -O- and β -C-glycosylation in the mannopyranose series: evidence for the existence of a mannopyranosyl oxocarbenium ion, *J. Am. Chem. Soc.*, 2012, **134**, 14746–14749.
- 39 (a) P. R. Andreana and D. Crich, Guidelines for O-glycoside formation from first principles, *ACS Cent. Sci.*, 2021, **7**, 1454–1462; (b) H. H. Trinderup, S. M. Andersen, M. Heuckendorff and H. H. Jensen, How do various reaction parameters influence anomeric selectivity in chemical glycosylation with thioglycosides and NIS/TfOH activation?, *Eur. J. Org. Chem.*, 2021, 3251–3259; (c) S. Chatterjee,



- S. Moon, F. Hentschel, K. Gilmore and P. H. Seeberger, An empirical understanding of the glycosylation reaction, *J. Am. Chem. Soc.*, 2018, **140**, 11942–11953.
- 40 S. Kaeothip, P. Pornsuriyasak and A. V. Demchenko, Silver (i) tetrafluoroborate as a potent promoter for chemical glycosylation, *Tetrahedron Lett.*, 2008, **49**, 1542–1545.
- 41 O. T. Tuck, E. T. Sletten, J. Danglad-Flores and P. H. Seeberger, Towards a systematic understanding of the influence of temperature on glycosylation reactions, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115433.
- 42 T. G. Frihed, M. Bols and C. M. Pedersen, Mechanisms of glycosylation reactions studied by low-temperature nuclear magnetic resonance, *Chem. Rev.*, 2015, **115**, 4963–5013.
- 43 (a) M. M. Nielsen, T. Holmström and C. M. Pedersen, Stereoselective O-Glycosylations by pyrylium salt organocatalysis, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115394; (b) T. Li, T. Li, H. Zhuang, F. Wang, R. R. Schmidt and P. Peng, O-Glycosyl trichloroacetimidates as glycosyl donors and platinum(IV) chloride as a dual catalyst permitting stereo- and regioselective glycosidations, *ACS Catal.*, 2021, **11**, 10279–10287; (c) M. M. Nielsen, P. Mała, E. Þ. Baldursson and C. M. Pedersen, Self-promoted and stereospecific formation of N-glycosides, *Chem. Sci.*, 2019, **10**, 5299–5307; (d) K. Kowalska and C. M. Pedersen, Catalytic stereospecific O-glycosylation, *Chem. Commun.*, 2017, **53**, 2040–2043; (e) P. Peng and R. R. Schmidt, An alternative reaction course in O-glycosidation with O-glycosyl trichloroacetimidates as glycosyl donors and Lewis acidic metal salts as catalyst: Acid-base catalysis with gold chloride-glycosyl acceptor adducts, *J. Am. Chem. Soc.*, 2015, **137**, 12653–12659.
- 44 (a) P. Merino, I. Delso, S. Pereira, S. Orta, M. Pedrón and T. Tejero, Computational evidence of glycosyl cations, *Org. Biomol. Chem.*, 2021, **19**, 2350–2365; (b) P. O. Adero, H. Amarasekara, P. Wen, L. Bohé and D. Crich, The experimental evidence in support of glycosylation mechanisms at the S_N1–S_N2 interface, *Chem. Rev.*, 2018, **118**, 8242–8284; (c) L. Bohé and D. Crich, A propos of glycosyl cations and the mechanism of chemical glycosylation; the current state of the art, *Carbohydr. Res.*, 2015, **403**, 48–59.
- 45 (a) K. M. Demkiw, C. T. Hu and K. A. Woerpel, Hyperconjugative interactions of the carbon–halogen bond that influence the geometry of cyclic α -haloacetals, *J. Org. Chem.*, 2022, **87**, 5315–5327; (b) D. M. Smith and K. A. Woerpel, Electrostatic interactions in cations and their importance in biology and chemistry, *Org. Biomol. Chem.*, 2006, **4**, 1195–1201.
- 46 A. Ramdular and K. A. Woerpel, Diastereoselective substitution reactions of acyclic β -alkoxy acetals via electrostatically stabilized oxocarbenium ion intermediates, *Org. Lett.*, 2022, **24**, 3217–3222.
- 47 S. van der Vorm, T. Hansen, H. S. Overkleeft, G. A. van der Marel and J. D. C. Codée, The influence of acceptor nucleophilicity on the glycosylation reaction mechanism, *Chem. Sci.*, 2017, **8**, 1867–1875.
- 48 (a) J. A. Morales-Serna, O. Boutureira, Y. Díaz, M. I. Matheu and S. Castellón, Highly efficient and stereoselective synthesis of β -glycolipids, *Org. Biomol. Chem.*, 2008, **6**, 443–446; (b) J. A. Morales-Serna, O. Boutureira, Y. Díaz, M. I. Matheu and S. Castellón, Recent advances in the glycosylation of sphingosines and ceramides, *Carbohydr. Res.*, 2007, **342**, 1595–1612.
- 49 O. Boutureira, J. A. Morales-Serna, Y. Díaz, M. I. Matheu and S. Castellón, Direct and efficient glycosylation protocol for synthesizing α -glycolipids: application to the synthesis of KRN7000, *Eur. J. Org. Chem.*, 2008, 1851–1854.

