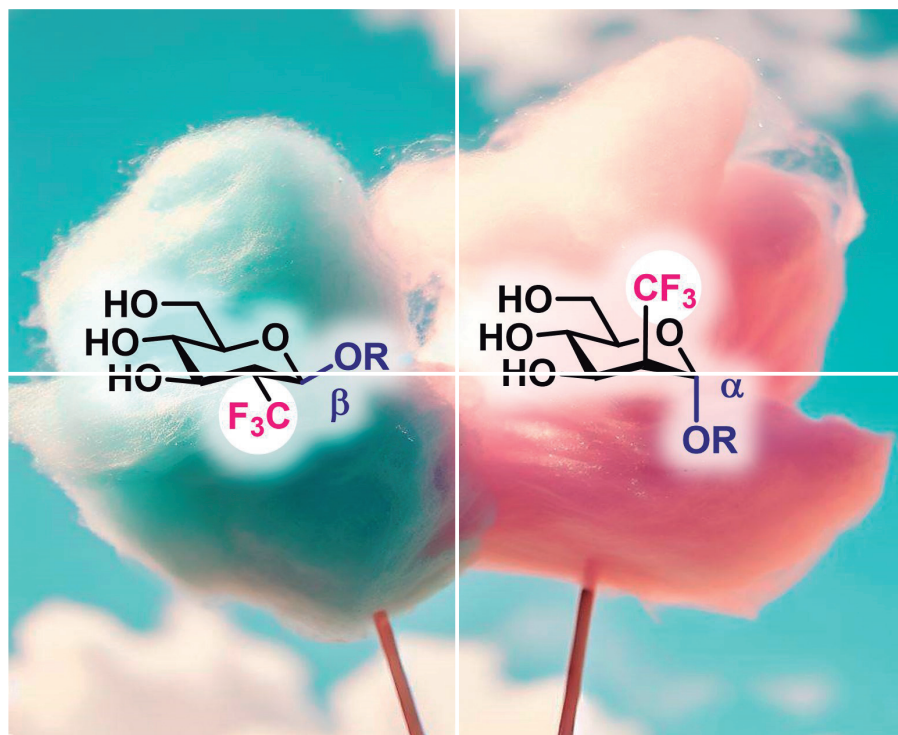


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10, 2405Stereoselective access to 2-deoxy-2-trifluoromethyl sugar mimetics by trifluoromethyl-directed 1,2-*trans* glycosylation†

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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.

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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

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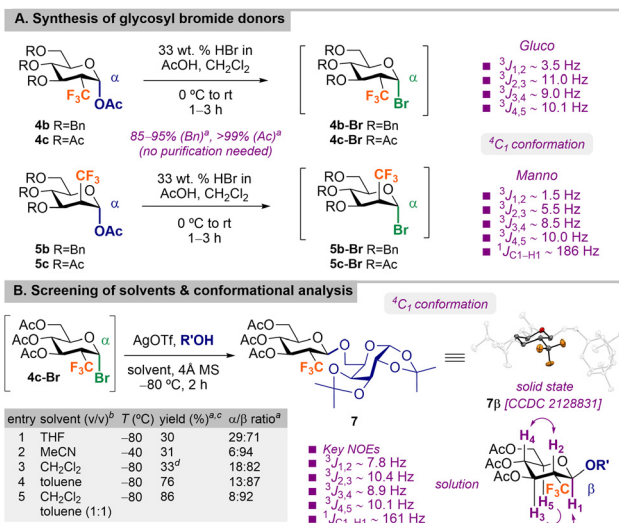
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manipulation of gaseous reagents. Herein, the overall synthetic sequence was improved by using first a more efficient iodination protocol (79% for **2a**; 59% for **2b**)³² and second, the use of a trifluoromethylation system (TMSCF₃/KF/CuBr) that 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 to form glycosides 10-20. The reaction conditions are 1) HBr, 2) AgOTf, R'OH, Conditions. The substituents are X = F, CF₃ and R = Ac, Bn. The products are shown as 10-20, with the OR' group attached to the anomeric carbon.

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

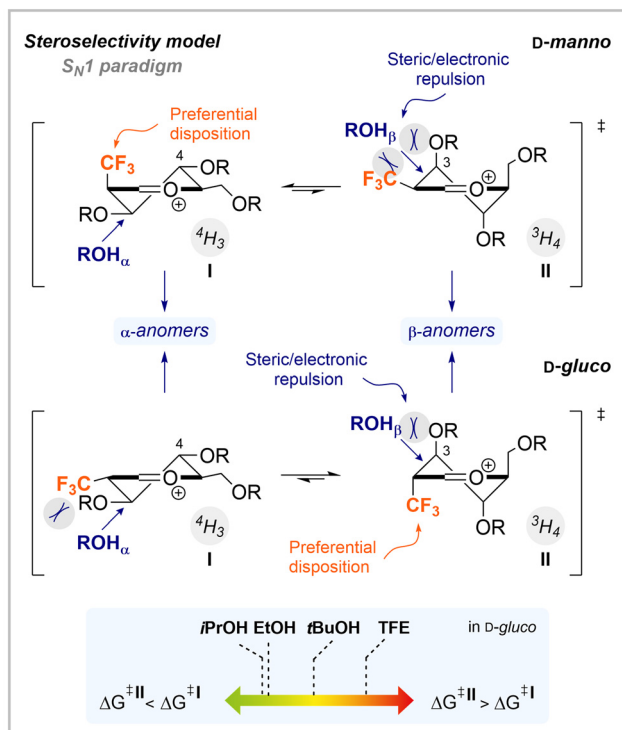
^a General conditions: (1) 2-X-pyranose (1 equiv.), 33 wt% HBr in AcOH, 0°C to rt, 1–3 h; (2) glycosyl bromide donor (1 equiv.), R'OH (2 equiv.), and AgOTf (2 equiv.) in 1 : 1 (v/v) CH_2Cl_2 /toluene (0.05 M), -80°C , 3 h unless otherwise indicated. Variable amounts of elimination side-reactions to the 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



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

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-



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 Zemiplén deacetylation; NaOMe, MeOH, rt, 6 h and the residue purified by flash column chromatography. ^eYield 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** (β -Glc(1,6)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.

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