Glycosides

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gem-Difluorocarbadisaccharides: Restoring the *exo*-Anomeric Effect**

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Dedicated to Max Malacria on the occasion of his 65th birthday

Abstract: *Molecular mimicry is an essential part of the development of drugs and molecular probes. In the chemical glycobiology field, although many glycomimetics have been developed in the past years, it has been considered that many failures in their use are related to the lack of the anomeric effects in these analogues. Additionally, the origin of the anomeric effects is still the subject of virulent scientific debates. Herein, by combining chemical synthesis, NMR methods, and theoretical calculations, we show that it is possible to restore the anomeric effect for an acetal when replacing one of the oxygen atoms by a CF_2 group. This result provides key findings in chemical sciences. On the one hand, it strongly suggests the key relevance of the stereoelectronic component of the anomeric effect. On the other hand, the CF_2 analogue adopts the natural glycoside conformation, which might provide new avenues for sugar-based drug design.*

Carbohydrates play a pivotal role in multiple biological processes which are initiated upon specific molecular recognition of sugar ligands by cellular receptors.[1] Therefore, sugar mimicry is an essential part of the development of carbohydrate-based therapeutics, an area which already proved successful with molecules such as Miglustat, Acarbose, or Voglibose.[2] The mimics are sugar scaffolds bearing a relatively minimal modification which changes its properties while still resembling the sugar. Hence, modifications of the sugar moiety largely concentrate on the replacement of one or both the acetal oxygen atoms by another atom, which is mainly carbon, nitrogen, or sulphur.[3] Those modifications induce a change in the stability, polarity, charge, conformation, ring flexibility, or hydrogen-bonding pattern to improve their affinity for the target protein.[4] The precise understanding of the parameters governing those changes is therefore essential to the design of new and more efficient therapeutic molecules. More specifically, the replacement of the exocyclic anomeric oxygen atom by a carbon atom leads to *C*-glycosides[5] while replacement of the endocyclic one produces carbasugars.[6] In both cases, when the aglycone is another glycoside, this transformation leads to non-hydrolysable disaccharide analogues: *C*-disaccharides and carbadisaccharides (Figure 1).

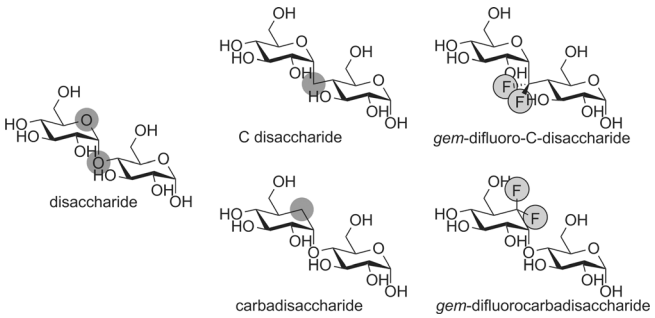

Figure 1. Schematic perspective of the different glycomimetics mentioned in the text.

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Also, in both cases the conformational behavior of those molecules drastically changes: more flexibility in the interglycosidic linkage as well as the population of unnatural conformations are observed.[7] These changes are often detrimental to the efficient interaction of such molecules with target proteins, mainly because of the entropic penalty it induces. This phenomenon has been tentatively attributed to the absence of the anomeric effects, especially the *exo*-anomeric one.[8] The anomeric effects are still subject to virulent scientific debate,[9–11] but the *exo*-anomeric effect plausibly finds its origin in the favorable interaction between a lone pair of electrons on the exocyclic anomeric oxygen atom with the parallel σ* orbital of the adjacent C1–O5 bond. More precisely, it is the fact that this interaction is more favorable than the interaction of a lone pair orbital of the same oxygen atom with the $\sigma^*_{C1\text{-}C2}$. This difference can be attributed to the different polarization between the C1−O5 and C1−C2 bonds, thus producing a larger σ* orbital centered on the less electronegative atom of the polarized bond (Figure 2). Therefore, the search for closer stereoelectronic

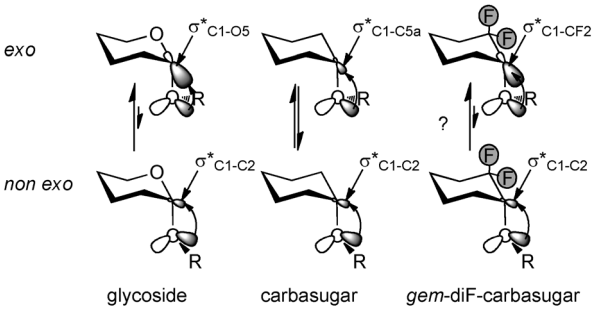


Figure 2. Schematic representation of the lone pair–σ* interactions responsible for the *exo*-anomeric effect. The *exo*-anomeric conformers are represented in the top row. For the regular glycoside (left), a good overlapping between the σ* and the lone pair is possible. The possibility of restoration of the *exo*-anomeric effect in *gem*-difluorocarbadisaccharides is presented at the right-hand side. The non-*exo*-anomeric geometries are depicted in the bottom row. In this case, no proper overlapping between the σ* and the lone pair is possible for any molecule.

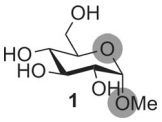
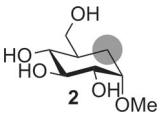
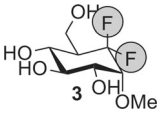
mimics, retaining this feature, is essential. According to the previous statement, replacement of the endocyclic oxygen atom by a CF_2 group instead of a CH_2 should induce a polarization of the C1−CF_2 bond and restore the *exo*-anomeric effect (Figure 2). A contrario, when the exocyclic oxygen atom is replaced by a CF_2 rather than a CH_2 it populates the unnatural non-*exo* conformation as a result of hyperconjugation of the C1−H1 and C1−C2 bonds with the C–F bonds.[12,13] Interestingly, while many *C*-disaccharides and carbasugars, and some CF_2 *C*-disaccharides have been prepared, there is no report of the synthesis of any *gem*-difluorocarbadisaccharide.[14] We therefore embarked on the synthesis and study of such a molecule to explore the possibility of restoring the *exo*-anomeric effect in a carbonated sugar mimic.

First, we tested our hypothesis in silico. Hence, we performed density functional theory (DFT) calculations on a simple methyl α-D-glucopyranoside (**1**) and its CH_2 (**2**) and CF_2 (**3**) counterparts. Solvent effects are included using the polarizable continuum model (PCM) representing water. The obtained geometries were then submitted to natural bond orbital[15–17] (NBO) analysis investigating how the *endo*- and *exo*-anomeric effects were affected by these structural modifications, since NBO analysis allows the elucidation of the role of intramolecular orbital interactions. The protocol considers all possible interactions between the filled donors and empty acceptors and estimates their energetic importance using second-order perturbation theory. For each donor NBO (i) and acceptor NBO (j), the stabilization energy $E^{(2)}$, associated with the corresponding electron delocalization, is estimated as:

$$E^{(2)} = q_i\ (F_{i,j})^2/\varepsilon_j - \varepsilon_i$$

Where q_i is the orbital occupancy, ε_i and ε_j are the diagonal elements (orbital energies), and $F_{i,j}$ is the off-diagonal NBO Fock matrix element. Table 1 lists the calculated stabilization energies corresponding to the anomeric effects. As expected

Table 1: Second-order interaction energy (E^2, kcal mol^{-1}) between donor and acceptor orbitals in a natural sugar (**1**) and analogous carbasugars (**2**; CH_2, and **3**; CF_2).

Molecule	Stabilization Energy (E^2) kcal mol^{-1}	
	exo-anomeric effect	*endo*-anomeric effect
 **1**	$n_{O_{exo}} \rightarrow \sigma^*_{C1\text{-}O_{endo}}$ 17.39	$n_{O_{endo}} \rightarrow \sigma^*_{C1\text{-}O_{exo}}$ 10.66
 **2**	$n_{O_{exo}} \rightarrow \sigma^*_{C1\text{-}C5a}$ 0.84	N.P.
 **3**	$n_{O_{exo}} \rightarrow \sigma^*_{C1\text{-}C5a}$ 9.24	$N_{F_{ax(LP)}} \rightarrow \sigma^*_{C1\text{-}O_{exo}}$ 1.33

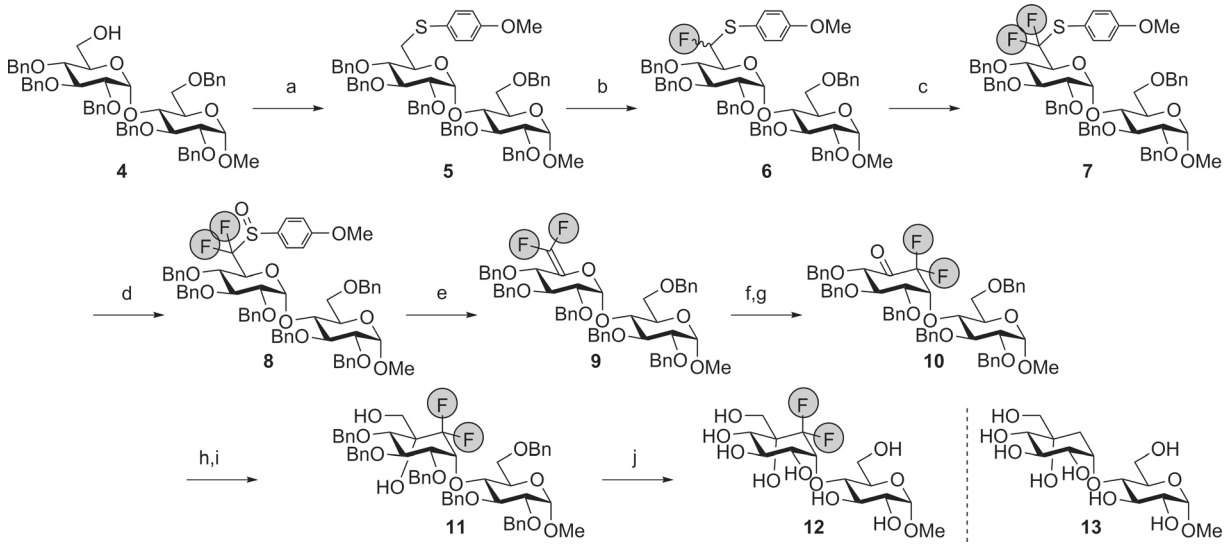
they coexist in the natural glycoside **1**, but disappear in the analogous CH_2 carbasugar **2**. However, and much to our delight the *exo*-anomeric effect reappears in the *gem*-difluorocarbaglycoside **3**. Interestingly, a small but unexpected interaction between a lone pair of electrons on the axial fluorine atom and the $\sigma^*_{C1\text{-}O1}$ is observed to mimick the *endo*-anomeric effect.

The energy contribution to the *exo*-anomeric effect in the natural sugar compared to the one in the corresponding CH_2 and CF_2 carbasugars clearly suggests that the fluorine atoms, because of their high electronegativity, favor the recovery of the *exo*-anomeric effect through polarization of the C1−CF_2 bond. The optimized structural parameters of the studied molecules obtained at the DFT (B3LYP/6-31++G PCM) level[18] of theory are given in Table S1 in the Supporting Information. The calculated bond lengths for **2** and **3** in the anomeric region, compared to those of **1**, are in agreement

with the presence of an *exo*-anomeric effect in **3** (Table S1). According to the calculated molecular orbital diagrams (see Figure S1 in the Supporting Information), the uneven electron density distribution in the C1–X5a σ-bonding orbitals for **3** and **1**, compared to those of **2**, translates to a better orbital overlap between the (*n*) lone pair molecular orbital of the exocyclic oxygen atom and the unoccupied antibonding (σ*) molecular orbital of C1. Moreover, the inductive effect of the electron-withdrawing fluorine atoms at C5a also contributes to the preservation of a large stereoelectronic *exo*-anomeric contribution in **3**.

Encouraged by this preliminary work, and to experimentally validate this concept, we synthesized a *gem*-difluorocarbadisaccharide (Scheme 1). We have previously synthesized *gem*-difluorocarbasugars[19] using an O→C 1,3-rearrangement[20] applied to *C*-glycosides.[21] This strategy produced a free pseudoanomeric hydroxy group which was ready for further functionalization. However, despite numerous attempts, this OH could neither be alkylated nor substituted. In parallel, we have also shown that disaccharides could undergo the O→C 1,3-rearrangement directly, thus producing carbadisaccharides.[22] We therefore turned our attention towards this strategy for the present work. However, the challenge here was the synthesis of a *gem*-difluorinated *exo*-glycal. After several attempts, the successful route was inspired by the work of McCarthy and Prakash on nucleosides,[23] and involved a Pummerer reaction. The starting alcohol **4** was produced from maltose using a known route.[22] Sulfidation of **4** was then achieved by treatment with bis(4-methoxyphenyl) disulfide and tributylphosphine in DMF to afford the sulfide **5** in 92% yield. Fluorination of **5** was performed using a modified Pummerer reaction with DAST in the presence of NIS to give the monofluorosulfides **6** in 88% yield as a mixture of two inseparable diastereomers. The second fluorination was achieved slightly differently through treatment of **6** with Selectfluor in the presence of DAST, followed by the addition of triethylamine to give the desired difluorosulfide **7** in 61% yield together with monofluorosulfoxides (22%). Further oxidation of **7** with *m*CPBA produced the sulfoxides **8** in 90% yield as an inseparable mixture of two diastereomers. Their thermolysis with Bn_3N in Ph_2O at 190°C under air for 120 hours gave the difluoroalkene **9** in 65% yield. Treatment of **9** with TIBAL gave the desired carbocycle as a mixture of diastereomeric alcohols, which were oxidized into a single ketone (**10**) with Dess–Martin periodinane. The synthesis of the diol **11** was achieved by hydroxymethylation with Fleming–Tamao oxidation procedure from **10**. Reaction of **10** with freshly prepared Tamao's reagent provided β-hydroxysilanes, which was subjected without purification to oxidative cleavage of the Si–C bond by basic hydrogen peroxide to give **11**. Final deprotection of **11** using palladium on charcoal (Pd/C) as a catalyst in methanol proceeded smoothly to give the target molecule **12** in quantitative yield (Scheme 1).

Thus, the conformation of **12** was investigated by a combination of NMR spectroscopy and molecular modeling methods, and compared to that of the carbasugar analogue **13** (Scheme 1), where fluorine atoms are replaced by hydrogen atoms, to probe the stereoelectronic effect of the CF_2 group. The synthesis of **13** is given in the Supporting Information and uses the same last steps as those used for **12** from a known intermediate.[24] We first performed molecular mechanics calculations (MM3*)[25] and found that for both **12** and **13** there were three more stable conformations around the Φ/Ψ glycosidic linkages, which were the *exo*-Φ/syn-Ψ (Φ/Ψ ca. −40/−20), *exo*-Φ/anti-Ψ (Φ/Ψ ca. −40/180), and non-*exo*-Φ/



Scheme 1. Reagents and conditions: a) Bis(4-methoxyphenyl) disulfide (1.5 equiv), nBu_3P, DMF, RT, overnight, 92%; b) DAST (5 equiv), *N*-iodosuccinimide (NIS, 2.1 equiv), CH_2Cl_2, −40°C to RT, overnight, 88%; c) Selectfluor (1.25 equiv), DAST (0.18 equiv), CH_3CN, RT, 45 min; then anhydrous triethylamine (1.5 equiv), RT, 45 min, 61%; d) *m*CPBA (1.1 equiv), CH_2Cl_2, −20°C to RT, overnight, 90%; e) Bn_3N (3 equiv) Ph_2O, 190°C, 120 h, 65%; f) TIBAL (12 equiv), toluene, 50°C, 30 min, 29%; g) Dess–Martin periodinane (3.7 equiv), CH_2Cl_2, RT, 1 h; h) [(isopropoxydimethylsilyl)methyl]magnesium chloride, 4 Å M.S., THF, 0°C, 1 h; i) TBAF (4 equiv), $KHCO_3$ (8 equiv), H_2O_2 (20 equiv), THF/MeOH (1:1, *V*/*V*), 0°C, 1 h, 13% over three steps; j) H_2, 10% Pd/C, MeOH, RT, 15 h, quant. DAST = diethylaminosulfurtrifluoride, DMF = *N*,*N*-dimethylformamide, *m*CPBA = n-chloroperbenzoic acid, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran, TIBAL = triisobutylaluminum.

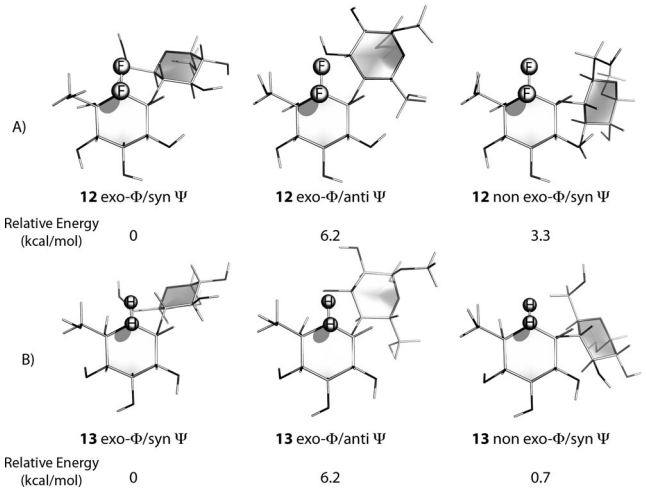


Figure 3. Ball and stick representations and relative steric energy values of the major conformers of **12** and **13** according to MM3* calculations.

syn-Ψ (Φ/Ψ ca. 40/0) conformations (see the Supporting Information for details). The calculated conformers are represented in Figure 3 together with the steric energy values provided by MM3*.[25] Other force fields (AMBER*, OPLS) provided similar geometries and relative steric energy values.

^{1}H-^{1}H NOESY and/or ^{1}H-^{19}F HOESY NMR experiments were carried out on both **12** and **13**. As shown on Figure 4 the pattern of correlations for H1′ is strikingly different between **12** and **13**. While the only inter-residue correlation of H1′ is with H4 for **12**, H1′ correlates with H3, H4, H5, and H6 in the case of **13** (Figure 4 A,B). Both the F_{eq} in **12** and and H5a$_{eq}$ (further referred to as H_{eq}) in **13** correlate with H4 and a H6 (Figure 4 C,D).

We next estimated the interatomic distances using the calculated structures (Figure 3) as well as the experimental proton–proton and proton–fluorine distances from the integration of the observed NOE crosspeaks using the isolated spin pair approximation (ISPA).[26] The results are reported in Table S3 of the Supporting Information and illustrated on the different conformers in Figure 5. For **12** the *exo*-Φ/anti-Ψ conformer can be easily dismissed because no correlations are observed between H1′ and H5, nor between F_{eq} and H3. The fact that H1′ only correlates with H4 cannot discriminate between the *exo*-Φ/syn-Ψ and the non-*exo*-Φ/syn-Ψ conformers, but the presence of a F_{eq}–H4 correlation together with the absence of the H1′–H6 correlation allows the clear discrimination between both geometries exclusively in favor of the *exo*-Φ/syn-Ψ conformer. In striking contrast, the simultaneous presence of H_{eq}–H4, H_{eq}–H6, H1′–H3, H1′–H4, H1′–H5, and H1′–H6 correlations for **13** clearly indicate a conformational equilibrium between the three conformers depicted in Figure 3. In particular, the presence of the H_{eq}–H4 NOE can only be explained by the *exo*-Φ/syn-Ψ geometry. The presence of the H_{eq}–H6S NOE and H1′–H6R NOE can only be satisfied by the alternative non-*exo*-Φ/syn-Ψ conformer. The observation of the H1′–H3 and H1′–H5 NOE is only compatible with the presence of the third *exo*-Φ/*anti*-Ψ

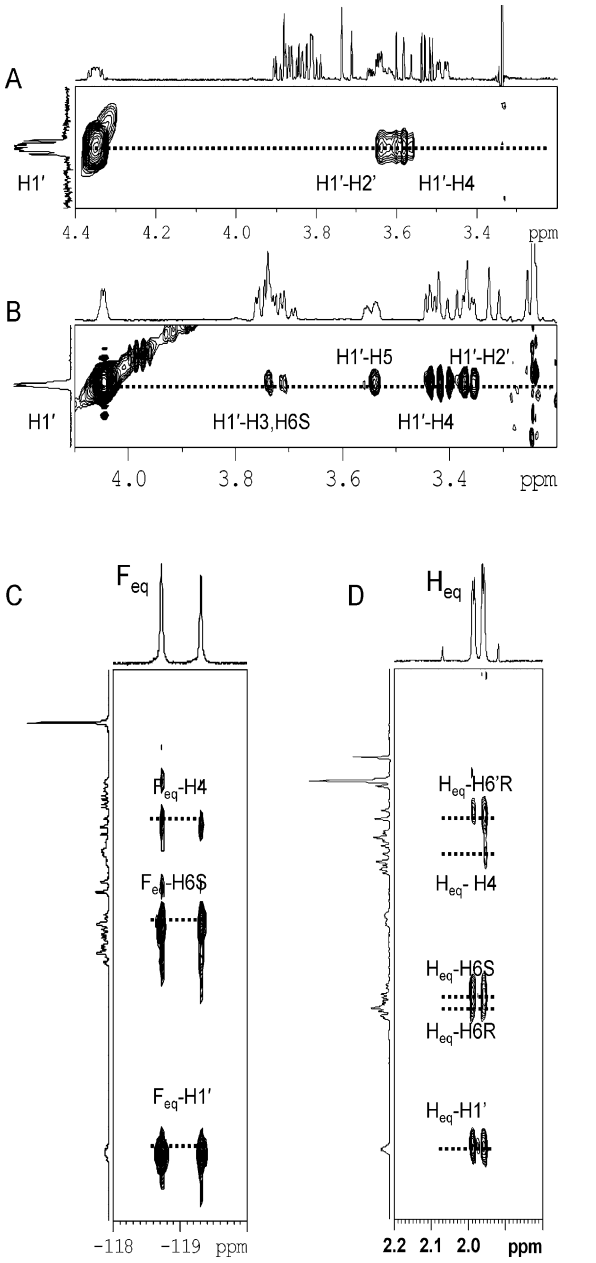


Figure 4. (Upper) Strips of two-dimensional NOESY spectra (700 ms mixing time) of **12** (A) and **13** (B) taken at frequency of H1′. (Lower) Strips of 2D ^{1}H-^{19}F HOESY (500 ms mixing time) of **12** (C) and ^{1}H-^{1}H NOESY (700 ms mixing time) for **13** (D). Key NOEs are highlighted. No other inter-residue NOE interactions are observed above the noise level.

conformation. (Figure 5) Therefore, the three conformations indeed exist in solution. The possibility of establishing an intra-residue OH5···O$_{exo}$ hydrogen bond was also scrutinized because it could stabilize one or the other conformation. According to the calculations, this possibility would exist for both *exo*- and non-*exo* conformers. However, since the experiments have been performed in water (D_2O), given the massive presence of water molecules, the importance of any intraresidue OH···O interaction should be at a minimum and not influence the conformational behavior. Nevertheless, its

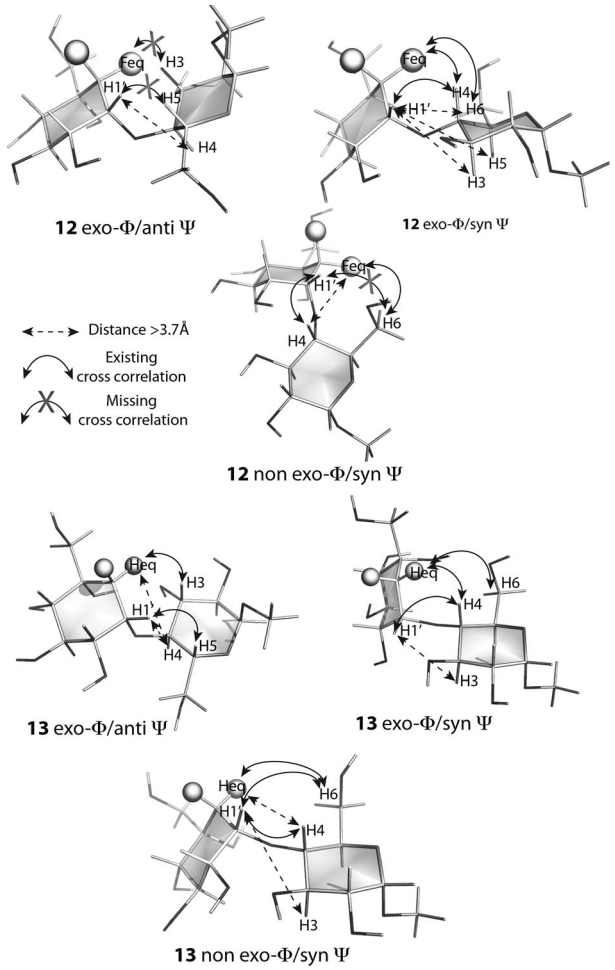


Figure 5. Schematic view of the NOE contacts and distances for each conformer.

occurrence was also experimentally discarded (see Figures S5–S10 and Table S4 in the Supporting Information).

In conclusion, our theoretical calculations predict that the *exo*-anomeric effect of maltose, an effect which is almost completely abolished in the carbasugar analogue, is significantly restored when a CF_2 group is present at the endocyclic position corresponding to O5 in the natural sugars. As an experimental demonstration, we have synthesized the *gem*-difluorocarbasugar maltose analogue **12**, which indeed only exists in solution in the *exo*-anomeric conformation. In striking contrast, the corresponding carbasugar **13** displays a mixture of the *exo*-Φ and non-*exo*-Φ geometries in solution. It has therefore been demonstrated that it is possible to restore an anomeric effect for an acetal when replacing one of the oxygen atoms by a CF_2 group. This result provides key findings in chemical sciences as it strongly suggests the importance of the stereoelectronic component for the *exo*-anomeric effect. Additionally, the obtained mimicking of the natural glycoside conformation may open new avenues for sugar-based drug design.

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Communications

Glycosides

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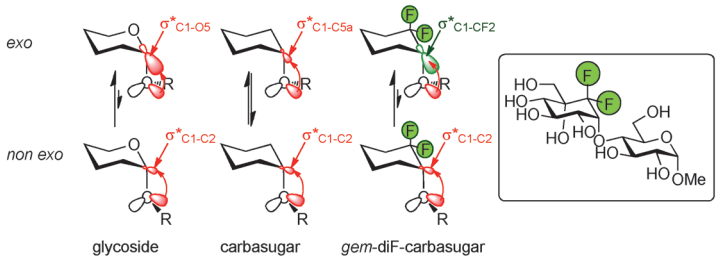
gem-Difluorocarbadisaccharides: Restoring the *exo*-Anomeric Effect



Taking effect: The combination of chemical synthesis, NMR methods, and calculations show that it is possible to restore the anomeric effect for an acetal when replacing one of the oxygen atoms by a CF_2 group. This result provides key findings as it strongly suggests the importance of the stereoelectronic component for the anomeric effect, and may open new avenues for sugar-based drug design.