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Synthesis of 1′,2′-*cis*-Nucleoside Analogues: Evidence of Stereoelectronic Control for S_N2 Reactions at the Anomeric Center of Furanosides

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Abstract: We are reporting a highly diastereoselective route to 1′,2′-*cis*-nucleoside analogues in the D-ribo, D-lyxo, D-xylo, and D-arabinoside series. Five-membered ring lactols undergo highly selective N-glycosidation reactions in the presence of dimethylboron bromide with different silylated nucleobases. Stereoelectronic control plays a crucial role for the observed induction, and the products are proposed to be formed through S_N2 "exploded" transition states. This approach shows great potential considering its simplicity and selectivity for the synthesis of nucleoside analogues, an important class of molecules in medicinal chemistry.

Introduction

Endogenous nucleosides play key roles in various aspects of life, including cell division and viral replication. It is therefore not surprising that nucleoside analogues have been designed to interfere with these processes to provide antiviral[1] and antitumor[2] drugs. Nucleoside analogues also show promising activity against emerging viruses and novel pharmaceutical targets, such as protein kinases (e.g., VEGF and FFGR), involved in deregulated signaling cascades in various diseases.[3] The 1′,2′-*cis* arrangement between the nucleobase attached at the anomeric center and the heteroatom at C-2′ is found in numerous biologically relevant nucleoside analogues (Figure 1).[2a,4] The synthesis of this motif (1′,2′-*cis*) is still problematic in spite of past achievements. A general strategy giving access to this class of molecule, regardless of the relative stereochemistry of different groups attached at C-3 and C-4 positions of the furanose ring, would be a great asset for synthetic and medicinal chemists.

The current paradigm governing the synthesis of nucleosides implies that the nucleobase (purine or pyrimidine) be linked to a glycosyl acceptor in the presence of a Lewis acid. In this particular strategy, the nucleophilic heterocycle has to be delivered on the most hindered face of the furanose moiety, a generally higher energy approach than the one leading to the 1′,2′-*trans* product.[5] The latter can be prepared by taking advantage of the anchimeric participation of C-2 neighboring groups (OAc or OBz) to block the *syn* face of the glycosyl acceptor.[6] The 1′,2′-*cis* N-glycosidations have been achieved by S_N2 displacements of 1,2-*trans*-halosugars, but the latter are not trivial to generate diastereoselectively and useful selectivities can only be reached by extensive optimization of the reaction conditions.[7] Other strategies to provide 1′,2′-*cis* N-glycosidation involve activation of anomeric thioethers[8] or carboxyl[9] groups by various Lewis acids (AgOTf, $BiBr_3$, TMSOTf, NBS, NIS, SiF_4). However, to the best of our knowledge, none of these

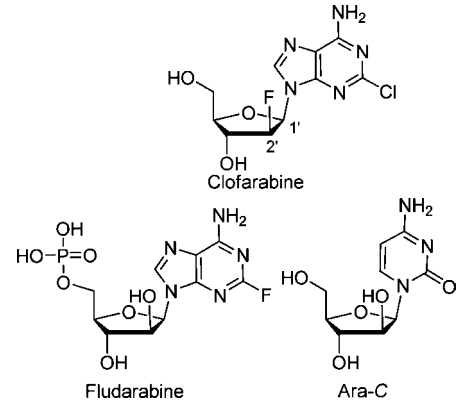

Figure 1. FDA approved drugs with 1′,2′-*cis* relative stereochemistry.

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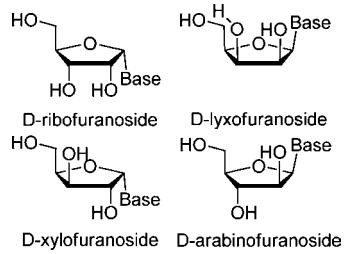


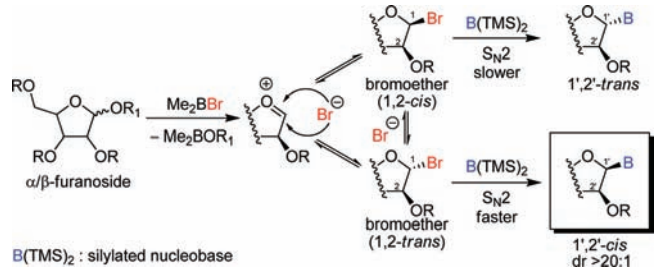
Figure 2. Four D-furanose scaffolds.

protocols give access to high 1′,2′-*cis* selectivity in the four D-furanose scaffolds to generate modified nucleosides (Figure 2).

Expanding the scope of our retrospective analysis led us to consider stereoselective C-, O-, and N-glycosidation reactions that do not involve neighboring group assistance. These displacement reactions are generally proposed to proceed through two limit mechanisms: S_N1 mechanisms involving oxocarbenium intermediates,[10] generally accessed by activation of the anomeric center by strong Lewis acids, or S_N2 displacements of an anomeric leaving group (e.g., bromide).[1a] Other intermediate scenarios involve solvent-separated ions pairs (SSIP),[11] displacements of contact ions pairs (CIP),[12] or S_N2-like mechanisms with oxocarbenium character, as suggested in the "exploded"[13] S_N2 transition state model.[14] The relative energy of these transition states is strongly influenced by the nature of the Lewis acid, the nucleophile, the counterion (i.e., leaving group), and the nature of the glycosyl donor.[8b,15]

The general and highly diastereoselective N-glycosidation strategy reported herein gives access to 1′,2′-*cis*-nucleoside analogues. Five-membered ring lactols (R_1 = H, Scheme 1), with an electronegative substituent at C-2, were treated with

Scheme 1. Synthesis of 1′,2′-*cis*-Nucleosides from Lactols (R_1 = H)



Me_2BBr[16] to generate mixtures of cyclic bromoethers. Subsequent addition of persilylated pyrimidine bases ($B(TMS)_x$) led to highly selective 1′,2′-*cis*-nucleosides in good yields for all four D-furanose scaffolds (Figure 2). We are proposing that the selectivity observed is the consequence of faster stereospecific displacements of 1,2-*trans*- versus 1,2-*cis*-bromoethers, which are undergoing rapid in situ anomerization (Scheme 1). This work provides evidence against the general assumption that in situ anomerization glycosidation strategies[28,36] can only lead to high anomeric selectivity in six-membered rings[5,17] and suggests that stereoelectronic effects are significant for S_N2 displacements at the anomeric position of five-membered ring systems.

Results and Discussion

Investigation of the Activation of Tetrahydrofuran Acetals with Me_2BBr. Initially, we were interested in studying N-glycosidations of halosugars under kinetic control to develop experimental conditions leading to high 1′,2′-*cis* selectivities. We first studied the feasibility of generating cyclic bromoethers in a single step from readily available methyl furanosides using Me_2BBr, a Lewis acid that has been reported to convert acetals and ketals to bromoethers at low temperature (Scheme 1, R_1 = Me).[18] This strategy was appealing because it would provide an efficient alternative to other elegant protocols for the installation of an activating group at the anomeric position.[8,10] In order to determine if the desired bromoether products were formed after the Lewis acid activation step, trapping experiments were performed at low temperature using thiols in the presence of a hindered base. Accordingly, 1,2-*trans* tetrahydrofuran acetal **1a** was treated with Me_2BBr at −78 °C. Thiophenol and DIEA were subsequently added to the reaction mixture at low temperature. Rather than forming the desired cyclic acetal, acyclic thioacetal **2** was obtained as a 11:1 (1,2-*anti*:1,2-*syn*) ratio (Table 1, entry 1). When performing the reaction at a higher temperature (0 °C), the diastereoselectivity dropped to 1.3:1 (1,2-*anti*:1,2-*syn*) and thiofuranosides **3** was observed in trace amounts (Table 1, entry 2). The acyclic thioacetal was also obtained from tetrahydrofuran 1,2-*cis*-acetal **1b**, but with opposite diastereoselectivity in a 1:10 (1,2-*anti*:1,2-*syn*) ratio (Table 1, entry 3). Our preliminary results at low temperature clearly indicated a selective activation of the ring oxygen by the Lewis acid with subsequent cleavage of the C−O endocyclic bond. In order to favor a chemoselective complexation of the

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(13) Concerted associative transition states with long breaking and forming bonds. The anomeric center is considered to be pseudo-sp^2-hybridized with participation of the endocyclic oxygen to stabilize the developing positive charge. In these transition states, bond forming and bond breaking are considered to be occurring in a symmetrical manner.
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(16) Other boron activating agents, such as *c*-Hex_2BI, were considered. Similar trends were observed with compound **15**, but the scope of this activating agent remains to be investigated.
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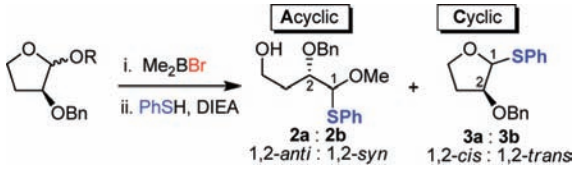
Table 1. Formation of Acyclic and Cyclic Thioacetals



Entry	Substrate	T[a] (°C)	Acyclic Product[b]	Cyclic Product[b]
1	**1a**	−78	89% (11:1)	*(not observed)*
2	**1a**	0	78% (1.3:1)	10% (1.4:1)
3	**1b**	−78	88% (1:10)	*(not observed)*
4	**4**	−78[c]	*(not observed)*	86% (13:1)

[a] With 2.0 equiv of Me_2BBr at different T (°C), then 3.0 equiv of DIEA and 2.5 equiv of PhSH. [b] Ratios were determined by ^1H NMR spectroscopic analysis of unpurified products. [c] Reaction stirred for 3 h, before the addition of PhSH.

exocyclic oxygen, we envisioned using lactols as substrates for these reactions. We were pleased to note that cyclic product **3** was synthesized selectively when lactol **4** was reacted at low temperature with Me_2BBr (Table 1, entry 4). These results are interesting both at the theoretical and practical levels.

Substitutions of acetals have been shown to involve intermediates (vide supra) with oxocarbenium character.[10] These intermediates are formed with the stereoelectronic assistance of the acetal oxygen lone pair that is antiperiplanar to the breaking C−O bond after Lewis acid activation.[19] As illustrated in Figure 3, the exocyclic oxocarbenium intermediates **B** and **C** can be accessed in both the pseudoaxial and pseudoequatorial conformations, whereas the endocyclic oxocarbenium intermediate **A** is only accessible from the pseudoaxial conformation. Endocyclic or exocyclic C−O bond cleavage and subsequent nucleophilic attack by a bromide would generate cyclic bromoethers through **A** and acyclic bromoethers through **B** or **C** (Figure 3).[20,21] Displacement of these bromoethers by the thiol nucleophile would then give thioacetals **2** or **3** (Table 1, entries 1−3).

The selectivity for the formation of acyclic versus cyclic products is likely to be determined at the complexation step.[21] In the pseudoaxial conformation, the carbon−oxygen bonds at

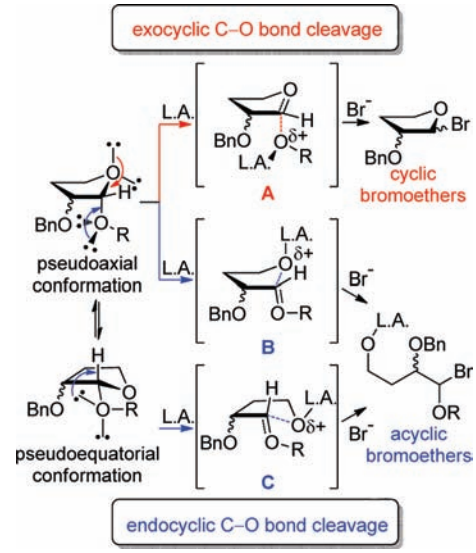


Figure 3. Endocyclic and exocyclic activation pathways of pseudoaxial or pseudoequatorial methyl furanosides.

the anomeric center are properly aligned for *endo*- and *exo*-anomeric effects to take place (Figure 3).[17,22] Hence, both oxygens should display lower basicity because of the electron delocalization toward the anomeric center.[22] In contrast, the pseudoequatorial conformation only allows donation from the glycosidic oxygen (Figure 3), as the unshared pair of electrons on the ring oxygen are not properly oriented to interact with the glycosidic σ^*_{C-O} orbital. Therefore, by only considering stereoelectronic factors in the analysis, it is expected that the ring oxygen in the pseudoequatorial conformation is the more basic. Formation of acyclic products would consequently occur selectively through **C**. Given that five-membered rings exist in different conformations that are close in energy and can rapidly equilibrate, the more reactive conformation could be easily accessed, even if it is not the most thermodynamically favored in the ground state.[23] Interestingly, ring-opening studies of methyl pyranosides, which generally have a single low-energy chair conformation,[23] indicated that the α-anomers were significantly less reactive than β-anomers at low temperatures.[21] This scenario would, however, only be valid at low temperatures for furanosides, in view of the fact that at 0 °C the 1,2-*anti* diastereoselectivity of the acyclic products was lost and that cyclic thioacetals **3** were formed in low yield (Table 1, entry 2). This is suggestive that at higher temperature the reaction becomes reversible and could consequently provide the thermodynamically preferred cyclic thioacetal. The observed high diastereoselectivities at low temperature are also of particular interest (Table 1, entries 1 and 3) because they could be the result of two consecutive substitution reactions occurring with S_N2-like character.

Further studies will be undertaken to determine if these reactivity and selectivity trends hold with more substituted acetals and to establish if the ring-opening reaction occurs through S_N2 displacements. As for the successful realization of

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(20) (a) Olsson, R.; Rundström, P.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 785. (b) Olsson, R.; Rundström, P.; Persson, B.; Frejd, T. *Carbohydr. Res.* **1998**, *307*, 13. (c) Olsson, R.; Berg, U.; Frejd, T. *Tetrahedron* **1998**, *54*, 3935.
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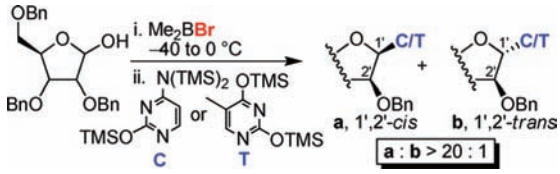
(23) (a) Angyal, S. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 157. (b) Angyal, S. J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 15.

Table 2. N-Glycosidation Induced by Me_2BBr



Entry	Substrate	Product[b]	Yield (%)[a]
1	**5**	**6a**:**6b** (>20:1)	83
2	**5**	**7a**:**7b** (>20:1)	93
3	**8**	**9a**:**9b** (>20:1)	85
4	**10**	**11a**:**11b** (>20:1)	79
5	**12**	**13a**:**13b** (>20:1)	80

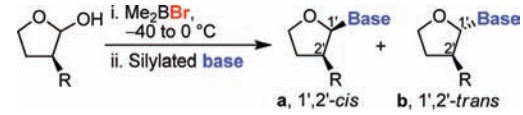
[a] With 1.8 equiv of Me_2BBr at −40 °C, then 30 min at 0 °C, before addition of 3.0 equiv of **B**$(TMS)_x$. [b] Ratios were determined by ^1H NMR spectroscopic analysis of unpurified products.

the objectives sought after in the present work, these results indicated that selective formation of cyclic bromoethers under kinetic conditions can be achieved from lactol derivatives and that stereoelectronic effects are at work in five-membered rings.

Synthesis of 1′,2′-*cis*-*N*-Glycosides from Hemiacetals. The efficient formation of cyclic thioacetals from lactols, using Me_2BBr, encouraged us to study N-glycosidation reactions with silylated pyrimidine nucleobases. Solutions of hemiacetals in CH_2Cl_2 were cooled to −40 °C, before the addition of Me_2BBr (Table 2). The reaction mixtures were then warmed at 0 °C and treated with silylated nucleobases. The N-glycosidation was completed within 2 h in the *ribo* (**5**, entries 1 and 2), *arabino* (**8**, entry 3), and *xylo* (**10**, entry 4) series; whereas 6 h was needed to reach full conversion in the *lyxo* (**12**, entry 5) series. This protocol provided 1′,2′-*cis*-nucleosides in very good isolated yields from the four D-furanose scaffolds (Table 2). Both pyrimidine natural nucleobases (thymine and cytosine) were competent nucleophiles to generate *N*-glycosides with high 1′,2′-*cis* selectivity (Table 2, entries 1 and 2).

These results are exciting due to the high 1′,2′-*cis* diastereocontrol obtained in the four D-furanose scaffolds. It should be noted that the reaction was very selective even with the most sterically encumbered glycosyl acceptors. For example, *N*-glycoside **13a** was obtained in good yield in a diastereomeric ratio greater than 20:1 from lactol **12**, in spite of having four substituents on the same face of the ring (Table 2, entry 5).

Table 3. N-Glycosidation of C-2-Substituted Lactols



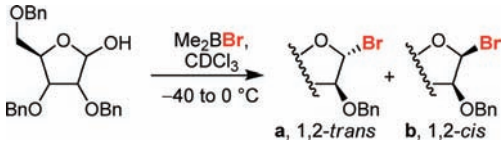
Entry	Substrate	Product[b]	Yield (%)[a]
1[c]	**4**	**14a**:**14b** (>20:1)	91
2	**15**	**16a**:**16b** (>20:1)	88
3	**15**	**17a**:**17b** (>20:1)	90
4[d]	**18**	**19a**:**19b** (10:1)	41
5	**18**	**20a**:**20b** (>20:1)	22[e]
6	**21**	**22a**:**22b** (1:1)	98

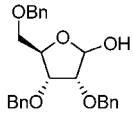
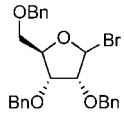
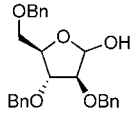
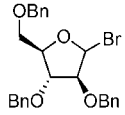
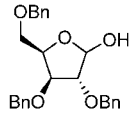
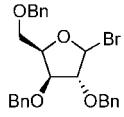
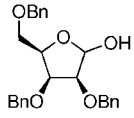
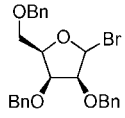
[a] With 1.8 equiv of Me_2BBr at −40 °C, then 30 min at 0 °C, before addition of 3.0 equiv of **B**$(TMS)_x$. [b] Ratios were determined by ^1H NMR spectroscopic analysis of unpurified products. [c] Reaction was cooled at −78 °C prior to the addition of Me_2BBr. [d] Reaction stirred for 16 h. [e] Unoptimized yield with silylated 5-fluorouracil.

Stereoselective formation of 1′,2′-*cis* *N*-glycosides, regardless of the C-3 and C-4 relative stereochemistry of the lactols studied, suggests that the C-2 alkoxy group is the dominant controlling factor to reach high selectivities. To ascertain this hypothesis, lactols bearing electronically and sterically different C-2 substituents were prepared and submitted to our optimized N-glycosidation conditions (Table 3). With benzyloxy or *tert*-butyl(dimethyl)silyloxy group at C-2, high 1′,2′-*cis* selectivities were observed (Table 3, entries 1−3). Replacing the alkoxy group at the C-2 position by a fluorine atom also provided good 1′,2′-*cis* selectivities (Table 3, entries 4 and 5). Interestingly, with a methyl substituent at the C-2 position, the selectivity of the N-glycosidation was completely lost (Table 3, entry 6). High 1′,2′-*cis* diastereocontrol is therefore only observed with electronegative atoms (F or O) attached at the C-2 position and is not influenced by the steric bulk of the alkoxy protecting group.

Investigation of the 1′,2′-*cis* N-Glycosidation. In order to understand the origin of the high 1′,2′-*cis* selectivity, we initiated various studies to determine the nature of the intermediates involved in the N-glycosidation reaction. ^1H NMR spectroscopic analysis of solutions of lactols, 30 min after the addition of Me_2BBr, indicated clean formation of cyclic bromoethers (**23**−**26**) with anomeric ratios ranging from 8:1 to 1:1 (1,2-*trans*:1,2-*cis*), as seen in Table 4.

Table 4. Activation of Lactols by Me_2BBr



Entry	Substrate	Product	dr (**a**:**b**)[a,b]
1	 **5** (*ribo*)	 **23a**:**23b**	8:1
2	 **8** (*arabino*)	 **24a**:**24b**	6:1
3	 **10** (*xylo*)	 **25a**:**25b**	1:1
4	 **12** (*lyxo*)	 **26a**:**26b**	2:1

[a] Conditions: Me_2BBr (1.8 equiv), $CDCl_3$ (0.1 M). [b] Ratios were determined by ^1H NMR spectroscopic analysis of the reaction mixtures.

The N-glycosidation reactions were then monitored by ^1H NMR spectroscopy. The ^1H NMR resonance of the C-1 anomeric hydrogens of the species present during the N-glycosidation of **5** (*ribo* scaffold) are shown in Figure 4. Addition of Me_2BBr provided bromoethers **23a** and **23b** in less than 5 min (t_i = 5 min, Figure 4). Silylated thymine **T**$(TMS)_2$ was then added at 25 °C, and ^1H NMR spectra were collected at different reaction times (t_{ii}). *N*-Glycoside **6a** (δ 6.26 ppm) was formed with high 1′,2′-*cis* selectivity; the minor diastereomer **6b** (δ 6.08 ppm) was not observed (t_{ii} = 5 min). It is noteworthy that 1′,2′-*cis*:1′,2′-*trans* diastereomeric ratios for the nucleosides remained constant during the reaction (t_{ii} = 5 min to 2 h). A similar trend was also noted with D-xylose **10** and D-lyxose **12**.[24] From these experiments, one can conclude that high levels of 1′,2′-*cis* N-glycosidation selectivity are not the result of selective formations of 1,2-*trans*-bromoethers undergoing a S_N2-like displacement.

Mechanisms and Rationale

Synthesis of 1′,2′-*cis*-*N*-Glycosides from Lactols. As reported herein, we have developed a general strategy to synthesize modified 1′,2′-*cis*-nucleoside analogues in the four D-furanose scaffolds (Table 2). This stereoselective N-glycosidation was shown to involve two consecutive reactions under kinetic control. Different lactols were reacted with Me_2BBr to give anomeric mixtures of furanosyl bromides, which were subsequently displaced by silylated nucleobases to form the C−N

(24) Results are provided as Supporting Information.

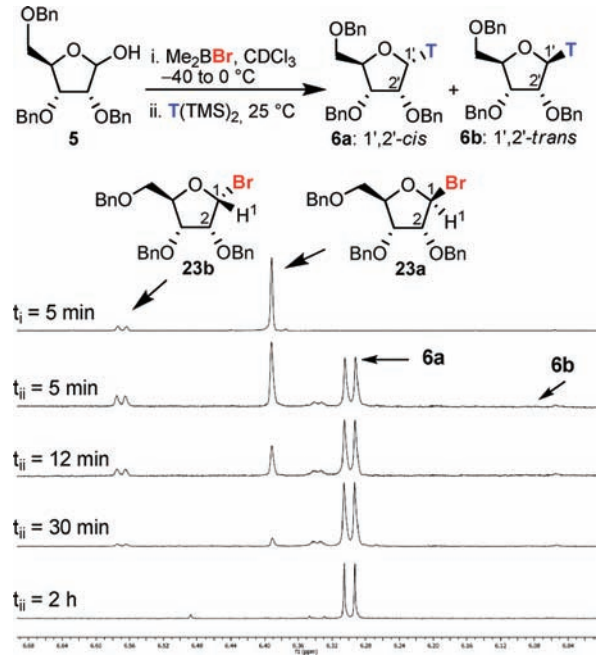
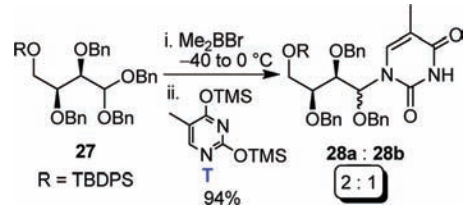


Figure 4. ^1H NMR spectra of the anomeric hydrogens resonance region during N-glycosidation of D-ribofuranoside **5** in $CDCl_3$ (0.1 M), where t_i is the time elapsed after the addition of 1.8 equiv of Me_2BBr and t_{ii} is the time elapsed after the addition 3.0 equiv of **T**$(TMS)_2$.

Scheme 2. N-Glycosidation of Acyclic Acetals



glycosidic bonds. Although the 1′,2′-*cis* selectivity is controlled by the presence of an electronegative substituent (−F, −OR) at the C-2 position, an N-glycosidation reaction performed on acyclic acetal **27** was observed to be poorly selective under our optimized conditions (Scheme 2). The conformational bias imposed by the ring system was therefore considered in the analysis. From a mechanistic standpoint, these results will be rationalized in light of previous findings and hypotheses.

Halosugars have been extensively studied as glycosyl donors, and different mechanisms have been proposed to explain the 1,2-*cis* selectivity obtained for various C-, N-, and O-glycosidation reactions.[25] Classical S_N2 substitution (**D**)[26] and free oxocarbenium (SSIP, **G**)[10b] transition state models often failed to predict the anomeric selectivities for displacements of anomeric halides by nucleophiles requiring other intermediate mechanisms to be invoked, such as "exploded" S_N2 transition

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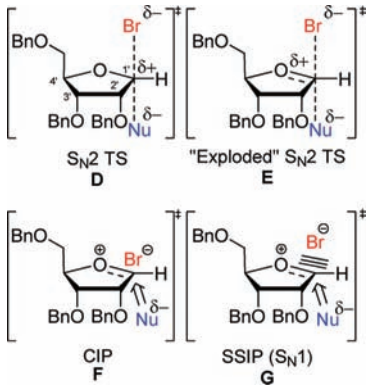

Figure 5. Different transition states for glycosidation reactions depicted in the ribose scaffold (CIP, contact ion pair; SSIP, solvent-separated ion pair; Nu, nucleobases).

states **E**[14c,27] and contact ion pair (CIP) **F**[9b,35] (Figure 5). Which of these transitions states is the lowest in energy in a given reaction? The answer to this question varies depending on the nature of the nucleophile, proximal substituents, and the conditions used (solvent, activating agents).

Lemieux, in his seminal papers, has suggested that the enhanced reactivity of bromopyranosides, relative to bromocyclohexanes, could be explained by donation of a lone pair of the endocyclic oxygen to the anomeric center to provide reactive ion pair intermediates.[28] These intermediates were proposed to be involved in the rapid anomerization of the bromopyranosides, and the *endo*-anomeric effect was postulated to bias their reactivities toward O-nucleophiles to give α-products selectively. Interestingly, in situ anomerization involving ion pairs (**F**) has only been invoked to explain erosion of selectivities in the displacement of 1,2-*trans*-bromofuranosides.[29] This lack of selectivity was generally attributed to the small energy gap between the different possible reactive five-membered ring conformers and to the fact that anomeric effects are weak in these ring systems.[17,26,29a]

Crich has offered interesting contributions in his studies of O-glycosidation reactions.[8b,14a,30] A contact ion pair mechanism was proposed to lead to the *β*-glycoside product, while a solvent-separated ion pair (SSIP in **G**, Figure 5) was invoked for the formation of the α-glycoside.[14a,27] In the remarkable *β*-glycosidation of mannoside derivatives, the presence of a benzylidene was suggested to destabilize the formation of the oxocarbenium intermediate (**G**, Figure 5).[12c] For steric and electronic reasons, the equilibrium was shifted toward a covalently bound anomeric trifluoromethane sulfonate. Contact ion pairs and exploded S_N2 transitions states were proposed to govern the nucleophilic displacement of this reactive intermediate (**E** and **F**, Figure 5).

Not less remarkable are the contributions from Woerpel that demonstrated the importance of stereoelectronic effects of proximal substituents in C-glycosidation reactions. Five-membered oxocarbenium intermediates were invoked for nucleophilic additions of allyltrimethylsilane or silylated enol ethers to anomeric acetates activated with strong Lewis acids (TMSOTf, $SnBr_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$).[10b,31] Excellent diastereoselectivity was noted from D-ribose derivatives. This suggested stabilization of the five-membered oxocarbenium conformations with the C-3 alkoxy group in the pseudoaxial position to maximize electrostatic stabilization and, to a lesser extent, with the C-2 alkoxy group occupying the pseudoequatorial position. The nucleophilic attack was proposed to occur from the inside face of low-energy envelope conformers (inside attack) to avoid eclipsing interactions that are encountered when attacking from the outside face (outside attack).[30] Importantly, a complete loss of the diastereoselectivity was noted in the D-arabinose series. In this case, the C-3 and the C-2 alkoxy groups have opposite directing effects. These results were reproduced within a window of nucleophilicity parameters using various reagents.[32]

Although the different models described above cannot be invoked to rationalize our results, they provide key elements for an interpretation of the N-glycosidation strategy presented in this work. As stated before, the selectivity observed was clearly linked to the configuration and electronic properties of the substituent at C-2 and not that of C-3. No difference of diastereoselectivity was noticed (vide supra) between the *arabino*- and the *ribo*-pentose scaffolds, and control reactions using allyltrimethylsilane instead of silylated nucleobases, with Me_2BBr as the activating agent, did not lead to the formation of C-glycosidation adducts.[33] These results indicate that free oxocarbenium ions are not involved in our reaction conditions, a conclusion in good agreement with reported kinetic evidence suggesting that free oxocarbenium intermediates are too short-lived in the presence of strong nucleophiles, such as bromide ions, to react diastereoselectively.[32b,34] The stereoselective synthesis of bromofuranoside and their resulting contact ion pair **F** cannot be proposed either since the bromoether has been obtained as an anomeric mixture in all cases (Table 4).[9b,35]

The mechanistic hypothesis that is suggested herein does, however, relate to the in situ anomerization, but in contrast to the work of Lemieux and others, the selectivities observed are not proposed to originate mainly from anomeric effects.[36] The rate difference for the S_N2 displacement of anomeric 1,2-*cis*- or 1,2-*trans*-bromides would arise from a stereoelectronic effect involving the C-2 substituent in 1′,2′-*cis* and 1′,2′-*trans* predictive exploded S_N2 transition states (Figure 6).[9] In these transition states, a developing sp^2 character between the endocyclic oxygen and the anomeric center would stabilize the developing positive charge at C-1 (Figure 6).[37] Given that the resulting intermediates display oxocarbenium character in five-membered rings, they are likely to adopt a low-energy envelop conformation, where

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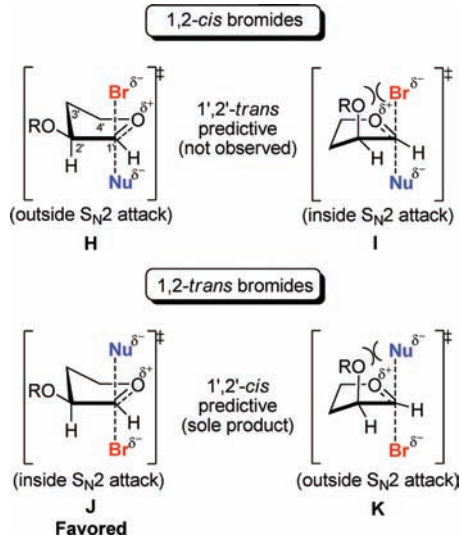

Figure 6. Proposed transition states.

the C-1, C-2, and C-4 carbon atoms are coplanar, as illustrated in Figure 6.[5,10b,38]

Addition reactions to 1-bromofuranoside should occur from the inside face (inside attack) to avoid the development of eclipsing interactions encountered during the rehybridization through the outside S_N2 attack (Figure 6).[38] This suggests that transition states **H** and **K** are higher in energy than **I** and **J** (Figure 6). Qualitatively, the relative energy of **I** and **J** can then be evaluated by considering stereoelectronic factors in the analysis. Transition state **I**, involving the 1,2-*cis*-bromide, is likely to be destabilized by a repulsive electronic interaction between two eclipsed electronegative atoms (OBn and Br).[10b,31] These interactions are not present for the 1,2-*anti*-bromide in transition state **J**, which should also benefit from the σ-hyperconjugation stabilization, the carbon−hydrogen bond at C-2 being almost orthogonal to the emerging electron-deficient π-system.[39] The transition state **J** leading to the 1′,2′-*cis* product should therefore be of lowest relative energy. In accordance with the Curtin-Hammet principle,[40] a rapid anomerization of the bromides during the N-glycosidation would lead to the selective formation of 1′,2′-*cis* products because of the difference in energy between **I** and **J** (Scheme 1 and Figure 6). The anomerization could be facilitated by bromide anions, which might come from excess Me_2BBr or from the formation of TMSBr in the course of the reaction, as suggested by Lemieux.[28,36] Since the 1′,2′-*cis* products were formed selectively regardless of the C-3 or C-4 relative configurations or substitutions, the proposed mechanistic analysis also rationalizes the selectivity observed in the four D-furanoside series (Table 2) and for the C-2-substituted lactols (Table 3).

Conclusion

We have described a highly stereoselective N-glycosidation strategy for the synthesis of modified 1′,2′-*cis*-nucleosides in all four D-pentose scaffolds and in C-2-substituted five-membered ring systems. Even the most sterically encumbered molecules were formed in good yields with excellent selectivity by in situ additions of silylated nucleobases to cyclic bromoethers obtained by reacting lactols with Me_2BBr. We have suggested a mechanism involving exploded S_N2 transition states to rationalize 1′,2′-*cis* selectivity at the N-glycosidation step. The scope of our methodology is currently being expanded with various nucleophiles to allow the synthesis of novel nucleoside analogues and other natural products that could serve as biological and medicinal tools, in addition to being putative drugs.

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Supporting Information Available: Detailed experimental procedures, proof of structures, and X-ray data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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