Stereoselective Glycosidations

Control of α/β Stereoselectivity in Lewis Acid Promoted C-Glycosidations Using a Controlling Anomeric Effect Based on the Conformational Restriction Strategy[**]

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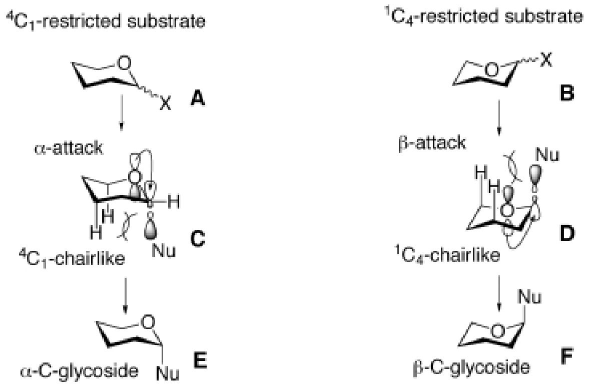
The synthesis of C-glycosides has been extensively studied because of their importance as stable mimics for natural O-glycosides.[1] Lewis acid promoted C-glycosidation is effective in providing a wide variety of C-glycosidic compounds. However, control of the stereochemistry is often problematic.[1] For example, although allyltrimethylsilanes can be used as nucleophiles in reactions with pyranosyl donors to provide the α products stereoselectively, it is difficult to carry out β-selective C-glycosidations by this method.[2–5] We report herein an anomeric-effect-dependent, highly α- and β-selective, Lewis acid promoted C-glycosidation based on the conformational restriction of the pyranose ring.[6–9]

Experimental and theoretical studies have shown that conformational features and the reactivity of the anomeric position of sugars are affected by the anomeric effect,[10] which is a stereoelectronic effect resulting from n→σ* hyperconjugation between the nonbonding orbital of the oxygen atom in the ring and the antibonding orbital of the anomeric carbon–heteroatom bond in their planar arrangement.[10–14] This kind of orbital interaction gives rise to a phenomenon known as the kinetic anomeric effect, which stabilizes the transition state during bond-forming (or bond-cleavage) processes at the anomeric center, where nucleophilic attack occurs through an axial trajectory.[10–14] We recently developed a highly stereoselective radical C-glycosidation reaction in which the stereochemistry is controlled by the kinetic anomeric effect, depending on the conformation of the substrate.[9]

Although the kinetic anomeric effect for α-axial attack at the oxocarbenium ion in C-glycosidations is considered to be very weak,[5] we speculated that the stereoselectivity of S_N1-type C-glycosidations of pyranoses may be controlled effectively by the kinetic anomeric effect when conformationally restricted substrates are employed. Our working hypothesis, summarized in Scheme 1, is based on the principle that the conformation of the transition state and that of the reactive intermediate are strongly influenced by the conformational effects that stabilize the ground-state conformation.[8,9,11] In the S_N1-type C-glycosidation reaction of substrate **A**, which is conformationally restricted in a $^4C_1$-chair form, the transition state would assume the $^4C_1$-chairlike form **C** as a result of conformational restriction of the pyranose backbone, in which conformation the anomeric center would be pyramidal. Thus, the α-product **E** can be formed highly selectively as a consequence of the kinetic anomeric effect. Similarly, when the conformation of the substrate is restricted to the unusual $^1C_4$-chair form **B**, the kinetic anomeric effect promotes selective formation of the β-product **F** via the $^1C_4$-chairlike transition state **D**. Both axial-attack transition states $^4C_1$-restricted **C** and $^1C_4$-restricted **D** should be significantly stabilized by the interaction between the antibonding $\sigma^{*\neq}$ of the anomeric C–C bond being formed and the orbital of a nonbonded electron pair (n_O) on the oxygen atom in the ring because of their planar arrangement,[9,13] while both the axial-attack transition states would be accompanied by significant 1,3- and 1,5-diaxial steric repulsion caused by the conformational restriction.



Scheme 1. The working hypothesis for the kinetic-anomeric-effect-dependent α- and β-selective C-glycosidation reaction.

We selected allyltrimethylsilane as the model nucleophile, because its Lewis acid promoted anomeric attack seems to proceed via an oxocarbenium intermediate, at least in a nonpolar solvent such as CH_2Cl_2,[5,8,15] which would make the experimental results easier to interpret. Furthermore, anome-

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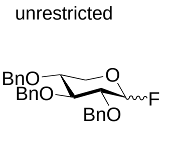
ric allylation reactions are very useful in synthetic organic chemistry.[1] Thus, we planned anomeric allylation reactions of the 1-fluoro-D-xylose substrates **2** (restricted in the $^4C_1$ conformation by the cyclic 3,4-diketal)[16] and **3** (restricted in the $^1C_4$ conformation by bulky *O*-silyl groups),[17] and of the unrestricted tri-*O*-benzylated 1-fluoro-D-xylose **1**.[18]



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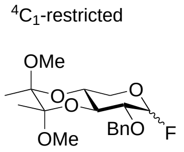

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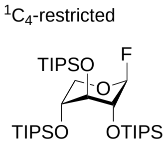

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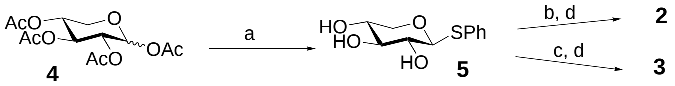
Glycosyl fluorides are relatively stable and readily prepared, and are also very effective glycosyl donors.[19] The substrates **2** and **3** were prepared from tetra-*O*-acetyl-D-xylose (**4**) (Scheme 2). ^1H NMR and ^{19}F NMR spectroscopic analysis showed that they are conformationally restricted in the $^4C_1$ and the $^1C_4$ conformations, respectively.[20]



Scheme 2. Synthesis of the substrates **2** and **3**: a) 1) HBr/AcOH, CH_2Cl_2; 2) PhSH, Et_3N, CH_3CN; 3) NaOMe, MeOH, 84%; b) 1) $[Me(MeO)_2C]_2$, $(MeO)_3CH$, CSA, MeOH; 2) BnBr, NaH, THF, 60%; c) TIPSOTf, NaH, THF, 85%; d) DAST, NBS, CH_2Cl_2, 84% (**2**), 60% (**3**). CSA = camphorsulfonic acid, Bn = benzyl, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate, DAST = (diethylamino)sulfur trifluoride, NBS = *N*-bromosuccinimide.

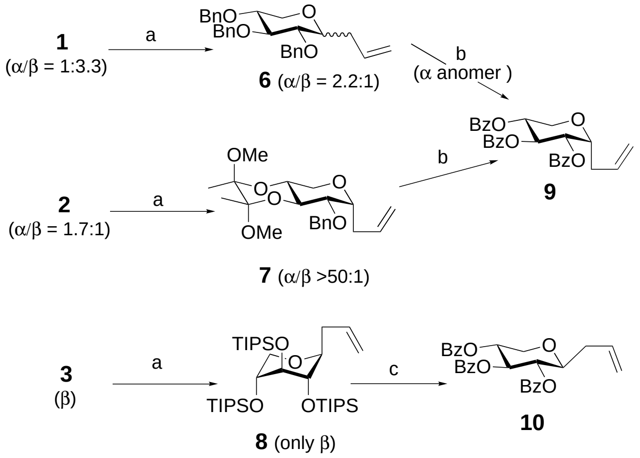
C-glycosidation of **1**, **2**, and **3** was performed with allyltrimethylsilane (2.0 equiv) and $BF_3 \cdot OEt_2$ (0.05 equiv) in CH_2Cl_2 at room temperature (Table 1).[21] The products were converted into the corresponding tri-*O*-benzoates **9** and **10** (Scheme 3), the structures of which were confirmed by ^1H NMR spectroscopic analysis.[22,23] The reaction of the unrestricted substrate **1** ($\alpha/\beta = 1{:}3.3$) showed moderate α selectivity to give **6** (Table 1, entry 1, $\alpha/\beta = 2.2{:}1$), which was in accord with previous results.[2b,c,5] The reaction of the $^4C_1$-restricted substrate **2** ($\alpha/\beta = 1.7{:}1$) proceeded with high α-selectivity to give **7** (Table 1, entry 2, $\alpha/\beta > 50{:}1$), which is the first highly α-selective example of this kind of Lewis acid promoted anomeric allylation in the absence of acetonitrile as solvent.[5] Thus, the conformational restriction in the $^4C_1$ form significantly increased α selectivity. When the $^1C_4$-restricted β-fluoro substrate **3** was used, the stereoselectivity was completely reversed to give the product of retention of configuration, the β-*C*-allyl glycoside **8**, as the sole product (Table 1, entry 3).

Table 1: The C-glycosidation reaction of substrates **1**, **2**, and **3** with allyltrimethylsilane.[a]

Entry	Substrate	Conformation	Product	Yield [%][b]	α/β[c]
1	**1**	unrestricted	**6**	70	2.2:1
2	**2**	$^4C_1$	**7**	85	> 50:1
3	**3**	$^1C_4$	**8**	73	only β

[a] The substrate was treated with allyltrimethylsilane (2.0 equiv) and $BF_3 \cdot OEt_2$ (0.05 equiv) in CH_2Cl_2 at room temperature in the presence of 4-Å molecular sieves. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy.

The stereochemical results suggest that the allylation proceeds through an S_N1-type mechanism.[24] These results clearly demonstrate that conformational restriction increases and can also invert the stereoselectivity in C-glycosidations, as we had hypothesized. It should be noted that highly selective α-and β-axial nucleophilic attack occurred in the reactions with **2** and **3**, even though the transition states for the reactions would have been accompanied by significant 1,3- and 1,5-diaxial steric repulsion because of the conformational restriction to the $^4C_1$- or the $^1C_4$-chair conformation.



Scheme 3. Anomeric allylation of the xylosyl fluorides **1**, **2**, and **3**: a) see Table 1; b) 1) BCl_3, CH_2Cl_2; 2) BzCl, DMAP, pyridine, 38% from the α anomer of **6**, 75% from **7**; c) 1) TBAF, THF; 2) BzCl, Et_3N, DMAP, MeCN, 72%. Bz = benzoyl, DMAP = 4-(dimethylamino)pyridine, TBAF = tetrabutylammonium fluoride.

In summary, depending on the restricted conformation of the substrate ($^4C_1$ or $^1C_4$), either the α or the β product was formed highly stereoselectively in our C-glycosidation reaction. This study has shown that the kinetic anomeric effect can be used effectively for controlling both α and β stereoselectivity in glycosidation reactions.

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[18] In hexopyranoses, the steric effect of the 5-hydroxymethyl moiety would significantly affect the course of their glycosidation reactions, especially in the case of β-axial attack at the $^{1}C_{4}$-restricted substrate because of 1,5-diaxial repulsion, and this would disturb the exact estimation of the anomeric effect on the stereoselectivity. Thus, xylose derivatives that lack a carbon substituent at the 5-position were selected as model substrates.

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[20] Typical ^{1}H NMR coupling constants for the conformationally restricted substrates in $CDCl_3$: **2** (α-anomer), $J_{1,2} = 2.8$, $J_{2,3} = 9.4$, $J_{4,5b} = 9.7$ Hz; **3**, $J_{1,2}$, $J_{2,3}$, $J_{3,4}$, $J_{4,5b}$, $J_{2,3} \approx 0$ Hz. The $^{1}C_{4}$-restricted 1-β-fluoro structure of **3** was also confirmed by ^{19}F NMR spectroscopy in $CDCl_3$: $J_{F,1} = 49.9$, $J_{F,2} = 5.1$ Hz (conformational analysis of pyranoses by ^{19}F NMR: M. Michalik, M. Hein, M. Frank, *Carbohydr. Res.* **2000**, *327*, 185–218).

[21] For experimental details, see Supporting Information.

[22] The ^{1}H NMR spectral data of the tri-*O*-benzoates **9** and **10** were in accord with those of authentic samples synthesized previously by another method.[9]

[23] The α/β ratio was determined based on the anomeric proton signals in the ^{1}H NMR spectrum.

[24] It may be possible that the β-product **7** was produced in part through the S_N2 reaction of the α anomer of the donor **2**.