Highly α- and β-Selective Radical *C*-Glycosylation Reactions Using a Controlling Anomeric Effect Based on the Conformational Restriction Strategy. A Study on the Conformation−Anomeric Effect−Stereoselectivity Relationship in Anomeric Radical Reactions

Hiroshi Abe, Satoshi Shuto,* and Akira Matsuda*

Contribution from the Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

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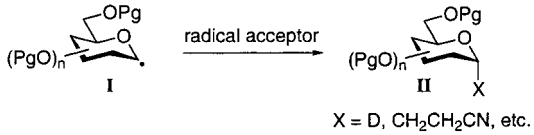
Abstract: We hypothesized that, because the stereoselectivity of anomeric radical reactions was significantly influenced by the anomeric effect, which can be controlled by restricting the conformation of the radical intermediate, the proper conformational restriction of the pyranose ring of the substrates would therefore make highly α- and β-stereoselective anomeric radical reactions possible. Thus, the conformationally restricted 1-phenylseleno-D-xylose derivatives **9** and **10**, restricted in a $^4C_1$-conformation, and **11** and **12**, restricted in a $^1C_4$-conformation, were designed and synthesized by introducing the proper protecting groups on the hydroxyl groups on the pyranose ring as model substrates for the anomeric radical reactions. The radical deuterations with Bu_3SnD and the *C*-glycosylation with $Bu_3SnCH_2CH{=}CH_2$ or $CH_2{=}CHCN$, using the $^4C_1$-restricted substrates **9** and **10**, afforded the corresponding α-products (α/β = 97:3−85:15) highly stereoselectively, whereas the $^1C_4$-restricted substrates **11** and **12** selectively gave the β-products (α/β = 1:99−0:100). Thus, stereoselectivity was significantly increased by conformational restriction and was completely inverted by changing the substrate conformation from the $^4C_1$-form into the $^1C_4$-form. Ab initio calculations suggested that the radical intermediates produced from these substrates possessed the typical $^4C_1$- or $^1C_4$-conformation, which was similar to that of the substrates, and that the anomeric effect in these conformations would be the factor controlling the transition state of the reaction. Therefore, the highly α- and β-selective reactions would occur because of the anomeric effect, which could be manipulated by conformational restriction of the substrates, as expected. This would be the first radical *C*-glycosylation reaction to provide both α- and β-*C*-glycosides highly stereoselectively.

Introduction

C-Glycosides have gained increasing interest in view of their occurrence as fragments in the structures of a number of natural products.[1] Moreover, because of their resistance to hydrolysis, *C*-glycosides are expected to be stable mimics for natural *O*-glycosides with biological activity.[2,3] Consequently, the methods for the synthesis of *C*-glycosides have been extensively studied, via anomeric anion, cation, and radical intermediates.[4]

Scheme 1



Radical *C*-glycosylations have the advantage of occurring under mild neutral conditions, and those using an intramolecular cyclization have been effective in constructing *C*-glycosidic bonds highly stereoselectively. In recent years, we have been working to develop radical *C*-glycosylations by intramolecular cyclization with a silyl tether.[3,5] However, while anomeric pyranosyl radicals **I**, such as glucosyl radicals, stereoselectively afford the corresponding α-product **II**[6,7] in intermolecular radical *C*-glycosylation reactions, as shown in Scheme 1, the β-selective radical *C*-glycosylation is more difficult to effect.[8]

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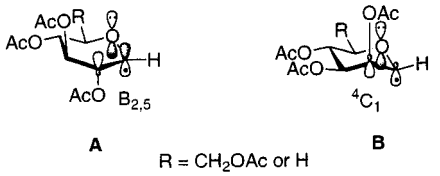


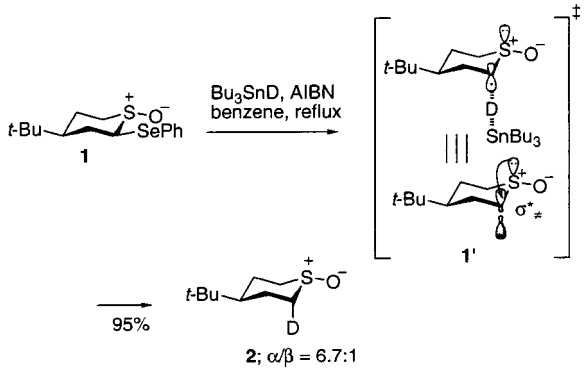
Figure 1. Conformations of pyranosyl radical intermediates.

In S_N1-like *O*- or *C*-glycosylation reactions of pyranoses via an oxocarbenium intermediate, the nucleophilic attack at the anomeric position often occurs stereoselectively from the α-side to afford the corresponding α-glycosides as the major products.[9] Experimental and theoretical studies showed that the stereoselectivity in these S_N1-like glycosylation reactions is mainly due to the kinetic anomeric effect.[10,11] As pointed out by Giese,[7c] in the radical *C*-glycosylation reaction shown in Scheme 1, the α-selectivity can also be a result of the anomeric effect, similar to that of the S_N1-like glycosylations. The anomeric effect should be influenced by the conformation of the sugar molecule, because it is the stereoelectronic effect on the anomeric position due to the nonbonding electrons on the ring oxygen.[11b,c] Consequently, we speculated that the anomeric effect might be employed to effectively control the stereoselectivity in anomeric radical reactions by using conformationally restricted substrates. On the basis of this idea, we performed anomeric radical reactions as well as theoretical calculations with the conformationally restricted D-xylose derivatives as model substrates, concentrating especially on the conformation−anomeric effect−stereoselectivity relationship.[12] Thus, we report here the anomeric effect-dependent highly α- and *β*-selective anomeric radical reactions based on the conformational restriction of the pyranose ring.

Results and Discussion

Anomeric Effect in the Anomeric Radical Reactions. Giese and co-workers have clarified conformations of the anomeric radical intermediates produced from several *O*-acetylated pyranoses using ESR spectroscopy,[13] and their results are summarized in Figure 1. The glucosyl and xylosyl radicals possessed $B_{2,5}$-boatlike conformation **A**, and the mannosyl and lyxosyl radicals possessed $^4C_1$-chairlike conformation **B**. They explained that these pyranosyl radicals were maximally stabilized in conformations **A** or **B** because of the effective interaction between the radical orbital (SOMO), the σ^*-orbital of the adjacent C_2-O_2 bond, and the p-orbital of a lone pair of the ring oxygen in their periplanar arrangement. These results show that the anomeric effect is likely to effectively stabilize the anomeric radical intermediate. They also pointed out that only in the case of axial attack on the $^4C_1$-chairlike conformer **B** is the overlap between the lone pair of the ring oxygen and the unpaired electron of the radical orbital (or newly formed bond) maintained en route to the transition state to form only α-products, and that in the case of $B_{2,5}$-boatlike conformer **A**, where the stereoselectivity is somewhat smaller, the decrease in the selectivity is probably due to the fact that boat conformers are more flexible than chair conformers.[7c]

Scheme 2



The important question in anomeric radical reactions is what the transition state is and how the stereoselectivity is controlled. Renaud reported pregnant results that radical deuteration of α-phenylseleno cyclic sulfoxide **1** with Bu_3SnD gave the α-deuterated isomer **2** selectively[14] (Scheme 2). He finely explained that the energy of transition state **1′**, in which the radical center is pyramidal, is lowered by the interaction between the antibonding orbital ($\sigma^{*‡}$) of the newly forming carbon−deuterium (C−D) bond and one of the nonbonded electron pairs of the sulfur atom.[15,16] This theory that the transition state energy can be lowered by the orbital interaction due to $\sigma^{*‡}$ of the newly forming bond is originally presented by Cieplack for expounding the stereoselectivity of nucleophilic additions.[15] The explanation by this kind of orbital interaction (the radical version of the Cieplack theory) would afford the best account of the transition state of anomeric radical reactions; the orbital interaction between the $\sigma^{*‡}$ of the newly forming bond at the anomeric position and one of the nonbonded electron pairs of the ring oxygen stabilizes the transition state, which is the kinetic anomeric effect in the radical reactions.

On the basis of these findings, the mechanism of anomeric radical reactions is, using the deuteration of the tetra-*O*-

(6) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (b) Descotes, G. *J. Carbohydr. Chem.* **1988**, *7*, 1−20.

(7) (a) Giese, B.; Dupes, J. *Tetrahedron Lett.* **1984**, *25*, 1349−1352. (b) Giese, B.; Dupuis, J.; Leising, M.; Nix, M.; Lindner, H. J. *Carbohydr. Res.* **1987**, *171*, 329−341. (c) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969−980.

(8) *β*-selective radical *C*-glycosylation of xylose derivatives has been reported: see ref 7b.

(9) (a) Lemieux, R.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc*. **1975**, *97*, 4056−4062. (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc*. **1982**, *104*, 4976−4978.

(10) Experimental studies: (a) Toshima, K.; Tatsuta, K. *Chem. Rev* **1993**, *93*, 1503−1531 andreferences therein. (b) Hanessian, S. *Preparative Carbohydrate Chemistry*; Marcel Dekker: New York, 1996 and references therein.

(11) Theoretical studies: (a) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019−5087 and references therein. (b) *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series 539; Thatcher, G. R. J., Ed.; American Chemical Society: Washington, DC, 1993. (c) Thibaudeau, C.; Chattopadhyaya, J. *Stereoelectronic Effects in Nucleosides and Nucleotides and their Structural Implications*; Uppsala University Press: Uppsala, Sweden, 1999.

(12) In hexopyranoses, such as glucose or mannose derivatives, the steric effect due to the hydroxymethyl moiety attached at the 5-position would affect the stereoselectivity of the anomeric radical reaction, which may disturb the exact estimation of the anomeric effect on the stereoselectivity. Therefore, we used the xylose derivatives as the model substrates in this study, because they lack the carbon substituent at the 5-position.

(13) (a) Dupuis, J.; Giese, B.; Ruegge, D.; Fischer, H.; Korth, H.-G.; Sustman, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896−898. (b) Korth, H.-G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453−1459.

(14) Renaud, P. *Helv. Chim. Acta* **1991**, *74*, 1305−1313.

(15) Cieplack pointed out the importance of hyperconjugation in the transition state of nucleophilic addition reactions to carbonyls, because the energy of the transition state is lowered by delocalization of electrons from an antiperiplanar vicinal *σ*-bond to the antibonding component ($\sigma^{*‡}$) of the newly forming bond: (a) Cieplack, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552. (b) Johnson, C. R.; Tait, B. D.; Cieplack, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5857−5876 and references therein.

(16) An explanation of the radical reaction transition state pertaining to this kind of orbital interaction: Bodpudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001−2006.

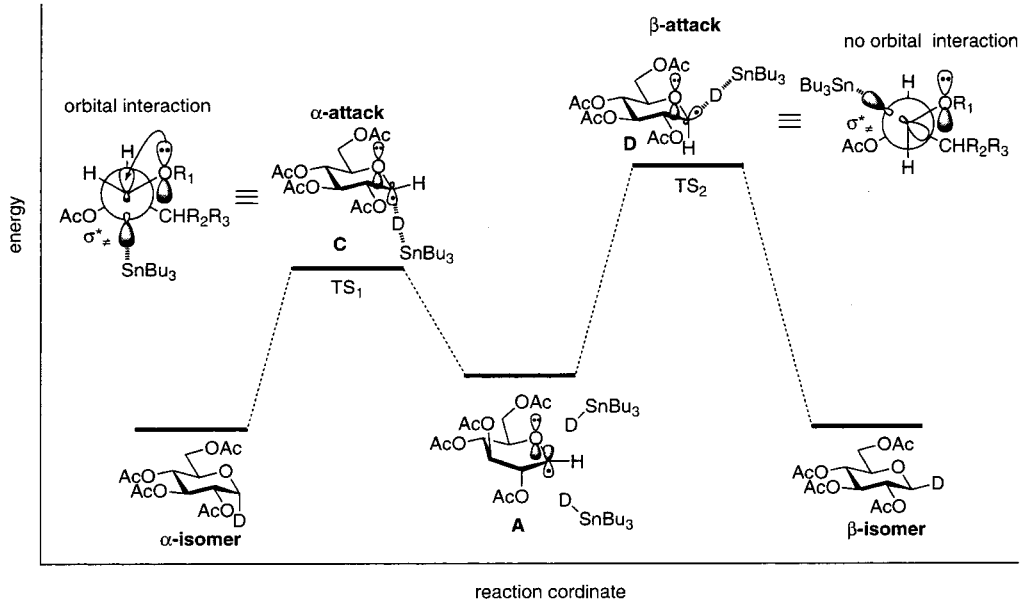
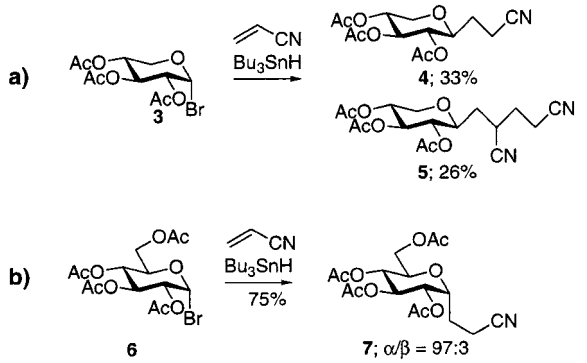
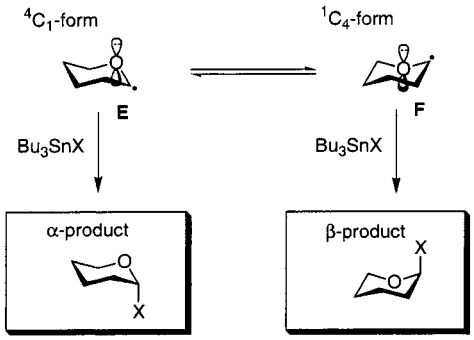


Figure 2. Possible reaction pathways of the anomeric glucosyl radical deuteration.

Scheme 3



Scheme 4



acetylated anomeric glucosyl radical by Bu_3SnD[7a] as an example, summarized in Figure 2. As reported by Giese,[13] radical intermediate **A** in the $B_{2,5}$-boat conformation has a planar (sp^2-like) radical center with a radical orbital having high p-character. Bu_3SnD could possibly attack it from either the α- or the β-side. The important point in our mechanism is that in the transition state the radical center should have more s-character to be pyramidal (sp^3-like),[17] where the pyranose ring would adopt a $^4C_1$ chairlike conformation. Thus, in the course of forming the C−D bond, the radical center becomes pyramidal to access to $^4C_1$ chairlike transition state **C** or **D**. The transition state for α-side attack **C** can be effectively stabilized by the interaction between the antibonding $\sigma^{*\ddagger}$ of the newly forming C−D bond and the p-orbital of a nonbonded electron pair (n_O) on the ring oxygen, while little stabilization would occur from the $\sigma^{*\ddagger}-n_O$ interaction in the transition state for β-side attack **D**. This significant stabilization, due to the $\sigma^{*\ddagger}-n_O$ interaction in the **C** transition state, for example, would cause the selective formation of the α-product rather than the β-product; this is the kinetic anomeric effect in the anomeric radical reactions.

Interestingly, the anomeric radical addition reaction to CH_2=CHCN with D-xylose derivative **3** gave only β-products **4** and **5** (Scheme 3a),[7b] while a similar reaction with D-glucose derivative **6** gave the usual α-product **7** highly stereoselectively (Scheme 3b).[7b] Giese previously described that the β-isomer might be produced via the ^{1,4}B-boat or the $^1C_4$-chair conformer in the xylosyl radical intermediate because of the stereoelectronic effect.[7c] On the other hand, we reasoned that the highly β-selective reaction with **3** as the substrate would occur because of the kinetic anomeric effect via the $^1C_4$-like transition state, having the pyramidal radical center. The $^1C_4$-like transition state can be effectively stabilized by the $\sigma^{*\ddagger}-n_O$ interaction, because the $^1C_4$-conformation might be more stable in xylose derivatives, as compared with the usual hexopyranoses, because of the lack of the hydroxymethyl moiety at the 5-position.

These experimental results and considerations led us to the hypothesis that the stereoselectivity of anomeric radical reactions was significantly affected by the kinetic anomeric effect, which can be controlled by restricting the conformation of the radical intermediate; the proper conformational restriction of the pyranose ring of substrates would make highly α- and β-stereoselective anomeric radical reactions possible, as shown in Scheme 4. In the reaction of anomeric radical intermediate **E** conformationally restricted in the $^4C_1$-chair form, the conformation of which is analogous to transition state **C** shown in Figure 2, the anomeric effect works effectively to give the α-product highly selectively, because the intermediates smoothly progress to the transition state in the sterically preferable $^4C_1$-chairlike conformation. Similarly, when the conformation of the radical intermediate is restricted to the unusual $^1C_4$-chair form **F**, the corresponding β-product should be selectively

(17) A calculation study showed that methyl radical had a productlike pyramidal geometry in the transition state of its addition to a C=C double bond: Dewar, M. J. S.; Olivella, S. *J. Am. Chem. Soc.* **1978**, *100*, 5290−5295.

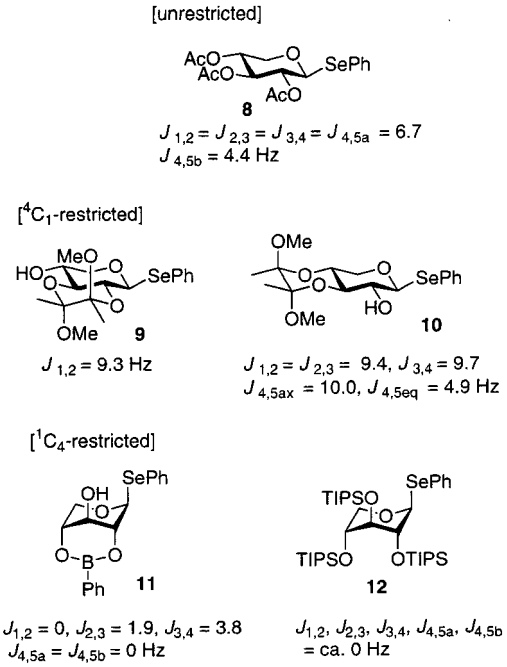


Figure 3. Conformationally restricted and unrestricted xylose derivatives as the anomeric radical reaction substrates.

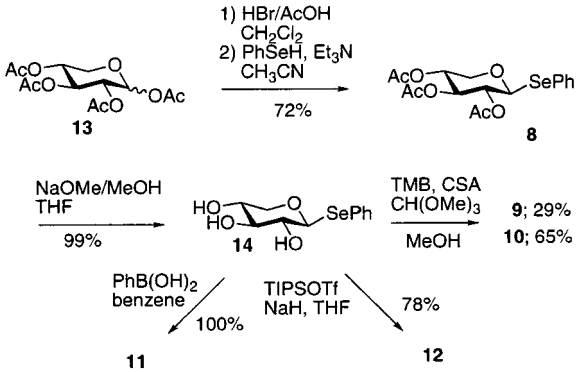
obtained because of the kinetic anomeric effect. Therefore, depending on the restricted conformation of the substrates, in the $^4C_1$- or the $^1C_4$-form, the α- or *β*-products can be obtained highly stereoselectively via anomeric radical reactions.

Design and Synthesis of D-Xylose Derivatives Restricted to a $^4C_1$- or a $^1C_4$-Chair Conformation as Substrates. The conformations of pyranoses can be restricted by introducing proper protecting groups on the hydroxyl groups. We designed the 1-*β*-phenylseleno-D-xylose derivatives **9**−**12** restricted in a $^4C_1$- or a $^1C_4$-conformation as the substrates for the experimental and theoretical calculation studies. The conformationally unrestricted tri-*O*-acetate **8** was also used in this study as the reference substrate. The structures of these substrates are shown in Figure 3.

Substrates **9**−**11** have a bicyclic structure, because introducing another ring into a pyranose would effectively restrict the conformation of the pyranose ring. The conformation of the pyranose ring of substrates **9** and **10** bearing a 2,3- or a 3,4-*O*-cyclic-diketal group would be restricted in the $^4C_1$-form because of its *trans*-decalin-type ring system.[18] Cyclic-phenylboronate **11** was designed as a conformationally restricted substrate in the $^1C_4$-form, because pyranoses are known to adopt a $^1C_4$-conformation when a cyclic-phenylboronate system is introduced at the 2,4-*cis*-diol.[19]

Substrate **12** was designed as a $^1C_4$-restricted substrate without introducing another ring. It has been recognized that introducing a significantly bulky protecting group at the 3,4-*trans*-hydroxyl groups of pyranoses causes a flip of their conformation leading to a $^1C_4$-form, in which the bulky substituents are in axial positions because of mutual steric repulsion. Suzuki and co-workers first reported this type of conformational feature of pyranosides and efficiently synthesized aryl *C*-glycosides using a $^1C_4$-conformational donor.[20] We successfully constructed the

Scheme 5



tricyclic sugar moiety of herbicidin B, a nucleoside antibiotic, via a facially selective reduction of the enone system in a $^1C_4$-conformational substrate.[21] We also developed an efficient method for preparing 1-α-*C*-glucosides via a radical cyclization reaction using $^1C_4$-restricted glucose derivatives.[3a−c] On the basis of these findings, we designed 2,3,4-tris-*O*-triisopropysilyl (TIPS)-protected D-xylose derivatives **12** that would adopt a $^1C_4$-conformation because of the steric effect of the bulky silyl groups.

The preparation of substrates **8**−**12** is summarized in Scheme 5. Tetra-*O*-acetylxylopyranoside **13** was treated with HBr/AcOH, followed by PhSeH/Et_3N to give 1-*β*-phenylselenide **8** as the sole product. Treatment of **8** with NaOMe in MeOH/THF afforded triol **14**, which was the common intermediate for the desired substrates. When **14** was heated with 2,2,3,3-tetramethoxybutane (TMB) and $CH(OMe)_3$ in MeOH in the presence of catalytic 10-camphorsulfonic acid (CSA), the desired 2,3-*O*-cyclic-diketal **9** (29%) and 3,4-*O*-cyclic-diketal **10** (65%) were obtained.[18] On the other hand, the 2,4-*O*-cyclic-phenylboronate **11** was prepared by the procedure reported by Ferrier and co-workers;[19] namely, heating a solution of triol **14** and phenylboronic acid in benzene under reflux with a Dean−Stark apparatus quantitatively gave the desired **11**.

3,4-Bis-*O*-silyl pyranoses have been synthesized via introduction of the silyl groups on the 3,4-*trans*-diol of the glycal.[3a−c,20,21] We most recently developed an efficient method for directly introducing the bulky silyl groups on the *trans*-vicinal-diol of pyranoses with a TIPSOTf/NaH/THF system.[22] Thus, treatment of **14** with TIPSOTf/NaH in THF at room temperature successfully gave 2,3,4-tris-*O*-TIPS substrate **12** in 78% yield.

The conformations of these substrates were investigated by ^1H NMR (Figure 3). The large coupling constants ($J > 9.3$ Hz) between the vicinal protons of **9** or **10** showed that these protons were in an axial orientation, where the pyranose ring had the $^4C_1$-conformation. On the other hand, the small coupling constants ($J < 3.8$ Hz) between the vicinal equatorial protons of **11** or **12** showed that these had the $^1C_4$-conformation. The conformationally unrestricted **8** had medium coupling constants ($4.4 < J < 6.7$ Hz), compared with the other two types of conformationally restricted substrates.

Deuteration of the Conformationally Restricted Xylosyl Radicals. We investigated the deuteration of the anomeric radicals produced from unrestricted substrates **8**, $^4C_1$-restricted substrates **9** and **10**, and $^1C_4$-restricted substrates **11** and **12** with

(18) (a) Montchamp, J. L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897−3899. (b) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2023−2031.

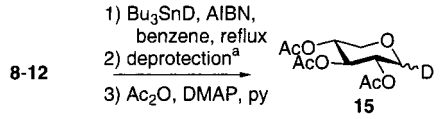
(19) Ferrier, R. J.; Prasad, D.; Rudowski, A.; Sangster, I. *J. Chem. Soc.* **1964**, 3330−3334.

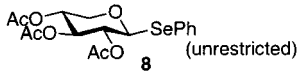
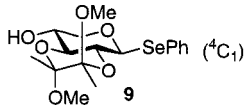
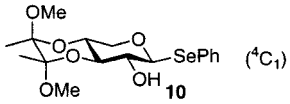
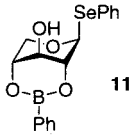
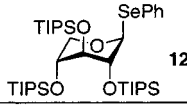
(20) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 636−666.

(21) Ichikawa, S.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* **1999**, *121*, 10270−10280.

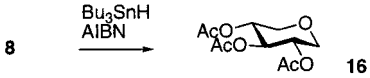
(22) Abe, H.; Shuto, S.; Tamura, S.; Matsuda, A. *Tetrahedron Lett.* **2001**, *42*, 6159−6161.

Table 1. Deuteration of the Xylosyl Anomeric Radicals



entry	substrate (conformation)	15[b] α/β[c] (yield, %)
1	 **8** (unrestricted)	65:35 (66)
2	 **9** ($^4C_1$)	97:3 (83)
3	 **10** ($^4C_1$)	97:3 (83)
4	 **11** ($^1C_4$)	1:99 (72)
5	 **12** ($^1C_4$)	1:99 (80)

[a] Conditions were noted in the Experimental Section. [b] For ^1H NMR assignment of the 1-deuterated product **15**, the corresponding reduction product (1,5-anhydro-2,3,4-tri-*O*-acetyl-D-xylitol, **16**) was prepared by treating **8** with Bu_3SnH/AIBN.



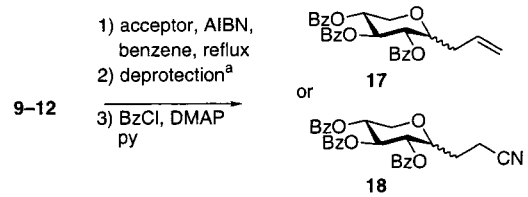
[c] Determined by ^2H NMR analysis.

Bu_3SnD/AIBN. Such deuterium-labeling experiments would be useful in estimating the stereoselectivity, leading to a clarification of the anomeric effect in anomeric radical reactions.[7a] The substrate (0.07 M) was heated with Bu_3SnD (2.0 equiv)/AIBN (0.5 equiv) in benzene under reflux and deprotected under appropriate conditions, and the resulting three hydroxyl groups of the product were acetylated with Ac_2O/pyridine. Deuterium-labeled product **15** was purified by silica gel column chromatography, and the stereoselectivity was determined by the ^2H NMR spectrum. The results are summarized in Table 1.

The deuteration of unrestricted **8** as the substrate showed a moderate α-selectivity (entry 1, $\alpha/\beta = 65:35$). The reaction with substrate **9**, restricted in the $^4C_1$-conformation by a 2,3-*O*-cyclic-diketal, showed high α-selectivity (entry 2, $\alpha/\beta = 97:3$). The reaction with the other $^4C_1$-restricted substrate **10** with a 3,4-*O*-cyclic-diketal also showed the same high α-selectivity (entry 3, $\alpha/\beta = 97:3$). Thus, the conformational restriction of the substrate in the $^4C_1$-form resulted in significantly increased α-selectivity compared with the result of the unrestricted substrate **8**. When $^1C_4$-restricted substrates **11** and **12** were used, the stereoselectivity was completely reversed. The radical deuterations with both the 2,4-*O*-cyclic-phenylboronate **11** and the 2,3,4-tris-*O*-TIPS derivative **12**, irrespective of the hydroxyl protecting groups, highly selectively gave the *β*-deuterated products (entries 4 and 5, $\alpha/\beta = 1:99$).

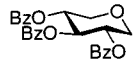
These results clearly demonstrate that the conformational restriction of the pyranose ring in the $^4C_1$-form or $^1C_4$-form increases and inverts the stereoselectivity in the anomeric radical reaction.

Table 2. Allylation and Cyanoethylation of the Xylosyl Anomeric Radicals



entry	substrate	conformation	acceptor[b]	product	α/β[c] (yield, %)
1	**9**	$^4C_1$	A	**17**	85:15 (73)
2	**10**	$^4C_1$	A	**17**	91:9 (69)
3	**11**	$^1C_4$	A	**17**	1:99 (61)
4	**12**	$^1C_4$	A	**17**	1:99 (26)[d]
5	**12**	$^1C_4$	B	**18**	0:100 (66)

[a] Conditions were noted in Experimental Section. [b] A, $Bu_3SnCH_2CH{=}CH_2$; B, $CH_2{=}CHCN$. [c] Determined by ^1H NMR analysis. [d] Reduced product **19** was obtained in 61% yield.


19

Stereoselective *C*-Glycosylation of the Xylosyl Radicals. The conformational restriction strategy, which proved to be effective in controlling the stereochemistry in the deuterium-labeling reactions described above, was next applied to the radical *C*-glycosylation reactions, that is, the allylation and the cyanoethylation of the anomeric xylosyl radicals using the $^4C_1$-restricted substrates, 2,3-*O*-cyclic-diketal **9** and 3,4-*O*-cyclic-diketal **10**, and the $^1C_4$-restricted substrates, 2,4-*O*-cyclic-phenylboronate **11** and 2,3,4-tris-*O*-TIPS ether **12**. The substrate was heated with $Bu_3SnCH_2CH{=}CH_2$/AIBN[23] or $CH_2{=}CH_2CN$/Bu_3SnH/AIBN[7b] in benzene under reflux and deprotected under appropriate conditions, and the resulting three hydroxyl groups of the product were benzoylated with BzCl/pyridine. The *C*-glycosylation product, 1-*C*-allylated **17** or 1-*C*-cyanoethylated **18**, was isolated after purification by silica gel column chromatography, and the stereoselectivity was determined by the ^1H NMR spectrum. The results are summarized in Table 2.

The radical *C*-allylation[24] with substrate **9** restricted in the $^4C_1$-conformation stereoselectively gave the α-product ($\alpha/\beta = 85:15$) in 73% yield (entry 1). A similar result was observed in the reaction with the other $^4C_1$-restricted substrate **10** under the same reaction conditions (entry 2, $\alpha/\beta = 91:9$, 69% yield). When the 2,4-*O*-cyclic-phenylboronate **11** restricted in the $^1C_4$-conformation was treated under the same conditions, the stereoselectivity was completely inverted, and the *β*-product was obtained with extremely high stereoselectivity (entry 3, $\alpha/\beta = 1:99$, yield 61%). The reaction with the $^1C_4$-restricted 2,3,4-tris-*O*-TIPS derivative **12** as the substrate also gave the *β*-product highly selectively, although the yield was low (entry 4, $\alpha/\beta = 1:99$, yield 26%), and the directly reduced product **19** was obtained as the major product in 61% yield.[25] By using $CH_2{=}CH_2CN$ as the radical acceptor, the yield was significantly improved without decreasing the stereoselectivity, and the *β*-cyanoethylated product **18** was obtained as the sole product in 66% yield from the substrate **12** (entry 5, $\alpha/\beta = 0:100$).

(23) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079−4094.

(24) The radical allylation with unrestricted substrate **21** gave an unknown product in low yield, which is probably derived from the acyloxy migration from the 2-position to the 1-position.

(25) Reduced product **19** might be produced via the intramolecular hydrogen abstraction from the 2-*O*-TIPS group.

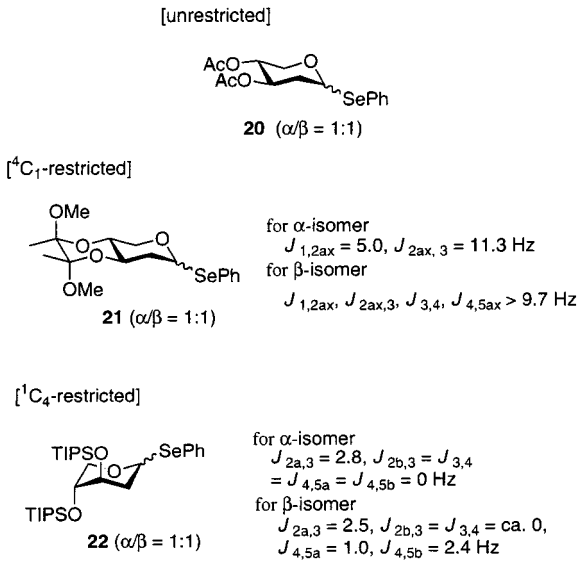
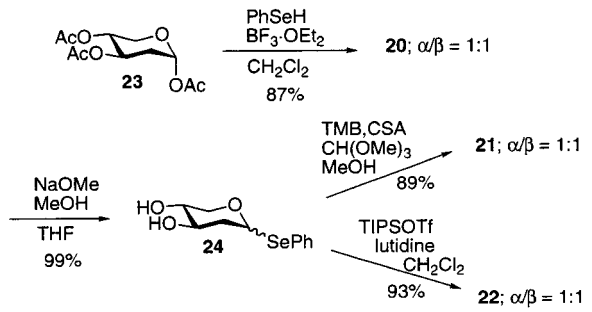


Figure 4. Conformationally restricted and unrestricted 2-deoxyxylose derivatives as the anomeric radical reaction substrates.

Scheme 6



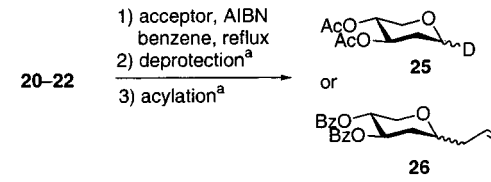
As described, very effective stereocontrol by this conformational restriction method was observed in the radical *C*-glycosylation reactions (Table 2), analogous to the deuteration (Table 1). This is the first radical *C*-glycosylation reaction that highly stereoselectively provides both the α- and *β*-*C*-glycosides.

Deuteration and *C*-Glycosylation of the 2-Deoxyxylosyl Radicals. In the anomeric radical *C*-allylation, the stereoselectivity with $^4C_1$-restricted compounds **9** and **10** as the substrates (Table 2, entries 1, 2) was slightly lower than in those with $^1C_4$-restricted substrates **11** and **12** (Table 2, entries 3, 4). We considered whether the stereoselectivity in the radical allylation could be influenced by the 1,2-steric repulsion derived from the 2-hydroxyl moiety on the α-face. To clarify the effect of the 2-hydroxyl group on the stereoselectivity of the reaction, we designed 2-deoxyxylose derivatives, that is, the unrestricted substrate **20**, the substrate **21** restricted in a $^4C_1$-conformation with a 3,4-*O*-cyclic-diketal, and the substrate **22** restricted in a $^1C_4$-conformation with bulky TIPS groups (Figure 4), and examined the radical deuteration and allylation with them.

The preparation of 2-deoxy-D-xylose derivatives **20**−**22** is summarized in Scheme 6. Tri-*O*-acetyl-2-deoxy-D-xylopyranose **23**, derived from tetra-*O*-acetyl-D-xylose,[26] was treated with PhSeH/BF_3·OEt_2 to give 1-phenylseleno derivative **20** as an anomeric mixture (α/β = 1:1). After removal of the acetyl groups of **20**, the resulting diol **24** was further treated with TMB/CSA/$CH(OMe)_3$ or with TIPSOTf/2,6-lutidine to afford $^4C_1$-restricted substrate **21** or $^1C_4$-restricted substrate **22**, respectively.

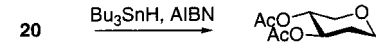
(26) Giese, B.; Gröniger, K. S.; Witzel, T.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 233−234.

Table 3. Deuteration and Allylation of 2-Deoxyxylosyl Anomeric Radicals

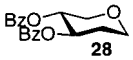


entry	substrate	conformation	acceptor[b]	product	α/*β* (yield %)
1	**20**	unrestricted	A	**25**[c]	84:16[d] (97)
2	**21**	$^4C_1$	A	**25**[c]	99:1[d] (61)
3	**21**	$^4C_1$	B	**26**	98:2[e] (74)
4	**22**	$^1C_4$	A	**25**[c]	72:28[d] (71)
5	**22**	$^1C_4$	B	**26**	46:54[e] (34)[f]

[a] Conditions were noted in the Experimental Section. [b] A, Bu_3SnD; B, $Bu_3SnCH_2CH{=}CH_2$. [c] For ^1H NMR assignment of the 1-deuterated product **25**, the corresponding reduction product (1,5-anhydro-2-deoxy-3,4-di-*O*-acetyl-D-xylitol, **27**) was prepared by treating **20** with Bu_3SnH/AIBN.



[d] Determined by ^2H NMR analysis. [e] Determined by ^1H NMR analysis. [f] Reduced product **28** was obtained in 20% yield.



The large and small coupling constants in the ^1H NMR analyses of **21** and **22**, respectively (Figure 4), suggested that these substrates preferred the typical $^4C_1$- and $^1C_4$-conformations.

The radical reactions of the 2-deoxy substrates with Bu_3SnD/AIBN or $Bu_3SnCH_2CH{=}CH_2$/AIBN were carried out by the same procedures described above, and the results are summarized in Table 3. While the deuteration with unrestricted **20** showed moderate α-selectivity (entry 1, α/β = 84:16), a highly α-stereoselective deuteration occurred with $^4C_1$-restricted substrate **21** (entry 2, α/β = 99:1), similar to the deuteration with $^4C_1$-restricted substrates **9** and **10** having a 2-hydroxyl moiety. The radical allylation with $^4C_1$-restricted 2-deoxy substrate **21** showed higher α-selectivity (entry 3, α/β = 98:2), compared to that of **9** and **10** (Table 2, entries 1, 2), to give *C*-allylated product **26** in 74% yield, as expected. However, unexpectedly, the radical reactions of $^1C_4$-restricted 2-deoxy substrate **22** were not stereoselective; the deuteration was moderately α-selective (entry 4, α/β = 72:28), and the allylation gave nonstereoselectively *C*-allylated product **26** (α/β = 46:54) in low yield (34%) along with reduced product **28** in 20% yield.

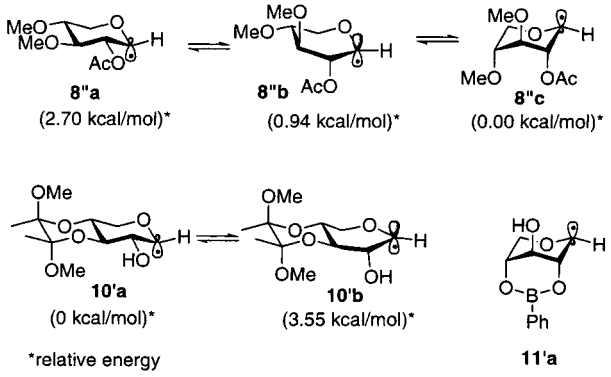
Analysis of Conformation and Orbitals of the Anomeric Radical Intermediates by Theoretical Calculations. Conformational analysis of the anomeric radical intermediates derived from the substrates would be helpful in understanding the reaction mechanism. Orbital analysis of the radical intermediates would also provide insight into the orbital interactions of the transition states. Conformational analysis using ^1H NMR spectra (Figure 3) showed that substrates **9**−**12** have the typical $^4C_1$- or $^1C_4$-chair conformations. However, the conformations of the radical intermediates produced from these substrates are unclear. Thus, we performed conformational and orbital analyses by ab initio calculations[27] using the Gaussian 98 program.[28] Final optimization was performed by UHF/3-21G*. Single point energies and NBO (natural bond orbital) analysis were calculated by UB3LYP/6-31G*. The calculation results are summarized in Figure 5 and Tables 4 and 5.

(27) Theoretical calculations of anomeric radicals including the conformational analysis of pyranosyl radicals: Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−8384.

Table 4. Hybridized Orbital Analysis of the Anomeric Carbon (C_1) and the Ring Oxygen (O_5) in the Xylosyl Radical Conformers[a]

	8″a		**8″b**		**8″c**	
atom	α spin	β spin	α spin	β spin	α spin	β spin
O_5	LP(1) $sp^{1.6}$	LP(1) $sp^{1.7}$	LP(1) $sp^{1.6}$	LP(1) $sp^{1.5}$	LP(1) $sp^{1.82}$	LP(1) $sp^{1.7}$
	LP(2) $sp^{20.8}$	LP(2) $sp^{31.3}$	LP(2) $sp^{36.5}$	LP(2) $sp^{82.9}$	LP(2) $sp^{17.3}$	LP(2) $sp^{13.3}$
C_1	LP(1) $sp^{8.3}$	LP*(1) $sp^{65.1}$	LP(1) $sp^{57.5}$	LP*(1) p	LP(1) $sp^{8.7}$	LP*(1) p
	10′a		**10′b**		**11′a**	
atom	α spin	β spin	α spin	β spin	α spin	β spin
O_5	LP(1) $sp^{1.7}$	LP(1) $sp^{1.7}$	LP(1) $sp^{2.5}$	LP(1) $sp^{1.7}$	LP(1) $sp^{1.56}$	LP(1) $sp^{1.7}$
	LP(2) $sp^{22.2}$	BD(C_1−O_5) $sp^{31.3}$	LP(2) $sp^{7.9}$	BD(C_1−O_5) p	LP(2) $sp^{47.3}$	LP(2) $sp^{10.9}$
C_1	LP(1) $sp^{8.6}$	BD(C_1−O_5) $sp^{65.1}$	LP(1) $sp^{14.6}$	BD(C_1−O_5) p	LP(1) $sp^{8.3}$	LP*(1) p

[a] Hybridized orbitals based on the NBO theory were calculated by UB3LYP/6-31G*.



conformer	conf.	E[a] (a.u.)	E + zpe[b] (a.u.)
8"a	$^4C_1$	-728.00299	-727.74567
8"b	$B_{2,5}$	-728.00499	-727.74848
8"c	$^1C_4$	-728.00757	-727.74998
10'a	$^4C_1$	-881.83416	-881.50976
10'b	$^{4,5}H$	-881.82773	-881.50410
11'a	$^1C_4$	-752.16520	-751.92639

[a] All calculations were performed by UB3LYP/6-31G*//UHF/3-21G*.
[b] Zero point energies calculated by UHF/3-21G*

Figure 5. Conformers in the xylosyl radical intermediate and their calculated energies.

We first calculated the energies of the conformers of the radical intermediates produced from $^4C_1$-restricted substrate **10** and $^1C_4$-restricted substrate **11**. The calculated stable structures and their energies are shown in Figure 5. For the radical intermediate derived from **10**, which was protected with a 3,4-*O*-cyclic-diketal, the two stable conformers **10′a** in a $^4C_1$-conformation with the equatorial C_2−O_2 bond and **10′b** in a $^{4,5}H$-conformation with the pseudoaxial-like C_2−O_2 bond were obtained, and the $^4C_1$-conformer **10′a** was 3.55 kcal/mol more stable than the $^{4,5}H$-conformation **10′b**. Calculation of the radical intermediate of the 2,4-*O*-cyclic-phenylboronate **11** gave only the stable conformer **11′a** in a typical $^1C_4$-conformation. Instead of the radical intermediate produced from the unrestricted tri-*O*-acetyl substrate **8** used in the above experiments, the corresponding 3,4-di-*O*-methylxylosyl radical **8″** was used in this calculation as an unrestricted model intermediate to simplify the calculations.[29] The conformationally unrestricted xylosyl radical would exist in a great number of conformations because of the extremely high conformational flexibility. Therefore, we selected the three typical conformers that are likely to be stable, that is, **8″a** in a $^4C_1$-form, **8″b** in a $B_{2,5}$-form, and **8″c** in a $^1C_4$-form, for the energy calculations, and compared their energies.[30] The structures and calculated energies of **8″a**−**c** are also shown in Figure 5. The relative energies of the unrestricted three conformers **8″a**, **8″b**, and **8″c** were 2.70, 0.94, and 0.00 kcal/mol, respectively. The energy difference between **8″b** and **8″c** might not be so important, especially under the reaction conditions at the high temperature (80 °C).

Table 5. Stabilization Energies by the Hyperconjugation Interactions between LP(2) O_5 and LP*(1) C_1 and between LP (1) C_1 and BD* (C_2−O_2) in the Xylosyl Radical Conformers

		energy[a] (kcal/mol)					
donor	acceptor	**8″a**	**8″b**	**8″c**	**10′a**	**10′b**	**11′a**
LP(2) O_5	LP*(1) C_1	32.11	39.01	39.60	π-bond	π-bond	38.69
LP(2) C_1	BD*(C_2−O_2)	1.87	14.98	9.71	1.52	9.58	9.15

[a] Second-order perturbation energies based on the NBO theory were calculated by UB3LYP/6-31G*.

We next analyzed the hybridized orbitals and the orbital interactions leading to stabilization of the above conformers **8″a**−**c**, **10′a,b**, and **11′a** on the basis of NBO theory.[31] The hybridized orbitals of these conformers were calculated for the two lone pairs of the O_5-atom and the radical orbital of the C_1-atom, and the results are shown in Table 4. In all the conformers, one lone pair (LP) of the O_5-atom was in an equatorial sp^2-like LP(1) orbital and the other in an axial p-like LP(2) orbital. Furthermore, in all the conformers, a radical electron at the C_1-atom existed, not in the β-spin-orbital, but in the α-spin-orbital; the α-spin had a high occupation (>0.91), whereas the β-spin-orbital was empty.[32] In $B_{2,5}$-boat conformer **8″b** and $^{4,5}H$-half boat conformer **10′b**, the radical orbital of the α-spin had a high

(28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

(29) Although we first tried to calculate the conformer energies using the radical intermediate produced from tri-*O*-acetyl substrate **8**, it gave a number of local minima because of the bond rotational barrier of the three *O*-acetyl moieties, which were energetically similar and had a similar pyranose conformation. A search of all of these minimum conformers was likely to be troublesome, and therefore, we used simplified model intermediate **8″** in the calculations.

(30) The $^4C_1$- and the $^1C_4$-conformers are the typical conformations in pyranoses. The $B_{2,5}$-conformer was found to be a stable conformer in the tri-*O*-acetylxylosyl radical intermediate by ESR analysis: see ref 13.

(31) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.

π-character (p>94%), and the radical center at the C_1-atom was planar. On the other hand, in the chair conformers, **8″a**, **8″c**, **10′a**, and **11′a**, the radical orbital of the α-spin had relatively high s-character, and the radical center at the C_1-atom was more pyramidal (sp^3-like), compared to boatlike conformers **8″b** and **10′b**.

Stabilization energies of the orbital interactions between the LP(2) O_5 and the LP*(1) C_1 or between the LP(1) C_1 and the BD*(C_2-O_2) of conformers **8″a**−**c**, **10′a**,**b**, and **11′a** were calculated on the basis of NBO theory,[31,33] and the results are summarized in Table 5. All of the conformers were significantly stabilized by the orbital interaction between the LP(2) O_5 and the LP*(1) C_1; the stabilized energies in the conformers **8″a**−**c** and **11′a** were 32.11−39.6 kcal/mol, and the interaction in the conformers **10′a** and **10′b** had π-bonding character.[34] The orbital interaction between the LP(1) C_1 and the BD*(C_2-O_2) significantly stabilized the conformers **8″b**, **8″c**, **10′b**, and **11′a** with an axial-like C_2-O_2 bond (9.15−14.98 kcal/mol), while only minimal stabilization was observed in conformers **8″a** and **10′a** with an equatorial-like C_2-O_2 bond (1.87 and 1.52 kcal/mol, respectively).

The calculations on unrestricted intermediate **8″** suggested that the intermediate would exist predominantly in $B_{2,5}$-boat conformer **8″b** and $^1C_4$-chair conformer **8″c**, in which the orbital between the LP(1) C_1 and the BD*(C_2-O_2) interacts effectively. The $^4C_1$-chair conformer **8″a** would be relatively unimportant in the equilibrium. Giese and co-workers investigated the conformation of the tri-*O*-acetylxylosyl radical **A** (shown in Figure 1) derived from unrestricted substrate **8** by an ESR study.[13] They reported that the $B_{2,5}$-boat conformer was the most preferred in the xylosyl radical, although it could change into other conformers, such as the ^{1,4}B-boat or the $^1C_4$-chair conformer, because of the high conformational flexibility. Therefore, our energy calculation results on the unrestricted radical intermediate were in accord with those of the ESR study.[13]

The calculation results indicated that the radical intermediate derived from **10** with a 3,4-*O*-cyclic-diketal structure would preferentially exist in $^4C_1$-chair conformer **10′a** and that the intermediate derived from **11** protected with a cyclic-phenylboronate would also exist in $^1C_4$-chair conformer **11′a** as virtually the sole conformer. Both conformers, **10′a** and **11′a**, restricted in the chair conformations, possessed a lone pair with high p-character in the axial direction and also the pyramidal (sp^3-like) radical center at the C_1-position. Thus, the conformation of the anomeric radical intermediates can be manipulated on the basis of the conformational restriction of the substrates, as we hypothesized.

Discussion. We have shown, using the D-xylose and the 2-deoxy-D-xylose derivatives as substrates, that the stereoselectivity of deuteration and *C*-glycosylation reactions of pyranosyl radicals can be effectively controlled by restricting the conformation of the pyranose ring of the substrates. As expected, the stereoselectivity is completely inverted by flipping the substrate conformations from the $^4C_1$-form into the $^1C_4$-form; the $^4C_1$-conformationally restricted substrates yield the α-products highly stereoselectively, while the $^1C_4$-conformationally restricted substrates give the β-products. To understand the reaction mechanism, we should examine the reaction transition states from the standpoint of steric hindrance and stereoelectronic effect, on the basis of the results of the experimental and theoretical calculation studies.

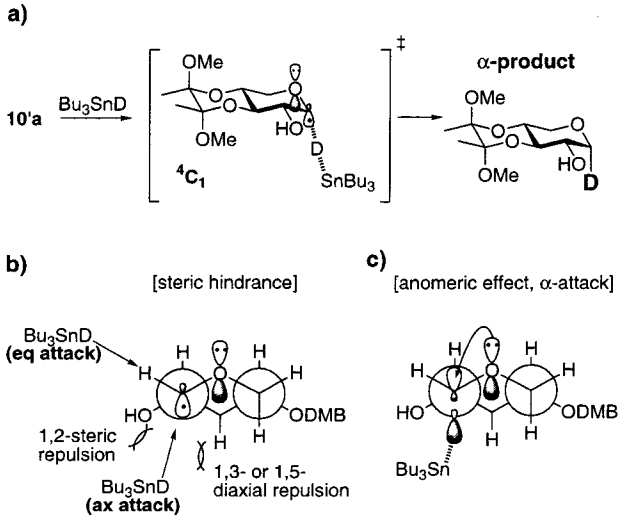


Figure 6. Transition state model of the reaction of the $^4C_1$-conformationally restricted xylosyl radicals for an understanding of the stereoselectivity.

In the reactions of anomeric radicals, a radical acceptor can attack from both axial and equatorial directions.[35] As an example, in the deuteration with $^4C_1$-restricted substrate **10** and $^1C_4$-restricted substrate **11**, the highly stereoselective attack of Bu_3SnD proceeded from the α- or β-axial direction, respectively. We will first consider the α-selective reaction with radical intermediate **10′a** in the $^4C_1$-conformation, as shown in Figure 6a. Taking into account only steric hindrance in the attack on the radical intermediate **10′a** in the $^4C_1$-conformation (Figure 6b, steric hindrance), the 1,2-steric repulsion in the α-axial attack would be more significant than that in the β-equatorial attack, because the axial attack of Bu_3SnD would proceed through the pseudoaxial direction,[35] where the newly forming C−D bond and the C_2-O_2 bond are nearly eclipsed. Moreover, the axial attack on **10′a** is accompanied by rather significant 1,3- and 1,5-diaxial repulsion. Hence, the equatorial attack should be preferred over the axial attack from the viewpoint of steric hindrance. On the other hand, considering the stereoelectronic effect in the radical reaction of **10′a**, the α-axial attack would be preferred to the equatorial attack. In the reaction of the radical intermediate in the $^4C_1$-conformation, the transition state is likely to assume the $^4C_1$-like conformation because of the conformational restriction, and the axial attack from the α-side could be significantly stabilized by the interaction between the antibonding $\sigma^{*‡}$ of the newly forming anomeric C−D bond and the axial-directed nonbonding electrons of the ring oxygen which have high p-character (Figure 6c, anomeric effect). The stereoelectronic stabilization would effectively work in the transition state, because of the restricted $^4C_1$-like conformation, to yield the α-product highly selectively; this is the kinetic anomeric effect in anomeric radical reactions.

(32) The α-spin occupation of radical electron at the C_1-position: **8″a** (0.96246), **8″b** (0.91382), **8″c** (0.94286), **12′a** (0.96417), **12′b** (0.94635), **13′a** (0.93575).

(33) A similar analysis using the NBO method: Senyurt, N.; Aviyente, V. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1463−1470.

(34) π-Bonding character means double bond. Using the default setting of the NBO program, when the single electron occupation between two atoms is higher than 0.9 e (occupancy threshold), it is judged on bonding. In this case, the π-bond in **10′b** and **10′b** would be energetically higher [p-BD(C_1-O_5) occupation: **10′a** (0.98381), **10′b** (0.98337)] than the nonbonded interaction in **8″a**−**c**, and **11′a**

(35) Theoretical calculations by Giese and Houk showed that attack of radical acceptors on the cyclohexyl radical occurred through the two pathways of axial and equatorial directions. They concluded that the axial attack occurred from the direction slightly diverted from the vertical, in other words, a pseudoaxial direction: Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067−4079.

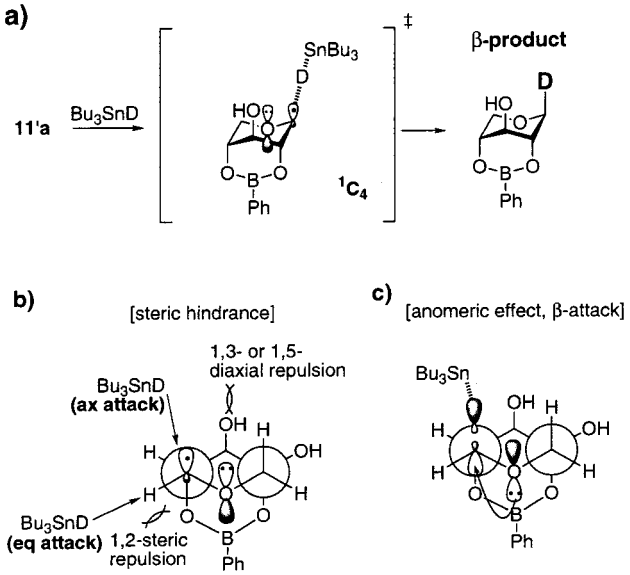


Figure 7. Transition state model of the reaction of the $^1C_4$-conformationally restricted xylosyl radicals for an understanding of the stereoselectivity.

We will next consider the β-selective reaction with the radical intermediate **11′a** in a $^1C_4$-conformation (Figure 7). With respect to steric hindrance in the attack on the radical **11′a**, the β-axial attack of Bu_3SnD proceeding through the pseudoaxial direction, analogous to that on **10′a** described above, encounters 1,3- and 1,5-diaxial repulsion (Figure 7b, steric hindrance). However, in the reaction of **11′a** in the $^1C_4$-conformation, the 1,2-steric repulsion derived from the 2-hydroxyl moiety would prevent the α-equatorial attack, at least to some extent. Therefore, from the standpoint of steric hindrance, we cannot judge whether the equatorial or the axial attack would be favored. On the other hand, the axial attack by Bu_3SnD from the β-side of **11′a** would be preferred because of the kinetic anomeric effect contributing to stabilize the transition state having the $^1C_4$-like conformation (Figure 7c, anomeric effect).

We, therefore, concluded that the dominant factor controlling the stereoselectivity of these radical reactions is not steric hindrance but the kinetic anomeric effect. Because of the conformational restriction, the transition state conformation would be analogous to that of the intermediate radical, that is, the $^4C_1$- or $^1C_4$-forms, where the anomeric effect is most effective in causing the highly stereoselective axial attack on the radical intermediate. The transition state model of attack on the pyranosyl radical in the $^4C_1$- or $^1C_4$-conformations, illustrated by Newman projection formula in Figures 6 and 7, nicely explains the stereochemical results.

Although radical deuterations with the $^4C_1$-restricted xylosyl and 2-deoxyxylosyl substrates (**10** and **21**, respectively), having a 3,4-*O*-cyclic-diketal structure, likewise gave the corresponding α-deuterated products highly selectively (α/β = 97:3 or 99:1), different stereoselectivity was observed in the radical allylation with the two $^4C_1$-restricted substrates; these anomeric *C*-allylations give **17** (α/β = 91:9) from **10** and **26** (α/β = 98:2) from **21**, respectively. Steric hindrance would influence the reaction course more in the allylation with $Bu_3SnCH_2CH{=}CH_2$ than in the deuteration with Bu_3SnD.[23,36] Therefore, the 1,2-steric repulsion between the radical acceptor $Bu_3SnCH_2CH{=}CH_2$ and

(36) In allylation of pyranosyl radicals using $Bu_3SnCH_2CH{=}CH_2$ as the acceptor, the stereoselectivity was significantly influenced by the steric hindrance of the 2-substituent of the substrates: Roe, B. A.; Boojamara, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442−6445.

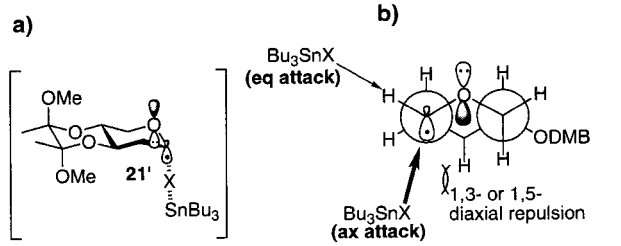


Figure 8. α-Attack to the 2-deoxyxylosyl radical in a $^4C_1$-conformation controlled by the anomeric effect.

the 2-hydroxyl moiety in the axial α-attack on the anomeric radical intermediate produced from **10** might decrease the stereoselectivity, as shown in Figure 6b, and the highly stereoselective attack from the α-side by $Bu_3SnCH_2CH{=}CH_2$ on the 2-deoxyxylosyl radical intermediate **21′** occurred, as shown in Figure 8, probably because of a decrease in 1,2-steric repulsion.

In the radical *C*-glycosylation with 2,3,4-*O*-silylated substrate **12**, the yield was low (26%, α/β = 1:99) when $Bu_3SnCH_2CH{=}CH_2$ was used as the acceptor (Table 2, entry 4), while a similar reaction with $CH_2{=}CHCN$ as the acceptor gave the corresponding β-*C*-glycoside in 66% yield as the sole product (Table 2, entry 5). This may be due to the difference in reactivity between the radical acceptors $CH_2{=}CHCN$ and $Bu_3SnCH_2CH{=}CH_2$. According to frontier molecular orbital (FMO) theory, the π^* of a radical acceptor at the lower energy level should effectively interact with a singly occupied molecular orbital (SOMO) at a higher level.[37] Our calculations by RHF/3-21G* showed that the π^* of $CH_2{=}CHCN$ was located at an energy level lower than that of $Bu_3SnCH_2CH{=}CH_2$.[38] The SOMO of anomeric radicals is known to be located at a raised energy level,[6] probably because of the anomeric effect. Therefore, the relatively high π^* energy level of $Bu_3SnCH_2CH{=}CH_2$ would not interact as effectively with the SOMO of the anomeric radical produced from **12**, resulting in the low yield of the *C*-glycoside **17**. However, a greater stabilization of the transition state would occur in the reaction with $CH_2{=}CHCN$ by the interaction between the higher level SOMO of the anomeric radical and the π^* of $CH_2{=}CHCN$, so that the radical addition reaction might proceed smoothly. Because the anomeric effect raises the SOMO energy of the anomeric radical, the transition state may be significantly stabilized by this kind of interaction between the SOMO and the π^* of the acceptor. Accordingly, the kinetic anomeric effect on these addition reactions of anomeric radicals may depend on the electronic property of the radical acceptor used.

Unexpectedly, the radical deuteration and the allylation with 2-deoxyxylosyl substrate **22** showed no β-selectivity (Table 3, entries 4, 5). Although ^1H NMR data (Figure 4) indicated that substrate **22** was likely to prefer the $^1C_4$-conformation, the reaction results suggested that the $^1C_4$-conformation in the radical intermediate of **22** was not sufficiently stable, especially at the higher reaction temperature (80 °C). We examined the stability of the $^1C_4$-conformations in the intermediates by MM3 calculation[39] with the corresponding 1-deoxy derivatives, that is, 3,4-bis-*O*-TIPS-1,2-dideoxyxylose (**30**) and 2,3,4-tris-*O*-TIPS-1-deoxyxylose (**29**), as model compounds of the radical

(37) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.

(38) Calculated energies of the π^* of $CH_2{=}CHCN$ and $Bu_3SnCH_2CH{=}CH_2$ by RHF/3-21G* were +0.18142 and +0.23263 eV, respectively.

(39) Mohanmadi, F.; Richard, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrikson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

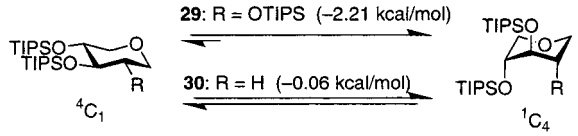


Figure 9. Relative energies of the $^1C_4$-conformers based on the $^4C_1$-conformer calculated by the MM3 force field.

intermediates derived from **22** and **12**, to estimate the steric effect of the *O*-silyl groups on the pyranose conformation. As shown in Figure 9, the calculated energies suggested that in 3,4-bis-*O*-silylated **30**, the $^1C_4$-conformer would not be so stable (0.06 kcal/mol) compared to the flipped $^4C_1$-conformer, whereas the $^1C_4$-conformer was 2.21 kcal/mol more stable than the $^4C_1$-conformer in 2,3,4-tris-*O*-silylated **29**. Therefore, the nonstereoselective experimental results with 2-deoxyxylose derivative **22** as the substrate may be attributed to insufficient conformational restriction to the $^1C_4$-form under the high-temperature reaction conditions.

As described, we have proved that the conformational restriction strategy made possible the control of the stereoselectivity of the anomeric radical reactions. In the *O*- or *C*-glycosylations via S_N1 displacement reactions on the oxocarbenium intermediate, highly stereoselective reactions may also be realized, on the basis of the conformation restriction strategy controlling the anomeric effect.[40]

Conclusion

Introduction of protecting groups, such as 2,3- or 3,4-*O*-cyclic-diketal, 2,4-*O*-cyclic-phenylboronate, and 2,3,4-tris-*O*-TIPS, on the hydroxyl groups effectively restricted the pyranose conformation in a $^4C_1$- or a $^1C_4$-form. Radical deuterations with $^4C_1$- or $^1C_4$-restricted substrates highly stereoselectively gave the corresponding α- or *β*-products, respectively. Selectivity was increased by the conformational restriction and completely inverted by flipping the substrate conformation from the $^1C_4$-form into the $^4C_1$-form, because of the kinetic anomeric effect. Analogously, the radical *C*-glycosylations, that is, the allylation and the cyanoethylation, showed high stereoselectivity by the conformational restriction method. Ab initio calculations suggested that the radical intermediates produced from these substrates possessed typical $^4C_1$- or $^1C_4$-conformations which were similar to those of the substrates and that the anomeric effect was operative in these conformations. These results suggest that the highly α- and *β*-selective reactions occurred because of the anomeric effect, which was manipulated by the conformational restriction of the substrates, as expected. This method is the first radical *C*-glycosylation reaction that highly stereoselectively provides both the α- and *β*-*C*-glycosides and would be applicable to stereoselective construction of various biologically important *C*-glycosides.

Experimental Section

General Methods. ^1H and ^2H spectra were recorded at 270 and 500 MHz (^1H) and at 400 MHz (^2H). Chemical shifts are reported in ppm downfield from TMS (^1H) and $CDCl_3$ (^2H), and *J* values are given in hertz. The ^1H NMR assignments were in agreement with COSY spectra. Mass spectra were obtained by fast atom bombardment (FAB) and electron spray ionization (ESI) methods. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done on Merck silica gel 7734 or 9385. Reactions were carried out under an argon atmosphere.

Phenyl 1-Seleno-2,3,4-tri-*O*-acetyl-*β*-D-xylopyranoside (8). A mixture of **13** (15.7 g, 49 mmol) and HBr (33% in AcOH, 10 mL) in CH_2Cl_2 (30 mL) was stirred at room temperature for 2 h. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with H_2O, aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), evaporated, and dried in vacuo at room temperature for 1 h. A solution of the residue, Et_3N (9.6 mL, 69 mmol), and PhSeH (6.2 mL, 58 mmol) in CH_3CN (150 mL) was stirred at room temperature for 1 h. The resulting mixture was partitioned between AcOEt and aqueous saturated $NaHCO_3$, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 2:1) to give **8** (14.7 g, 72% as an oil): ^1H NMR ($CDCl_3$, 270 MHz) *δ* 7.64−7.20 (m, 5 H), 5.18 (d, 1 H, *J* = 6.7), 5.12 (dd, 1 H, *J* = 6.7, 6.7), 5.03 (dd, 1 H, *J* = 6.7, 6.7), 4.87 (ddd, 1 H, *J* = 4.4, 6.7, 6.7), 4.36 (dd, 1 H, *J* = 4.4, 12.3), 3.54 (dd, 1 H, *J* = 6.7, 12.3), 2.08 (m, 9 H); FAB-HRMS calcd for $C_{17}H_{20}O_7SeNa$ 439.0272 (MNa^+), found 439.0296. Anal. Calcd for $C_{17}H_{20}O_7Se$: C, 49.17; H, 4.85. Found: C, 49.32; H, 4.88.

Phenyl 1-Seleno-*β*-D-xylopyranoside (14). A mixture of **8** (11.0 g, 26.5 mmol) and NaOMe (28% in MeOH, 500 *μ*L) in THF/MeOH (20 mL/30 mL) was stirred at room temperature for 2 h and then neutralized with Diaion PK 212 resin (H^+ form). The resin was filtered off, and the filtrate was evaporated to give **14** (7.66 g, 99% as a yellow solid): ^1H NMR (CD_3OD, 400 MHz) *δ* 7.55−7.17 (m, 5 H), 4.83 (d, 1 H, *J* = 7.9), 3.97 (dd, 1 H, *J* = 4.7, 11.4), 3.43−3.24 (m, 3 H), 3.20 (dd, 1 H, *J* = 8.5, 11.4); FAB-HRMS calcd for $C_{11}H_{14}O_4SeNa$ 312.9955 (MNa^+), found 313.0005. Anal. Calcd for $C_{11}H_{14}O_4Se$: C, 45.69; H, 4.88. Found: C, 45.65; H, 4.96.

Phenyl 2,3-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutan-2,3-diyl]-1-seleno-*β*-D-xylopyranoside (9) and Phenyl 3,4-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutan-2,3-diyl]-1-seleno-*β*-D-xylopyranoside (10). A mixture of **14** (150 mg, 519 *μ*mol), TMB (82 *μ*L, 1.04 mmol), $CH(OMe)_3$ (454 *μ*L, 4.15 mmol), and CSA (6 mg, 25 *μ*mol) in MeOH (2 mL) was heated under reflux for 1.5 h. The mixture was partitioned between AcOEt and aqueous saturated $NaHCO_3$, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 3.5:1−2:1) to give **9** (61 mg, 29% as a white solid) and **10** (136 mg, 65% as a white solid). **9**: ^1H NMR ($CDCl_3$, 500 MHz) *δ* 7.62−7.27 (m, 5 H, Ar), 4.95 (d, 1 H, H-1, *J* = 9.3), 4.13 (dd, 1 H, H-5a, *J* = 5.9, 11.4), 3.89 (m, 1 H, H-4), 3.65 (m, 2 H, H-2, H-3), 3.29 (m, 4 H, H-5b, OMe), 3.21 (s, 3 H, OMe), 2.27 (d, 1 H, 4-OH, *J* = 2.9), 1.34 (m, 6 H, Me × 2); FAB-HRMS calcd for $C_{17}H_{24}O_6SeNa$ 427.0636 (MNa^+), found 427.0631. Anal. Calcd for $C_{17}H_{24}O_6Se$: C, 50.62; H, 6.00. Found: C, 50.98; H, 6.12. **10**: ^1H NMR ($CDCl_3$, 500 MHz) *δ* 7.64−7.30 (m, 5 H, Ar), 4.69 (d, 1 H, H-1, *J* = 9.4), 3.98 (dd, 1 H, H-5a, *J* = 4.9, 10.7), 3.71 (ddd, 1 H, H-4, *J* = 4.9, 10.0, 10.0), 3.65 (dd, 1 H, H-3, *J* = 9.4, 9.4), 3.49 (ddd, 1 H, H-2, *J* = 1.9, 9.4, 9.4), 3.44 (dd, 1 H, H-5b, *J* = 10.0, 10.0), 3.30 (s, 3 H, OMe), 3.24 (s, 3 H, OMe), 2.41 (d, 1 H, 2-OH, *J* = 1.9), 1.32 (s, 3 H, Me), 1.28 (s, 3 H, Me); FAB-HRMS calcd for $C_{17}H_{24}O_6SeNa$ 427.0636 (MNa^+), found 427.0609. Anal. Calcd for $C_{17}H_{24}O_6Se$: C, 50.62; H, 6.00. Found: C, 50.77; H, 6.04.

Phenyl 1-Seleno-*β*-D-xylopyranoside 2,4-*O*-cyclic-phenylboronate (11). A suspension of **14** (375 mg, 1.30 mmol) and phenylboronic acid (174 mg, 1.42 mmol) in benzene (30 mL) was heated under reflux using a Dean−Stark apparatus for 1 h. The resulting clear solution was evaporated, and the residual white powder was treated with hexane and filtrated to give **11** (485 mg, 100% as a white powder): ^1H NMR (DMSO-d_6, 400 MHz) *δ* 7.94−7.24 (m, 10 H, Ar), 6.36 (d, 1 H, 3-OH, *J* = 3.8), 5.56 (s, 1 H, H-1), 4.44 (d, 1 H, H-5a, *J* = 12.3), 4.42 (dd, 1 H, H-3, *J* = 1.9, 3.8), 4.08 (br s, 1 H, H-2), 4.05 (d, 1 H, H-4, *J* = 3.5), 3.68 (d, 1 H, H-5b, *J* = 12.3); FAB-HRMS calcd for $C_{17}H_{17}BO_4Se$ 376.0385 (M^+), found 376.0361. Anal. Calcd for $C_{17}H_{17}BO_4Se$: C, 54.44; H, 4.57. Found: C, 54.43; H, 4.41.

Phenyl 1-Seleno-2,3,4-tris-*O*-triisopropylsilyl-*β*-D-xylopyranoside (12). To a suspension of **14** (300 mg, 1.04 mmol) and NaH (60% in mineral oil, 326 mg, 8.15 mmol) in THF (5 mL) was slowly added

(40) Examples of highly α-stereoselective *O*-mannosylation using conformationally restricted substrates with a 4,6-*O*-benzylidene group have been reported: (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223. (b) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436. (c) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291−1297.

TIPSOTf (1.12 mL, 4.17 mmol) over 20 min, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with AcOH and partitioned between AcOEt and H_2O, and the organic layer was washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/benzene, 20:1) to give **12** (615 mg, 78% as an oil): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58−7.24 (m, 5 H, Ar), 5.66 (s, 1 H, H-1), 4.58 (d, 1 H, H-5a, J = 12.3), 4.20 (s, 1 H, H-3), 3.99 (s, 1 H, H-2), 3.75 (s, 1 H, H-4), 3.19 (d, 1 H, H-5b, J = 12.3), 1.08 (m, 63 H, TIPS × 3); ESI-HRMS calcd for $C_{38}H_{74}O_4SeSi_3Na$ 781.3957 (MNa^+), found 781.3984. Anal. Calcd for $C_{38}H_{74}O_4SeSi_3$: C, 60.20; H, 9.84. Found: C, 59.92; H, 9.59.

General Procedure for the Radical Deuteration with Bu_3SnD. To a solution of a substrate (140 μmol, 0.07 M) and Bu_3SnD (113 μL, 418 μmol) in benzene (2 mL) was added AIBN (5 mg, 30 μmol) at 80 °C, and the mixture was heated at the same temperature. After the disappearance of the starting material on TLC, the mixture was evaporated, and the residue was treated by the procedure as described to give **15** or **25**. The α/β ratio of the product was determined by ^{2}H NMR.

1-[^{2}H]-1,5-Anhydro-2,3,4-tri-*O*-acetyl-D-xylitol (15) from 8 (Table 1, Entry 1). After the treatment of **8** (56 mg, 140 μmol) according to the general procedure for the deuteration described above, the resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 3.5:1) to give **15** (24 mg, 66% as a white solid, α/β ratio = 65:35): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (dd, 1 H, H-3, J = 8.5, 8.5), 4.91 (m, 2 H, H-3, H-4), 4.03 (m, 1.6 H, H-1β, H-5a), 3.34 (m, 1.4 H, H-1α, H-5b), 2.06 (m, 9 H, Ac × 3); ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.48 (β-anomer), 2.79 (α-anomer); FAB-HRMS calcd for $C_{11}H_{16}DO_7$ 262.1037 (MH^+), found 262.1019. Anal. Calcd for $C_{11}H_{15}DO_7$: C, 50.57; H, 6.56. Found: C, 50.32; H, 6.22.

Compound 15 from 9 (Table 1, Entry 2). After the treatment of **9** (56 mg, 140 μmol) according to the general procedure for the deuteration described above, the residue was shortly filtrated through a column (SiO_2, hexane/AcOEt, 1:1) to give a crude product. A solution of the obtained product in aqueous TFA (80%, 3 mL) was stirred at room temperature for 15 min, and the solvent was evaporated and azeotroped with toluene (3 times). A mixture of the resulting residue, AcCl (50 μL, 703 μmol), and DMAP (4-(dimethylamino)pyridine) (17 mg, 140 μmol) in pyridine (2 mL) was stirred at room temperature for 2 h. After addition of ice, the mixture was partitioned between AcOEt and aqueous 1 M HCl, and the organic layer was washed with aqueous saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 3.5:1) to give **15** (30 mg, 83% as a white solid, α/β ratio = 97:3): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.48 (β-anomer), 2.79 (α-anomer); FAB-HRMS calcd for $C_{11}H_{16}DO_7$ 262.1037 (MH^+), found 262.1044.

Compound 15 from 10 (Table 1, Entry 3). Compound **15** (30 mg, 83% as a white solid, α/β ratio = 97:3) was obtained from **10** (56 mg, 140 μmol) by the procedure described for **9** (Table 1, entry 2): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.48 (β-anomer), 2.79 (α-anomer); FAB-HRMS calcd for $C_{11}H_{16}DO_7$ 262.1037 (MH^+), found 262.1053.

Compound 15 from 11 (Table 1, Entry 4). After the treatment of **11** (40 mg, 140 μmol) according to the general procedure for the deuteration described above, the mixture of the residue and 1,3-propanediol (50 μL, 690 μmol) in acetone (2 mL) was stirred at 0 °C for 15 min, and the solvent was evaporated to give the crude deprotected product, which was acetylated by the procedure described for **9** (Table 1, entry 2) to give **15** (26 mg, 72% as a white solid, α/β ratio = 1:99): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.48 (β-anomer), 2.79 (α-anomer); FAB-HRMS calcd for $C_{11}H_{16}$ DO_7 262.1037 (MH^+), found 262.1032.

Compound 15 from 12 (Table 1, Entry 5). After the treatment of **12** (56 mg, 140 μmol) according to the general procedure for the deuteration described above, the residue was shortly filtrated through a column (SiO_2, hexane/benzene, 8:1) to give a crude product. A solution of the crude product and TBAF (1 M in THF, 556 μL, 556 μmol) was stirred at room temperature for 1 h and evaporated to give the crude deprotected product, which was acetylated by the procedure described for **9** (Table 1, entry 2) to give **15** (29 mg, 80% as a white solid, α/β ratio = 1:99): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.48 (β-anomer), 2.79 (α-anomer); FAB-HRMS calcd for $C_{11}H_{16}DO_7$ 262.1037 (MH^+), found 262.1041.

1,5-Anhydro-2,3,4-tri-*O*-acetyl-D-xylitol (16). Compound **16** (66 mg, 91% as an oil) was prepared from **8** (116 mg, 279 μmol) by the procedure for **15** (Table 1, entry 1) with Bu_3SnH instead of Bu_3SnD: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (dd, 1 H, H-3, J = 8.5, 8.5), 4.91 (ddd, 2 H, H-2, H-4, J = 5.0, 8.5, 8.5), 4.03 (dd, 2 H, H-1β, H-5a, J = 5.0, 11.4), 3.34 (dd, 2 H, H-1α, H-5b, J = 8.8, 11.4), 2.06 (m, 9 H, Ac × 3); FAB-HRMS calcd for $C_{11}H_{17}O_7$ 261.0974 (MH^+), found 261.0929.

General Procedure for the Radical Allylation with Allyltributyltin. To a solution of a substrate (301 μmol, 0.10 M) and allyltributyltin (467 μL, 1.51 mmol) in benzene (3 mL) was added AIBN (5 mg, 30 μmol) at 80 °C, and the mixture was heated at the same temperature. After disappearance of the starting material on TLC, the mixture was evaporated, and the residue was treated by the procedure as described to give **17** or **26**. The α/β ratio of the product was determined by ^{1}H NMR.

3-(2,3,4-Tri-*O*-benzoyl-D-xylopyranosyl)propene (17) from 9 (Table 2, Entry 1). After the treatment of **9** (121 mg, 301 μmol) according to the general procedure for the allylation described above, the residue was shortly filtrated through a column (SiO_2, hexane/AcOEt, 2:1) to give the crude product. A solution of the crude product in aqueous TFA (80%, 4 mL) was stirred at room temperature for 15 min, evaporated, and azeotroped with toluene (3 times). A mixture of the resulting residue, BzCl (210 μL, 1.80 mmol), and DMAP (37 mg, 301 μmol) in pyridine (3 mL) was stirred at room temperature for 2 h. After the addition of ice, the mixture was partitioned between AcOEt and aqueous 1 M HCl, and the organic layer was washed with aqueous saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 10:1) to give **17** (107 mg, 73% as a white solid, α/β ratio = 85:15); FAB-HRMS calcd for $C_{29}H_{27}O_7$ 487.1757 (MH^+), found 481.1791. The α/β mixture of **17** (105 mg) was further purified by column chromatography (SiO_2, hexane/AcOEt, 12:1) to give the α-anomer (85 mg, as a white solid) and the β-anomer (15 mg, as a white solid). α-Anomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17−7.15 (m, 15 H, Ar), 5.88 (m, 1 H, C*H*═CH_2), 5.62 (br s, 1 H, H-3), 5.21 (br s, 1 H, H-3), 5.11 (m, 3 H, H-4, CH═CH_2), 4.31 (d, 1 H, H-5a, J = 13.2), 4.13 (dd, 1 H, H-5b, J = 2.0, 13.2), 4.07 (ddd, 1 H, H-1, J = 1.5, 7.0, 7.0), 2.59−2.41 (m, 2 H, CH_2); FAB-HRMS calcd for $C_{29}H_{27}O_7$ 487.1757 (MH^+), found 487.1730. Anal. Calcd for $C_{29}H_{26}O_7$: C, 71.59; H, 5.39. Found: C, 71.30; H, 5.36. β-Anomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94−7.25 (m, 15 H, Ar), 5.90 (m, 1 H, C*H*═CH_2), 5.83 (dd, 1 H, H-3, J = 9.6, 9.6), 5.40 (dd, 1 H, H-2, J = 9.6, 9.6), 5.38 (m, 1 H, H-4), 5.11 (m, 2 H, CH═CH_2), 4.40 (dd, 1 H, H-5a, J = 5.6, 11.1), 3.72 (ddd, 1 H, H-1, J = 3.8, 7.6, 9.6), 3.52 (dd, 1 H, H-5b, J = 11.1, 11.1), 2.41 (m, 2 H, CH_2); FAB-HRMS calcd for $C_{29}H_{27}O_7$ 487.1757 (MH^+), found 487.1733. Anal. Calcd for $C_{29}H_{26}O_7 \cdot 0.7H_2O$: C, 69.78; H, 5.53. Found: C, 71.01; H, 5.93.

Compound 17 from 10 (Table 2, Entry 2). Compound **17** (83 mg, 69% as a white solid, α/β ratio = 91:9) was prepared from **10** (121 mg, 301 μmol) by the procedure described above for **9** (Table 2, entry 1); FAB-HRMS calcd for $C_{29}H_{27}O_7$ 487.1757 (MH^+), found 487.1769.

Compound 17 from 11 (Table 2, Entry 3). After the treatment of **11** (87 mg, 301 μmol) according to the general procedure described above, a mixture of the residue and 1,3-propanediol (55 μL, 761 μmol) in acetone (1.5 mL) was stirred at room temperature for 15 min and evaporated to give the crude deprotected product, which was benzoylated by the procedure described for **9** (Table 2, entry 1) to give **17** (90 mg, 61% as a white solid, α/β ratio = 1:99); FAB-HRMS calcd for $C_{29}H_{27}O_7$ 487.1757 (MH^+), found 487.1787.

Compound 17 and 1,5-Anhydro-2,3,4-tri-*O*-benzoyl-D-xylitol (19) from 12 (Table 2, Entry 4). After treatment of **12** (228 mg, 301 μmol) according to the general procedure for the allylation described above, the residue was shortly filtrated through a column (SiO_2, hexane/benzene, 50:1−10:1) to give a crude product. A solution of the crude product and TBAF (1 M in THF, 1.35 mL, 1.35 mmol) in THF (2 mL) was stirred at room temperature for 2 h and evaporated to give the crude deprotected product, which was benzoylated by the procedure

described above for **9** (Table 2, entry 1) to give **17** (38 mg, 26% as a white solid, α/β ratio = 1:99) and **19** (83 mg, 61% as a white solid). **17**: FAB-HRMS calcd for $C_{29}H_{26}O_7Na$ 509.1576 (MNa^+), found 509.1604. **19**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13−7.36 (m, 15 H, Ar), 5.82 (dd, 1 H, H-3, *J* = 7.9, 7.9), 6.68 (ddd, 2 H, H-2, H-4, *J* = 4.7, 8.1, 8.1), 5.39 (dd, 2 H, H-1a, H-5a, *J* = 4.7, 11.6), 4.58 (dd, 2 H, H-1b, H-5b, *J* = 8.1, 11.6); FAB-HRMS calcd for $C_{26}H_{22}O_7Na$ 469.1263 (MNa^+), found 469.1263.

3-(2,3,4-Tri-*O*-benzoyl-D-xylopyranosyl)propionitrile (18) from 12 (Table 2, Entry 5). To a solution of **12** (228 mg, 301 μmol), acrylonitrile (199 μL, 3.0 mmol), and Bu_3SnH (162 μL, 600 μmol) in benzene (3 mL) was added AIBN (10 mg, 61 μmol) at 80 °C, and the mixture was heated at the same temperature. After disappearance of the starting material on TLC, the mixture was evaporated, and the residue was treated by the procedure described above for the allylation of **12** (Table 2, entry 4). After purification by column chromatography (SiO_2, hexane/Et_2O, 20:1), **18** was obtained (28 mg, 66% as an oil, α/β = 0:100): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.10−7.20 (m, 15 H, Ar), 5.88 (dd, 1 H, H-3, *J* = 5.6, 10.8), 5.39 (ddd, 1 H, H-4, *J* = 5.6, 10.8, 10.8), 5.34 (dd, 1 H, H-2, *J* = 9.6, 9.6), 4.42 (dd, 1 H, H-5a, *J* = 5.6, 10.8), 3.76 (ddd, 1 H, H-1, *J* = 2.9, 9.4, 9.4), 3.56 (dd, 1 H, H-5b, *J* = 10.8, 10.8), 2.58 (m, 2 H, CH_2CH_2CN), 1.96 (m, 2 H, CH_2CH_2CN); FAB-HRMS calcd for $C_{29}H_{26}NO_7$ 500.1709 (MH^+), found 500.1689. Anal. Calcd for $C_{29}H_{25}NO_7 \cdot 0.3H_2O$: C, 68.98; H, 5.11; N, 2.77. Found: C, 69.05; H, 5.11; N, 2.54.

Phenyl 2-Deoxy-3,4-di-*O*-acetyl-1-seleno-β-D-xylopyranoside (20). To a solution of **23**[26] (2.82 g, 10.8 mmol) and PhSeH (2.39 mL, 21.6 mmol) in CH_2Cl_2 (72 mL) was added $BF_3 \cdot OEt_2$ (2.33 mL, 18.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. The mixture was partitioned between Et_2O and aqueous saturated $NaHCO_3$, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 5:1) to give **20** (3.36 g, 87% as a white solid, α/β ratio = ∼1:1 based on ^1H NMR): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58−7.27 (m, 5 H), 5.68 (dd, 0.55 H, *J* = 4.4, 4.4), 5.55 (dd, 0.45 H, *J* = 4.7, 4.7), 5.14−3.50 (m, 4 H), 2.65−2.00 (m, 8 H); FAB-HRMS calcd for $C_{15}H_{18}O_5SeNa$ 381.0217 (MNa^+), found 381.0220. Anal. Calcd for $C_{15}H_{18}O_5Se$: C, 50.43; H, 5.08. Found: C, 50.46; H, 5.16.

Phenyl 2-Deoxy-1-seleno-β-D-xylopyranoside (24). A mixture of **20** (1.98 g, 5.54 mmol) and NaOMe (28% in MeOH, 100 μL) in THF/MeOH (5 mL/5 mL) was stirred at room temperature for 2 h and neutralized with Diaion PK 212 resin (H^+ form). The resin was filtered off, and the filtrate was evaporated and dried in vacuo at room temperature for 1 h to give **24** (1.51 g, 99% as a white solid, α/β ratio = 1:1): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.55 (m, 2 H), 7.26 (m, 3 H), 5.84 (dd, 0.54 H, *J* = 2.0, 5.1), 5.19 (dd, 0.46 H, *J* = 2.8, 8.7), 4.23−3.25 (m, 4 H), 2.51−1.80 (m, 4 H); FAB-HRMS calcd for $C_{11}H_{14}O_3SeNa$ 297.0006 (MNa^+), found 297.0028. Anal. Calcd for $C_{11}H_{14}O_3Se$: C, 48.36; H, 5.17. Found: C, 48.26; H, 5.05.

Phenyl 2-Deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-diyl]-1-seleno-β-D-xylopyranoside (21). Compound **21** (1.68 g, 89% as a white solid, α/β ratio = 1:1 based on ^1H NMR) was obtained from **24** (1.34 g, 4.9 mmol) as described for the synthesis of **10**, after purification by column chromatography (SiO_2, hexane/AcOEt, 20:1). The α/β mixture of **24** (600 mg) was further purified by silica gel chromatography (SiO_2, hexane/AcOEt, 25:1) to give the α-anomer (223 mg), the β-anomer (111 mg), and the α/β mixture (252 mg). α-Anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57−7.25 (m, 5 H, Ar), 5.93 (d, 1 H, H-1, *J* = 4.7), 4.10−3.65 (m, 4 H, H-3, H-4, H-5a, H-5b), 3.31 (s, 3 H, OMe), 3.28 (s, 3 H, OMe), 2.30 (ddd, 1 H, H-2b, *J* = 1.7, 5.0, 11.7), 2.23 (ddd, 1 H, H-2a, *J* = 5.3, 11.7, 11.7), 1.32 (s, 3 H, Me), 1.31 (s, 3 H, Me); FAB-HRMS calcd for $C_{17}H_{24}O_5SeNa$ 411.0687 (MNa^+), found 411.0681. Anal. Calcd for $C_{17}H_{24}O_5Se \cdot 0.1H_2O$: C, 52.47; H, 6.27. Found: C, 52.24; H, 6.16. β-Anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62−7.30 (m, 5 H, Ar), 5.00 (dd, 1 H, H-1, *J* = 2.1, 11.7), 4.00 (dd, 1 H, H-5a, *J* = 5.0, 10.6), 3.74 (ddd, 1 H, H-3, *J* = 4.4, 9.7, 9.7), 3.66 (ddd, 1 H, H-4, *J* = 5.0, 9.8, 9.8), 3.36 (dd, 1 H, H-5b, *J* = 10.6, 10.6), 3.25 (s, 3 H, OMe), 3.07 (s, 3 H, OMe), 2.23 (ddd, 1 H, H-2a, *J* = 2.1, 4.4, 11.7), 1.89 (ddd, 1 H, H-2b, *J* = 11.7, 11.7, 11.7), 1.29 (s, 3 H, Me), 1.28 (s, 3 H, Me); FAB-HRMS calcd for $C_{17}H_{24}O_5SeNa$ 411.0687 (MNa^+), found 411.0702. Anal. Calcd for $C_{17}H_{24}O_5Se$: C, 52.57; H, 6.21. Found: C, 52.72; H, 6.25.

Phenyl 3,4-Bis-*O*-triisopropylsilyl-2-deoxy-1-seleno-β-D-xylopyranoside (22). A mixture of **24** (369 mg, 1.35 mmol), TIPSOTf (1.09 mL, 4.06 mmol), and 2,6-lutidine (1.57 mL, 13.5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min. After the addition of MeOH (550 μL), the mixture was partitioned between AcOEt and aqueous 1 M HCl, and the organic layer was washed with H_2O, aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/benzene, 15:1−10:1) to give **22** (736 mg, 93% as an oil, α/β ratio = 1:1 based on ^1H NMR). The α/β mixture of **22** (736 mg) was further purified by column chromatography (SiO_2, hexane/benzene, 15:1) to give the α-anomer (209 mg), the β-anomer (382 mg), and the α/β mixture (145 mg). α-Anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59−7.19 (m, 5 H, Ar), 5.81 (d, 1 H, H-1, *J* = 5.5), 4.55 (d, 1 H, H-5a, *J* = 12.0), 4.01 (d, 1 H, H-3, *J* = 2.8), 3.69 (br s, 1 H, H-4), 3.58 (d, 1 H, H-5b, *J* = 12.0), 2.77 (ddd, 1 H, H-2a, *J* = 2.8, 5.5, 14.0), 2.06 (d, 1 H, H-2b, *J* = 14.0), 1.10 (m, 42 H, TIPS × 2); FAB-HRMS calcd for $C_{29}H_{54}O_3SeSi_2Na$ 609.2675 (MNa^+), found 609.2682. Anal. Calcd for $C_{29}H_{54}O_3SeSi_2$: C, 59.45; H, 9.29. Found: C, 59.17; H, 9.05. β-Anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62−7.25 (m, 5 H, Ar), 5.46 (dd, 1 H, H-1, *J* = 2.2, 10.5), 3.99 (br s, 1 H, H-3), 3.98 (dd, 1 H, H-5a, *J* = 1.0, 11.8), 3.83 (dd, 1 H, H-5b, *J* = 2.4, 11.8), 3.61 (br s, 1 H, H-4), 2.38 (ddd, 1 H, H-2a, *J* = 2.5, 10.5, 13.3), 1.90 (m, 1 H, H-2b), 1.05 (m, 42 H, TIPS × 2); FAB-HRMS calcd for $C_{29}H_{54}O_3SeSi_2Na$ 609.2675 (MNa^+), found 609.2645. Anal. Calcd for $C_{29}H_{54}O_3SeSi_2 \cdot 0.3H_2O$: C, 58.91; H, 9.31. Found: C, 58.98; H, 8.95.

1-[^{2}H]-1,5-Anhydro-2-deoxy-3,4-di-*O*-acetyl-D-xylitol (25) from 20 (Table 3, Entry 1). After treatment of **20** (50 mg, 140 μmol) according to the procedure described for the deuteration of **8** (Table 1, entry 1), **25** (28 mg, 97% as an oil, α/β ratio = 84:16) was obtained: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.00 (ddd, 1 H, H-3, *J* = 4.6, 8.1, 8.1), 4.83 (ddd, 1 H, H-4, *J* = 4.2, 7.5, 7.5), 3.98 (dd, 1 H, H-5a, *J* = 4.2, 11.7), 3.87 (m, 0.84 H, H-1β), 3.54 (m, 0.16 H, H-1α), 3.39 (dd, 1 H, H-5b, *J* = 7.5, 11.7), 2.12 (m, 1 H, H-2a), 2.07 (m, 6 H, Ac × 2), 1.73 (m, 1 H, H-2b): ^2H NMR ($CHCl_3$, 400 MHz) δ 3.33 (β-anomer), 3.00 (α-anomer); ESI-HRMS calcd for $C_9H_{13}DO_5Na$ 226.0802 (MNa^+), found 226.0806.

Compound 25 from 21 (Table 3, Entry 2). After treatment of **21** (54 mg, 104 μmol) according to the procedure described for the deuteration of **9** (Table 1, entry 2), **25** (18 mg, 61% as an oil, α/β ratio = 99:1) was obtained: ^2H NMR ($CHCl_3$, 400 MHz) δ 3.33 (β-anomer), 3.00 (α-anomer); ESI-HRMS calcd for $C_9H_{13}DO_5Na$ 226.0802 (MNa^+), found 226.0806.

Compound 25 from 22 (Table 3, Entry 4). After treatment of **22** (82 mg, 140 μmol) according to the procedure described for the deuteration of **12** (Table 1, entry 5), **25** (20 mg, 71% as an oil, α/β ratio = 72:28) was obtained: ^2H NMR ($CHCl_3$, 400 MHz) δ 3.33 (β-anomer), 3.00 (α-anomer); ESI-HRMS calcd for $C_9H_{13}DO_5Na$ 226.0802 (MNa^+), found 226.0808.

3-(2-Deoxy-2,3,4-tri-*O*-benzoyl-D-xylopyranosyl)propene (26) from 21 (Table 3, Entry 3). After treatment of **21** (117 mg, 301 μmol) according to the procedure described for the allylation of **9** (Table 2, entry 1), **26** (61 mg, 74% as an oil, α/β ratio = 98:2) was obtained: ^1H NMR ($CDCl_3$, 500 MHz) δ for the α-anomer 8.15−7.29 (m, 10 H, Ar), 5.86 (m, 1 H, C*H*=CH_2), 5.42 (d, 1 H, H-3, *J* = 1.5), 5.11 (m, 3 H, H-4, CH=CH_2), 4.19 (d, 1 H, H-5a, *J* = 13.2), 4.09 (dd, 1 H, H-5b, *J* = 1.3, 13.2), 3.86 (m, 1 H, H-1), 2.37 (m, 2 H, CH_2CH=CH_2), 2.04 (m, 2 H, H-2a, H-2b); ^1H NMR ($CDCl_3$, 500 MHz) δ for the β-anomer 8.15−7.29 (m, 10 H, Ar), 5.86 (m, 1 H, C*H*=CH_2), 5.41 (ddd, 1 H, H-3, *J* = 5.3, 10.7, 10.7), 5.33 (ddd, 1 H, H-4, *J* = 5.4, 10.7, 10.7), 5.11 (m, 2 H, CH=CH_2), 4.35 (dd, 1 H, H-5a, *J* = 5.3, 10.7), 3.63 (m, 1 H, H-1), 3.44 (dd, 1 H, H-5b, *J* = 10.7, 10.7), 2.37 (m, 2 H, CH_2-CH=CH_2), 1.71 (m, 2 H, H-2); FAB-HRMS calcd for $C_{22}H_{22}O_5Na$ 389.1365 (MNa^+), found 389.1369. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.03; H, 6.22.

Compound 26 and 1,5-Anhydro-2-deoxy-3,4-di-*O*-benzoyl-D-xylitol (28) from 22 (Table 3, Entry 5). After treatment of **22** (176 mg, 301 μmol) according to the procedure described for the allylation of **12** (Table 2, entry 4), **26** (36 mg, 34% as an oil, α/β ratio = 46:54)

and **28** (21 mg, 20% as an oil) were obtained. **26**: FAB-HRMS calcd for $C_{22}H_{22}O_5Na$ 389.1365 (MNa^+), found 389.1345. **28**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.05 (m, 10 H, Ar), 5.39 (ddd, 1 H, H-3, J = 4.4, 7.6, 7.6), 5.26 (ddd, 1 H, H-4, J = 4.1, 7.6, 7.6), 4.21 (dd, 1 H, H-5a, J = 4.4, 11.7), 4.01 (ddd, 1 H, H-1a, J = 4.4, 4.4, 11.7), 3.67 (ddd, 1 H, H-1b, J = 2.9, 9.4, 10.6), 3.60 (dd, 1 H, H-1a, J = 7.9, 11.7), 2.35 (m, 1 H, H-2a), 1.96 (m, 1 H, H-2b); FAB-HRMS calcd for $C_9H_{19}O_5$ 327.1232 (MH^+), found 327.1208.

1,5-Anhydro-2-deoxy-3,4-di-*O*-acetyl-D-xylitol (27). Compound **27** (26 mg, 96% as an oil) was prepared from **20** (50 mg, 140 μmol) by the procedure described for the deuteration of **20** with Bu_3SnH instead of Bu_3SnD: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.00 (ddd, 1 H, H-3, J = 4.6, 8.1, 8.1), 4.83 (ddd, 1 H, H-4, J = 4.2, 7.5, 7.5), 3.98 (dd, 1 H, H-5a, J = 4.2, 11.7), 3.87 (ddd, 1 H, H-1β, J = 4.6, 4.6, 11.8), 3.54 (ddd, 1 H, H-1α, J = 3.0, 9.2, 11.8), 3.39 (dd, 1 H, H-5b, J = 7.5, 11.7), 2.12 (m, 1 H, H-2a), 2.07 (m, 6 H, Ac $\times$ 2), 1.73 (m, 1 H, H-2b); ESI-HRMS calcd for $C_9H_{14}O_5Na$ 225.0739 (MNa^+), found 225.0741.

Calculations. All ab initio and semiempirical PM3 calculations were performed using the Gaussian 98 program[28] on an SGI O2 workstation. MM3 calculations were performed using the Macromodel 5.0 program.[37] The preoptimized geometries by UHF/STO-3G* or PM3 were taken to be the input geometries for final optimization by UHF/3-21G*. The stationary points were characterized by frequency analysis (minimum with 0). Single point energies and properties based on the natural bond orbital (NBO) theory[30] were calculated by UB3LYP/6-31G*. Hybrid orbitals and stabilization energy by orbital interactions were analyzed by the NBO method.[32] Orbital interactions were examined in terms of second-order perturbation from filled orbitals to empty neighboring orbitals.

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Supporting Information Available: ^1H NMR spectral charts of **15** (from **8**), **16**, **17** (α-anomer), **17** (β-anomer), **17** (from **9**, **10**, **11**, and **12**), **18**, **19**, **21** (α-anomer), **21** (β-anomer), **22** (α-anomer), **22** (β-anomer), **25** (from **20**), **26** (from **21** and **22**), **27**, and **28**; ^2H NMR spectral charts of **15** (from **8**, **9**, **10**, **11**, and **12**) and **25** (from **20**, **21**, and **22**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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