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A Study on the Conformation−Anomeric Effect−Stereoselectivity Relationship in Anomeric Radical Reactions, Using Conformationally Restricted Glucose Derivatives as Substrates

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We previously theorized that, since the stereoselectivity of anomeric radical reactions is significantly influenced 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 the substrates would therefore make highly α- and *β*-stereoselective anomeric radical reactions possible. This theory was based on our previous results of the anomeric radical reactions with D-xylose derivatives as the substrates. We herein report the anomeric radical deuteration reactions with the conformationally restricted 1-phenylseleno-D-glucose derivatives, **2g** and **3g**, restricted in a $^4C_1$-conformation by an *O*-cyclic diketal moiety, and **4g**, **5g**, **6g**, **7g**, and **8g**, restricted in a $^1C_4$-conformation by bulky *O*-silyl protecting groups. The radical deuterations with Bu_3SnD, using the $^4C_1$-restricted substrates **2g** and **3g**, afforded the corresponding α-products (α/*β* = 98:2) highly stereoselectively, whereas the $^1C_4$-restricted substrate **6g**, having a trigonal (sp^2) carbon substituent, i.e., −CHO, at the 5-position, selectively gave the *β*-products (α/*β* = 0:100). Thus, the stereoselectivity was significantly increased by the conformational restriction and was completely inverted by changing the substrate conformation from the $^4C_1$-form to the $^1C_4$-form. On the other hand, the deuterations with the $^1C_4$-restricted substrates **4g** and **5g** showed that the 1,5-steric effect due to the tetrahedral carbon substituent (−CH_2OTIPS or −CH_2OH) at the 5-axial position dominantly prevented the hydride transfer from the *β*-face competing with the kinetic anomeric effect. This study suggests that, depending on the restricted conformation of the substrates to the $^4C_1$- or the $^1C_4$-form, the α- or *β*-products would be obtained highly stereoselectively via anomeric radical reactions of hexopyranoses.

Introduction

There has been growing interest in radical reactions because of their facility to proceed under mild neutral conditions.[1] In carbohydrate chemistry, the reactions of anomeric radicals have been extensively studied.[2] For example, intramolecular radical cyclizations are effective in constructing the *C*-glycosidic bonds highly stereoselectively, and we have also been working to develop efficient *C*-glycosylation reactions by intramolecular radical cyclization[3] using a silyl tether.[4] On the other hand, in intermolecular anomeric radical reactions, while anomeric pyranosyl radicals **I**, such as glucosyl radicals, stereoselectively afford the corresponding α-product II,[5,6] as shown in Scheme 1, the *β*-selective anomeric radical reaction is more difficult to realize.[7]

Giese and co-workers have significantly contributed to the development of the anomeric radical reactions. They pointed out that in the radical *C*-glycosylation reaction

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(7) A *β*-selective radical *C*-glycosylation of xylose derivatives has been reported: see ref 6b.

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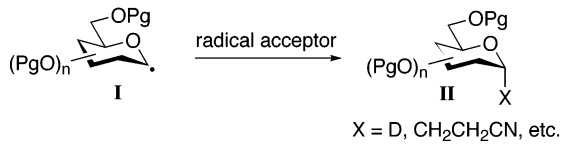
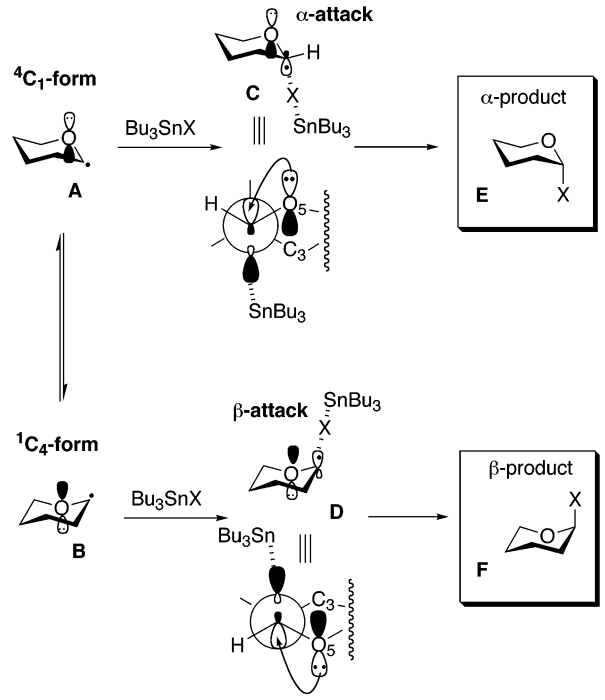
SCHEME 1



SCHEME 2



the α-selectivity can be a result of the anomeric effect, similar to S_N1-like glycosylations.[8] The anomeric effect should be influenced by the conformation of the sugar molecule, since it is a stereoelectronic effect on the anomeric position due to the nonbonding electrons on the ring oxygen.[9] The transition state of anomeric radical reactions of pyranoses would be significantly stabilized when it adopts a $^4C_1$ or a $^1C_4$-chairlike conformation, where the newly forming bond orbital effectively interacts with the p-orbital of a lone pair on the ring oxygen in a periplanar arrangement. Consequently, we theorized that the anomeric effect might be employed to effectively control the stereoselectivity in anomeric radical reactions by using conformationally restricted substrates.[10,11] As shown in Scheme 2, in the reaction of an anomeric radical intermediate **A**, the conformation of which is restricted in the $^4C_1$-chair form, the α-axial attack transition state **C** also assumes the $^4C_1$-like form, where the kinetic anomeric effect works effectively to give the α-product **E** highly selectively. Similarly, when the conformation of the radical intermediate is restricted to the unusual $^1C_4$-chair-form **B**, the corresponding *β*-product **F** should be selectively obtained due to the kinetic anomeric effect via the *β*-axial attack transition state **D**. The transition states $^4C_1$-restricted **C** and $^1C_4$-restricted **D** can be effectively stabilized by the interaction between the antibonding $\sigma^{*\ddagger}$ of the newly forming anomeric bond and the p-orbital of a nonbonded electron pair (n_O) on the ring oxygen because of the periplanar arrangement,[12,13] which is the kinetic anomeric effect in anomeric radical reactions.[10] Accordingly, depending on the conformation of the substrates which are restricted to the $^4C_1$- or the $^1C_4$-form, the α- or *β*-products can be obtained highly stereoselectively by the anomeric radical reactions. On the basis of this idea, we previously studied anomeric radical reactions using xylose derivatives as model substrates to show that the α- and *β*-selective anomeric radical reactions actually occur.[10]

In hexopyranoses, such as glucose or mannose derivatives, steric effect due to the hydroxymethyl moiety attached at the 5-position would affect the stereoselectivity of the anomeric radical reactions, which was likely to disturb the exact estimation of the anomeric effect on the stereoselectivity. Therefore, we used the xylose derivatives as the model substrates in the previous study, since they lack the carbon substituent at the 5-position. However, hexopyranoses are major components in natural carbohydrates, and therefore, especially from the viewpoint of synthetic organic chemistry, reactions with hexopyranoses as the substrates are important. Thus, we planned to investigate further the conformation−anomeric effect−stereoselectivity relationship in the anomeric radical reactions using conformationally restricted hexose substrates. These studies would also clarify the effect of the hydroxymethyl moiety attached to the 5-carbon of the pyranose on the stereoselectivity of anomeric radical reactions. Here we report the results of deuterium-labeling radical reactions using conformationally restricted glucose derivatives as the substrates.

Results and Discussion

Design and Synthesis of D-Glucose Derivatives Restricted in a $^4C_1$- or a $^1C_4$-Chair Conformation as the Substrates. The conformations of pyranoses can be restricted by introducing proper protecting groups on the hydroxy groups. We designed the phenyl 1-seleno-*β*-D-glucosides **2g**−**8g** restricted in a $^4C_1$- or a $^1C_4$-conformation as the substrates for this study. The conformationally unrestricted tetra-*O*-acetylglucoside **1g** was also employed as the reference substrate.[14] The structures of these substrates are shown in Figure 1.

(8) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969−980.

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(11) The α- and *β*-stereoselectivity in S_N1-type anomeric allylation is also controlled by the kinetic anomeric effect by using conformationally restricted substrates: Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1021−1023.

(12) Cieplack pointed out the importance of hyperconjugation in the transition state of nucleophilic addition reactions to carbonyls, since the energy of the transition state is lowered by delocalization of electrons from an antiperiplanar vicinal *σ*-bond to the antibonding component ($\sigma^{*\ddagger}$) 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.

(13) For explanations of radical reaction transition states by this kind of orbital interaction see: (a) Renaud, P. *Helv. Chim. Acta* **1991**, *74*, 1305−1313. (b) Bodpudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001−2006.

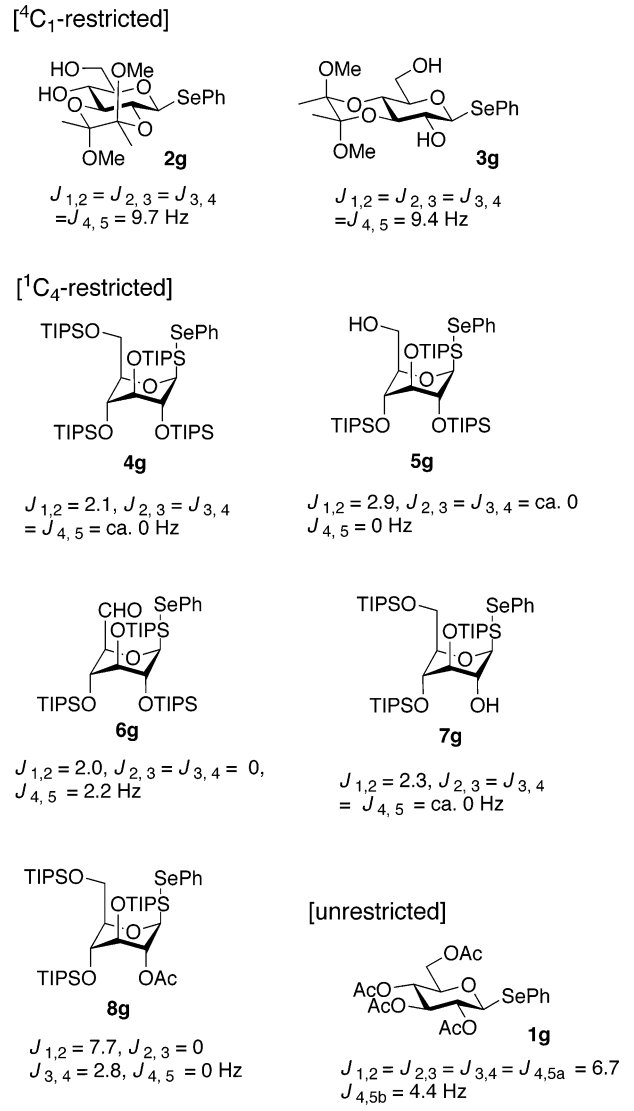
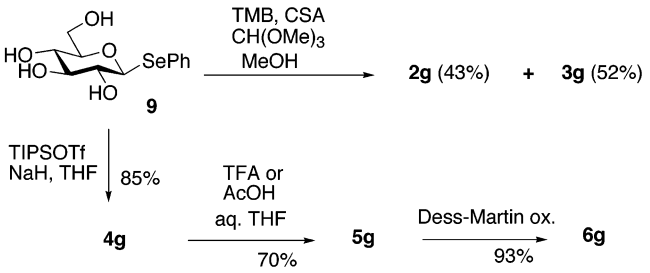


FIGURE 1. Conformationally restricted and unrestricted glucose derivatives as the anomeric radical reaction substrates.

The conformation of the pyranose ring of the substrates **2g** and **3g** bearing a 2,3- or a 3,4-*O*-cyclic-diketal group would be restricted in the $^4C_1$-form due to its *trans*-decalin-type ring system.[13] The glucose derivatives **4g**, **5g**, **6g**, **7g**, and **8g** were designed as the $^1C_4$-restricted substrates. It is known that introducing a quite bulky protecting group at the 3,4-*trans*-hydroxy groups of pyranoses causes a flip of their conformation leading to the $^1C_4$-form, in which the bulky substituents are in axial positions due to mutual steric repulsion.[3a−c,10,16−18] Therefore, the 2,3,4,6-tetrakis- and 2,3,4,-tris-*O*-triisopropysilyl (TIPS)-protected D-glucose derivatives **4g** and **5g**, respectively, would adopt a $^1C_4$-conformation due to the steric effect of the bulky silyl groups.

SCHEME 3



As described below, in the substrates **4g** and **5g** conformationally restricted in the $^1C_4$-form, both the α- and β-sides of the anomeric position were likely to be significantly sterically hindered due to the 1,3- and 1,5-diaxial repulsion, especially due to the tetrahedral carbon substituent attached to the 5-position and also due to a bulky protecting group at the 2-hydroxyl. The 2,3,4-tris-*O*-TIPS-6-aldehyde derivative **6g** was therefore designed as the $^1C_4$-restricted substrate, in which the 1,5-steric repulsion for the 5-substituent on the anomeric β-side should be moderated because of the trigonal C_6 structure of the formyl group, compared with **4g** and **5g** bearing a tetrahedral carbon substituent (−CH_2OTIPS or −CH_2OH). The substrates **7g** and **8g**, in which the 2-silyloxy moiety of the $^1C_4$-restricted substrate **4g** was replaced with a free hydroxyl or an acetoxy group, were also designed. In these substrates, the steric hindrance on the α-side of the anomeric position should be significantly reduced compared with that of **4g**.

The preparation of the substrates **2g**−**6g** is summarized in Schemes 3. Phenyl 1-seleno-β-D-glucopyranoside (**9**)[19] was heated with 2,2,3,3-tetramethoxybutanedione (TMB) and $CH(OMe)_3$ in MeOH in the presence of catalytic CSA[15] to give the corresponding 2,3-*O*-cyclic-diketal **2g** (43%) and the 3,4-*O*-cyclic-diketal **3g** (52%). Although 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,16,18] 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.[17] Thus, treatment of **9** with TIPSOTf/NaH in THF at room temperature successfully gave the 2,3,4,6-tetrakis-*O*-TIPS substrate **4g** in 85% yield. The 6-*O*-silyl group of **4g** was selectively removed by acidic treatment in aqueous THF to give **5g**, Dess−Martin oxidation[20] of which afforded the corresponding 6-formyl derivative **6g**.

The 2-free-hydroxy and 2-*O*-acetyl substrates, **7g** and **8g**, respectively, were synthesized from the glycal **10** as shown in Scheme 4. TIPS groups were introduced at all three hydroxyls by treatment of **10** with TIPSOTf in 2,6-lutidine,[21] and the resulting tris-*O*-silylated **11** was

(14) An α-selective deuteration with 1-bromo-2,3,4,6-tetra-*O*-acetyl glucose as a substrate was reported: Giese, B.; Dupes, J. *Tetrahedron Lett.* **1984**, *25*, 1349−1352.

(15) (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

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

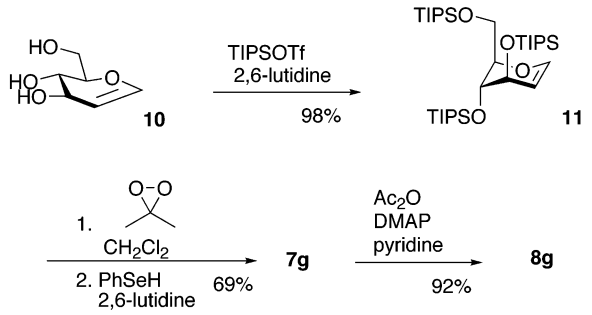
(18) (a) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 636−666. (b) Futagami, S.; Ohashi Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063−1067.

(19) Borner, W. A.; Robinson, A. *J. Am. Chem. Soc.* **1954**, *72*, 354−356.

(20) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(21) Dötz, K. H.; Otto, F.; Nieger, M. *J. Organomet. Chem.* **2001**, *621*, 77−88.

SCHEME 4



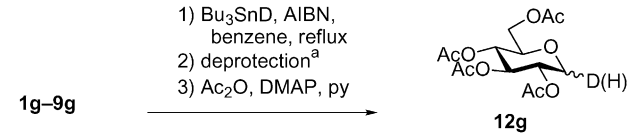
successively treated with dimethyldioxirane in CH_2Cl_2 and PhSeH in 2,6-lutidine to stereoselectively give the 1-β-phenylselenide **7g**. The 2-hydroxyl of **7g** was acetylated to give **8g**.

The conformations of the synthesized substrates were investigated by ^{1}H NMR, and the results are summarized in Figure 1. The large coupling constants (J > 9 Hz) between the vicinal protons of **2g** or **3g** showed that these protons were in an axial orientation, where the pyranose ring assumed the expected $^4C_1$-conformation. On the other hand, the small coupling constants ($J \leq 3$ Hz) between the vicinal equatorial protons of **4g**, **5g**, **6g**, **7g**, and **8g** showed that these had the $^1C_4$- or $^1C_4$-like conformation[22] as expected. The conformationally unrestricted **1g** had medium coupling constants (J = 4.4 and 6.7 Hz), compared with the other two types of conformationally restricted substrates.

Deuteration of the Conformationally Restricted Glucosyl Radicals. We first investigated the deuteration of the anomeric glucosyl radicals produced from the unrestricted substrates **1g**, the $^4C_1$-restricted substrates **2g** and **3g**, and the $^1C_4$-restricted substrates **4g** and **5g** with Bu_3SnD/AIBN. Such deuterium-labeling experiments would be useful in estimating the stereoselectivity, leading to a clarification of the influence of the steric hindrance and the anomeric effect in anomeric radical reactions. The substrates (0.07 M) were heated with Bu_3SnD (2.0 equiv)/AIBN (0.5 equiv) in benzene under reflux and then deprotected under appropriate conditions, and the resulting four hydroxyl groups of the products were acetylated with Ac_2O/pyridine. The deuterium-labeled product **12g** was purified by silica gel column chromatography, and the stereoselectivity was determined by the ^{2}H NMR spectrum. The results are summarized in Table 1.

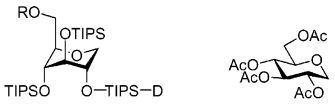
The deuteration of the unrestricted **1g** as the substrate showed an α-selectivity (entry 1, α/β = 88:12), which was in accord with the radical deuterium-labeling result of a similar tetra-*O*-acetylglucosyl substrate previously reported by Giese.[14] The reaction with the substrate **2g**, restricted in the $^4C_1$-conformation by a 2,3-*O*-cyclic-diketal, showed high α-selectivity (entry 2, α/β = 98:2). The reaction with the other $^4C_1$-restricted substrate **3g** having a 3,4-*O*-cyclic-diketal also showed the same high α-selectivity (entry 3, α/β = 98:2). 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 **1g** as expected. However, when the $^1C_4$-restricted substrates **4g** and **5g** were used, no deuterium was incorporated at the anomeric position in the corresponding reduction products, which were produced in high yield (entries 4 and 5). These unexpected results showed that intramolecular abstraction of a hydrogen atom of the 2-*O*-TIPS moiety by the anomeric radical occurred to produce **13** or **14**,[23] probably because both of the α- and β-sides of the anomeric position were significantly sterically hindered to prevent the approach of Bu_3SnD.

TABLE 1. Radical Deuteration of the Glucosyl Anomeric Radicals



entry	substrate	conformation	yield (D rate)[b]	α/β[c]
1	**1g**	unrestricted	91% (100%)	88:12
2	**2g**	$^4C_1$	67% (100%)	98:2
3	**3g**	$^4C_1$	71% (100%)	98:2
4	**4g**	$^1C_4$	91% (0%)[d]	
5	**5g**	$^1C_4$	90% (0%)[d]	
6	**6g**	$^1C_4$	60% (87%)	0:100
7	**7g**	$^1C_4$	65% (100%)	52:48
8	**8g**	$^1C_4$	71% (100%)	83:17

[a] In entry 6, the radical reaction products were treated with $NaBH_4$ in THF to reduce the formyl group before the deprotection. [b] Deuterium incorporation rate at the 1-position determined by ^{1}H NMR analysis. [c] Determined by ^{2}H NMR analysis. [d] The corresponding 1-deoxy compound **15** was obtained as the major product (entry 4, 91%; entry 5, 90%) via **13** or **14**.



On the basis of the above results, we next investigated the reaction with the other $^1C_4$-restricted substrates **6g**, **7g**, and **8g**. The radical deuterations with the 6-aldehyde substrate **6g**, which has a formyl group attached at the 5-position instead of the hydroxymethyl or the silyloxymethyl group in **4g** and **5g**, gave the β-deuterated products highly selectively as expected (entry 6, α/β = 0:100). These results showed that significant 1,5-steric repulsion occurred in the $^1C_4$-restricted substrates **4g** and **5g** due to the tetrahedral carbon structure ($-CH_2-$) at the 5-position to prevent the approach of Bu_3SnD to the anomeric β-side. The radical reaction product from **6g** was then treated with $NaBH_4$, which readily converted it into the corresponding glucose derivative. These results demonstrated that the conformational restriction of the pyranose ring of the glucose derivatives in the $^4C_1$- or $^1C_4$-form increases and inverts the stereoselectivity in anomeric radical reactions.

In the reactions with **7g** and **8g**, in which the bulky 2-silyloxy moiety of **4g** was replaced with a hydroxy or

(22) In the ^{1}H NMR spectrum of **8g**, although the coupling constants between the H_2, H_3, H_4, and H_5 (J = 0–2.8 Hz) showed that these protons were in axial orientations, the anomeric proton would not be in an axial orientation because of the rather large constant between H_1 and H_2 ($J_{1,2}$ = 7.7 Hz). Therefore, the preferred conformation of **8b** might be somewhat different from the typical $^1C_4$-form, especially around the anomeric position.

(23) The molecular ion peaks corresponding to **13** or **14** were observed in their mass spectra.

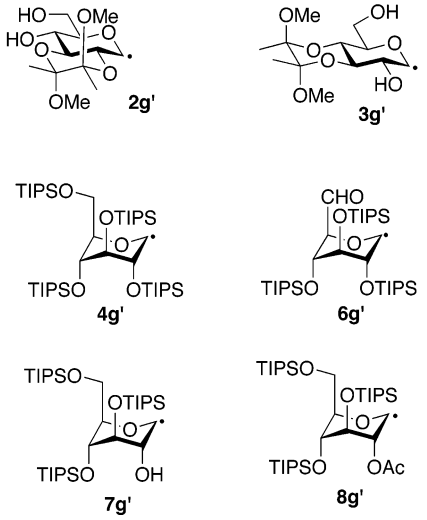


FIGURE 2. Xylose derivatives as the substrates used in the previous study.

an acetoxy group to reduce the steric hindrance around the anomeric α-position, deuteration at the anomeric position proceeded efficiently. Although the 2-hydroxy substrate **7g** was nonstereoselectively deuterated (entry 7, $\alpha/\beta = 52{:}48$), the deuteration with 2-*O*-acetyl substrate **8g** selectively gave the α-product (entry 9, $\alpha/\beta = 83{:}17$).

Conformational Analysis of the Anomeric Radicals. As described above, the ^{1}H NMR analysis suggested that the conformations of the substrates were restricted to the $^4C_1$- or the $^1C_4$-form as expected. However, the conformations of the radical intermediates, as shown in Figure 2, should more importantly affect the stereoselectivity of the anomeric radical reactions. The substrates **2g** and **3g** should be rigidly restricted to the $^4C_1$-conformation due to the inflexible *trans*-decalin-type ring system. Accordingly, the radical intermediates **2g′** and **3g′** derived from **2g** and **3g** would also rigidly assume the $^4C_1$-like conformation.

On the other hand, the conformational restriction of the radical intermediates **4g′**−**8g′** derived from **4g**−**8g**, respectively, due to the bulky silyl groups, might not be as rigid as those in the radicals **2g′** and **3g′**. Therefore, we estimated the stability of the $^1C_4$-conformations by MM3 calculations[24] with the corresponding 1-deoxy derivatives, i.e., 1,5-anhydro-2,3,4,6-tetra-*O*-TIPS-D-glucitol (**16**), its 6-formyl derivative **17**, 1,5-anhydro-3,4,6-tris-*O*-TIPS-D-glucitol (**18**), and its 2-acetate **19**, as model compounds of the radical intermediates derived from **4g**, **6g**, **7g**, and **8g**, respectively (Figure 3). These calculations would clarify the steric effect of the silyl protecting groups on the conformation of the radical intermediates. The calculated energies showed that in the 2,3,4-*O*-silylated **16** and **17** the flipped $^1C_4$-conformer is significantly more stable (8.85 kcal/mol for **16** and 10.61 kcal/mol for **17**) than the usual $^4C_1$-conformer. Therefore, the radical intermediates **4g′** and **6g′** were likely to be restricted rigidly in the $^1C_4$-conformation. Although the 3,4,6-*O*-silylated radical intermediates **7g′** and **8g′** would also prefer the $^1C_4$- to the $^4C_1$-confromation, they might have

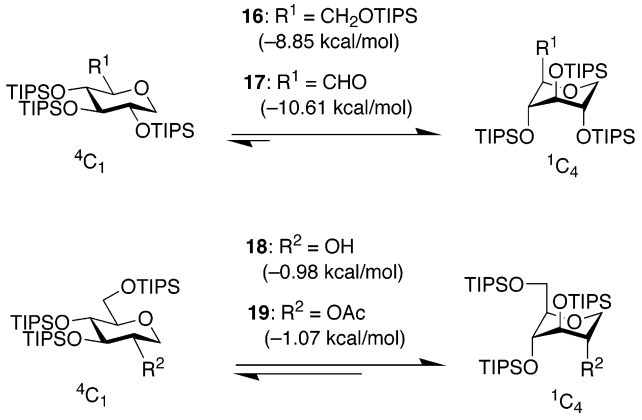


FIGURE 3. $^4C_1$-restricted and $^1C_4$-restrected glucosyl radicals.

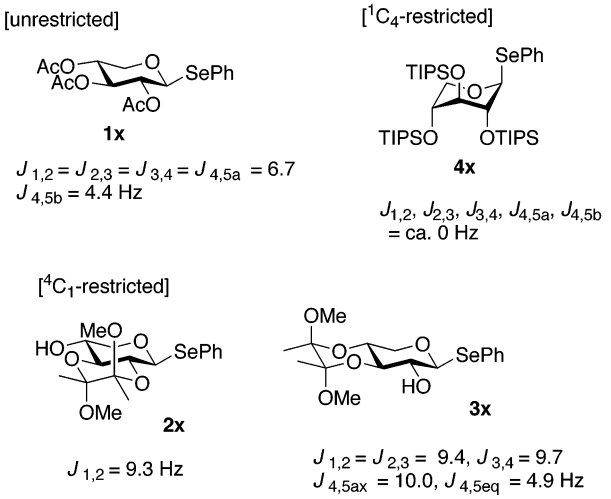


FIGURE 4. Relative energies of $^1C_4$-conformers based on the $^4C_1$-conformers calculated by the MM3 force field.

some conformational flexibility compared with **4g′** and **6g′**, because the calculated energy differences between the two conformations of the model compounds **18** and **19** were not so high (0.98 kcal/mol for **18** and 1.07 kcal/mol for **19**).

Discussion

We previously reported that anomeric radical deuterations with $^4C_1$- or $^1C_4$-restricted xylose derivatives as the substrates gave highly stereoselectively the corresponding α- or β-products, respectively, and that the stereoselectivity was increased by the conformational restriction and completely inverted by flipping the substrate conformation from the $^1C_4$- into the $^4C_1$-form, due to the kinetic anomeric effect.[10] The typical reaction substrates and results of the previous study are shown in Figure 4 and Table 2.

In the present study, the deuterium-labeling radical reactions with the glucose substrates **2g** and **3g** restricted in the $^4C_1$-conformation by a 2,3- or a 3,4-*O*-cyclic-diketal showed high α-selectivity as expected (Table 1, entries 2 and 3). These results were similar to those observed with the corresponding $^4C_1$-restricted xylose substrates **2x** and **3x** (Figure 4) reported previously, as shown in Table 2 (entries 2 and 3). However, no deuterium was incorpo-

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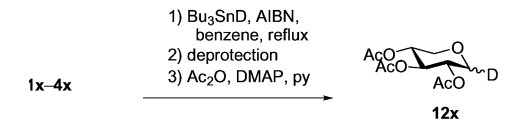
TABLE 2. The Previous Radical Deuteration of the Xylosyl Anomeric Radicals[a]



entry	substrate	conformation	yield (D rate)[b]	α/β[c]
1	**1x**	unrestricted	66% (100%)	65:35
2	**2x**	$^4C_1$	83% (100%)	97:3
3	**3x**	$^4C_1$	83% (100%)	97:3
4	**4x**	$^1C_4$	80% (100%)	1:99

[a] Data were taken from ref 10. [b] Deuterium incorporation rate at the 1-position determined by ^{1}H NMR analysis. [c] Determined by ^{2}H NMR analysis.

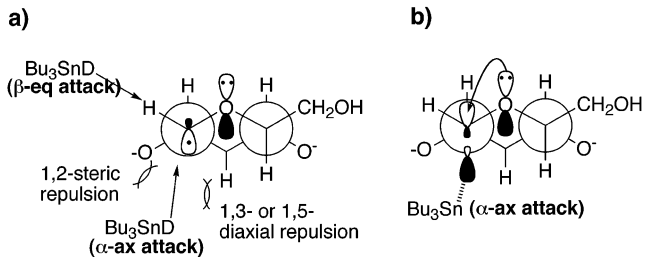


FIGURE 5. Transition state model of the reaction of the $^4C_1$-conformationally restricted glucosyl radicals **2g′** and **3g′** for an understanding of the α-stereoselectivity: considerations of the steric effect (a) and the stereoelectronic effect (b).

rated at the anomeric position in the reaction with the $^1C_4$-restricted *O*-silylated glucose derivatives **4g** and **5g** having bulky silyl groups as the substrates, where the corresponding xylose derivative **4x** effectively deuterated with high β-selectivity (Table 2, entry 4). In contrast, when the 6-aldehyde substrate **6g** was used, the radical deuteration at the anomeric position occurred with a high β-selectivity (Table 1, entry 6).

In the reactions of anomeric radicals, a radical acceptor can attack from both the axial and equatorial directions.[25,26] We first considered the highly α-selective reaction with the cyclic-diketal substrates **2g** and **3g**, via the radical intermediates **2g′** and **3g′** in the $^4C_1$-conformation (Figure 2). The steric effect in the attack on the radical intermediates **2g′** or **3g′** in the $^4C_1$-conformation is summarized in Figure 5a. The α-axial attack on **2g′** or **3g′** is accompanied by 1,3- and 1,5-diaxial repulsion. Moreover, 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,[26] where the newly forming carbon−deuterium bond and the C_2-O_2 bond are nearly eclipsed. Hence, the equatorial attack should be preferred over the axial attack from the viewpoint of steric hindrance. However, considering the stereoelectronic effect in the radical reaction of **2g′**

(25) The steric effect of substitutions at the 2-position was analyzed by using the cyclohexyl radical as a model substrate: see ref 8.

(26) Theoretical calculations by Giese, Houk, and Zipse 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, i.e., 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.

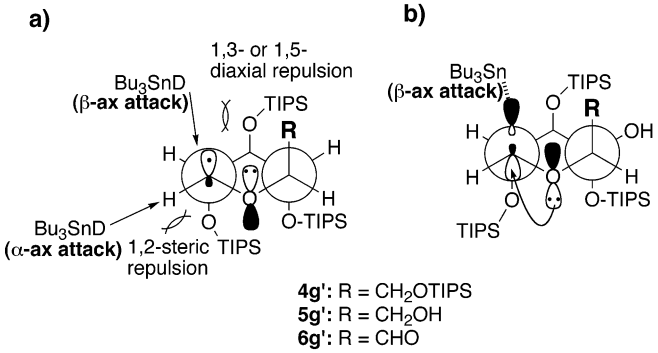


FIGURE 6. Transition state model of the reaction of the $^1C_4$-conformationally restricted glucosyl radicals **4g′**, **5g′**, and **6g′** for an understanding of the β-stereoselectivity.

and **3g′**, the α-axial attack would be preferred to the equatorial attack (Figure 5b). In the reaction of the radical intermediate conformationally restricted in the $^4C_1$-conformation,[27] the transition state likely assumes the $^4C_1$-like conformation due to the conformational restriction, where the axial attack from the α-side could be significantly stabilized by the interaction between the antibonding $\sigma^{*\ddagger}$ of the newly forming anomeric bond and the axial-directed nonbonding electrons of the ring oxygen which have high p-character to yield the α-product highly selectively. We, therefore, concluded that the dominant factor controlling the stereoselectivity of the radical reactions with the cyclic-diketal substrates **2g** and **3g** restricted in the $^4C_1$-conformation is not steric hindrance but the kinetic anomeric effect.

We next considered the reactions with the substrates **4g**, **5g**, and **6g** (Figure 6). As described above, the MM3 calculations of the corresponding 1-deoxy model compounds **16** and **17** suggested that the intermediates **4g′**, **5g′**, and **6g′** seemed to be rigidly restricted in the $^1C_4$-conformation. In the reaction of the 6-*O*-TIPS and 6-OH radicals **4g′** and **5g′**, the axial attack by Bu_3SnD from the β-side would be preferred due to the kinetic anomeric effect contributing to stabilize the transition state assuming the $^1C_4$-like conformation (Figure 6b). On the other hand, with respect to steric hindrance in the attack on the radicals **4g′** and **5g′**, the β-axial attack of Bu_3SnD encounters 1,3- and 1,5-diaxial repulsion, where the α-equatorial attack can also be disturbed by the 1,2-steric repulsion derived from the bulky 2-*O*-TIPS moiety (Figure 6a). The reaction results with the substrates **4g** and **5g** would be due to the fact that the significant steric hindrance on both the α- and the β-sides completely prevented the approach of the reagent in the intramolecular hydrogen transfer, while the kinetic anomeric effect should promote the β-side attack. Notably, the reaction of the 6-aldehyde **6g** gave the β-product with high stereoselectivity (α/β = 0:100, Table 1, entry 6); moderation of the 1,5-steric repulsion by replacement of the tetrahedral carbon ($-CH_2O-$) with the trigonal carbon ($-CHO$) at the 6-positon accompanied by the kinetic anomeric effect resulted in complete stereocontrol.

Finally, the reactions of the substrates **7g** and **8g**, in which the 2-silyloxy moiety of the $^1C_4$-restricted substrate

(27) Ab initio calculations of the xylosyl anomeric radical with 2,3- or 3,4-cyclic-diketal structure showed that they have a stable $^4C_1$-conformation: see ref 10.

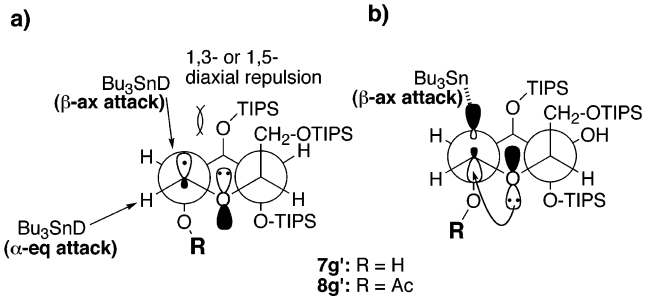
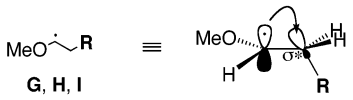


FIGURE 7. Transition state model of the reaction of the $^1C_4$-conformationally restricted glucosyl radicals **7g′** and **8g′** for an understanding of the α-stereoselectivity.

4g was replaced with a free hydroxyl or an acetoxy group, were considered. We designed **7g** and **8g** to be 1,2-steric repulsion-reduced substrates as shown in Figure 7a, compared with the corresponding 2-*O*-TIPS substrate **4g** (Figure 5a). However, the radical deuteration with the 2-hydroxy substrate **7g** was nonstereoselective (Table 1, entry 7), while the corresponding 2-*O*-acetyl substrate **8g** was α-stereoselectively deuterated, as expected (entry 8, α/β = 83:17). Although ^{1}H NMR data (Figure 1) indicated that the two substrates **7g** and **8g** preferred the $^1C_4$-conformation, the reaction results suggested that the conformational feature of the radical intermediates **7g′** and **8g′** derived from **7g** and **8g** might be different. Therefore, we investigated conformations of the radical intermediates **7g′** and **8g′** by MM3 calculations using the corresponding 1-deoxy derivatives **18** and **19** as the model compounds (Figure 3). The calculations suggested that in the two intermediates the $^1C_4$-conformer was similarly stable; the $^1C_4$-conformer was about 1 kcal/mol more stable than the $^4C_1$-conformer in both of the model compounds **18** and **19**.

We next focused on the stereoelectronic effect of the 2-substituent on the conformation of the intermediates of **7g′** and **8g′** from the point of view of orbital interactions, since the single occupied radical orbital (sp^n) could interact with the σ^* of the C_2-O_2 bond in the radical intermediates.[8,28] Thus, the stabilization energies of the orbital interactions between the radical orbital (sp^n) and the σ^* of the C−O bond were calculated based on NBO (natural bond orbital) theory,[29,30] using model radicals **G**, **H**, and **I**, and the results are summarized in Table 3. The calculated energies showed that the interaction between the σ^* of the C_2-O_2 bond stabilized the radical, where the stabilization effect was more significant in the 2-acetoxy radical **G** than in the corresponding 2-hydroxy radical **H**. Accordingly, the $^1C_4$-conformer, in which the sp^n-σ^* interaction is maximum because of the periplanar arrangement, might be more stable in **8g′** than in **7g′**. This may explain why the 2-*O*-acetoxy substrate **8g** was more selectively deuterated compared with the 2-hydroxy substrate **7g**. In the reactions of **8g**, the kinetic anomeric effect (Figure 7b), which should promote the β-attack, would not be so dominant because of the strong 1,5-steric repulsion.[31]

TABLE 3. Stabilization Energies Due to the Hyperconjugation Interactions between a Single Occupied Orbital (sp^n) and an Antibonding Orbital Bond (σ^*) of the Adjacent C−R[a]



radical	R	radical orbital (sp^n)	energy (kcal/mol)
G	−OAc	$sp^{8.91}$	14.12
H	−OH	$sp^{8.23}$	11.23
I	−H	$sp^{7.38}$	6.30

[a] Structure optimization and NBO analysis was performed by UHF/3-21G*.

Conclusion

The present study together with our previous ones[10] on the anomeric radical reactions showed that (1) the kinetic anomeric effect can be manipulated by the substrate conformation and that (2) the kinetic anomeric effect determines and increases the α-stereoselectivity of $^4C_1$-restricted substrates, such as **2g**, **3g**, **2x**, or **3x**, and also the β-stereoselectivity of the $^1C_4$-restrected substrates lacking a tetrahedral carbon substituent at the 5-axial-position, such as **6g** or **4x**. Thus, depending on the conformation of the substrates restricted to the $^4C_1$- or the $^1C_4$-form, the α- or β-products would be obtained highly stereoselectively via anomeric radical reactions.[11] However, the results of the $^1C_4$-restricted substrates **4g** and **5g** having the 5′-tetrahedral carbon substituent (−CH_2OTIPS or −CH_2OH) and 2′-OTIPS group showed that the significant steric hindrance on both the α- and the β-sides completely prevented the intermolecular deuteration in the intramolecular hydrogen transfer, while the kinetic anomeric effect should promote the β-side attack.

Experimental Section

Phenyl 2,3-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-diyl]-1-seleno-β-D-glucopyranoside (2g) and Phenyl 3,4-*O*-[(2*S*,3*S*)-2,3-Dimethoxybutane-2,3-diyl]-1-seleno-β-D-glucopyranoside (3g). A mixture of **9**[18] (1.0 g, 3.1 mmol), TMB (490 μL, 6.3 mmol), $CH(OMe)_3$ (2.7 mL, 25 mmol), and CSA (36 mg, 15 μmol) in MeOH (10 mL) was heated under reflux

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(30) 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.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

(31) Geise described that α-axial attack to the anomeric radical of pyranoses could occur via a $B_{2,5}$-boat intermediate stabilized by the anomeric effect (ref 8). In the radical deuteration of **8g**, the $B_{2,5}$-boat intermediate might contribute to the α-product formation, at least to some extent.

for 2 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 residue was purified by column chromatography (SiO_2, hexane/AcOEt, 2:1−2:3) to give compound **2g** (575 mg, 43% as an oil) and **3g** (704 mg, 52% as an oil). **2g**: $[\alpha]_D$ −127.6 (*c* 1.00 MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61−7.27 (m, 5 H), 5.00 (d, 1 H, J = 9.7 Hz), 3.90 (m, 1 H), 3.78 (m, 1 H), 3.73 (m, 1 H), 3.70 (dd, 1 H, J = 9.7, 9.7 Hz), 3.63 (dd, 1 H, J = 9.7, 9.7 Hz), 3.41 (m, 1 H), 3.28 (s, 3 H), 3.22 (s, 3 H), 2.48 (br s, 1 H), 1.99 (m, 1 H), 1.34 (s, 3 H), 1.33 (s, 3 H); FAB-HRMS calcd for $C_{18}H_{26}O_7$-SeNa 457.0741 (MNa^+), found 457.0751. Anal. Calcd for $C_{18}H_{26}O_7Se\cdot 0.2H_2O$: C, 49.48; H, 6.09. Found: C, 49.37; H, 6.13. **3g**: $[\alpha]_D$ 70.8 (*c* 1.05 MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62−7.35 (m, 5 H), 4.78 (d, 1 H, J = 9.4 Hz), 3.88 (m, 1 H), 3.73 (dd, 1 H, J = 9.4, 9.4 Hz), 3.72 (m, 1 H), 3.61 (dd, 1 H, J = 9.4, 9.4 Hz), 3.57 (m, 1 H), 3.50 (ddd, 1 H, J = 1.8, 9.4, 9.4 Hz), 3.30 (s, 3 H), 3.22 (s, 3 H), 2.45 (d, 1 H, J = 1.8 Hz), 1.84 (m, 1 H), 1.32 (s, 3 H), 1.28 (s, 3 H); FAB-HRMS calcd for $C_{18}H_{26}O_7SeNa$ 457.0741 (MNa^+), found 457.0759. Anal. Calcd for $C_{18}H_{26}O_7Se\cdot 0.4H_2O$: C, 49.07; H, 6.13. Found: C, 49.04; H, 6.08.

Phenyl 1-Seleno-2,3,4,6-tetrakis-*O*-triisopropylsilyl-*β*-D-glucopyranoside (4g). To a suspension of **9** (300 mg, 1.04 mmol) and NaH (60% in oil, 1.25 g, 31 mmol) in THF (20 mL) was added TIPSCl (4.21 mL, 15.7 mmol) slowly 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, 50:1) to give **4g** (2.51 g, 85% as an oil): $[\alpha]_D$ −39.4 (*c* 1.01 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62−7.21 (m, 5 H), 5.47 (d, 1 H, J = 2.9 Hz), 4.31 (br s, 1 H), 4.25 (dd, 1 H, J = 6.0, 9.9 Hz), 4.14 (br s, 1 H,), 4.04 (br s, 1 H), 4.02 (m, 2 H), 1.06 (m, 84 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.0, 132.7, 128.7, 126.7, 84.6, 82.5, 75.3, 75.2, 70.5, 65.9, 65.1, 18.8, 18.5, 18.4, 18.4, 18.3, 18.3, 18.0, 12.9, 12.7, 12.6, 12.1; ESI-HRMS calcd for $C_{48}H_{96}O_5$-$SeSi_4Na$ 967.5398 (MNa^+), found 967.5389. Anal. Calcd for $C_{48}H_{96}O_5SeSi_4\cdot H_2O$: C, 59.89; H, 10.26. Found: C, 59.57; H, 10.20.

Phenyl 1-Seleno-2,3,4-tris-*O*-triisopropylsilyl-*β*-D-glucopyranoside (5g). A solution of **4g** (200 mg, 212 μmol) in TFA/H_2O/THF (1:1:2.5, 4.5 mL) was stirred at room temperature for 6 h. The mixture was partitioned between AcOEt (50 mL) and H_2O (50 mL), and the organic layer was washed with H_2O, aqueous saturated $NaHCO_3$, and brine, dried (Na_2-SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt, 30:1) to give **5g** (117 mg, 70% as an oil): $[\alpha]_D$ −32.3 (*c* 0.98 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.15 (m, 5 H), 5.51 (d, 1 H, J = 2.1 Hz), 4.41 (br s, 1 H), 4.27 (m, 1 H), 4.13 (br s, 1 H), 4.04 (m, 1 H), 3.90 (br s, 1 H), 3.65 (m, 1 H), 2.25 (m, 1 H), 1.07 (m, 63 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.3, 132.2, 129.0, 126.9, 84.6, 81.0, 74.93, 74.3, 70.2, 62.3, 18.4, 18.3, 18.3, 18.2, 18.2, 17.7, 12.8, 12.6, 12.5, 12.3; FAB-HRMS calcd for $C_{39}H_{76}O_5SeSi_3Na$ 967.5398 (MNa^+), found 967.5389. Anal. Calcd for $C_{39}H_{76}O_5SeSi_3$: C, 59.43; H, 9.72. Found: C, 59.45; H, 9.71.

Phenyl 1-Seleno-2,3,4-tris-*O*-triisopropylsilyl-*β*-D-glucopyranosid-6-urose (6g). A suspension of **5g** (370 mg, 469 μmol) and Dess−Martin reagent[19] (220 mg, 516 μmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min. After addition of AcOEt (50 mL), aqueous $Na_2S_2O_3$ (saturated, 40 mL), and aqueous $NaHCO_3$ (saturated, 10 mL) to the mixture, the resulting mixture was partitioned. The organic layer was washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane/benzene, 4:1) to give **6g** (342 mg, 93% as an oil): $[\alpha]_D$ −10.2 (*c* 0.98 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.25 (s, 1 H), 7.63−7.27 (m, 5 H), 5.75 (d, 1 H, J = 2.0 Hz), 4.50 (d, 1 H, J = 2.2 Hz), 4.25 (m, 1 H), 4.24 (br s, 1 H), 4.12 (br s, 1 H), 1.08 (m, 63 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.3, 132.9, 132.4, 129.4, 127.4, 84.8, 84.1. 73.0, 72.0, 68.7, 18.5, 18.4, 18.4, 18.3, 12.7, 12.6, 12.5; FAB-HRMS calcd for $C_{39}H_{74}O_5SeSi_3Na$ 809.3907 (MNa^+), found 809.3885. Anal. Calcd for $C_{39}H_{74}O_5SeSi_3$: C, 59.58; H, 9.49. Found: C, 59.68; H, 9.54.

Phenyl 1-Seleno-3,4,6-tris-*O*-triisopropylsilyl-*β*-D-glucopyranoside (7g). To a solution of **11**[20] (2.2 g, 3.6 mmol) in CH_2Cl_2 (15 mL) was added a solution of dimethyldioxirane (0.09 M in acetone, 60 mL, 5.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was evaporated and dried in vacuo at room temperature for 3 h. To a solution of the resulting residue in 2,6-lutidine (10 mL) was added PhSeH (666 μL, 6.2 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for 3 h. The mixture was partitioned between AcOEt and aqueous HCl (1 M), and the organic layer was washed with H_2O, aqueous saturated $NaHCO_3$, H_2O, and brine, and then dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, hexane/Et_2O, 50:1) to give **7g** (1.94 g, 69% as an oil): $[\alpha]_D$ −92.6 (*c* 1.09 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64−7.25 (m, 5 H, Ar), 5.63 (d, 1 H, J = 2.3 Hz), 4.61 (dd, 1 H, J = 9.5, 9.5 Hz), 4.25 (br s, 1 H), 4.19 (br s, 1 H), 4.16 (m, 2 H), 4.10 (dd, 1 H, J = 4.7, 9,5 Hz), 4.06 (br s, 1 H), 1.09 (m, 63 H); FAB-HRMS calcd for $C_{39}H_{76}O_5SeSi_3Na$ 811.4063 (MNa^+), found 811.4049. Anal. Calcd for $C_{39}H_{76}O_5SeSi_3$: C, 59.43; H, 9.72. Found: C, 59.63; H, 9.64.

Phenyl 2-*O*-Acetyl-1-seleno-3,4,6-tris-*O*-triisopropylsilyl-*β*-D-glucopyranoside (8g). A mixture of **7g** (200 mg, 254 μmol), Ac_2O (100 μL, 1.06 mmol), and DMAP (93 mg, 76 μmol) in pyridine (3 mL) was stirred at room temperature for 1 h. The mixture was partitioned between AcOEt and aqueous HCl (1 M), and the organic layer was washed successively with H_2O, aqueous saturated $NaHCO_3$, H_2O, and brine, and then dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, hexane/Et_2O, 50:1) to give **8g** (195 mg, 92% as an oil): $[\alpha]_D$ −7.5 (*c* 0.86 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54−7.14 (m, 5 H), 5.34 (d, 1 H, J = 7.7 Hz), 5.06 (d, 1 H, J = 7.7 Hz), 4.12 (d, 1 H, J = 2.8 Hz), 4.02 (d, 1 H, J = 2.8 Hz), 3.96 (m, 2 H), 3.85 (dd, 1 H, J = 5.3, 9.6 Hz), 1.95 (s, 3 H), 0.99 (m, 63 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 133.0, 132.9, 128.7, 127.74, 126.3, 77.4, 74.0, 73.6, 69.1, 19.9, 17.1, 17.1, 17.0, 17.0, 16.7, 11.3, 11.2, 11.0; FAB-HRMS calcd for $C_{41}H_{78}O_6SeSi_3Na$ 853.4168 (MNa^+), found 853.4182. Anal. Calcd for $C_{41}H_{78}O_6SeSi_3$: C, 59.31; H, 9.47. Found: C, 59.24; H, 9.38.

General Procedure for Radical Deuteration. AIBN (5 mg, 30 μmol) was added to a solution of a substrate (140 μmol, 0.07 M) and Bu_3SnD (113 μL, 418 μmol) in benzene (2 mL) at 80 °C. After the complete disappearance of the starting material on TLC, the mixture was evaporated and the residue was treated by the procedure as described below to give **12g**. The α/β ratio of the product was determined by ^{2}H NMR.

1-[^{2}H]-1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucitol (12g) from 1g (Table 1, entry 1). After the treatment of **1g** (68 mg, 140 μmol) according to the above general procedure, the resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt, 2:1) to give **12g** (42 mg, 91% as an oil, deuteration rate = 100%, α/β ratio = 88:12): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.21 (dd, 1 H, J = 9.6, 9.6 Hz), 5.03 (dd, 1 H, J = 9.6, 9.6 Hz), 5.02 (m, 1 H), 4.21 (dd, 1 H, J = 4.9, 12.4 Hz), 4.16 (m, 0.88 H), 4.13 (dd, 1 H, J = 2.5, 12.4 Hz), 3.60 (ddd, 1 H, J = 2.5, 4.9, 9.6 Hz), 3.31 (m, 0.12 H), 2.10−2.03 (m, 12 H); ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.60 (β-anomer), 2.75 (α-anomer); FAB-HRMS calcd for $C_{14}H_{20}O_9D$ 334.1248 (MH^+), found 334.1261.

Compound 12g from 2g (Table 1, entry 2). After the treatment of **2g** (61 mg, 140 μmol) according to the above general procedure, the residue was shortly filtrated through a column (SiO_2, hexane/AcOEt, 1:1) to give a crude product. A solution of the product in aqueous TFA (80%, 3 mL) was stirred at room temperature for 15 min, and the mixture was

evaporated and azeotroped with toluene (3 times). A mixture of the resulting residue, Ac_2O (50 μL, 703 μmol), and DMAP (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 HCl (1 M), and the organic layer was washed successively with H_2O (10 mL), aqueous saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and then evaporated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt, 3.5:1) to give **12g** (31 mg, 67% as an oil, deuteration rate = 100%, α/β ratio = 98:2): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.60 (β-anomer), 2.75 (α-anomer); FAB-HRMS calcd for $C_{14}H_{20}DO_9$ 334.1248 (MH^+), found 334.1248.

Compound 12g from 3g (Table 1, entry 3). Compound **11g** (33 mg, 71% as an oil, deuteration rate = 100%, α/β ratio = 98:2) was obtained from **3g** (61 mg, 140 μmol) according to the procedure described for **2g**: ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.60 (β-anomer), 2.75 (α-anomer); FAB-HRMS calcd for $C_{14}H_{20}DO_9$ 334.1248 (MH^+), found 334.1232.

1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucitol (15) as the Reference Compound. Compound **15** (44 mg, 95% as an oil) was obtained from **1g** (68 mg, 140 μmol) according to the procedure described for the deuteration of **1g** with Bu_3SnH instead of Bu_3SnD: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.21 (dd, 1 H, J = 9.6, 9.6 Hz), 5.03 (dd, 1 H, J = 9.6, 9.6 Hz), 5.02 (m, 1 H), 4.21 (dd, 1 H, J = 4.9, 12.4 Hz), 4.16 (dd, 1 H, J = 5.7, 10.6 Hz), 4.13 (dd, 1 H, J = 2.5, 12.4 Hz), 3.60 (ddd, 1 H, J = 2.5, 4.9, 9.6 Hz), 3.31 (dd, 1 H, J = 10.8, 10.8 Hz), 2.10−2.03 (m, 12 H). FAB-HRMS calcd for $C_{14}H_{21}O_9$ 333.1186 (MH^+), found 333.1185.

Compound 15 from 4g via [^{2}H]-1,5-Anhydro-2,3,4,6-tetrakis-*O*-triisopropylsilyl-D-glucitol (13) (Table 1, entry 4). After the treatment of **4g** (131 mg, 140 μmol) according to the above general procedure, the resulting residue was purified by column chromatography (SiO_2, hexane/benzene, 25:1−20:1) to give **13** (100 mg, 91% as white amorphous): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.05−3.67 (m, 8 H), 1.06 (m, 83 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 81.1, 75.2, 72.1, 71.1, 64.1, 63.7, 18.5, 18.5, 18.5, 18.5, 18.4, 18.4, 18.3, 18.2, 12.9, 12.8, 12.7, 12.3; ESI-HRMS calcd for $C_{42}H_{91}DO_5Si_4Na$ 812.5982 (MNa^+), found 812.5982. A solution of **13** (89 mg, 0.10 mmol) and TBAF (1 M in THF, 600 μL, 600 μmol) in THF (1 mL) was stirred at room temperature for 1 h and then evaporated. The residue was acetylated by the procedure described for **2g** to give **15** (34 mg, quant, deuteration rate = 0%): FAB-HRMS calcd for $C_{14}H_{21}O_9$ 333.1186 (MH^+), found 333.1175.

Compound 15 from 5g via [^{2}H]-1,5-Anhydro-2,3,4-tris-*O*-triisopropylsilyl-D-glucitol (14) (Table 1, entry 5). According to the above procedure for **4g**, compound **5g** (110 mg, 140 μmol) was deuterated and purified by column chromatography (SiO_2, hexane/AcOEt, 15:1) to give **14** (81 mg, 90% as an oil): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99−3.72 (m, 6 H), 3.60 (dd, 1 H, J = 4.4, 11.7 Hz), 3.51 (m, 1 H), 2.29 (m, 1 H), 1.00 (m, 63 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 80.2, 74.2, 74.2, 71.3, 71.2, 71.2, 63.9, 61.9, 61.8, 18.3, 18.2, 18.2, 18.1, 17.8, 12.7, 12.5, 12.5, 12.4, 12.2. FAB-HRMS calcd for $C_{33}H_{72}O_5DSi_3$ 634.4829 (MH^+), found 634.4789. Anal. Calcd for $C_{33}H_{71}DO_5Si_3$: C, 62.50; H, 11.60. Found: C, 62.46; H, 11.07. Compound **14** (63 mg, 1.0 mmol) was deprotected and acetylated according to the procedure described for **13** to give **15** (33 mg, quant, deuteration rate = 0%).

Compound 12g from 6g (Table 1, entry 6). After the treatment of **6g** (110 mg, 140 μmol) according to the above general procedure, the residue was shortly filtrated through column chromatography (SiO_2, hexane/Et_2O, 40:1) to give a crude product. The mixture of the product and $NaBH_4$ (15 mg, 397 μmol) in THF (2 mL) was stirred at room temperature for 1 h and partitioned between AcOEt and H_2O, and the organic layer was washed with aqueous saturated $NaHCO_3$ and brine, and then dried (Na_2SO_4) and evaporated to give a crude product. The crude product was deprotected and acetylated according to the procedure described for **13** to give **12g** (14 mg, 60% as an oil, deuteration rate = 87%, α/β ratio = 0:100): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.60 (β-anomer), 2.75 (α-anomer); FAB-HRMS calcd for $C_{14}H_{19}DO_9Na$ 356.1068 (MNa^+), found 356.1080.

Compound 12g from 7g (Table 1, entry 7). Compound **7g** (105 mg, 140 μmol) was deuterated, deprotected, acetylated, and purified according to the above procedure for **4g** to give **12g** (29 mg, 65% as an oil, deuteration rate = 100%, the α/β ratio was 52:48): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.60 (β-anomer), 2.75 (α-anomer); FAB-HRMS calcd for $C_{14}H_{19}DO_9Na$ 356.1068 (MNa^+), found 356.1041.

Compound 12g from 8g (Table 1, entry 8). Compound **8g** (116 mg, 140 μmol) was deuterated, deprotected, acetylated, and purified according to the above procedure for **4g** to give **12g** (33 mg, 71% as an oil, deuteration rate = 100%, the α/β ratio was 83:17): ^{2}H NMR ($CHCl_3$, 400 MHz) δ 3.60 (β-anomer), 2.75 (α-anomer); FAB-HRMS calcd for $C_{14}H_{20}O_9D$ 334.1248 (MH^+), found 334.1272.

Computational Methods. MM3 calculations were performed with the Macro Model 5.0 program.[24] Ab initio molecular orbital calculations were performed with the Gaussian 98 program[30] running on an SGI O2 computer. The geometries of all stationary points were fully optimized at the UHF/3-21G(d) level. The stationary points were characterized by frequency analysis (minimum with 0). The natural bond orbital (NBO) method was used to analyze and understand hybrid orbitals and energy stabilizations, which determine molecular conformations. Energy stabilizations were examined in terms of second-order perturbation from almost filled orbitals to almost empty neighboring orbitals.

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Supporting Information Available: ^{1}H NMR charts of **12g** (from **1g**), **13**, and **15**, ^{2}H NMR charts of **12g** (from **1g**, **2g**, **3g**, **6g**, **7g**, and **8g**), and general methods of experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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