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An Efficient Synthesis of β-*C*-Glycosides Based on the Conformational Restriction Strategy: Lewis Acid Promoted Silane Reduction of the Anomeric Position with Complete Stereoselectivity

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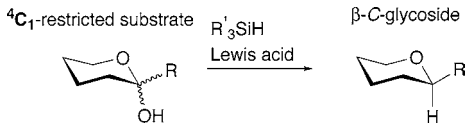
ABSTRACT



The reduction of glyconolactols having an anomeric carbon substituent by Et_3SiH/TMSOTf proceeded with complete stereoselectivity to produce the corresponding β-*C*-glycosides when the substrates were conformationally restricted in the $^4C_1$-chair form by a 3,4-*O*-cyclic diketal or a 4,6-*O*-benzylidene protecting group. Thus, the efficient construction of β-*C*-glycosides was achieved on the basis of the conformation restriction strategy.

C-Glycosides are of interest as stable mimics of natural *O*-glycosides with biological activity.[1,2] Although various effective methods for providing α-*C*-glycosides have been developed, the stereoselective synthesis of β-*C*-glycosides has been more challenging.[1−7] In the course of our synthetic studies on *C*-glycoside trisphosphates as novel *myo*-inositol trisphosphate receptor ligands,[2] we needed a highly stereoselective method for the construction of various β-*C*-glycosides.

An efficient procedure for providing β-*C*-glycosides has been developed by Kishi and co-workers. It involves addition of an organometallic reagent to a glyconolactone to give an anomeric mixture of the corresponding lactols that is reduced stereoselectively by trialkylsilane under Lewis acidic conditions to give the β-*C*-glycoside (Scheme 1).[4] β-*C*-Glucosides and -galactosides have been stereoselectively synthesized by this method. A drawback is that the stereochemical outcome

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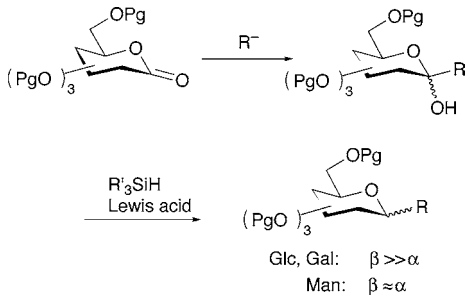
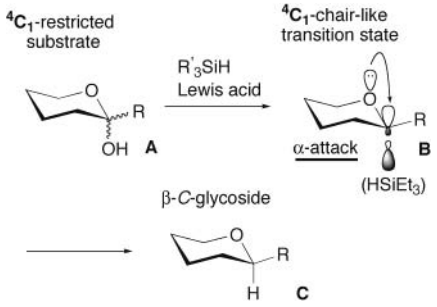
Scheme 1. Synthesis of *C*-Glycosides via the Lewis Acid Prompted Silane Reduction



Scheme 2. Working Hypothesis for the Kinetic Anomeric Effect-Dependent Silane Reduction Forming the *β*-*C*-Glycosides



of reduction depends on the starting sugar structure, and the stereoselectivity is not always high.[4] For example, when the method was applied to mannose derivatives, the reduction was almost nonstereoselective.[4] We report here a completely stereoselective construction of *β*-*C*-glycosides via the Lewis acid-promoted Et_3SiH reduction by manipulation of the anomeric effect through use of the conformationally restricted substrates.

The anomeric effect[8,9] is a stereoelectronic effect ascribed to n → *σ** hyperconjugation between the nonbonding orbital on the ring oxygen and the antibonding orbital of the anomeric carbon-heteroatom bond.[8−10] When this kind of orbital interaction stabilizes the transition state during anomeric bond-forming (or bond-cleavage) processes, it is referred to as the kinetic anomeric effect.[8−10] We have shown that, in radical and Lewis acid promoted *C*-glycosidation reactions, the kinetic anomeric effect can be manipulated by the substrate conformation. Depending on whether the conformation of the substrates is restricted to the $^4C_1$- or the $^1C_4$-form, α- or *β*-selective reactions can be made to occur highly stereoselectively.[3,6]

In the Lewis acid-promoted silane reduction (Scheme 1), hydride attack on the oxocarbenium intermediate seems to occur predominantly from the α-axial direction[4a] due to the kinetic anomeric effect, at least in the cases of glucose and galactose derivatives. We expected that the stereoselectivity of the reduction could be improved even further by enhancing the kinetic anomeric effect through placing conformational restrictions in the substrates employed. The conformation of the transition state and the intermediate can be strongly influenced by conformational effects, which stabilize the ground-state conformation.[3,6,9,11] Therefore, as shown in Scheme 2, in the reduction of substrate **A** conformationally restricted to a $^4C_1$-chair form, the transition state would assume the $^4C_1$-chairlike form **B**, where the anomeric center would be pyramidal. Accordingly, the *β*-*C*-glycosidic product **C** could be produced highly selectively. The axial attack transition state **B** in the $^4C_1$-restricted form would be significantly stabilized by the interaction between the antibonding $\sigma^{*‡}$ of the newly forming anomeric C−H bond and the orbital of a nonbonded electron pair (n_O) on the ring oxygen because of their planar arrangement.[12]

Based on this hypothesis, we planned to examine the Lewis acid promoted Et_3SiH reduction with the various conformationally restricted and unrestricted substrates. In this study, the glucose- and mannose-type substrates were employed to compare their stereochemical outcomes, since these two were considered the typical stereoselective and nonselective substrates in the reductions reported previously.[4,7] Thus, we designed the conformationally restricted substrates **2a**−**c**, **4a**−**c**, and **5** and the corresponding conformationally unrestricted substrates **1a**−**c** and **3a**−**c** (Table 1), derived from D-glucose or D-mannose. The conformation of the pyranose ring of the substrates **2a**−**c** and **4a**−**c** bearing a 3,4-*O*-cyclic diketal group and the substrate **5** bearing a 4,6-*O*-benzylidene group would be restricted in the desired $^4C_1$-form due to the *trans*-decalin-type ring system.[3,6,13,14]

The conformationally unrestricted substrates **1a**−**c** and **3a**−**c** were prepared by the previously reported method.[4a,7c,15] The conformationally restricted substrates **2a**−**c** and **4a**−**c** were synthesized from 1-thiophenyl-2,3,4,6,-tetra-*O*-acetyl sugars **6** or **7** via mannolactones **10**[16] or **11** (Scheme S1 in the Supporting Information). Similarly, another conforma-

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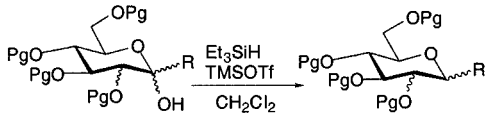
(15) Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4297−4309.

Table 1. Reduction of the Conformationally Restricted and Unrestricted Substrates with Et_3SiH/TMSOTf[a]



Entry	Substrate (α/β)[b]	R	Major product Yield[c] (α/β)[d]
	unrestricted		
1	**1a** (95:5)	Me	81% (only β)
2	**1b** (91:9)	Ph	59% (only β)
3	**1c** (91:9)	allyl	79%[e] (10:90)
	$^4C_1$		
4	**2a** (95:5)	Me	93%[f] (only β)
5	**2b** (91:9)	Ph	90% (only β)
6	**2c** (91:9)	allyl	92% (only β)
	unrestricted		
7	**3a** (> 99:1)	Me	68%[e] (22:78)
8	**3b** (> 99:1)	Ph	53% (only β)
9	**3c** (> 99:1)	allyl	61%[e] (33:67)
	$^4C_1$		
10	**4a** (> 99:1)	Me	68% (only β)
11	**4b** (> 99:1)	Ph	91% (only β)
12	**4c** (> 99:1)	allyl	-
	$^4C_1$		
13	**5** (> 99:1)	allyl	95% (only β)

[a] Reaction was carried out with Et_3SiH (1.1 equiv) and TMSOTf (1.1 equiv) in CH_2Cl_2 at −78 °C for 60 min, and the products were purified by silica gel column chromatography. [b] The α or β is based on the configuration of the anomeric hydroxyl, and the ratio was determined by ^1H NMR. [c] Substrate was recovered in entries 2 (18%), 8 (22%), 10 (18%), and 12 (64%). [d] Determined by isolated yields for entry 3 and by ^1H NMR for entries 7 and 9. [e] Yield of the mixture of the α- and β-*C*-glycosides. [f] The reaction time was 75 min.

tionally restricted substrate **5** was prepared (Scheme S2 in the Supporting Information), and the conformation of these substrates was analyzed by their ^1H NMR spectra. As summarized in Table S1 (Supporting Information), these coupling constants suggested that, irrespective of the protecting groups, all of the substrates seem to prefer the $^4C_1$-chairlike conformation. Thus, the effect of the constrained cyclic protecting groups on the conformational stability was unclear at least from the ^1H NMR analysis.

The reduction of these substrates was carried out with Et_3SiH (1.1 equiv) and TMSOTf (1.1 equiv) in CH_2Cl_2 at −78 °C,[17] and the results are summarized in Table 1.[18] The stereoselectivity was first examined with the glucose-type substrates, which were the conformationally unrestricted **1a**−**c** and the restricted **2a**−**c** (entries 1−6). The silane reduction of 1-carbon-substituted glucolactols having benzyl protecting groups is known to occur stereoselectively to produce the corresponding β-*C*-glucosides.[4,7] In accord with these previous results, the 1-methyl substrate **1a** and the 1-phenyl substrate **1b** were reduced with a complete stereoselectivity to give the β-products (entries 1 and 2). The corresponding conformationally restricted substrates **2a** and **2b** also gave the β-*C*-glucosides as the sole product (entries 4 and 5), where the yields were higher than those in the cases of the unrestricted substrates. Although, in the reduction of the conformationally unrestricted substrate **1c** having an anomeric allyl substituent the β-selectivity decreased somewhat (α/β = 10:90, entry 3), the corresponding conformationally restricted substrate **2c** was reduced to only the β-*C*-glucoside in high yield (entry 6). These reactions with the glucose substrates showed that the conformational restriction improved the yield of the β-*C*-glucosides, probably due to the stabilized transition state.

The reduction of the mannose substrates, the conformationally restricted lactols **4a**−**c** and **5**, and the unrestricted lactols **3a**−**c** was next examined (entries 7−13). In the reduction of the conformationally unrestricted tetra-*O*-benzyl substrates, the 1-phenyl mannose derivative **3b** was converted into the β-product with complete selectivity in moderate yield (entry 8). However, the β-stereoselectivity in the reduction of the 1-methyl substrate **3a** and the 1-allyl substrate **3c** was poor, in accord with the previous results with the 1-substituted mannolactols.[4] When the $^4C_1$-restricted substrates were used, the stereoselectivity was significantly improved as expected (entries 10, 11, and 13). Reduction of the 1-methyl and the 1-phenyl lactols **4a** and **4b** with the 3,4-cyclic ketal protection occurred with complete stereoselectivity to give the desired β-products (entries 10 and 11). On the other hand, reduction of the conformationally restricted 1-allyl substrate **4c** was very slow, and most of the starting material was recovered. When the 4,6-*O*-benzylidene-protected lactol **5** was employed as the conformationally restricted substrate, the reduction proceeded effectively to produce the desired 1-allyl-β-*C*-mannoside as the sole product in 95% yield. Thus, the $^4C_1$-conformational restriction effectively improved the stereoselectivity as well as the yield in the Et_3SiH reduction.

As shown in Table 1, while all of the 1-substituted lactol substrates used in this study mainly included the α-hydroxy

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(17) When $F_3B{\cdot}OEt_2$ was used as the Lewis acid, the 3,4-cyclic ketal moiety of the conformationally restricted substrates was partially reduced.

(18) The stereochemistry of the *C*-glycosidic products was determined by the $J_{1,2}$ values for the *C*-glucosides or by NOE experiments for the *C*-mannosides.

isomer, the stereoretained β-*C*-glycoside was always obtained as the major product, indicating that the reduction proceeded mainly via an S_N1 or an analogous mechanism. In the glucose-type substrates, the reduction selectively occurred from the α-face even without conformational restriction. However, in the conformationally unrestricted mannose-type substrates, the β-selectivity was low, and the conformational restriction effectively improved the stereochemical outcome. The tetra-*O*-benzyl glucosubstrates **1a**−**c** would be more stable in the $^4C_1$-chair conformation, due to the 2,3,4-all-equatorial substituents on the pyranose ring, than the corresponding manno substrates **3a**−**c** having an axial substituent at the 2-position. Accordingly, the kinetic anomeric effect may work rather effectively even in the conformationally unrestricted gluco substrates **1a**−**c**.

In conclusion, we have developed an efficient method for providing β-*C*-glycosides based on the conformationally restricted strategy. The present study together with our previous results[3,6] suggests that the kinetic anomeric effect can be manipulated by the substrate conformation to increase the stereoselectivity in the anomeric reactions.

Supporting Information Available: Schemes S1 and S2, Table S1, and experimental details on the synthesis of the reaction substrates and the Lewis acid promoted silane reduction; ^{1}H NMR spectra of **3b**, **5**, and the silane reduction products from **2c** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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