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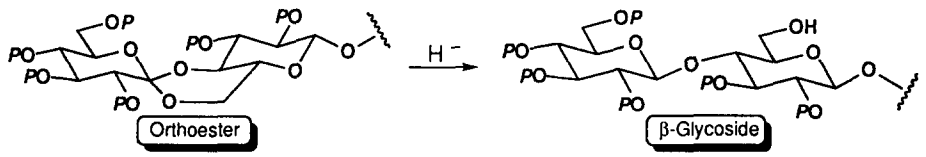
A Highly Stereoselective β-(1→4)-Glycosidic Bond Formation by Reductive Cleavage of Cyclic Orthoesters

Takamasa Iimori†, Hiro Ohtake, and Shiro Ikegami*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

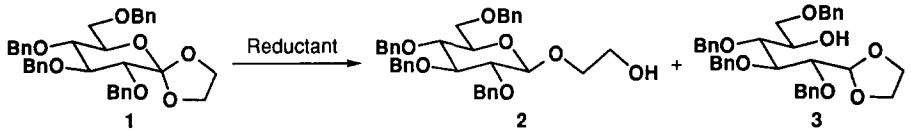
Abstract: Sterically congested glycosides, glycosyl-β-(1→4)-glycosides, were stereoselectively synthesized by reduction of glycosidic spiro-orthoesters with $LiAlH_4$-$AlCl_3$. This novel transformation is especially valuable when it is applied to the preparation of mannosyl-β-(1→4)-glycoside which must be one of the most difficult tasks in carbohydrate chemistry. © 1997 Elsevier Science Ltd.

Oligosaccharides and glycoconjugates play essential roles in many molecular processes. Studies of these biological functions have necessitated development of effective methods for the construction of glycosides and oligosaccharides.[1] The glycosidic bond formation, the most important process in saccharide synthesis, is generally based on the activation of glycosyl donors with leaving groups such as fluoride, trichloroacetimidate by appropriate promoters,[2] but a different type of glycosylation is an attractive alternative because it might provide flexible strategies to construct complex oligosaccharides. Along this line, we reported a two-step glycosylation procedure, which involved the opposite mode of connection of sugars to form glycosyl carbonate and decarboxylative transformation of the temporally connected carbonate into glycoside.[3] Another crucial problem in carbohydrate chemistry is the difficulty of stereoselective construction of glycosides with the sterically hindered glycosyl acceptors. From these points of view, we designed a novel glycosylation protocol based on a completely different concept from the known ones. Here we disclose a novel glycosylation, which is characterized by linking two sugar moieties as an orthoester and cleaving one C-O orthoester bond to form glycosyl-β-(1→4)-glycoside.



Hydrogenolysis of 4,6-*O*-benzylidene-D-glucopyranoside to 4- or 6-*O*-benzyl-D-glucopyranoside is a useful selective manipulation in carbohydrate chemistry.[4] Our new glycosylation concept was inspired by this regioselective transformation. As shown in the above figure, if an appropriate reductant was selected for the cleavage of the orthoester, it might produce a sterically more congested glycosyl-(1→4)-glycoside selectively.

Table 1. Reduction of Orthoesters to Form a Glycosidic Bond.



Entry	Reductant (mol eq.)	Solvent	Conditions	Yield (%)[a] 2 (α : β)[b]	3	1
1	$LiAlH_4$-$AlCl_3$ (1.5)	CH_2Cl_2-Et_2O	0 °C, 3 h	68 (5 : 95)	16	—
2	$LiAlH_4$-$AlBr_3$ (1.5)	CH_2Cl_2-Et_2O	0 °C, 3 h	65 (4 : 96)	6	—
3	DIBAH (5.0)	toluene	0 °C, 2 h; rt 1 h	79 (2 : 98)	< 1	1
4	Al(i-Bu)$_3$ (10)	toluene-hexane	0 °C, 1 h; rt 2 h	—	53	22
5	$NaBH_3CN$-TMSCl (10)	CH_3CN	0 °C, 2 h; rt 1 h	32 (1 : 99)	—	47

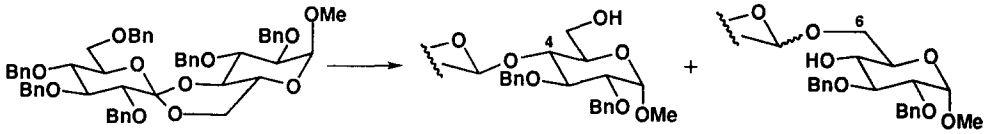
[a] Isolated yield. — : Not detected. [b] Determined by HPLC analysis.

To materialize this idea, we first examined the reductive opening of the orthoester **1**[5] to the glycoside **2** by using the reported procedures of the reductive cleavage of orthoesters and acetals.[6] While there are three C-O bonds for opening the spiro-cyclic orthoester, it is necessary for the reductant to select the glycosylidene C-O bonds as the transformation to glycoside. Gorin and co-worker have reported the reduction of simple cyclic orthoesters with a combination of $LiAlH_4$ and $AlCl_3$ widely used in the regioselective cleavage of acetals.[6a] By using this reductant, the β-glycoside **2** was obtained stereoselectively accompanied with **3** in which the undesired C-O bond was cleaved (entry 1 in Table 1). Lewis acids which would suppress the formation of **3** were surveyed and $AlBr_3$ was found to be effective (entry 2) but the yield of **2** was lower than that of entry 1. Cleavage of orthoesters with DIBAH at 0 °C has also been reported by Yamamoto and co-workers.[6b] In our case, although the reduction of the orthoester **1** required an excess of DIBAH (5 mol equiv) and higher temperature (entry 3), the desired glycoside was produced in 79% yield with high stereoselectivity (α : β = 2 : 98). Reduction with $NaBH_3CN$-TMSCl[6c] also produced **2**, but a large excess of reagents might be required to complete the reaction (entry 5). The other reductants examined (Al(i-Bu)$_3$, BH_3[6d] or Et_3SiH with various Lewis acid[4b,6e]) did not produce the glycoside at all. It is interesting that Al(i-Bu)$_3$ cleaves a different C-O bond to form **3** selectively (entry 4). As shown in entries 1 and 3, the appropriate reductants cleaved the desired C-O bond and afforded the β-glycoside stereoselectively. Although the rationale for this high β-selectivity observed has not been elucidated, it might be ascribed to the axial side attack of a hydride to an orthoester carbon.

With these promising results in hand, we next explored the applicability of our new glycosylation protocol to disaccharide synthesis. The first step of our glycosylation method is formation of orthoesters from the corresponding sugar lactones. 4,6-*O*-(D-Glucopyranosylidene)-α-D-glucopyranoside **4**, the substrate for the glucopyranoside **5**, was prepared in 72% yield by Yoshimura and his co-workers.[7] Since each step of our glycosylation method must be a high-yielding process, we first attempted to improve the yield of this orthoester formation. After several experiments, we found a more efficient procedure which is described in the accompanying paper[8] resulting in glucopyranosylidene acetal **4** as a single stereoisomer (shown in Scheme 2) in 87% yield. By this modified procedure, galactopyranosylidene and mannnopyranosylidene acetals (**7** and **9**) were also obtained in 82 and 77% yield, respectively.

The next stage in our study was clarification of the regioselectivity in reductive cleavage of the orthoesters and stereoselectivity of the thus-formed glycosidic bond. As shown in Scheme 2, glucosyl-(1→4)-glucoside **5** and (1→6)-glucoside **6** are possible as the glycosylation products. However, reduction with $LiAlH_4$-$AlCl_3$ produced sterically congested (1→4)-glycoside **5** in 92% yield as expected. The stereochemistry of the anomeric center of **5** was determined to be β by the coupling constant of ^1H NMR.[9] A careful survey of the minor products showed the presence of a small amount (less than 3%) of an undesired bond-cleaved product like **3**, but neither α-glycoside of **5** nor (1→6)-glycoside **6** was detected. (1→4)-Glycoside linkage in **5** was undoubtedly determined by ^1H NMR analysis of the benzoylated derivative. To our knowledge, this is the first example of complete regio- and stereoselective ring cleavage of a glycosydic orthoester to form a glycosidic bond. DIBAH reduction also produced the glycoside **5** in 90% yield, but completion of the reaction required a large excess of the reagent (*ca.* 15 mol equiv). From the practical point of view, the $LiAlH_4$-$AlCl_3$ combination was the reductant of choice for the complex disaccharide synthesis.

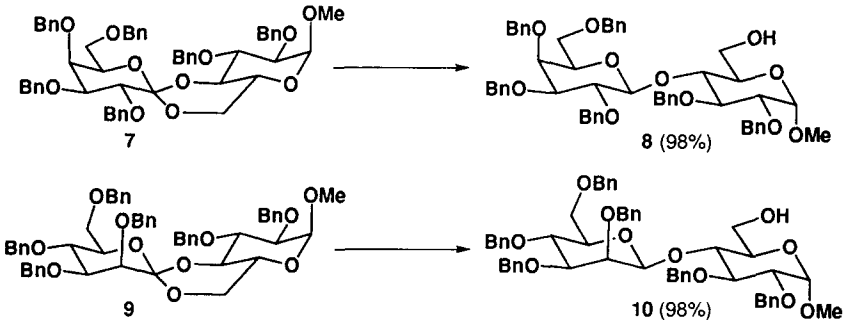
Scheme 2[a]



[a] Conditions: $LiAlH_4$-$AlCl_3$ (2 mol eq.), CH_2Cl_2-Et_2O, rt, 2 h.

Application of this glycosylation procedure to the galactopyranose derivative **7** and the mannopyranose derivative **9** is summarized in Scheme 3. The reduction of the orthoesters **7** and **9** with $LiAlH_4$-$AlCl_3$ smoothly occurred to produce the glycosides **8** and **10**, respectively, in completely regio- and stereoselective fashion.[9] Since construction of β-mannoside is one of the most difficult tasks due to the 1,2-*cis*-arrangement and stereoelectronically disfavored C-O bond formation, the stereoselectivity observed in the mannopyranoside **10** was noteworthy. Moreover, the regioselective (1→4)-glycoside formation is also valuable in carbohydrate chemistry since β-mannosides linked to sterically congested *O*-4 positions of glycosides have often been encountered in glycoconjugates. While highly stereoselective β-mannosidation has been achieved by using an aglycon delivery concept recently,[10] our glycosidation protocol is comparable in terms of efficiency and selectivity.

Scheme 3[a]



[a] Conditions: $LiAlH_4$-$AlCl_3$ (2 mol eq.), CH_2Cl_2-Et_2O, rt, 2 h.

The glycosylation by reduction of orthoesters presented herein is a less direct route, but it may lead to a new synthetic plan in the area of oligosaccharide synthesis because a completely different mode of glycosidic bond formation is utilized in this process. The greatest advantage of this glycosylation procedure over the others is that sterically congested (1→4)-glycosides are stereoselectively formed in high yield. As it might be a new practical entry for the stereoselective formation of β-mannosides, extension of this process to synthesis of oligosaccharides having such linkages is under investigation in this laboratory.

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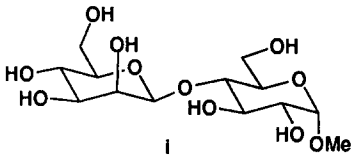

i

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