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A Facile and Improved Preparation of Glycosylidene Acetals of Monosaccharides

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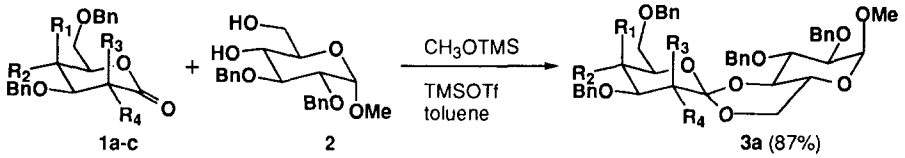
Abstract: Glycosidic spiro-orthoesters were prepared from sugar lactones, diols, trimethylsilyl methyl ether and a catalytic amount of trimethylsilyl triflate in high yield. A key feature of this procedure is that diols can be directly used for this reaction without silylation. © 1997 Elsevier Science Ltd.

Acetal interlinkage between a glycosylidene group and a diol grouping of glycoside has been found in pseudo-saccharide antibiotics, orthothomycins.[1] Since this unique orthoester linkage restricts conformation of the saccharide, it may lead to a new type of molecular design in carbohydrate chemistry. We were interested in this interglycosidic spiro-orthoester linkage from a different point of view, namely, development of a novel reductive glycosidic bond formation.[2] Herein we report a simple and high-yielding preparation of such spiro cyclic orthoesters.

Yoshimura and his co-workers have extensively studied the interglycosidic spiro-orthoesters,[3] and reported the synthesis of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene acetals by using TMSOTf and the corresponding silylated diols.[3a] However, this procedure requires generally 3 days of reaction time at room temperature when it utilizes a complex diol such as **2**, and the yield of orthoester **3a** is around 70%. As we required a much more efficient method for our new glycosylation protocol, we explored several modifications of this process. In principle, preparation of orthoesters from lactones is similar to that of ketals from ketones. Kurihara and co-worker have reported the ketal formation by using diol, *sec*- or *tert*-alkoxy silane and TMSOTf in modification[4] of Noyori's method.[5] A direct application of this method to orthoester formation was not effective; however, replacement of *sec*- or *tert*-alkoxy silane to methoxy silane and removal of disiloxane from the reaction mixture dramatically improved the yield of the orthoesters. By this modification, the glucopyranosylidene, galactopyranosylidene and mannnopyranosylidene acetals **3a-c** were obtained in 87 - 77% yield.



1a-c **2**

a: R_1 = H, R_2 = OBn, R_3 = H, R_4 = OBn
b: R_1 = OBn, R_2 = H, R_3 = H, R_4 = OBn
c: R_1 = H, R_2 = OBn, R_3 = OBn, R_4 = H

3a (87%)
3b (82%)
3c (77%)

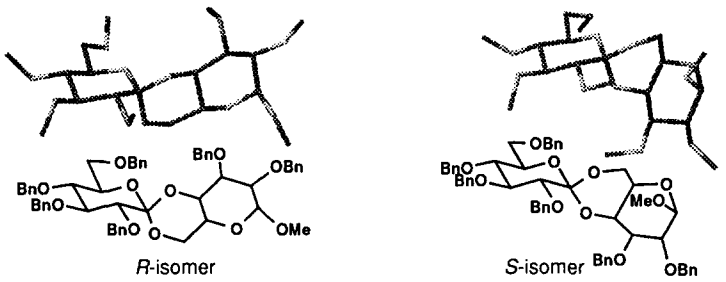


Figure 1. Two possible stereoisomers of **3a** (phenyl groups and hydrogens were omitted for clarity).

Although two stereoisomers of 4,6-*O*-(D-glucopyranosylidene)-α-D-glucopyranoside **3a** are possible, only one isomer was isolated in this orthoester formation. In order to determine this configuration, molecular mechanics calculations[6] were conducted. From the calculations, it was suggested that the *R*-isomer was more stable by 3.4 kcal/mol than the *S*-isomer (Figure 1). Thus, we tentatively assigned the stereochemistry of the anomeric position to be *R*. The orthoesters **3b** and **3c** were also obtained as a single isomer, and the *R*-isomers were judged to be apparently more stable than the *S*-isomers from a similar inspection of molecular modeling.

The modified procedure presented herein efficiently provides the orthoesters, which are employed in our new glycosylation protocol.[2] Moreover, since the spiro-orthoester linkages are useful conformational locks of saccharides, the design and synthesis of such molecules are under investigation in this laboratory.[7]

Typical Procedure of Orthoester Formation: To a solution of the lactone **1a** (54 mg, 0.10 mmol) and the diol **2** (37 mg, 0.10 mmol) in toluene (1 ml) were added TMSOMe (0.14 ml, 1.0 mmol) and TMSOTf (0.4 μl, 2 mol%) at room temperature. After 1 h of stirring, the solvent was removed under reduced pressure (5 mmHg, 1 h). The reaction vessel was leaked with Ar and the remainder was again dissolved in toluene. TMSOMe (0.14 ml, 1.0 mmol) and TMSOTf (0.4 μl, 2 mol%) was added to the solution, and the mixture was stirred for further 30 min. The solvent was removed under reduced pressure again. The remainder was dissolved in toluene containing 5% of Et_3N, and the mixture was applied to a silica gel column chromatography (ether-hexane 1 : 3 then 1 : 2) to afford **3a** as a colorless syrup (78 mg, 87%).

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† Deceased March 16, 1997

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