SYNTHESIS AND STRUCTURE OF GLYCOSYLIDENE ACETALS OF GALACTOSIDE

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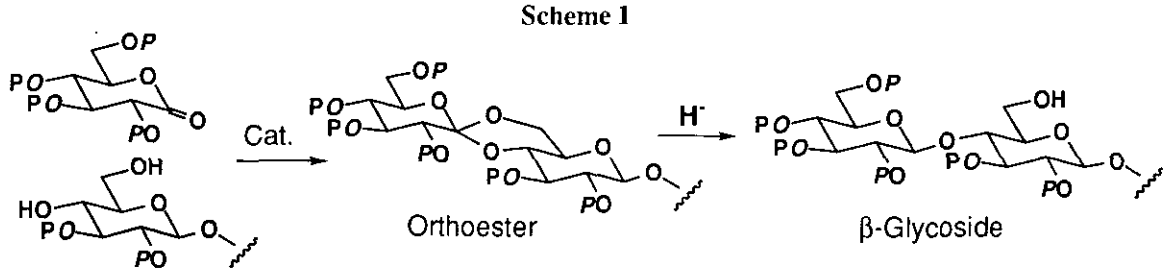
Abstract - Interglycosidic spiro-orthoesters were efficiently prepared from methyl 2,6-di-*O*-benzylgalactopyranoside and sugar lactones in the presence of methoxytrimethylsilane and a catalytic amount of trimethylsilyl triflate. The structure of the prepared orthoester, galactosylidenegalactoside, was determined by X-Ray crystallographic analysis.

The spiro-orthoester interlinkage between a glycosylidene group and the diol moiety of glycoside has been found in the orthosomycin family of antibiotics.[1] Since this unique orthoester linkage restricts conformation of the saccharide, it arose interest from the point of designing pseudo-saccharide molecules. Yoshimura and his co-workers have extensively studied interglycosidic orthoesters for the purpose of synthesizing orthosomycin antibiotics[2] and developed the method for the synthesis of such compounds by using TMSOTf and the corresponding silylated diols[2c] in modification of Noyori's method.[3] Recently, we were also interested in this unique type of linkage as the intermediate in our novel reductive glycosidic bond formation (Scheme 1), and modified the process for the formation of these orthoesters.[4] In previous paper,[4a] we reported that sugar lactones and methyl 2,3-di-*O*-benzylglucopyranoside rapidly formed orthoesters in the presence of excess amount of TMSOMe and catalytic amount of TMSOTf.[5] In this paper, we report the efficient preparation and the X-Ray structure determination of novel orthoester compounds using 2,6-di-*O*-protected galactoside as a α-diol type glycoside.

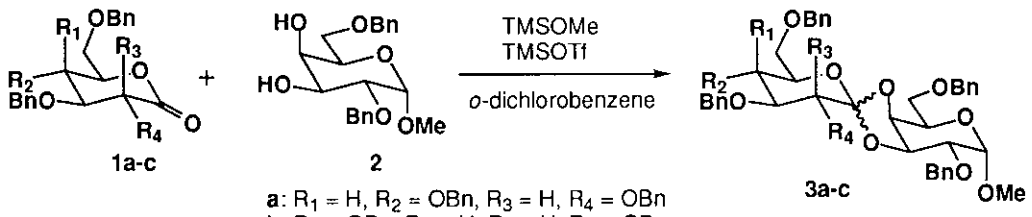
Scheme 1



Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

According to our improved procedure, we examined the ability of methyl 2,6-di-*O*-benzylgalactopyranoside (**2**) to form orthoesters with sugar lactones (**1a-c**). As shown in Table 1, 3,4-*O*-glucopyranosylidene (**3a**), 3,4-*O*-galactopyranosylidene (**3b**) and 3,4-*O*-mannnopyranosylidene acetals (**3c**) were obtained in 82, 87 and 79% yields, respectively, using *o*-dichlorobenzene as a solvent (Scheme 2). To improve the yields of orthoesters, produced MeOH and hexamethyldisiloxane were removed from the reaction mixtures under reduced pressure (5-15 mmHg), and the reagents (TMSOMe and TMSOTf) were supplemented during the course of reactions. Two stereoisomers were possible for each orthoester around anomeric center. The ratios of major isomers to minor ones were 4 : 1 in all three cases. The major isomers were separated by silica gel column chromatography, and the yields of them are shown in Table 1 beside those of mixtures. ^{13}C-Chemical shifts (δ in ppm relative to TMS) of anomeric carbons (C-1, C-1')[6] in these six orthoesters were summarized in Table 2.

Scheme 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

Table 1

Lactone	Orthoester	Yield (Major : Minor)[a]	Yield (Major)
1a	**3a**	82 % (4 : 1)	64 %
1b	**3b**	87 % (4 : 1)	65 %
1c	**3c**	79 % (4 : 1)	58 %

These reactions were carried out in *o*-dichlorobenzene under Ar at rt for 4 h ([**1a-c**] =100 mM, [2]=100 mM, [TMSOMe] =1.0 M, [TMSOTf]=2-8 mM). During the reaction, generated MeOH and hexamethyldisiloxane were removed under reduced pressure (5-15 mmHg, 1 hr x 2). a) Determined by ^{1}H-NMR.

Table 2

	3a(major)	**3a**(minor)	**3b**(major)	**3b**(minor)	**3c**(major)	**3c**(minor)
C-1	98.3	98.5	98.3	98.6	97.9	98.6
C-1'	119.4	120.4	119.9	120.9	118.9	120.2

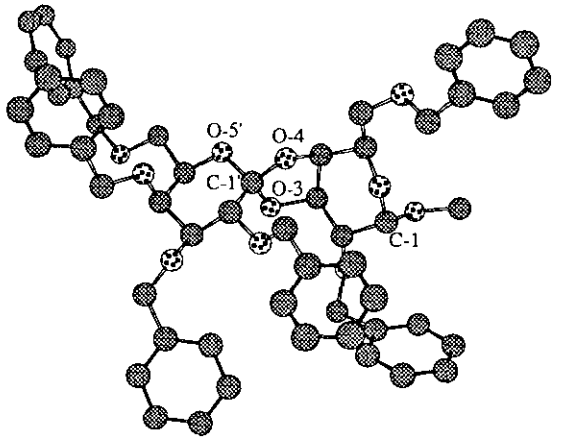
^{13}C-Chemical shifts (δ in ppm relative to TMS) of anomeric carbons (C-1, C-1').

It was revealed by the TLC analysis that the ratio between the amounts of major and minor isomers reached to 4 : 1 after the removal of MeOH and disiloxane under reduced pressure. We think that the presence of excess amount of TMSOMe, which was also removed under reduced pressure, might change the ratio between them. First, we used toluene or CH_2Cl_2 as a solvent for this reaction. However, in the cases with these solvents, the major / minor ratio did not reach to the above value. Differ from *o*-dichlorobenzene, these solvents were lost together with TMSOMe under these reduced pressure conditions, and then the reaction might not attain equilibrium completely after the removal of TMSOMe.

One of the presented orthoesters, the major isomer of galactosylidenegalactoside (**3b**(major)), was a crystalline compound, and the structure of it was determined by X-Ray crystallographic analysis.[7] The result is shown in Figure 1. It was indicated that O-3 atom linked to the orthoester carbon atom (C-1') from axial axis, and that the absolute configuration of C-1' was *R*. As shown in Table 2, the ^{13}C-NMR signals of orthoester carbons (C-1') in the major isomers (**3a**(major), **3b**(major) and **3c**(major)) were all observed in higher-field compared to those in the corresponding minor ones (**3a**(minor), **3b**(minor) and **3c**(minor)). It therefore can be assumed that the configurations of the orthoester carbon atoms in these major isomers are the same.

The role of TMSOMe under these reaction conditions is still not clear. While the reaction of α-diol type glycosides with sugar lactones rapidly attained an equilibrium to afford interglycosidic orthoesters in the presence of TMSOMe and a catalytic amount of TMSOTf, the reaction of corresponding trimethylsilylated diols with lactones proceeded far more slowly in the presence of same amount of catalyst. Thus, we presume that TMSOMe may activate sugar lactones instead of a diol group. It is plausible that dimethyl or methyl trimethylsilyl acetals of sugar lactones[8] are produced under these reaction conditions, and that the formed acetals react more efficiently with diols than sugar lactones.

Figure 1



The X-Ray single-crystal structure of orthoester (**3b**(major)) represented with ball and stick model.

The presented orthoesters will be employed in our reductive glycosylation procedure. The results in the reduction step will be published in due course. The design and synthesis of pseudo-succaride molecules containing spiro-orthoester linkages are also under investigation in this laboratory.

Typical Experimental Procedure for Orthoester Preparation: To a solution of lactone (**1a**) (54 mg, 0.10 mmol), diol (**2**) (37 mg, 0.10 mmol) and TMSOMe (0.14 mL, 1.0 mmol) in dry *o*-dichlorobenzene (1 mL), TMSOTf (0.4 μL, 2 mol%) was added at rt under argon. After 1 h of stirring, produced MeOH and hexamethyldisiloxane were removed under reduced pressure (5-15 mmHg, 1 h). The reaction vessel was leaked with argon, then TMSOMe (0.14 mL, 1.0 mmol) and TMSOTf (0.4 μL, 2 mol%) were again added to the remained solution. The mixture was stirred for further 30 min and produced MeOH and disiloxane were removed under reduced pressure again. After leaking with argon, triethylamine (50 μL) was added to the resulting solution, 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 (73 mg, 82%).

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REFERENCES AND NOTES

† Deceased March 16, 1997.

1. (a) D. E. Wright, *Tetrahedron*, 1979, **35**, 1207. (b) W. D. Ollis, C. Smith and D. E. Wright, *Tetrahedron*, 1979, **35**, 105.
2. (a) J. Yoshimura and M. Tamaru, *Carbohydr. Res.*, 1979, **72**, C9. (b) M. Tamaru, S. Horito and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3687. (c) J. Yoshimura, S. Horito and H. Hashimoto, *Chem. Lett.*, 1981, 375. (d) S. Horito, K. Asano, K. Umemura, H. Hashimoto and J. Yoshimura, *Carbohydr. Res.*, 1983, **121**, 175. (e) J. Yoshimura, S. Horito, J. Tamura and H. Hashimoto, *Chem. Lett.*, 1985, 1335. (f) J. Tamura, S. Horito, H. Hashimoto and J. Yoshimura, *Carbohydr. Res.*, 1988, **174**, 181.
3. T. Tsunoda, M. Suzuki and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357.
4. (a) H. Ohtake, T. Iimori and S. Ikegami, *Tetrahedron Lett.*, 1997, **38**, 3413. (b) T. Iimori, H. Ohtake and S. Ikegami, *Tetrahedron Lett.*, 1997, **38**, 3415.
5. Kurihara and a co-worker have reported the ketal formation by using diol, *sec*- or *tert*-alkoxysilane and TMSOTf; M. Kurihara and N. Miyata, *Chem. Lett.*, 1995, 263.
6. ^{13}C-Chemical shifts of anormeric carbons (C-1') in interglycosidic orthoesters: see for example; N. Neuss, K. F. Koch, B. B. Molloy, W. Day, L. L. Huckstep, D. E. Dorman and J. D. Roberts, *Helv. Chim. Acta*, 1970, **53**, 2314; A. K. Ganguly, O. Z. Sarre, D. Greeves and J. Morton, *J. Am. Chem. Soc.*, 1975, **97**, 1982.
7. The X-Ray analytical data are available on request.
8. Dimethyl or methyl trimethylsilyl acetals of sugar lactones are known to be formed from sugar lactones and TMSOMe in the presence of TMSOTf; J. Yoshimura, S. Horito, K. Asano and H. Hashimoto, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 24th* (Japan), 1981, p. 638.

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