Synthesis and Stereochemistry of 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosylidene Acetals of α-Diols and Monosaccharides

Masatoshi TAMARU,† Shigeomi HORITO, and Juji YOSHIMURA*

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227

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The title compounds were synthesized by addition of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone to epoxides and by direct dehydration between the lactone and diols in the presence of concentrated sulfuric acid as a catalyst. Stereochemistry of these spiro cyclic acetals was discussed.

The unique type of acetal interlinkage between a glycosylidene(1-dehydroglycosyl) group and a glycose has been found in such oligosaccharide antibiotics as everninomicins,[1] flambamycin,[2] hygromycin B,[3] destomycins,[4] A-396-I,[5] and SS-56C.[6] Recently, these antibiotics were designated as "orthosomycins,"[2] because the spiro cyclic ortho ester at the anomeric carbon is quite different from well-known fused-ring type ortho esters in the carbohydrate chemistry.[7] In general, two configurations are possible in this interlinkage depending on whether the anomeric carbon is (*R*) or (*S*). However, it is left ambiguous except for one of the two linkages in everninomicin D.[8] Moreover, no synthetic anologs have thus far been reported except a communication[9] from our laboratory.

This paper describes in detail the synthesis of the spiro cyclic ortho esters from 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**)[10] and the stereochemistry of their ring-systems.

Results and Discussion

As the applicable methods for the preparation of spiro cyclic ortho esters from **1**, addition of **1** to epoxides[11] and the dehydration condensation of **1** with diols[12] were examined.

Reaction of **1** in dichloromethane with equivalent amount of 1-chloro-2,3-epoxypropane or 1,2-epoxypropane at 28—30 °C for 1 h in the presence of boron trifluoride etherate gave the corresponding spiro cyclic ortho esters (**2** and **3**) as syrups in 45 and 65% yields, respectively. The presence of both of the isomers possible was indicated by the ^{1}H NMR spectra of **2** and **3**, respectively. A similar reaction of **1** with 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[13] for 1 h gave only one of two possible isomers, 1,2-*O*-isopropylidene-3-*O*-methyl-5,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-α-D-glucofuranose (**4**) in 26% yield. The presence of the ortho ester linkage in **4** was proved by the characteristic signal of ortho ester carbon at δ 110.8 ppm (from Me_4Si) in the ^{13}C NMR spectrum. However, this method was unsuccessful in the case of such epoxides including two secondary carbons as 1,2-epoxycyclohexane and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside.[14]

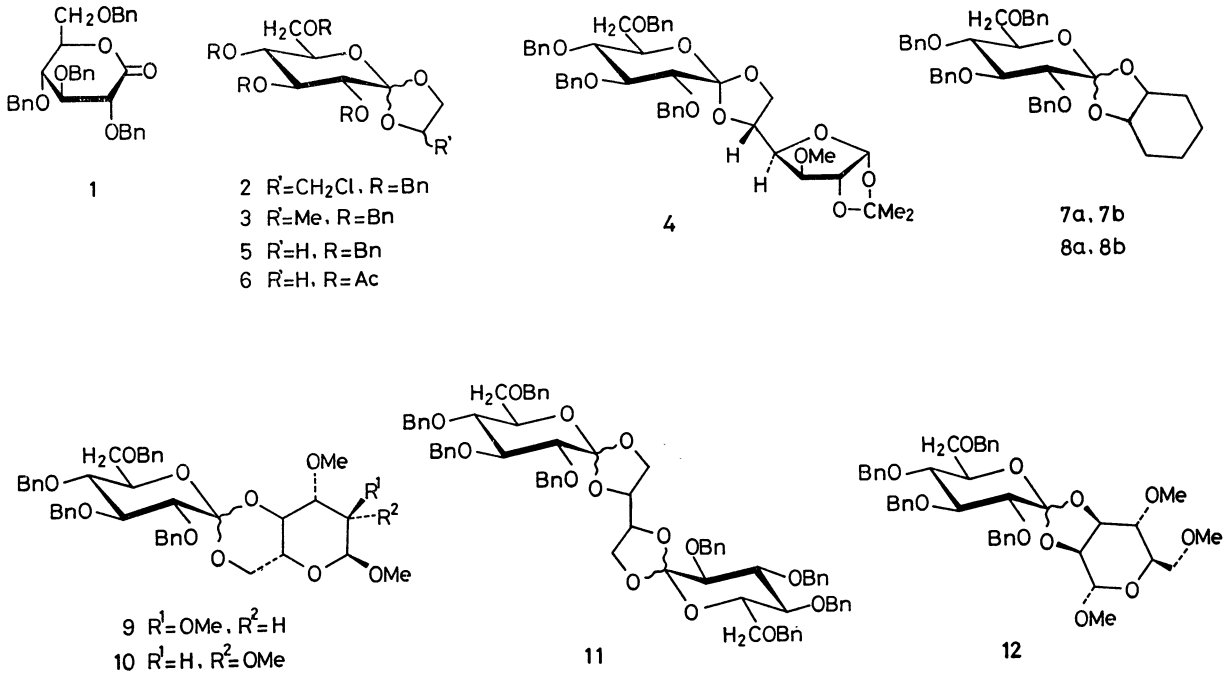
On the other hand, azeotropic dehydration of a solution of equimolar amounts of **1** and ethylene glycol in benzene containing a catalytic amount of concd sulfuric acid during 10 h gave the corresponding spiro cyclic othro ester (**5**) in 43% yield. On continuation of the dehydration for 24 h, **1** disappeared and the yield of **5** rose to 77%. Compound **3** was also obtained quantitatively from **1** and 1,2-propanediol by the same method. Catalytic hydrogenation of **5** in methanol in the presence of palladium-on-charcoal and a few drops of acetic acid gave the de-*O*-benzylated product as a syrup, this was acetylated with acetic anhydride in pyridine to give the corresponding tetraacetate (**6**) in 73% overall yield.

Similar dehydration of a mixture of **1** and *cis*-1,2-cyclohexanediol for 3 h gave a mixture of two isomers of the corresponding ortho esters (**7**) which was separated on a silica gel column to give **7a** and **7b** in 45 and 28% yields, respectively. Similar reaction of *trans*-1,2-cyclohexanediol for 37 h also gave two products (**8a** and **8b**) in 21 and 22% yields, respectively. Reaction of **1** and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside[15] or -α-D-mannopyranoside[16] gave only one of the two possible isomers (**9** and **10**) in 20 and 8% yields, respectively. Reaction of **1** and erythritol gave 1,2 : 3,4-di-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-erythritol (**11**) in 80% yield. Dehydration of a mixture of **1** and methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside gave unsuccessful result. However, a similar reaction with methyl 4,6-di-*O*-methyl-α-D-mannopyranoside gave a trace amount of 1 : 1 mixture of two possible isomers of methyl 4,6-di-*O*-methyl-2,3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-α-D-mannopyranoside (**12**) as a syrup. The separation of these two isomers was unsuccessful, but the presence was indicated by the two characteristic signals assigned to the ortho ester carbon in the ^{13}C NMR spectrum.

Examination of acidic catalysts indicated that *p*-toluenesulfonic acid, phosphorus pentaoxide, and ortho- and polyphosphoric acids were uneffective, while the super acid ($SbF_5 \cdot FSO_3H$) showed the effectiveness of the same level as concd sulfuric acid.

The chemical shifts of ortho ester carbons of glucosylidene acetals synthesized here were summarized in Table 1. The chemical shifts of the ortho ester carbons with 1,3-dioxolane rings (**2,4—8,12**), were 118—122 ppm, whereas that with 1,3-dioxane rings (**9** and **10**) 110.7—110.9 ppm. This difference in the chemical shifts of ortho ester carbons is diagnostic for the ring-size. Consequently, the chemical shift of the carbon in **11** clearly shows that the structure is 1,2 : 3,4-di-*O*-glucosylidene derivative having two 1,3-dioxolane

† Present address: Kumiai Chemical Industry Co. Ltd., Laboratory of Chemical Research, Shibukawa, Shimizu 424.



Scheme 1.

TABLE 1. THE CHEMICAL SHIFTS OF ORTHO ESTER CARBONS

Compound	Chemical shifts, δ (ppm)
2	120.5, 120.6
4	119.6
5	119.6
6	118.0
7	118.5, 119.6
8	119.1, 119.2
9	110.7
10	110.9
11	121.9
12	119.1, 120.5

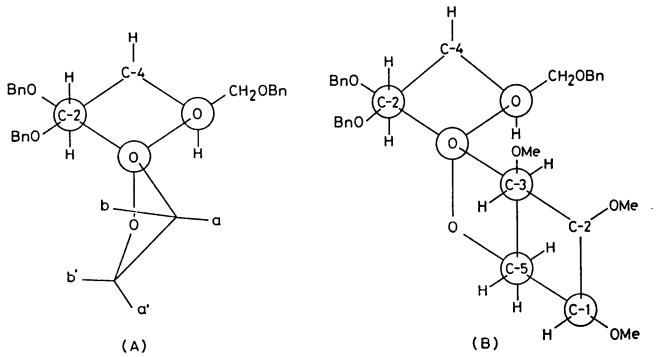


Fig. 1.

rings, but not 1,3 : 2,4-di-*O*-substituted derivative with two 1,3-dioxane rings, indicating the former ring is thermodynamically more stable than the latter.

The above results provide interesting problems in stereochemistry. In the case of five-membered spiro cyclic compounds [(A) in Fig. 1], the non-bonded interaction between groups attached to C-2 of the pyranosylidene ring and to the acetal ring can be avoided by a twist conformation of the latter, as was shown in the X-ray analysis of the olgose.[8] For example, in the case of **8** the conformation of the cyclohexane ring with a→b′ bonds will be a less-hindered one than that including b→a′ bonds. In possible formulations of **4**, the bulky D-glucofuranose ring should be attached to either b or a′ position, and therefore, the latter, the (1*R*)-pyranosylidene isomer shown by the structural formula in Scheme 1, will be much the more stable. This trend will be also true in the configuration of **11** from erythritol. In cases of **7** and **12** in which the five-membered acetal ring includes a→a′ bonds or b→b′ bonds, there was no significant difference in the yields of isomers, indicating the dispense of the strain of the two isomers by the direction of twisting of the five-membered ring. The Newman projection of the stable, (1*R*)-isomer of **9** or **10** having a six-membered acetal ring is presented in (B). It is obvious that the ring oxygen side of the glucopyranosylidene moiety is less hindered, though the absolute configuration is not yet determined.

Experimental

General Methods. Melting points were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a JNM-PS-100 and a JNM FX-100 spectrometers, respectively, in chloroform-*d* containing tetramethylsilane as the internal reference. The chemical shifts and coupling constants were recorded in δ(ppm) and Hz units. Optical rotations were measured in 0.5-dm tubes with a Carl Zeiss LEP-A1 polarimeter. Solvents were evaporated under diminished pressure.

1,2-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)-3-chloro-1,2-propanediol (2). To a solution of tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**) (1.8 g, 3.34 mmol) and boron trifluoride etherate (0.5 g) in dichloromethane (40 ml) was

added dropwise 3-chloro-1,2-epoxypropane (0.4 g, 4.32 mmol) with stirring, at 28—30 °C, during 1 h. The reaction mixture was stirred for 1 h, washed successively with 2.5 M sodium hydroxide and water, then dried and evaporated to give a syrup which was purified on a silica-gel column (7 : 2 hexane–ethyl acetate, R_f 0.41) to give **2** as a syrup in 45.0% yield. Found: C, 70.21; H, 6.61%. Calcd for $C_{37}H_{39}O_7Cl$: C, 70.41; H, 6.23%.

1,2-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)-1,2-propanediol (3). *i*): A similar reaction of **1** (1.8 g, 3.34 mmol) with 1,2-epoxypropane (0.2 g, 3.44 mmol) as above in the presence of boron trifluoride etherate (0.5 g) gave **3** as a syrup (7 : 2 hexane–ethyl acetate, R_f 0.43) in 65.2% yield.

ii): Azeotropic dehydration of a solution of **1** (3 g, 5.57 mmol) and 1,2-propanediol (0.5 g, 6.57 mmol) in dry benzene (60 ml) containing a catalytic amount of concentrated sulfuric acid for 24 h gave **3** (3.2 g) in 96.2% yield. Found: C, 74.47; H, 7.16%. Calcd for $C_{37}H_{40}O_7$: C, 74.47; H, 6.76%.

5,6-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)-1,2-O-isopropylidene-3-O-methyl-α-D-glucofuranose (4). A similar reaction of **1** (1.5 g, 2.78 mmol) and 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (0.65 g, 3.01 mmol) as **2** in the presence of boron trifluoride etherate (0.4 g), and purification of the product (9 : 1 benzene–acetone, R_f 0.68) gave **4** as prisms (petroleum ether) in 25.9% yield. Mp 131—132 °C, $[\alpha]_D^{22}$ +17.4° (*c* 0.62, $CHCl_3$); Found: C, 70.00; H, 6.78%. Calcd for $C_{44}H_{50}O_{11}$: C, 70.01; H, 6.68%.

Signals of two C-Me groups (δ 1.21 and 1.30), and one OMe (3.42), could be distinguished in the ^1H NMR spectrum, and in addition, those of four benzyl methylene carbons (73.4, 74.8, 75.4, and 75.7 ppm), 6- and 6′-carbons (66.6 and 69.0) and the ortho ester carbon (119.6) in the ^{13}C NMR spectrum.

1,2-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)ethanediol (5). A solution of **1** (2 g, 3.71 mmol) and ethylene glycol (340 mg, 5.45 mmol) in benzene (40 ml) containing a few drops of concentrated sulfuric acid was refluxed for 10 h, and the water formed was removed azeotropically. The benzene solution was successively washed with sodium hydroxide solution and water, then evaporated to give a syrup, which was purified on a silica-gel column (1 : 1 hexane–ether, R_f 0.42). Yield, 0.93 g (43%), mp 51—52 °C (petroleum ether), $[\alpha]_D^{22}$ +51° (*c* 1.0, $CHCl_3$). Found: C, 73.59; H, 6.52%. Calcd for $C_{36}H_{38}O_7$: C, 74.20; H, 6.57%. On continuation of the dehydration for 24 h, **5** was obtained in 77% yield.

1,2-O-(2,3,4,6-Tetra-O-acetyl-D-glucopyranosylidene)ethanediol (6). Catalytic hydrogenation of **5** (1 g, 1.72 mmol) in methanol (20 ml) in the presence of palladium–charcoal (10%, 1 g) and a few drops of acetic acid consumed theoretical amount of hydrogen (170 ml) during 8 h. The reaction mixture was filtered, and the filtrate was neutralized with lead carbonate and concentrated to give a syrup (350 mg, 93%). The syrup in pyridine was acetylated with acetic anhydride by the usual manner to give **6** as needles (toluene). Yield, 0.49 g (73%), mp 143—145 °C, $[\alpha]_D^{22}$ +51° (*c* 1.0, $CHCl_3$). ^1H NMR: 5.7—5.28 (H_2, H_3, H_4 : m), 4.52 (H_6 : q, $J_{5,6}$=4.2, $J_{6,6'}$=12.5), 4.40 ($H_{6'}$: q, $J_{5,6'}$=2.4), 4.32—6.00 (H_5, CH_2CH_2 : m), 2.31, 2.17, 2.10, 2.08 (4×OAc). Found: C, 49.35; H, 5.63%. Calcd for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68%.

1,2-O-(2,3,4,6-Tetra-O-benzyl-D-gluropyranosylidene)-cis-1,2-cyclohexanediol (7a and 7b). Azeotropic dehydration of **1** (2.0 g, 3.7 mmol) and *cis*-1,2-cyclohexanediol (0.8 g, 6.9 mmol) for 30 h as **5**, and separation of the product on a silica gel colume (1 : 1 hexane–ether) gave two isomers of **7a** (650 mg, R_f 0.53) and **7b** (1070 mg, R_f 0.50) as needles in 28 and 45% yields, respectively.

7a: mp 58—60 °C, $[\alpha]_D^{22}$ +45° (*c* 0.90, $CHCl_3$), ortho ester ^{13}C: 119.6 ppm. Found: C, 75.72; H, 7.03%. Calcd for $C_{40}H_{44}O_7$: C, 75.45; H, 6.97%.

7b: mp 98—100 °C, $[\alpha]_D^{22}$ +55° (*c* 1.1, $CHCl_3$), ortho ester ^{13}C: 118.5 ppm. Found: C, 75.80; H, 7.12%. Calcd for $C_{40}H_{44}O_7$: C, 75.45; H, 6.97%.

1,2-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)-trans-1,2-cyclohexanediol (8a and 8b). A similar azeotropic dehydration of **1** (2.0 g, 3.7 mmol) and *trans*-cyclohexane-1,2-diol (0.8 g, 6.9 mmol) as above gave two isomers of **8a** (490 mg, R_f 0.43, 1 : 1 hexane–ether) and **8b** (470 mg, R_f 0.50) in 21.9 and 21.0% yields, respectively.

8a: syrup, $[\alpha]_D^{22}$ +7.9° (*c* 0.5, $CHCl_3$), ortho ester ^{13}C: 119.1 ppm. Found: C, 75.00; H, 7.11%. Calcd for $C_{40}H_{44}O_7$: C, 75.45; H, 6.97%.

8b: mp 91—93 °C, (prism, petroleum ether), $[\alpha]_D^{22}$ +65° (*c* 0.8, $CHCl_3$), ortho ester ^{13}C: 119.2 ppm. Found: C, 75.43; H, 7.02%. Calcd for $C_{40}H_{44}O_7$: C, 75.45; H, 6.97%.

From the rotational values of **8a** and **8b**, it is deduced that **8a** is the condensation product of (1*R*,2*R*)-cyclohexanediol and **8b** that of (1*S*,2*S*)-isomer.[17]

Methyl 4,6-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)-2,3-di-O-methyl-α-D-glucopyranoside (9). Azeotropic dehydration of **1** (2.0 g, 3.7 mmol) and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (1.24 g, 5.58 mmol), for 8 h, and purification of the product on a silica-gel column (6 : 1 benzene–ethyl acetate, R_f 0.47) gave **9** in 19.6% (0.54 g) yield. Mp 63—64 °C (prism, peteroleum ether), $[\alpha]_D^{22}$ +93° (*c* 0.92, $CHCl_3$), ortho ester ^{13}C: 110.7 ppm. Found: C, 69.79; H, 6.88%. Calcd for $C_{43}H_{50}O_{11}$: C, 69.52; H, 6.78%.

Methyl 4,6-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)-2,3-di-O-methyl-α-D-mannopyranoside (10). Azeotropic dehydration of **1** (1.0 g, 1.85 mmol) and methyl 2,3-di-*O*-methyl-α-D-mannopyranoside (0.35 g, 1.57 mmol) for 65 h, and purification of the product on a silica-gel column (6 : 1 benzene–ethyl acetate, R_f 0.48), gave **10** (0.10 g) as a syrup in 8.6% yield. $[\alpha]_D^{22}$ +56.4° (*c* 0.5, CH_2Cl_2), ortho ester ^{13}C: 110.9 ppm. Found: C, 69.11; H, 6.98%. Calcd for $C_{43}H_{50}O_{11}$: C, 69.52; H, 6.78%.

1,2 : 3,4-Di-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosylidene)-erythritol (11). Azeotropic dehydration of **1** (1.5 g, 2.77 mmol) and erythritol (1.3 g, 10.6 mmol) for 24 h gave only one product (9 : 1 benzene–ethyl acetate, R_f 0.30) in 61.7% (1.05 g) yield. Mp 69—74 °C $[\alpha]_D^{22}$ +53° (*c* 0.3, $CHCl_3$), ortho ester ^{13}C: 121.9 ppm. Found: C, 73.95; H, 6.38%. Calcd for $C_{72}H_{74}O_{14}$: C, 74.34; H, 6.41%.

Methyl 2,3-O-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosylidene)-4,6-di-O-methyl-α-D-mannopyranoside (12). Azeotropic dehydration of **1** (1.5 g, 2.77 mmol) and methyl 4,6-di-*O*-methyl-α-D-mannopyranoside (1.5 g, 6.75 mmol), and purification of the product on a silica-gel column (1 : 1 hexane–ether, R_f 0.42) gave a syrup (40 mg) in 0.15% yield. Syrup, ortho ester ^{13}C: 119.1 and 120.5 ppm. Found: C, 69.15; H, 6.62%. Calcd for $C_{43}H_{50}O_{11}$: C, 69.52; H, 6.78%.

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