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A NEW SYNTHESIS OF 2,3,4,6-TETRA-*O*-BENZYL-D-GLUCOPYRANOSYLIDENE ACETALS, USING TRIMETHYLSILYL TRIFLUOROMETHANESULFONATE AS THE CATALYST

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ABSTRACT

The title compounds were synthesized by condensation of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone with bis-*O*-(trimethylsilyl)-1,2-diols in the presence of trimethylsilyl trifluoromethanesulfonate as the catalyst. Application to *cis*- and *trans*-1,2-diols containing primary, secondary, and tertiary hydroxyl groups was examined, and a new rearrangement was found in the reaction of a D-glucono-1,5-lactone derivative having an acetyl group at O-6.

INTRODUCTION

A unique type of acetal interlinkage between a glycopyranosylidene group and a 1,2-diol grouping of glycoses has been found in such oligosaccharide antibiotics as everninomicins[1], flambamycin[2], avilamycins[3], destomycins[4], hygromycin B (ref. 5), and antibiotics A-396 I (ref. 6) and SS-56C (ref. 7). These antibiotics were designated[2] "orthothomycins", because the spiro, cyclic orthoester interlinkage at the anomeric carbon atom is quite different from the fused-ring type of orthoester well known in carbohydrate chemistry[8]. In general, two configurations are possible for this interlinkage, depending on the (*R*) or (*S*) configuration of the orthoester carbon atom. The configurations of one of the two orthoester linkages in everninomicin D (ref. 9) and avilamycin A (ref. 10), and that of[11] destomycin A were determined by X-ray analysis to be (*R*).

For synthetic purposes relating to these antibiotics, it was found that the addition of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**) to epoxides, and direct dehydration of **1** with 1,2-diols (method A) gave the corresponding glucopyranosylidene acetals of 1,2-diols and of monosaccharides[12]. However, applica-

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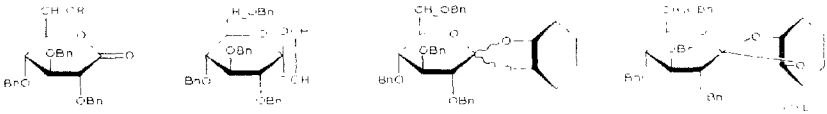
tion of these methods to a secondary 1,2-diol grouping of monosaccharides gave poor results. As a promising method, we described[13] a facile synthesis (method B) of spiro, cyclic orthoesters by condensation of a lactone and bis-*O*-(trimethylsilyl)-1,2-diols in the presence of trimethylsilyl trifluoromethanesulfonate (catalyst X). Thereafter, methods for the construction of the unique skeleton *via* the glycosyloxy–selenation–oxidation–elimination sequence for glycals[14], and *via* photocyclization of 2-hydroxyalkyl glycosides[15], were reported by other groups. We now describe method B in detail.

RESULTS AND DISCUSSION

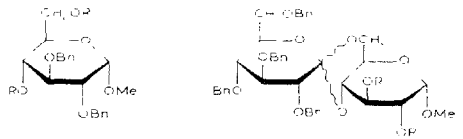
Reaction of **1** with 1.5 equivalents of 1,2-di-(trimethylsiloxy)ethane in dichloromethane for 2 h at room temperature under a nitrogen atmosphere, in the presence of catalyst X (5–10 mol%), gave 1,2-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)ethanediol (**3**) in 91.7% yield. Similar reaction of **1** with (trimethylsilyl)ated *cis*-1,2-cyclohexanediol gave two isomers of the corresponding spiro, cyclic orthoester (**4a,b**) in 30.4 and 59.3% yield, respectively. Similarly, two isomers (**5a,b**) were obtained from *trans*-1,2-cyclohexanediol in 30.6 and 33.3% yield, re-



1 R = Bn
2 R = Ac
Bn = PhCH$_2$

3 4 a b 5 a b

spectively. However, reaction of **1** with methyl 2,3-di-*O*-benzyl-4,6-di-*O*-(trimethylsilyl)-α-D-glucopyranoside (**6**) gave only one (**7**) of the two possible isomers, in 72.2% yield, as in the case of the analogous compound[13] (**8**) prepared by method A. Thus, method B gave products in yields higher than those obtained by method A, as shown in Table 1.



6 R = Me_3Si

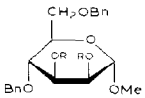
7 R = Bn
8 R = Me

Moreover, application of the new method for condensation of **1** with methyl 4,6-di-*O*-benzyl-2,3-di-*O*-(trimethylsilyl)-α-D-mannopyranoside (**9**), and separation of the products, gave two isomers of 4,6-di-*O*-benzyl-2,3-*O*-(2,3,4,6-tetra-*O*-

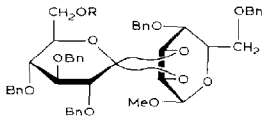
TABLE I

COMPARISON OF YIELDS OF 2,3,4,6-TETRA-*O*-BENZYL-D-GLUCOPYRANOSYLIDENE ACETALS IN METHODS A AND B

Products	*Chemical shift of orthoester carbon atom (p.p.m.)*	*Ytelds (%)*	
		Method A[12]	*Method B*
3	119.6	77	91.2
4a	118.5	45	59 3
4b	119.6	28	30 4
5a	119.1	21 9	30.6
5b	119.2	21.0	33.3
7	110.5	—	72.2
8	110.6	19.6	—



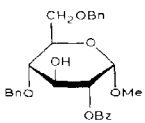
9 R = Me_3Si



10a,b R = Bn
11a,b R = Ac

benzyl-D-glucopyranosylidene)-α-D-mannopyranoside (**10a** and **10b**) in 44.8 and 26.6% yield, respectively. Similar condensation of **1** with secondary and tertiary *cis*-1,2-diol groupings of branched-chain sugars was successful, although that of the secondary, *trans*-1,2-diol grouping of methyl 4,6-*O*-benzylidene- and 4,6-di-*O*-benzyl-2,3-di-*O*-(trimethylsilyl)-α-D-glucopyranoside was unsuccessful.

Methyl 4,6-di-*O*-benzyl-3-*C*-methyl-α-D-allopyranoside (**14**) was prepared by conversion of methyl 4,6-di-*O*-benzyl-α-D-glucopyranoside into the corresponding 2-benzoate (**12**), followed by oxidation to the hexopyranosid-3-ulose (**13**) and addi-



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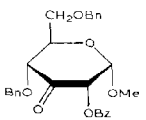

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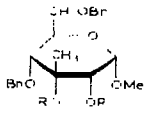
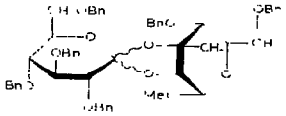
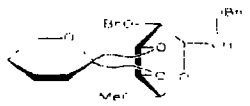
tion thereto of methylmagnesium iodide. Condensation of **1** with the 2,3-di-*O*-(trimethylsilyl) derivatives (**15**) of **14** gave two isomers of the spiro, cyclic orthoesters (**16a,b**) both in 8.9% yield. Also similar reaction of 5-hydroxypentano-1,5-lactone (δ-valerolactone) with **9** for 2 days at −10° gave one (**17**) of the two possible orthoesters in 40% yield. This condensation gave a complex mixture at room temperature, probably due to *C*-silylation *via* the silyl enolate. The reaction of 4-hydroxy-butano-1,4-lactone gave a similar result.



14 R = H
15 R = Me_3Si



16a,b



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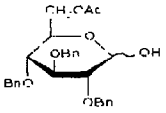
On the other hand, condensation of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone (**2**), which was prepared from 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α,β-D-glucopyranose[16] by partial deacetylation to **18** followed by oxidation, gave unexpectedly a rearrangement product, namely, benzyl 5-*O*-acetyl-2,6-anhydro-3,4-di-*O*-benzyl-D-mannonate (**19**), as the main product (52%), together with two isomers of the desired orthoester (**11a,b**; 16%). Ethanolysis of **19** with sodium ethoxide in ethanol gave, quantitatively, the corresponding ethyl ester (**20**), and reduction of **19** with lithium aluminum hydride gave the corresponding 2,6-anhydro-D-mannitol* which was characterized as the diacetate (**21**). Moreover, it was converted into the corresponding tetraacetate (**22**) by catalytic hydrogenolysis, and acetylation of the product. The 2,6-anhydro-D-*manno* configuration of **20**, **21**, and **22** was supported by their ^{1}H-n.m.r. data and by the value of the specific optical rotation ($[\alpha]_D$ −40°; lit.[17] $[\alpha]_D$ −42°) of **22**



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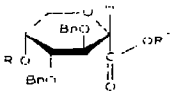
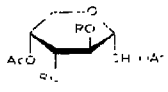


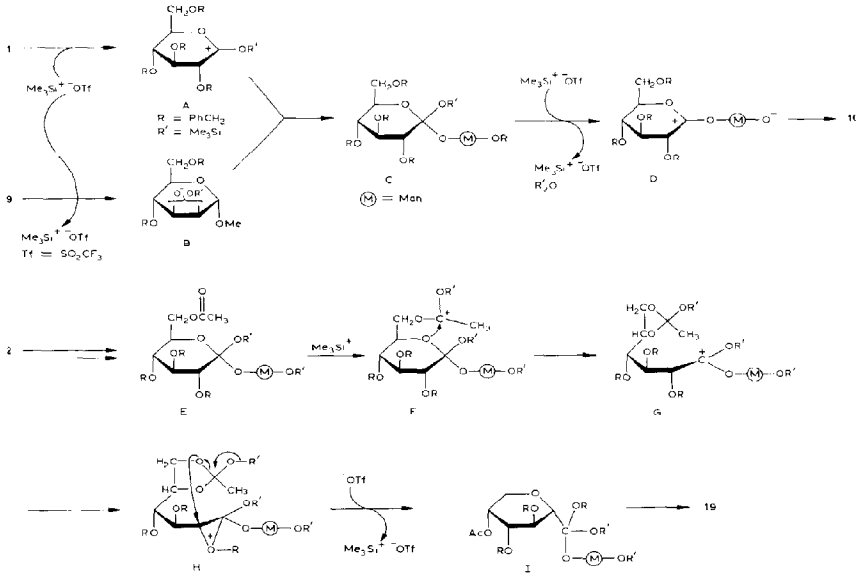
19 R^1 = Ac, R^2 = Bn
20 R = H, R = Et



21 R = Et
22 R = Ac

Compound **19** could not be produced by direct treatment of **2**, or by treatment of **11a,b** with the catalyst. From these results, the reaction pathways for the formation of orthoesters and **19** shown in Scheme 1 were formulated. The supercation Me_3Si^+ rapidly produces the carbonium cation (A) by reaction with **1**, and the counter anion $F_3CO_2SO^-$ gives the anion (B) from **9**, yielding the catalyst again[18]. The intermediate C, formed from A and B, slowly reacts with the catalyst to give the amphoteric intermediate (D), together with the catalyst and hexamethyldisiloxane, which cyclizes into **10**. Thus, the driving force of this condensation may be attributed to formation of the stable disiloxane[19]. In the case of **2**, compound **11** will be formed from the intermediate (E) through a similar pathway. However, the carbonium cation (F), afforded by rapid attack of the second

*Although the formal numeration is 1,5-anhydro-D-mannitol, 2,6- is used here in continuation of that used for the original compounds



Scheme 1. Possible pathways for the formation of 10 and 19

Me_3Si^+ on the acetyl carbonyl group, instead of the trimethylsilyl group at C-1, will be stabilized by conversion into the oxonium cation (H) *via* the carbonium cation (G). Intramolecular attack of the *O*-anion, formed by removal of trimethylsilyl cation from the terminal orthoester function with $F_3CSO_2O^-$, on the oxonium cation function gives the rearranged intermediate (I), with inversion at C-2 of the original **2**. Because the non-spiro, cyclic orthoester is generally unstable, (I) is readily converted into **19**.

Although the rearrangement of an alkoxyl group is not normal in the carbohydrate field, rearrangement of the methoxyl and the benzyloxy group at C-1 of methyl and benzyl 2,3-*O*-isopropylidene-5-*O*-(trifluoromethylsulfonyl)-β-D-ribofuranoside to C-5, *via* the tricyclic oxonium cation formed by removal of $F_3CSO_2O^-$, was recently reported[20]. This rearrangement was attributed to an anchimeric effect of the 1-alkoxyl group on the C-5 atom. However, the new rearrangement found here is synchronous to an acyl migration from O-6 to O-5.

EXPERIMENTAL

General methods. — Melting points were determined with a Mel-Temp hotplate and are uncorrected. The solutions were evaporated under diminished pres-

sure at a bath temperature not exceeding 50°. Specific rotations were measured with a Carl Zeiss LEP-A1 or a JASCO DIP-4 polarimeter, using chloroform as the solvent unless stated otherwise. I.r. spectra were recorded with a Hitachi Model EPL-G2 spectrometer. ^{1}H-N.m.r. spectra were recorded with a JEOL PS-100 spectrometer for solutions in chloroform-*d*, unless stated otherwise, using tetramethylsilane as the internal standard. ^{13}C-N.m.r. spectra were recorded with a JEOL FX-100 spectrometer at 25.16 MHz for solutions in chloroform-*d*, using 8 k data points, with proton-noise decoupling. Column chromatography was performed on a flash column of silica gel (Wakogel C-300), and preparative t.l.c. on silica gel (Merck type 60).

Methyl 2,3-di-O-benzyl-4,6-di-O-(trimethylsilyl)-α-D-glucopyranoside (**6**). — To a solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (5.1 g, 13.6 mmol) and hexamethyldisilazane (23 mL, 110 mmol) in dichloromethane (15 mL) were added a few drops of trifluoroacetic acid at 0°, and the mixture was stirred overnight at room temperature. After the reaction was complete, the mixture was evaporated. Purification of the residual syrup on a flash column of silica gel with 60:40:1 benzene–hexane–acetone gave **6** in 59.5% yield (4.2 g); m.p. 42.5–45.0° (prisms from petroleum ether), $[\alpha]_D^{17}$ +45.1° (*c* 1.7); ^{1}H-n.m.r.: δ 7.28 and 7.23 (s, 10 H, 2Ph), 5.00 and 4.72 (ABq, *J* 11.2 Hz, CH_2Ph), 4.70 and 4.54 (ABq, *J* 12.0 Hz, CH_2Ph), 4.58 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.9–3.3 (m, 6 H, H-2,3,4,5,6), 3.36 (s, 3 H, OMe), and 0.10 (s, 18 H, 6 SiMe).

Anal. Calc. for $C_{27}H_{42}O_6Si_2$: C, 62.51; H, 8.16. Found: C, 62.45; H, 8.43.

Methyl 4,6-di-O-benzyl-2,3-di-O-(trimethylsilyl)-α-D-mannopyranoside (**9**). — A similar reaction of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside (1.00 g, 2.67 mmol) with hexamethyldisilazane (9 mL, 4.31 mmol) gave **9** as a syrup; this was purified by use of a flash column (20:1 hexane–acetone), to give **9** in 97.5% yield (1.35 g); $[\alpha]_D^{18}$ +49.8° (*c* 1.98); ^{1}H-n.m.r.: δ 7.5–7.2 (m, 10 H, 2 Ph), 4.76 and 4.46 (ABq, *J* 11.6 Hz, CH_2Ph), 4.64 and 4.48 (ABq, *J* 12.0 Hz, CH_2Ph), 4.56 (s, H-1), 4.0–3.6 (m, 6 H, H-2,3,4,5,6), 3.34 (s, 3 H, OMe), and 0.16 and 0.14 (each s, 18 H, 6 SiMe).

Anal. Calc. for $C_{27}H_{42}O_6Si_2$: C, 62.51; H, 8.16. Found: C, 62.23; H, 8.43.

Methyl 2-O-benzoyl-4,6-di-O-benzyl-α-D-glucopyranoside (**12**). — To a solution of methyl 4,6-di-*O*-benzyl-α-D-glucopyranoside (2.00 g, 5.34 mmol) in pyridine (60 mL) was added dropwise a solution of benzoyl chloride (2.9 g, 20.43 mmol) in pyridine (30 mL) at 0°, and then the mixture was kept overnight at room temperature, poured into ice–water, and extracted with chloroform. Evaporation of the extract, and purification of the product by use of a flash column (5:1 hexane–acetone) gave **12** as a syrup in 97.8% yield (2.50 g); $[\alpha]_D^{18}$ +112.2° (*c* 1.18); ν_{max}^{NaCl} 3450 (OH) and 1720 cm^{-1} (C=O); ^{1}H-n.m.r.: δ 8.2–7.9 and 7.6–7.1 (m, 15 H, 3 Ph), 5.07 (d, $J_{1,2}$ 3.4 Hz, H-1), 4.98 (dd, $J_{2,3}$ 10.6 Hz, H-2), 4.81 and 4.59 (ABq, *J* 11.4 Hz, CH_2Ph), 4.67 and 4.51 (ABq, *J* 12.0 Hz, CH_2Ph), 4.26 (m[a], $J_{3,4}$ 8.6 Hz,

[a] The signal, which consisted of 12 lines, was analyzed by simulation as the M part of an ABMX 4-spin system, where A, B, and X respectively represent H-1, H-2, and H-4.

H-3), 3.9–3.6 (3 H, H-5,6), 3.64 (dd, H-4), 3.37 (s, 3 H, OMe), and 3.19 (bs, OH).

Anal. Calc. for $C_{28}H_{30}O_7$: C, 70.28; H, 6.32. Found: C, 69.98; H, 6.24.

*Methyl 2-O-benzoyl-4,6-di-O-benzyl-α-*D*-ribo-hexopyranosid-3-ulose* (**13**). — To a solution of **12** (1.00 g, 2.09 mmol) in dry dichloromethane (10 mL) was added pyridinium chlorochromate (900 mg) with stirring, and the mixture was stirred for 24 h at room temperature. The mixture was poured into ether, and the insoluble material was filtered off. The filtrate was evaporated, to give syrupy **13** (842 mg, 84.5%) which was purified by preparative t.l.c. with 1:1 hexane–ether; $[\alpha]_D^{18}$ +140.3° (*c* 3.45); ν_{max}^{NaCl} 1750 and 1720 cm^{-1} (C=O); ^{1}H-n.m.r.: δ 8.2–8.0 and 7.5–7.1 (m, 15 H, 3 Ph), 5.56 (dd, $J_{2,4}$ 1.0 Hz, H-2), 5.22 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.88 and 4.37 (ABq, *J* 10.6 Hz, CH_2Ph), 4.58 and 4.42 (ABq, *J* 12.4 Hz, CH_2Ph), 4.43 (dd, $J_{4,5}$ 9.4 Hz, H-4), 4.01 (dt, $J_{5,6}$ 2.0 Hz, H-5), 3.78 (q, $J_{6,6'}$ 10.6 Hz, H-6), 3.69 (q, $J_{5,6'}$ 2.0 Hz, H-6'), and 3.37 (s, 3 H, OMe).

Anal. Calc. for $C_{28}H_{28}O_7$: C, 70.57; H, 5.92. Found: C, 70.11; H, 5.54.

*Methyl 4,6-di-O-benzyl-3-C-methyl-α-*D*-allopyranoside* (**14**). — To a solution of methylmagnesium iodide in ether (30 mL), prepared from magnesium turnings (600 mg, 2.47 mmol) and methyl iodide (2.57 g), was added a solution of **13** (530 mg, 1.11 mmol) in benzene (30 mL), and the mixture was stirred for 5 h at room temperature, poured into cold ammonium chloride solution, the solution extracted with dichloromethane, and the extract washed with water, and evaporated. Purification of the product by preparative t.l.c. (1:1 hexane–acetone) gave syrupy **14** in 91.8% yield (396 mg); $[\alpha]_D^{18}$ +111.6° (*c* 1.25); ν_{max}^{NaCl} 3450 cm^{-1} (OH); ^{1}H-n.m.r.: δ 7.30 and 7.24 (each s, 10 H, 2 Ph), 4.75 (d, $J_{1,2}$ 4.4 Hz, H-1), 4.66 and 4.50 (ABq, 2 H, *J* 12.6 Hz, CH_2Ph), 4.60 (s, 2 H, CH_2Ph), 3.88 (dt, $J_{5,6'}$ 2.5 Hz, H-5), 3.82 (q, $J_{5,6}$ 2.5 Hz, H-6), 3.68 (q, $J_{6,6'}$ 11.4 Hz, H-6'), 3.5–3.3 (bm, H-2), 3.46 (d, $J_{4,5}$ 10.0 Hz, H-4), 3.44 (s, 3 H, OMe), 2.86 (s, OH), 2.53 (bd, $J_{OH,2}$ 10.8 Hz, OH), and 1.32 (s, 3 H, OMe).

Anal. Calc. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27; Found: C, 67.74; H, 7.46.

*Methyl 4,6-di-O-benzyl-3-C-methyl-2,3-di-O-(trimethylsilyl)-α-*D*-allopyranoside* (**15**). — To a solution of **14** (240 mg, 618 μmol) in *N*,*N*-dimethylformamide (1 mL) were added imidazole (105 mg) and chlorotrimethylsilane (148 mg, 1.36 mmol), with stirring. The mixture was kept overnight at room temperature, poured into ice–water, and extracted with ether. The usual processing of the extract, and purification of the product by use of a flash column (20:1 hexane–ethyl acetate), gave **15** in 90.9% yield (299 mg); $[\alpha]_D^{18}$ +72.3° (*c* 4.04); ^{1}H-n.m.r.: δ 7.4–7.1 (m, 10 H, 2 Ph), 4.67 and 4.48 (ABq, *J* 10.6 Hz, CH_2Ph), 4.60 (s, 2 H, CH_2Ph), 4.58 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.20 (dq, $J_{5,6'}$ 2.6 Hz, H-5), 3.79 (dd, $J_{5,6}$ 3.0 Hz, H-6), 3.64 (dd, $J_{6,6'}$ 10.6 Hz, H-6'), 3.40 (d, H-2), 3.33 (s, 3 H, OMe), 3.32 (d, $J_{4,5}$ 9.8 Hz, H-4), 1.27 (s, 3 H, CMe), and 0.12 and 0.10 (each 1 s, 18 H, 6 SiMe).

Anal. Calc. for $C_{28}H_{44}O_6Si_2$: C, 63.12; H, 8.32; Found: C, 62.82; H, 8.51.

*6-O-Acetyl-2,3,4-tri-O-benzyl-α,β-*D*-glucopyranose* (**18**). — An ice-cooled mixture of benzylamine (50 mL) and 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (8.0 g, 15.0 mmol) was vigorously stirred for 1 h, chloroform (100 mL)

was added, and the mixture was washed with M hydrochloric acid (20 mL), to remove the excess of amine, and water, dried (magnesium sulfate), and evaporated, to give colorless, syrupy **18** (α:β = 3:2), which was purified by use of a flash column (4:1 hexane–acetone); yield, 89.4% (6.61 g); $[\alpha]_D^{18}$ +31.9° (*c* 0.80); ν_{max}^{KBr} 3400 (OH) and 1740 cm^{-1} (C=O).

Anal. Calc. for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55; Found: C, 70.45; H, 6.63.

*6-O-Acetyl-2,3,4-tri-O-benzyl-*D*-glucono-1,5-lactone* (**2**). — Oxidation of **18** (9.44 g, 19.2 mmol) as described for **13** gave **2** in 72.3% yield (6.81 g); this was purified by use of a flash column (6:1 hexane–acetone): $[\alpha]_D^{18}$ +108.5° (*c* 1.74), ν_{max}^{NaCl} 1740 and 1750 cm^{-1} (C=O); ^{1}H-n.m.r.: δ 7.4–6.8 (m, 15 H, 3 Ph), 4.8–4.0 (m, 7 H, H-5,6,6' and 2 CH_2Ph), 4.04 (d, $J_{2,3}$ 5.3 Hz, H-2), 3.78 (dd, $J_{3,4}$ 5.6 Hz, H-3), 3.58 (dd, $J_{4,5}$ 9.0 Hz, H-4), and 1.54 (s, 3 H, Ac).

Anal. Calc. for $C_{29}H_{30}O_7$: C, 71.00; H, 6.16; Found: C, 71.32; H, 6.28.

Condensation of bis-O-(trimethylsilyl) derivatives with lactones. — To a stirred solution of **1** (561 mg, 1.04 mmol) and 1,2-di-(trimethylsiloxy)ethane [prepared from ethylene glycol (93.1 mg, 1.50 mmol)] in anhydrous dichloromethane (3 mL) was added catalyst X (22 mg, 0.1 mmol) at 0° under a nitrogen atmosphere. The mixture was stirred for 2 h at room temperature, the reaction quenched by addition of anhydrous pyridine (0.2 mL), and the solution poured into saturated sodium hydrogencarbonate solution (10 mL), and extracted with ether. The usual processing of the extract gave 1,2-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)dioxyethane (**3**) in 91.2% yield (553.7 mg); m.p. 51–52° (petroleum ether); lit.[13] m.p. 51–52°.

Similar reaction of **1** (518 mg, 0.96 mmol) with 1,2-di-*O*-(trimethylsilyl)ated *cis*-cyclohexanediol [prepared from *cis*-cyclohexanediol (388 mg, 3.34 mmol)], and separation of the product on a flash column with 5:2 hexane–ether, gave two isomers: **4a** (m.p. 58–60°; lit.[12] m.p. 58–60°) and **4b** (m.p. 98–100°; lit.[12] m.p. 98–100°) in 30.4 (186 mg) and 59.3% (378 mg) yield, respectively.

Similar reaction of **1** (853 mg, 1.58 mmol) and 1,2-di-*O*-(trimethylsilyl)ated 1,2-*trans*-DL-cyclohexanediol [prepared from 348.5 mg (3.00 mmol) of 1,2-*trans*-DL-cyclohexanediol] for 2 days gave two isomers: **5a** (syrup) and **5b** (m.p. 91–93°; lit.[12] m.p. 91–93°) in 30.6 (308 mg) and 33.3% (335 mg) yield, respectively.

*Methyl 2,3-di-O-benzyl-4,6-O-(2,3,4,6-tetra-O-benzyl-*D*-glucopyranosylidene)-α-*D*-glucopyranoside* (**7**). — Similar reaction of **1** (560 mg, 1.04 mmol) with **6** (593 mg, 1.14 mmol) for 3 days, and separation of the product on a column of silica gel (60:40:1 benzene–hexane–acetone), gave **7** in 72.2% yield (672 mg) as a syrup; $[\alpha]_D^{18}$ +38.1° (*c* 0.75); ^{13}C-n.m.r.: δ 110.5 (orthoester C).

Anal. Calc. for $C_{55}H_{58}O_{11}$: C, 73.81; H, 6.53. Found: C, 73.85; H, 6.42.

*Methyl 4,6-di-O-benzyl-2,3-O-(2,3,4,6-tetra-O-benzyl-*D*-glucopyranosylidene)-α-*D*-mannopyranoside* (**10a,b**). — Similar reaction of **1** (668 mg, 1.24 mmol) with **9** (571 mg, 1.10 mmol) for 3 days, and separation of the products on a Lobar column (5:3 hexane–ether), gave two isomers (**10a** and **10b**) in 44.8 (441.1 mg) and 26.6% (262.1 mg) yield, respectively. Compound **10a**: m.p. 61–62° (petroleum ether), $[\alpha]_D^{22}$ +28.1° (*c* 1.06); ^{13}C-n.m.r.: δ 119.0 (orthoester C); compound **10b**:

syrup; $[\alpha]_D^{22}$ +10.3° (*c* 0.20); ^{13}C-n.m.r.: δ 120.4 (orthoester C).

Anal. Calc. for $C_{55}H_{58}O_{11}$: C, 73.81; H, 6.53. Found for **10a**: C, 74.01; H, 6.57; and for **10b**: C, 73.89; H, 6.67.

Methyl 4,6-di-O-benzyl-3-C-methyl-2,3-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosylidene)-α-D-allopyranoside (**16a,b**). — Similar reaction of **1** (160.5 mg, 298 μmol) and **15** (138.9 mg, 263 μmol) for 3 days, and separation of the products by preparative t.l.c. (3:1 hexane–ethyl acetate), gave syrupy **16a** and **16b** in 8.9 (24 mg) and 8.9% (24 mg) yield, respectively. Compound **16a**: $[\alpha]_D^{18}$ +68.4° (*c* 0.420); ^{13}C-n.m.r.: δ 120.3 (orthoester C); compound **16b**: $[\alpha]_D^{18}$ +26.2° (*c* 0.435); ^{13}C-n.m.r.: δ 120.3 (orthoester C).

Anal. Calc. for $C_{56}H_{60}O_{11}$: C, 73.99; H, 6.65. Found for **16a**: C, 73.78; H, 6.65; and for **16b**: C, 73.84; H, 6.95.

Methyl 4,6-di-O-benzyl-2,3-O-(tetrahydropyran-2-ylidene)-α-D-mannopyranoside (**17**). — Similar reaction of δ-valerolactone (1.00 g, 10 mmol) with **9** (1.07 g, 2.10 mmol) for 2 days at −10°, and separation of the product on a flash column (5:2 hexane–ether), gave **17** in 40.2% yield (380 mg); m.p. 40–45° (petroleum ether), $[\alpha]_D^{20}$ +44.0° (*c* 0.35); ^{13}C-n.m.r.: δ 118.5 (orthoester C).

Anal. Calc. for $C_{26}H_{32}O_7$: C, 68.40; H, 7.07. Found: C, 68.19; H, 7.12.

Methyl 2,3-O-(6-O-acetyl-2,3,4-tri-O-benzyl-D-glucopyranosylidene)-4,6-di-O-benzyl-α-D-mannopyranoside (**11a,b**) *and benzyl 5-O-acetyl-2,6-anhydro-3,4-di-O-benzyl-D-mannonate* (**19**). — Similar reaction of **2** (167 mg, 0.34 mmol) with **9** (295 mg, 0.57 mmol) for 3 days, and separation of the products by preparative t.l.c. (1:2 hexane–ethyl acetate), gave a 1:1 isomeric mixture of **11a,b** and **19** in 16.3 (68.7 mg) and 51.7% (85.9 mg) yield, respectively. Mixture **11a,b**: $[\alpha]_D^{18}$ +36.2° (*c* 0.87); ν_{max}^{NaCl} 1740 cm^{-1} (C=O); ^{13}C-n.m.r.: δ 118.9 and 120.4 (orthoester C).

Anal. Calc. for $C_{50}H_{54}O_{12}$: C, 70.91; H, 6.43. Found: C, 70.85; H, 6.45.

Compound **19**: $[\alpha]_D^{18}$ +48.3° (*c* 1.60); ν_{max}^{NaCl} 1740 (C=O); ^{1}H-n.m.r. (C_6D_6): δ 7.6–7.1 (m, 15 H, 3 Ph), 5.10 (dq, $J_{5,6e}$ 3.9 Hz, H-5), 4.85 and 4.72 (ABq, 2 H, *J* 12.4 Hz, CH_2Ph), 4.63 (q, $J_{4,5}$ 5.3 Hz, H-3), 4.54 and 4.26 (ABq, 2 H, *J* 12.0 Hz, CH_2Ph), 4.48 (d, $J_{2,3}$ 8.6 Hz, H-2), 3.94 (q, $J_{4,5}$ 6.4 Hz, H-4), 3.90 (q, $J_{6e,6a}$ 10.2 Hz, H-6*e*), 3.67 (q, $J_{5,6a}$ 5.5 Hz, H-6*a*), 3.28 (s, 2 H, CO_2CH_2Ph), and 1.64 (s, 3 H, Ac).

Anal. Calc. for $C_{29}H_{30}O_7$: C, 71.00; H, 6.16. Found: C, 70.85; H, 6.45.

Ester exchange of **19** *to give ethyl 2,6-anhydro-3,4-di-O-benzyl-D-mannonate* (**20**). — A solution of **19** (40 mg, 82 μmol) in anhydrous ethanol (0.5 mL), mixed with a catalytic amount of M sodium ethoxide, was kept for 30 min at room temperature, made neutral with dilute hydrochloric acid, and then extracted with chloroform. The usual processing of the extract, and purification of the product by preparative t.l.c. (1:2 hexane–ether), gave **20** in 64.4% yield (20.4 mg); $[\alpha]_D^{18}$ +52.6° (*c* 0.57); ν_{max}^{NaCl} 3420 (OH), 1745, and 1735 cm^{-1} (C=O); ^{1}H-n.m.r.: δ 7.36 and 7.29 (each 1 s, 10 H, 2 Ph), 4.79 and 4.49 (ABq, 2 H, *J* 10.4 Hz, CH_2Ph), 4.75 and 4.43 (ABq, 2 H, *J* 9.8 Hz, CH_2Ph), 4.55 (dd, $J_{6e,6a}$ 8.0 Hz, H-6*e*), 4.35 (dd, $J_{5,6a}$ 6.0 Hz, H-6*a*), 4.27 (q, 2 H, OCH_2Me), 4.20 (m, $J_{5,6e}$ 1.8 Hz, H-5), 4.18 (d, $J_{2,3}$ 9.6 Hz,

H-2), 3.94 (q, $J_{3,4}$ 10.4 Hz, H-3), 3.75 (dd, $J_{4,5}$ 3.4 Hz, H-4), 1.80 (OH), and 1.32 (t, 3 H, J 7.0 Hz, CCH_3).

Anal. Calc. for $C_{32}H_{36}O_6$: C, 68.38; H, 6.78. Found: C, 68.28; H, 6.63.

*1,5-Di-O-acetyl-2,6-anhydro-3,4-di-O-benzyl-*D*-mannitol* (**21**). — A solution of **19** (90 mg, 0.18 mmol) and lithium aluminum hydride (14 mg, 0.36 mmol) in anhydrous oxolane (2 mL) was boiled under reflux for 1 h, cooled, and the reaction quenched by addition of ethyl acetate–water. The resulting mixture was filtered, and the filtrate was evaporated to a syrup (30 mg), which was acetylated in the usual way. Purification of the product by preparative t.l.c. (1:1 hexane–ether; developed three times) gave **21** in 51% yield (40 mg); $[\alpha]_D^{18}$ −7° (*c* 2.0); ν_{max}^{NaCl} 1740 cm^{-1} (C=O); ^{1}H-n.m.r.: δ 7.32 (s, 10 H, 2 Ph), 5.33 (oct, $J_{5,6e}$ 4.0 Hz, H-5), 4.78 and 4.66 (ABq, J 11.0 Hz, CH_2Ph), 4.70 and 4.50 (ABq, J 11.4 Hz, CH_2Ph), 4.32 (dd, $J_{1,1'}$ 11.2, $J_{1,2}$ 3.8 Hz, H-1), 4.21 (dd, $J_{1',2}$ 2.2 Hz, H-1'), 4.21 (t, $J_{3,4}$ 7.8 Hz, H-3), 4.07 (dd, $J_{4,5}$ 6.8 Hz, H-4), 4.04 (dd, $J_{6e,6a}$ 11.4 Hz, H-6*e*), 4.00 (m, $J_{2,3}$ 7.8 Hz, H-2), 3.96 (dd, $J_{5,6a}$ 5.6 Hz, H-6*a*), and 2.03 (s, 6 H, 2 Ac).

Anal. Calc. for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.34; H, 6.62.

*1,3,4,5-Tetra-O-acetyl-2,6-anhydro-*D*-mannitol* (**22**). — In a manner similar to that described for **21**, compound **19** (160.2 mg, 327 μmol) was reduced with lithium aluminum hydride to give a syrup (75 mg), which was then hydrogenolyzed in methanol in the presence of 20% palladium hydroxide on carbon (20 mg) overnight. The usual processing of the mixture gave a syrup (37.8 mg) which was acetylated in the usual way. Purification of the product by preparative t.l.c. (1:1 hexane–ether) gave 48 mg of pure **22** (44% overall yield): $[\alpha]_D^{18}$ −40° (*c* 0.5); ^{1}H-n.m.r.: δ 5.50 (dd, $J_{3,4}$ 9.5, $J_{4,5}$ 5.0 Hz, H-4), 5.42 (t, $J_{2,3}$ 9.8 Hz, H-3), ~5.38 (m, H-5), 4.37 (dd, $J_{5,6e}$ 3.8, $J_{6e,6e}$ 12.0 Hz, H-6*e*), 4.14 (dq, $J_{1,2}$ 5.0, $J_{1',2}$ 6.5 Hz, H-2), 4.02 (dd, $J_{5,6a}$ 6.3 Hz, H-6*a*), 3.99 (dd, $J_{1,1'}$ 10.2 Hz, H-1), 3.88 (dd, H-1'), and 2.16, 2.13, and 2.07 (each 1 s, 12 H, 4 OAc).

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.32; H, 6.02.

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