Carbohydrate Research, 63 (1978) 115–125

SYNTHESIS AND SOME REACTIONS OF 3,5-DI-*O*-METHYL-D-GLUCOSE AND -FRUCTOSE

JÁNOS KUSZMANN, PÁL SOHÁR, AND LÁSZLÓ KISS*
Research Institute for Pharmaceutical Chemistry, H-1325 Budapest 4, P.O. Box 82 (Hungary)
(Received August 29th, 1977; accepted for publication, September 22nd, 1977)

ABSTRACT

Hydrolysis of 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-α-D-glucofuranose by strong acid yielded 3,5-di-*O*-methyl-D-glucofuranose (**6**) and its 1,6-anhydride (**10**). The mechanism of the reaction giving **10** is discussed. On treatment with a catalytic amount of sodium methoxide, 1,2,6-tri-*O*-acetyl-3,5-di-*O*-methyl-D-glucofuranose (**8**) gives the 6-*O*-acetyl derivative, whereas complete deacetylation, and subsequent isomerization to the D-fructose derivative **16**, takes place in the presence of 0.1M sodium methoxide. The structure of **16** was proved both chemically and spectroscopically. Reduction of **6** or **8** with a borohydride afforded 3,5-di-*O*-methyl-D-glucitol.**

INTRODUCTION

For our studies on partially methylated 1,6-anhydro-1(6)-thiohexitols[1], 3,5-di-*O*-methyl-D-glucitol was needed as the starting material, but it has not been described in the literature. As methylated hexitols can be obtained most conveniently by borohydride reduction[2] of the corresponding hexose derivatives, the large-scale preparation of 3,5-di-*O*-methyl-D-glucose (**6**) was investigated. This compound has been synthesized by three different routes[3–5], and was obtained as a syrup. Among these three approaches, the synthesis described by Bishop[4], starting from 1,2-*O*-isopropylidene-α-D-glucofuranose, is the simplest. After tritylation to give **1**, and subsequent methylation to **2**, the isopropylidene group was hydrolyzed off with ethanol–aqueous HCl at elevated temperature. Neither **1** nor **2** had been isolated in crystalline state, and the syrupy hydrolyzate contained a byproduct (suggested to be a mono-*O*-methyl derivative[4]) that had to be removed by column chromatography. Pure **6** was finally obtained by distillation. To avoid these procedures, the intermediates in the aforementioned synthesis were purified, and both **1** and **2** were

*Present address: Biochemical Institute, L. Kossuth University, H-4010 Debrecen, Hungary.

**According to carbohydrate nomenclature, this may also be named 2,4-di-*O*-methyl-L-gulitol. To avoid confusion, the alditols are named as D-glucitol derivatives.

obtained in crystalline state*. Compound **1** had been synthesized in 1925, but was characterized only as its crystalline 3,5-di-*O*-benzoyl derivative[6].

RESULTS AND DISCUSSION

Despite the fact that, in our experiments, pure **2** was used as the starting material, the hydrolysis with acid, conducted according to the literature[4], always yielded a mixture of two compounds which, after separation by column chromatography, proved to be** **6** and its 1,6-anhydride (**10**). The same results were obtained when the trityl group was removed separately and the pure 6-hydroxy derivative **3** was submitted to hydrolysis. The anhydride **10** can theoretically be formed either *via* protonation of the dioxolane ring and attack of O-6 at the polarized C-1 atom (see **14**), or, after hydrolysis of the *O*-isopropylidene group, by attack of *β*-O-1 on C-6, which can be polarized by protonation of the OH-6 group (see **15**). When OH-6 was protected by a group resistant to acid hydrolysis[7], by converting **3** into the 6-*O*-*p*-nitrobenzoyl derivative **4**, the isopropylidene group could be hydrolyzed off with acid, and **7**, but no anhydro derivative **10**, could be detected in the hydrolyzate. This suggested that the first-mentioned mechanism (**14** → **10**) obtains for the formation of the anhydro ring. When the 6-*O*-tosyl derivative **5** was submitted to hydrolysis, *p*-toluenesulfonic acid was split off, and **10** was formed as the sole product, in accordance with the general rule established for the solvolysis of sulfonates[8], the

TABLE I

I.R. AND ^{1}H-N.M.R. DATA[a] FOR COMPOUNDS **1–5**

Compound	*CMe_2 bands (cm^{-1})*	*OMe band (cm^{-1})*	*Other bands (cm^{-1})*	*H-1 d(4)*	*H-2 d(4)*	*H-3,4,5 H-6 (2 H)*	*CMe_2 (2 s)*	*OMe (s)*	*Other protons*
1	1210 1180	—	OH: 3520 3420	5.90	4.45	4.15[b] 3.36*s*	1.25 1.45	—	420–455*m* trityl
2	1210 1185	2820	—	5.85	4.55	3.80*d*(3)[c] 4.35*dd*(3,10)[d] 190–230*m*[e]	1.30 1.50	3.40	425–465*m* trityl
3	1215	2820	OH: 3480 broad	5.75	4.50	190–250*m*	1.30 1.45	3.40	—
4	1218 1190	2840	ester C=O 1730	6.05	4.75	225–245*m*[f] 250–315*m*[g]	1.35 1.55	3.60	8.50*s* (4 H) *p*-nitrobenzoyl
5	1218 1195	2840	tosyl: 1365 1180, 560	5.70	4.45	220–260*m*	1.25 1.40	3.33 3.38	7.32; 7.75[h] 2.40*s* tosyl-CH_3

[a] *δ* scale, $CDCl_3$ solution; multiplets and coupling constants are given in Hz (in parentheses). [b] Singlet-like broad signal. [c] H-3. [d] H-4. [e] H-5,6. [f] H-3,5. [g] H-4,6. [h] AA′BB′ *m* (4 H).

*The i.r. and ^{1}H-n.m.r. data proving structures **1–5** are given in Table I.

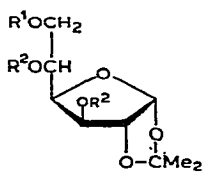
Compounds **6–9 are anomeric mixtures, as proved by their ^{1}H-n.m.r. data (see Table II), showing the presence of two anomeric protons in *cis* ($J_{1,2}$ = 4 Hz) and *trans* ($J_{1,2}$ < 1 Hz) relation to H-2.

TABLE II

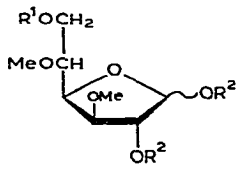
I.R. AND ^{1}H-N.M.R. DATA[a] FOR COMPOUNDS 6–9

Compound	*OH band (cm^{-1})*	*OMe band (cm^{-1})*	*Ester C=O band (cm^{-1})*	*H-1 d(4[b])*	*H-1 s(<1[b])*	*OMe (s)*	*Other protons*
6	3600–3200	2825	—	5.20	4.90	3.35	—
7	3600–3200	2835	1725	5.40	4.90	3.45	8.15*s* (4 H) *p*-nitrobenzoyl
8α	—	2840	1745	6.35	—	3.40 3.65	2.10*s* (9 H) acetyl
8β	—	2840	1745	—	5.95	3.35 3.48	2.02, 2.05, 2.08 3 *s* (9 H) acetyl
9	3600–3200	2835	1735	5.50	5.10	3.40 3.49	2.10 *s* (3 H) acetyl

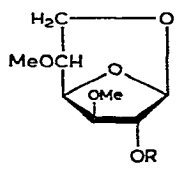
[a] δ scale, $CDCl_3$ solution. [b] Coupling constants, in Hz.



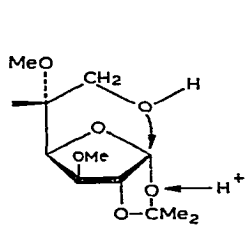
1 R^1 = Tr, R^2 = H
2 R^1 = Tr, R^2 = Me
3 R^1 = H, R^2 = Me
4 R^1 = $COC_6H_4NO_2$-*p*, R^2 = Me
5 R^1 = Ts, R^2 = Me



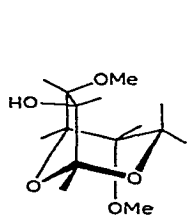
6 R^1 = R^2 = H
7 R^1 = $COC_6H_4NO_2$-*p*
8 R^1 = R^2 = Ac
9 R = Ac, R^2 = H



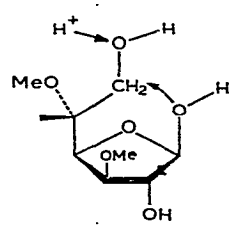
10 R = H
11 R = Ac
12 R = $COC_6H_4NO_2$-*p*
13 R = Me



14



10



15

mechanism of which involves a strongly polarized C-6–O bond, similar to that in route **15** → **10**.

The 1,6-anhydro-β-furanose structure of **10** was proved spectroscopically *via* its 2-*O*-acetyl (**11**) and 2-*O*-*p*-nitrobenzoyl (**12**) derivatives, as well as by converting it into the known[9] 2,3,5-tri-*O*-methyl derivative **13**.

The i.r. and ^{1}H-n.m.r. spectra of compounds **10**–**13** (see Table III) are in full agreement with the anhydro structure proposed; *e.g.*, no free OH band is present in the i.r. spectrum of the acetylated derivative **11**, whereas, in the ^{1}H-n.m.r. spectrum, the signal of only one acetyl group appears (2.10 p.p.m.), besides those of two

TABLE III

I.R. AND ^{1}H-N.M.R. DATA[a] FOR COMPOUNDS **10–13**

Compound	*OMe band (cm^{-1})*	*Other bands (cm^{-1})*	*H-1 (s)*	*H-2 (d[b])*	*H-3 dd[c]*	*H-5 (broad[d])*	*H-6[e]*	*OMe (2 s[f])*	*Other protons*
10	2840	OH 3600–3200	5.05	4.45	4.65	3.20	3.84 4.06	3.40 3.50	—
11	2835	ester C=O 1740	4.90	5.20	4.50	3.20	3.81 4.03	3.37 3.45	2.10*s* (3 H) acetyl
12	2810	ester C=O 1710	5.25	5.60	4.75	3.35	3.99 4.25	3.45 3.50	8.25*s* (4 H) *p*-nitrobenzoyl
13	2800	—	5.10	3.95[g]	4.60	3.20	3.95[g]	3.35 3.40 3.45	

[a] δ scale, $CDCl_3$ solution. [b] $J_{2,3} = 2$ Hz. [c] $J_{2,3} = 2$; $J_{3,4} = 7$ Hz. [d] Half-width 5 Hz. [e] *AB* part of an *ABX* multiplet ($J_{AB} = 12$; $J_{AX} \sim 3$ and $J_{BX} \sim 2$ Hz) coalesced with the H-4 multiplet, except for **12**, where H-4 gives a *dd* at 4.20 p.p.m. ($J_{3,4} = 7$; $J_{4,5} = 2$ Hz). [f] (6 H); in the case of **13**, 3 *s* (9 H). [g] H-2,4,6 give an overlapping signal.

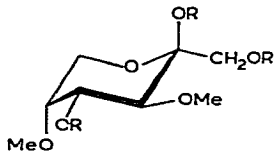
methoxyl groups (3.37 and 3.45 p.p.m.). Because of the absence of a double bond, only a bicyclic structure can be taken into consideration. The theoretically possible 1,2- or 2,5-anhydrofuranose arrangements can be excluded, as, in the spectra of the corresponding ester derivatives, only the signal of H-2 (but that of neither H-6 nor H-1) was shifted considerably, compared to the protons in **10**. Location of the acetoxyl group in **11** at C-2 was proved independently, by using $Eu(dpm)_3$ as a shift reagent, which forms preponderantly a complex with the carbonyl group, in consequence of which, the signal of the (sterically closest) H-3 atom was shifted most significantly.

In a search to avoid the formation of **10**, the influence of the conditions of the hydrolytic reaction was investigated. As, according to t.l.c., the hydrolysis of the 1,2-*O*-isopropylidene group is faster than the formation of **10**, the mechanism according to route **14** → **10** must be a two-step reaction, and the real intermediate in the anhydro-ring formation should be the α-OH anomer. For avoiding "unnecessary" protonation of this (less-basic) hydroxyl group, the proton concentration of the reaction had to be diminished. For this reason, we applied benzoic acid, in the presence of which the difference in rate of the two reactions was sufficiently high, yielding **6** practically free from **10**. For further purification, compound **6** was acetylated, to give a mixture of the α and β anomers of the 1,2,6-triacetate (**8**) from which the α anomer could be obtained in crystalline state.

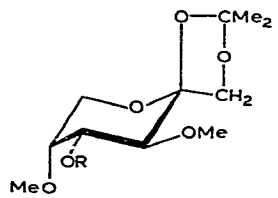
Deacetylation of **8** in methanol in the presence of a catalytic amount of sodium methoxide is a slow process, but, according to t.l.c., two of the acetyl groups are cleaved much faster than the third. Stopping the process after 2 h led to the 6-*O*-acetyl derivative **9**, the structure of which was proved spectroscopically*.

*See second footnote on page 116.

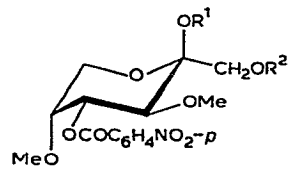
The 6-*O*-acetyl group, resistant to Zemplén deacetylation, could be removed by applying 0.1M sodium methoxide, but, according to t.l.c., besides **6**, another component was formed; this proved to be 3,5-di-*O*-methyl-D-fructopyranose (**16**). After 20 h at room temperature, the equilibrium was completely shifted towards the latter; this is remarkable, as, in the case of nonmethylated D-glucose, the equilibrium mixture from the base-catalyzed epimerization[10] contains D-glucose, D-fructose, and D-mannose in the ratios of 127:62:5. Protection of OH-6 by methylation prevents the formation of the D-fructose isomer, and the equilibrium contains[10,11] only D-glucose and D-mannose in the ratio of 1:1. The complete shift of the epimerization from **6** to **16** can be explained by steric factors, as the pyranose ring of the latter (having an equatorial CH_2OH group) is more stable than the furanose derivative **6** (having bulky groups in the *cis*-diaxial arrangement).



16 R = H
17 R = Me



18 R = H
19 R = $COC_6H_4NO_2$-*p*



20 R^1 = R^2 = H
21 R^1 = H, R^2 = Ac

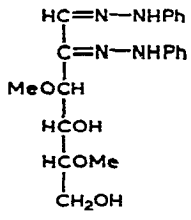
The structure of **16** was proved by converting it into the crystalline 1,2-*O*-isopropylidene derivative **18**, which showed no anomeric proton in its ^{1}H-n.m.r. spectrum. On acylation with *p*-nitrobenzoyl chloride, **19** was obtained, the isopropylidene group of which could be removed selectively by hydrolysis, affording **20**. The glycosidic hydroxyl group in **20** is less reactive than OH-1; therefore, the crystalline 1-*O*-acetyl derivative **21** was formed as the main component on acetylation with acetic anhydride in pyridine. Treatment of the corresponding D-glucose (**6**) or D-fructose (**16**) derivative with phenylhydrazine afforded the same osazone[4] (**22**).

The ^{1}H-n.m.r. spectrum of **19** proved not only the structure but the conformation too, as, besides the singlets of the isopropylidene methyl groups (1.45 and 1.55 p.p.m.) and the methoxyl groups (3.45 and 3.60 p.p.m.), the two methylene groups of the sugar give singlets (3.95 and 4.10 p.p.m.). The H-4 signal appeared at 5.45 p.p.m. as a double doublet, indicating a diaxial (11 Hz) and an axial–equatorial coupling (3 Hz). Accordingly, H-4 must be axially attached, proving the $_5C^2$(D) conformation of the pyranose.

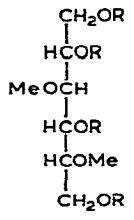
Methylation of the 1-*O*-acetyl derivative **21** with methyl iodide–silver oxide, followed by Zemplén deacylation and remethylation, afforded the known methyl tetra-*O*-methyl-β-D-fructopyranoside (**17**).

Reduction of 3,5-di-*O*-methyl-D-glucose (**6**) or its triacetate (**8**) by borohydride resulted in a syrup which, on acetylation and distillation, yielded pure 1,2,4,6-tetra-*O*-acetyl-3,5-di-*O*-methyl-D-glucitol (**23**). Deacetylation of **23** according to Zemplén afforded **24**, which was characterized as its 1,6-di-*O*-trityl derivative (**25**). Reduction

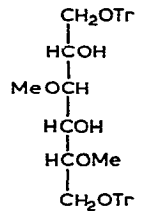
of the D-fructose isomer **16** resulted in a mixture of two components in the ratio of 1:1 (determined, after acetylation, by g.l.c.). The very similar retention-times of the two components suggest the presence of the D-mannitol isomer **26**.



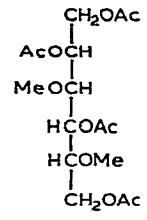
22



23 R = Ac
24 R = H



25



26

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was effected on Kieselgel G with ethyl acetate (*A*), with ethyl acetate–carbon tetrachloride 1:1 (*B*), 1:3 (*C*), and 1:5 (*D*), and with 9:1 ethyl acetate–ethanol (*E*). For detection, 1:1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (63–200 μm). I.r. spectra were recorded, for KBr pellets, with a Perkin–Elmer 577 spectrometer. ^{1}H-N.m.r. spectra (60 MHz) were recorded at room temperature with a JEOL 60-HL spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. G.l.c. was conducted with an F-21 Perkin–Elmer gas chromatograph, using a glass column (2 m × 4 mm) packed with 1% of XE-60 on Chromosorb W; temperatures: 11 min isothermal at 160°, then a heating rate of 3°.min^{-1}; carrier gas: nitrogen at 45 mL.min^{-1}.

All evaporations were performed in a rotary evaporator under diminished pressure, after the organic solutions had been dried with sodium sulfate. Light petroleum refers to the fraction having b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1), if not stated otherwise.

1,2-O-Isopropylidene-6-O-trityl-α-D-glucofuranose (**1**). — A solution of 1,2-*O*-isopropylidene-α-D-glucofuranose (22 g) in pyridine (110 mL) was treated with trityl chloride (30 g). After two days at room temperature, water was added to turbidity, and, after 2 h, the mixture was poured onto a mixture of conc. sulfuric acid (35 mL) and ice (1 L). The precipitated syrup was dissolved in chloroform, to give, after the usual processing, and crystallization of the residue from ether–light petroleum, 38.9 g (84%) of pure **1**, m.p. 143–146°, $[\alpha]_D^{20}$ −22.5° (*c* 2, MeOH); R_F 0.50 (*B*); lit.[4] amorphous, $[\alpha]_D^{20}$ −21° (*c* 2.6, MeOH).

1,2-O-Isopropylidene-3,5-di-O-methyl-6-O-trityl-α-D-glucofuranose (**2**). — To a stirred solution of **1** (46 g) in dimethyl sulfoxide (200 mL), a solution of sodium hydroxide (32 g) in water (32 mL) and dimethyl sulfate (38 mL) were simultaneously added at such a rate that the temperature of the reaction mixture did not exceed 50°. Stirring was continued for 1 h, and the mixture was then poured into water. The

precipitate was filtered off (48.3 g, 94.7%), and gave, after recrystallization from methanol, pure **2** (40.2 g, 82%), m.p. 113–114°, $[\alpha]_D^{20}$ −44° (EtOH); R_F 0.5 (*D*); lit.[4] syrup, $[\alpha]_D^{20}$ −30° (*c* 1.4, EtOH).

*1,2-*O*-Isopropylidene-3,5-di-*O*-methyl-α-*D*-glucofuranose* (**3**). — A slurry of **2** (49 g) in acetic acid (200 mL) and water (50 mL) was heated for 45 min on a steam bath. Tritanol separated from the hot solution on cooling, and was filtered off. The filtrate was evaporated below 40°, and the residue was filtered with the aid of water. The residue obtained on evaporation of the filtrate was dissolved in acetone (500 mL), the solution shaken with powdered potassium carbonate (20 g), and the suspension filtered. The filtrate was evaporated, and the product chromatographed on a column, using carbon tetrachloride and then solvent *B* for elution. The eluates with R_F 0.50 (*B*) were combined, and evaporated, to give **3** (14 g, 56.5%) as a colorless syrup that, after acetylation, gave a single peak in g.l.c., with a retention time of 7 min; $[\alpha]_D^{20}$ −26.6° (*c* 2, EtOH).

Anal. Calc. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.10; H, 8.38.

*1,2-*O*-Isopropylidene-3,5-di-*O*-methyl-6-*O*-(p-nitrobenzoyl)-α-*D*-glucofuranose* (**4**). — A solution of **3** (25 g) in pyridine (125 mL) was treated with *p*-nitrobenzoyl chloride (20 g). The mixture was kept at a temperature below 40° by cooling, and was then kept overnight at room temperature; it was next diluted with chloroform, and processed in the usual way, to give, after recrystallization from methanol, pure **4** (19.6 g, 49.5%), m.p. 125–126°, $[\alpha]_D^{20}$ −21.3°; R_F 0.5 (*C*).

Anal. Calc. for $C_{18}H_{23}NO_9$: C, 54.40; H, 5.83; N, 3.53. Found: C, 54.42; H, 6.06; N, 3.58.

*1,2-*O*-Isopropylidene-3,5-di-*O*-methyl-6-*O*-p-tolylsulfonyl-α-*D*-glucofuranose* (**5**). — To a stirred solution of **3** (12.5 g) and tosyl chloride (13 g) in benzene (50 mL) was added triethylamine (5.5 mL) at 0°. The mixture was kept overnight at room temperature, to give, after the usual processing, **5** (14 g, 70%) as a colorless syrup, $[\alpha]_D^{20}$ −25.5°; R_F 0.8 (*B*).

Anal. Calc. for $C_{18}H_{26}O_8S$: S, 7.97. Found: S, 7.82.

*3,5-Di-*O*-methyl-D-glucofuranose* (**6**). — *Method a.* The trityl derivative **2** (49 g) was hydrolyzed with aqueous acetic acid as described for compound **3**, except that the mixture was boiled for 5 min. The aqueous solution was evaporated, the residue was dissolved in water (120 mL), and benzoic acid (6 g) was added. The mixture was boiled for 4 h, while 20 mL (mainly acetone) was gradually distilled off. The benzoic acid, which crystallized from the cooled solution, was filtered off, the filtrate was evaporated, and two portions of water were added to, and evaporated from, the residue, which was then dissolved in water, and the solution washed with ether. Evaporation of the aqueous solution afforded **6** (20 g, 96.5%), $[\alpha]_D^{20}$ −20° (water); R_F 0.40 (*E*); lit.[3] $[\alpha]_D^{24}$ −21.3° (*c* 3, water); lit.[4,5] $[\alpha]_D^{20}$ −20° (*c* 1.1, water).

Method b. A solution of the detritylated derivative **3** (25 g) in water (150 mL) was boiled in the presence of benzoic acid (3 g) as just described, to yield **6** (17.6 g, 85%), identical with that obtained *via* route *a*.

*3,5-Di-*O*-methyl-6-*O*-(p-nitrobenzoyl)-D-glucofuranose* (**7**). — A slurry of **4**

(4 g) in acetic acid (40 mL) and water (10 mL) was boiled until hydrolysis was complete (2 h; checked by t.l.c.). The mixture was then evaporated, the residue was dissolved in chloroform, and the solution was successively washed with aqueous sodium hydrogencarbonate and water, and evaporated, to give **7** (2.5 g, 70%) as a yellow syrup, $[\alpha]_D^{20}$ −4.8°; R_F 0.2 (*B*).

Anal. Calc. for $C_{15}H_{19}NO_9$: N, 3.92; OMe, 17.32. Found: N, 3.74; OMe, 16.43.

*1,2,6-Tri-*O*-acetyl-3,5-di-*O*-methyl-*D*-glucofuranose* (**8**). — A solution of **6** (21 g) in pyridine (80 mL) and acetic anhydride (50 mL) was kept for 20 h at room temperature and then evaporated. The residue was dissolved in pyridine (10 mL), and the solution poured into water, and processed in the usual way, to give a syrup that, on treatment with ethyl acetate–light petroleum, afforded the crystalline α anomer **8α** (13 g, 39%), m.p. 76–77°, $[\alpha]_D^{20}$ +58°, R_F 0.60 (*B*).

Anal. Calc. for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63. Found: C, 50.32; H, 6.80.

The mother liquor was evaporated, and the residue was distilled, yielding (according to g.l.c.) a 3:7 mixture of **8α** and **8β** (11.6 g, 35.6%), b.p. 150–154°/27 Pa*. On fractional distillation, a 1:4 α:β mixture was obtained, $[\alpha]_D^{20}$ −37°; g.l.c. retention times: **8α**, 15.5, **8β**, 13.8 min.

Anal. Calc. for $C_{14}H_{22}O_9$: OMe, 18.59. Found: OMe, 18.4.

*6-*O*-Acetyl-3,5-di-*O*-methyl-*D*-glucofuranose* (**9**). — A solution of crystalline **8** (3.3 g) in methanol (15 mL) was treated with M methanolic sodium methoxide (0.1 mL), and the reaction was monitored by t.l.c. Besides a spot for **8** [R_F 0.6 (*B*)], two new components, R_F 0.35 and 0.15, appeared, the latter becoming predominant after 2 h. The reaction was stopped by addition of solid carbon dioxide, to give, after evaporation, and column chromatography with solvent *E*, pure **9** (2.2 g, 87.8%), $[\alpha]_D^{20}$ +6.3 (5 min) → +9° (24 h; water); R_F 0.15 (*B*), 0.70 (*E*).

Anal. Calc. for $C_{10}H_{18}O_7$: C, 47.99; H, 7.25. Found: C, 47.72; H, 7.07.

*1,6-Anhydro-3,5-di-*O*-methyl-β-*D*-glucofuranose* (**10**). — *Method a.* A solution of **6** (2.1 g) or the isopropylidene acetal **3** (2.5 g) in acetic acid (10 mL) and 2M aqueous hydrochloric acid (10 mL) was boiled for 10 h. The mixture was then made neutral with solid sodium hydrogencarbonate, and evaporated. The residue was mixed with ethanol, the suspension filtered, the filtrate evaporated, and the residue purified by column chromatography, using solvent *E* for elution. Evaporation of the fractions having R_F 0.65 gave pure **10** (1.15 g, 60.5%), $[\alpha]_D^{20}$ +16.8° (water).

Anal. Calc. for $C_8H_{14}O_5$: OMe, 32.6. Found: OMe, 32.4.

Method b. When the 6-*O*-tosyl derivative **5** (4 g) was used as starting material, the reaction was complete in 1 h at 80°. Sodium acetate trihydrate (1.4 g) was added to the cooled solution, and the residue obtained by evaporation was mixed with ethanol, the suspension filtered, and the filtrate processed as in *a*, to yield **10** (0.9 g, 47.5%), identical with that already described.

Acetylation of **10** (3 g) with acetic anhydride (5 mL) in pyridine (7 mL) gave,

*1 Torr = 101,325/760 Pa (pascals).

after column chromatography with solvent *B*, pure **11** (3 g, 82%), $[\alpha]_D^{20}$ −16°; R_F 0.50; g.l.c. retention time, 6.5 min.

p-*Nitrobenzoylation* of **10** (3 g) with *p*-nitrobenzoyl chloride (3 g) in pyridine (15 mL) yielded, after the usual processing, and treatment with methanol, crude **12** (4.4 g, 72.6%) which, after recrystallization from acetone–methanol, had m.p. 192–194°, $[\alpha]_D^{20}$ +8.4°; R_F 0.60 (*B*).

Anal. Calc. for $C_{15}H_{17}NO_8$: C, 53.10; H, 5.05; N, 4.13. Found: C, 53.22; H, 5.35; N, 4.02.

Methylation of **10** (0.7 g) in aqueous solution (5 mL) with 50% aqueous NaOH (4 mL) and dimethyl sulfate (2.2 mL) yielded, after the usual processing, and recrystallization from light petroleum, **13** (0.47 g, 68.5%), m.p. 52–54°, $[\alpha]_D^{20}$ +16.2° (acetone); lit.[9] m.p. 51–52°, $[\alpha]_D^{20}$ +18.9° (acetone).

*3,5-Di-*O*-methyl-β-*D*-fructopyranose* (**16**). — A solution of **6** (10.4 g) or its triacetate **8** (16.7 g) in methanol (60 mL) was treated with 5M methanolic sodium methoxide (1 mL). After 20 h at room temperature, sodium ions were removed by an ion-exchange resin, the suspension filtered, the solution evaporated, and the residue freed from solvents at 133.3 mPa (10^{-3} torr) to give pure **16** (10.2 g, 98%), $[\alpha]_D^{20}$ −73° (water); R_F 0.30 (*E*).

Anal. Calc. for $C_8H_{16}O_6$: OMe, 29.85. Found: OMe, 29.50.

*1,2-*O*-Isopropylidene-3,5-di-*O*-methyl-β-*D*-fructopyranose* (**18**). — A solution of **16** (4.6 g) in acetone (190 mL) containing sulfuric acid (1 mL) was kept overnight at room temperature, the acid neutralized with sodium carbonate, and the mixture evaporated. The residue was mixed with chloroform, and the solution washed with water, dried, and evaporated. The residue was purified by column chromatography (solvent *B*), to yield **18** (2.8 g, 54%) which, after recrystallization from ether–light petroleum, had m.p. 165–168°, $[\alpha]_D^{20}$ +47.7°; R_F 0.55 (*A*); g.l.c. retention-time, 7.7 min.

Anal. Calc. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.30; H, 8.25.

*1,2-*O*-Isopropylidene-3,5-di-*O*-methyl-4-*O*-(p-nitrobenzoyl)-β-*D*-fructopyranose* (**19**). — A solution of **18** (7.5 g) in pyridine (40 mL) was treated with *p*-nitrobenzoyl chloride (7 g) to give, after the usual processing, a syrup which was purified by column chromatography (solvent *C*). Evaporation of the fractions having R_F 0.40 afforded pure **19** (9.65 g, 81%) as a syrup, $[\alpha]_D^{20}$ −132°.

Anal. Calc. for $C_{18}H_{23}NO_9$: N, 3.53. Found: N, 3.26.

*3,5-Di-*O*-methyl-4-*O*-(p-nitrobenzoyl)-β-*D*-fructopyranose* (**20**). — A solution of **19** (8 g) in acetic acid (80 mL) and water (20 mL) was treated as described for compound **7**, to yield **20** as a yellow syrup (6.15 g, 86%), $[\alpha]_D^{20}$ −76°; R_F 0.20 (*B*).

Anal. Calc. for $C_{15}H_{19}NO_9$: N, 3.92; OMe, 17.32. Found: N, 3.78; OMe, 16.84.

*1-*O*-Acetyl-3,5-di-*O*-methyl-4-*O*-(p-nitrobenzoyl)-β-*D*-fructopyranose* (**21**). — A solution of **20** (7.2 g) in pyridine (35 mL) was treated with acetic anhydride (20 mL) to give, after the usual processing, and recrystallization from ethanol, pure **21** (3.48 g, 43.5%), m.p. 120–122°, $[\alpha]_D^{20}$ −113°; R_F 0.40 (*B*).

Anal. Calc. for $C_{17}H_{21}NO_{10}$: C, 51.13; H, 5.30; N, 3.51. Found: C, 51.15; H, 6.23; N, 3.35.

Methyl tetra-O-*methyl*-β-D-*fructopyranoside* (**17**). — A solution of compound **21** (1 g) in methyl iodide (15 mL) was stirred in the presence of silver oxide (1 g) for 20 h at room temperature. The mixture was then diluted with chloroform (30 mL), the silver salts were filtered off, and the filtrate was successively washed with 2% aqueous KCN solution and water, dried, and evaporated to afford the methyl β-glycoside as a syrup (1 g, 96.5%) which was dissolved in methanol (10 mL), treated with M methanolic sodium methoxide (0.1 mL), and kept for 20 h at room temperature. The mixture was freed of methyl *p*-nitrobenzoate by column chromatography (solvent *A*), and the glycoside was permethylated as described for **13** from **10**, to yield, on evaporation, **17** as a chromatographically pure syrup, $[\alpha]_D^{20}$ −140° (water); lit.[13] $[\alpha]_D^{20}$ −149.1° (*c* 3.1, water).

3,5-Di-O-*methyl*-D-arabino-*hexosulose bis*(*phenylhydrazone*) (**22**). — A solution of **6** or **16** (2.5 g), sodium hydrogensulfite (2.5 g), and phenylhydrazine (25 mL) in 20% aqueous acetic acid (100 mL) was heated for 3 h at 100°. The solution was cooled, and diluted with water (50 mL), and the precipitate was filtered off and recrystallized twice from ethanol–water, yielding **22** (1.5 g), m.p. 82–85°, $[\alpha]_D^{20}$ −86° (ethanol); R_F 0.65 (*E*); lit.[4] m.p. 64–65°, $[\alpha]_D^{20}$ −83° (*c* 1.5, ethanol).

1,2,4,6-Tetra-O-*acetyl-3,5-di*-O-*methyl*-D-*glucitol* (**23**). — A solution of the tri-*O*-acetyl derivative **8** (10 g) in methanol (30 mL) was added to a stirred solution of sodium borohydride (4 g) in methanol (100 mL) containing M aqueous sodium hydroxide (1 mL) at 0°. (It is advisable to perform this reaction in a large beaker so that the mixture will not foam over.) The solution was then transferred to a round-bottomed flask and boiled under reflux on a steam bath for 1 h. After being cooled, acetic acid (5 mL) was added, and the solution was evaporated. Then methanol, ethanol, and chloroform were successively added to, and evaporated from, the residue. This was dissolved in acetic anhydride (20 mL), and a solution of conc. sulfuric acid (10 mL) in acetic anhydride (20 mL) was slowly added. After 2 days at room temperature, the mixture was poured into a stirred slurry of sodium hydrogencarbonate (120 g) in water (1 L). The mixture was extracted with chloroform, and the extract evaporated, giving a residue that was distilled, to yield pure **23** (9.3 g, 82%), b.p. 155–160°/13 Pa, $[\alpha]_D^{20}$ +3°; R_F 0.45; ^{1}H-n.m.r. data: δ 2.08. 2.10. 2.15, and 2.17 (4 acetyl Me), and 3.35 and 3.45 (2 OMe); g.l.c. retention-time: 18.4 min.

Anal. Calc. for $C_{16}H_{26}O_{10}$: C, 50.79; H, 6.93. Found: C, 50.54; H, 6.86.

3,5-Di-O-*methyl*-D-*glucitol* (**24**). — *Method a.* A solution of the distilled tetraacetate **23** (3.8 g) in dry methanol (20 mL) was treated with M methanolic sodium methoxide (0.1 mL). According to t.l.c., the reaction was complete in 30 min. The solution was freed of sodium ions by means of a cation-exchange resin, to give, after evaporation, **24** as a colorless syrup (2 g, 95%), $[\alpha]_D^{20}$ −3.4° (water); R_F 0.50 (1 : 1 ethyl acetate–ethanol).

Anal. Calc. for $C_8H_{18}O_6$: OMe, 29.56. Found: OMe, 29.32.

Method b. A solution of **23** (3.8 g) in 3M methanolic hydrogen chloride (20 mL)

was kept for 5 h at room temperature and then evaporated. The residue was dissolved in methanol, and the solution was made neutral with an anion-exchange resin, the suspension filtered, and the filtrate evaporated, to yield **24** (1.9 g, 90%), identical with that described in *a*.

*3,5-Di-*O*-methyl-1,6-di-*O*-trityl-*D*-glucitol* (**25**). — To a solution of **24** (obtained by deacetylation of 9 g of **23**) in pyridine (50 mL) was added trityl chloride (15 g). After 24 h at room temperature, the mixture was processed in the usual way, to give, after purification by column chromatography, **25** as a solid foam (13 g, 78.2%); m.p. 52–54°, $[\alpha]_D^{20}$ −52°; R_F 0.40 (*D*).

Anal. Calc. for $C_{46}H_{46}O_6$: C, 79.51; H, 6.67. Found: C, 79.88; H, 6.82.

Reduction of **16** *with sodium borohydride.* — To a solution of **16** (0.8 g) in methanol (10 mL) was added sodium borohydride (0.3 g) during 30 min. According to t.l.c., the reduction was complete within 1.5 h. The solution was made neutral with acetic acid and evaporated, and methanol was added to, and evaporated from, the residue four times. The semi-solid residue was then treated with acetic anhydride (5 mL) and pyridine (7 mL), to give, after the usual processing, a syrup (1.1 g) that, according to g.l.c., contained only two components, having equal intensity (retention times: 18.4 and 18.9 min), corresponding to **23** and **26**.

REFERENCES

1 J. KUSZMANN AND P. SOHÁR, *Carbohydr. Res.*, 56 (1977) 105–115.
2 M. L. WOLFROM AND A. THOMPSON, *Methods Carbohydr. Chem.*, 2 (1973) 65–77.
3 G. N. HUFFMAN, B. A. LEWIS, F. SMITH, AND D. R. SPRIESTERSBACH, *J. Am. Chem. Soc.*, 77 (1955) 4346–4348.
4 C. T. BISHOP, *Can. J. Chem.*, 35 (1957) 61–64.
5 G. H. COLEMAN, S. S. BRANDT, AND C. M. MCCLOSKEY, *J. Org. Chem.*, 22 (1957) 1336–1338.
6 B. HELFERICH, L. MOOG, AND A. JÜNGER, *Ber.*, 58 (1925) 872–886.
7 J. KUSZMANN AND L. VARGHA, *Carbohydr. Res.*, 16 (1971) 261–271.
8 J. DEFAYE, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 181–228.
9 R. J. DIMLER, H. A. DAVIS, AND G. E. HILBERT, *J. Am. Chem. Soc.*, 68 (1946) 1377–1379.
10 M. L. WOLFROM AND W. L. LEWIS, *J. Am. Chem. Soc.*, 50 (1928) 837–854.
11 N. PRENTICE, L. S. CUENDET, AND F. SMITH, *J. Am. Chem. Soc.*, 78 (1956) 4439–4440.
12 J. C. IRVINE AND J. PATTERSON, *J. Chem. Soc.*, 121 (1922) 2696–2703.
13 W. N. HAWORTH, E. L. HIRST, AND A. LEARNER, *J. Chem. Soc.*, (1927) 1040–1049.