Alternative Syntheses of Methylated Sugars. VI.* 3,4-Di-*O*-methyl- and 4,6-Di-*O*-methyl-D-glucopyranose

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3,4-Di-*O*-methyl-D-glucopyranose and 4,6-di-*O*-methyl-D-glucopyranose have been synthesized by simple procedures using diazomethane with a catalytic proportion of boron trifluoride etherate as the methylating agent.

It was believed until recently that diazomethane cannot be used for the methylation of the alcoholic hydroxyl groups of a carbohydrate [1]. Investigations by *Gross* and co-workers [2] have established that by the use of diazomethane in the presence of a catalytic proportion of boron trifluoride etherate carbohydrates can be readily methylated. Moreover, it has been shown [2—4] that under the conditions of methylation with diazomethane—boron trifluoride etherate monosaccharides bearing base-labile substituents can be methylated without migration of the labile substituents. This finding makes some compounds having base-labile substituents convenient starting materials for the syntheses of partially methylated sugars.

The present paper describes the application of the principles outlined above to the simple synthesis of 3,4-di-*O*-methyl-D-glucopyranose (*IV*) and 4,6-di-*O*-methyl-D-glucopyranose (*VII*). We wish to show also that the employed methylation technique can be successfully used on a considerably larger scale than described previously [2—5].

Older, rather laborious, pathways leading to *IV* and *VII* were reviewed by *Bourne* and *Peat* [1]. Recently *Mitra et al.* [6] obtained a small amount of *IV* by saponification of *O*-mesyl groups in methyl 2,6-di-*O*-mesyl-3,4-di-*O*-methyl-α-D-glucopyranoside followed by acid hydrolysis, making thus the route to *IV* a four-step synthesis (starting from methyl α-D-glucopyranoside). As we wish to show here, a starting material from which *IV* can be obtained in an equally advantageous way is methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (*I*). Methylation of *I* with diazomethane—boron trifluoride etherate gave, in good yield, methyl 2,6-di-*O*-benzoyl-3,4-di-*O*-methyl-α-D-glucopyranoside (*II*) which was debenzoylated to yield the known methyl 3,4-di-*O*-methyl-α-D-glucopyranoside (*III*). Subsequent hydrolysis then readily afforded *IV*.

While the manuscript of this work was in preparation *Lipták*'s work [7] appeared where synthesis of *IV via* the same reaction sequence is described. The author claims to have obtained chromatographically pure *II* in 90.6% yield by methylation of *I*. The manner in which *II* was isolated from the reaction mixture indicates, however, that his product was contaminated with noncarbohydrate material, which possibly explains the difference between the optical rotation of *II* given in [7] ($[\alpha]_D^{22}$ +100.1°; $c = 1$, chloroform) and that of our compound *II* (see experimental section).

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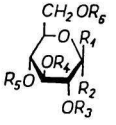
The starting material for the synthesis of *VII* was readily obtainable 1,2,3-tri-*O*-acetyl-β-D-glucopyranose (*V*) which upon methylation with diazomethane—boron trifluoride etherate afforded crystalline, hitherto unknown, 1,2,3-tri-*O*-acetyl-4,6-di-*O*-methyl-β-D-glucopyranose (*VI*), from which an excellent yield of *VII* was obtained by subsequent deacetylation. In addition to the reduced number of steps the convenience of the presented way to *VII* is in the fact that the last step of the synthesis is mild deacetylation, whereas the previous procedures required hydrolytic rupture of a methyl glucosidic structure in the course of which at least some of the desired product necessarily underwent decomposition. The simple synthetic pathway described here makes thus also our recent synthesis of 3,4,6-tri-*O*-methyl-D-glucopyranose [8], starting from *VII*, more attractive.

The physical constants of the title compounds compared well with the reported values. Small discrepancies between our values and those found by the earlier workers may be attributed to differences in anomeric composition.



	R_1	R_2	R_3	R_4	R_5	R_6
I	H	OMe	Bo	H	H	Bo
II	H	OMe	Bo	Me	Me	Bo
III	H	OMe	H	Me	Me	H
IV	(H, OH)		H	Me	Me	H
V	OAc	H	Ac	Ac	H	H
VI	OAc	H	Ac	Ac	Me	Me
VII	(H, OH)		H	H	Me	Me

Ac = acetyl, Bo = benzoyl, Me = methyl.

Experimental

Solutions were concentrated under diminished pressure on a rotary evaporator at 35—40°C. Melting points were determined on a Kofler hot stage. Specific rotations were measured with a Bendix—Ericsson Model 143 A automatic polarimeter.

Thin-layer chromatography (TLC) on Silica gel coated glass slides (4.5 × 12 cm) and preparative column chromatography on silica gel (0.05—0.1 mm) was carried out using: A. hexane—ethyl acetate 4 : 1, B. chloroform—methanol 6 : 1 and C. benzene—ethyl acetate 9 : 5. The solvent ratios are based on volumes. On thin-layer plates the components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible.

Methyl 2,6-di-O-benzoyl-3,4-di-O-methyl-α-D-glucopyranoside (II)

Methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside [9] (17 g) was dissolved in dichloromethane (100 ml) and the solution was cooled in an acetone—dry ice bath to −20°C. Alternately, and with stirring, freshly distilled boron trifluoride etherate (0.05 ml) and

diazomethane in dichloromethane (20 ml) was added, while the temperature of the reaction mixture was kept at -20 ± 3°C, until TLC (solvent A) showed that the ratio between the produced mono-*O*-methyl derivative and di-*O*-methyl derivative (R_F 0.16 and 0.54, respectively) remained practically unchanged (about 20 portions of each). Polymethylene, the reaction by-product, was filtered off and the filtrate was evaporated. Elution from a silica gel column (100 × 4 cm), using solvent A, gave 13.6 g (74.5%) of the faster moving methyl 2,6-di-*O*-benzoyl-3,4-di-*O*-methyl-α-D-glucopyranoside. The compound was vacuum distilled (b.p. 230°C/5 × 10^{-2} Torr) and collected as a thick colourless syrup; $[\alpha]_D^{25}$ +139° (c = 1.64, ethanol).

For $C_{23}H_{26}O_8$ (430.43) calculated: 64.17% C, 6.09% H, 21.63% CH_3O; found: 64.08% C, 6.09% H, 21.91% CH_3O.

The slower moving component (3.5 g) was a mixture of methyl 2,6-di-*O*-benzoyl-3-*O*- and 4-*O*-methyl-α-D-glucopyranoside, which was proved in the following manner: a small amount of the component was debenzoylated in methanol with sodium methoxide and subsequently hydrolyzed. The hydrolyzate was analyzed by gas–liquid chromatography applying previously elaborated analytical procedure [10] which showed the presence of 3-*O*-methyl- and 4-*O*-methyl-D-glucose.

Methyl 3,4-di-O-methyl-α-D-glucopyranoside (III)

Compound *II* (19.7 g) was dissolved in dry methanol (200 ml) and two drops of 10% sodium methoxide in dry methanol was added. The mixture was, with the exclusion of moisture, warmed up to 50°C and allowed to cool down to room temperature. TLC in solvent system A and B showed that the debenzoylation was complete and the product (R_F 0.42 in solvent B) was isolated in the usual manner. Crystallization from ether gave *III* (9.5 g, 82.5%); m.p. 53–56°C; $[\alpha]_D^{24}$ +179° (c = 4.33, chloroform). Ref. [6] gives m.p. 53.5–55.5°C and $[\alpha]_D^{24}$ +179° (c = 4.4, chloroform).

3,4-Di-O-methyl-D-glucopyranose (IV)

A solution of the glycoside *III* (6 g) was boiled in 5% hydrochloric acid (120 ml) for 3 hours, at which time TLC in system B showed that only traces of the starting material (R_F 0.42) were present in the reaction mixture. Deionization with an ion-exchange resin (Ionenaustauscher II, Merck A. G., Darmstadt), and evaporation to dryness afforded the product (R_F 0.2) which was crystallized from dry ethyl acetate. Recrystallization from the same solvent gave pure *IV* (4.5 g, 80%); m.p. 112–115°C; $[\alpha]_D^{25}$ +77.6° (6 min) → → +74.7° (8 hours const; c = 5, water). Ref. [6] gives m.p. 114–118.5°C and $[\alpha]_D$ +80° (6 min) → +76.0° (7 hours const; c = 5, water).

Ref. [11] gives physical properties of two independently obtained samples of 3,4-di-*O*-methyl-D-glucose: m.p. 110–113°C; $[\alpha]_D$ +77.8° (final, water) and m.p. 110–112°C; $[\alpha]_D$ +76.6° (final, water).

A portion of *IV* was converted to the corresponding *N*-phenyl-glycopyranosylamine; m.p. 176–178°C; $[\alpha]_D^{25}$ −101° (12 min; c = 1.5, ethanol).

Ref. [11] gives m.p. 177–178°C; $[\alpha]_D$ −106° (c = 2.2, ethanol).

1,2,3-Tri-O-acetyl-4,6-di-O-methyl-β-D-glucopyranose (VI)

1,2,3-Tri-*O*-acetyl-β-D-glucopyranose *V* [12] (8.5 g) was methylated in the manner described above. The starting material shortly disappeared from the reaction mixture

(as showed by TLC in solvent system B; R_F 0.6) and finally almost complete conversion into the di-*O*-methyl derivative (R_F 0.5; solvent system C) was observed. The reaction mixture was filtered, the filtrate was washed successively with saturated solution of sodium bicarbonate and water and concentrated to give a crude syrupy product. The syrup was dissolved in ether and hexane was added almost to turbidity, whereupon *VI* crystallized (8.2 g, 88.5%). Recrystallization from ether gave needles; m.p. 74.5—75.5°C; $[\alpha]_D^{25}$ −4.4° (c = 0.99, chloroform).

For $C_{14}H_{21}O_9$ (333.31) calculated: 50.44% C, 6.35% H, 18.62% CH_3O; found: 50.50% C, 6.40% H, 18.63% CH_3O.

4,6-Di-O-methyl-D-glucopyranose (VII)

Compound *VI* (5 g) was treated with a catalytic amount of sodium methoxide in dry methanol for one hour at room temperature and, after usual work-up, *VII* was crystallized from acetone. Yield 4.2 g (90%); m.p. 156—158°C; $[\alpha]_D^{24}$ +117° (3 min; c = 1.04, water) → +65.7° (80 hours const).

Ref. [13] gives m.p. 157°C; $[\alpha]_D^{18}$ +101° → +67.2° (equil., water).

4,6-Di-*O*-methyl-D-glucopyranose can be obtained in essentially the same yield by deacetylation of the crude product given rise to by methylation of *V* or its α-anomer [12].

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