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Note

A convenient synthesis of 6-substituted derivatives of methyl β-maltoside

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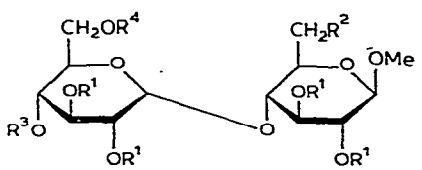
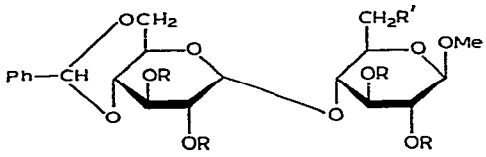
The practical preparation of 6-substituted derivatives of methyl β-maltoside (**1**) has been hindered by difficulties in obtaining a key intermediate, methyl 2,3,2′,-3′,4′,6′-hexa-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-maltoside (**2**), in a high yield. The attempted regioselective tosylation of **1** afforded[1] methyl 6-*O*-*p*-tolylsulfonyl-β-maltoside (**3**) in 1% yield together with the 6,6′-di-*O*-*p*-tolylsulfonyl (**4**) and the 6′-*O*-*p*-tolylsulfonyl (**5**) derivatives in 28% and 18% yield, respectively; **3** could then be acetylated to give syrupy **2**, which was further transformed[1] into methyl 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-6-deoxy-6-iodo-β-maltoside (**6**) and methyl 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-6-deoxy-β-maltoside (**7**). Alternatively, sequential treatment of 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-1,6-anhydro-β-maltose with titanium tetrachloride and methanol–mercuric acetate gave[2], in 7% yield, the hexaacetate **8** having HO-6 free; on *p*-toluenesulfonylation, **8** afforded **2**, which was converted[2] into methyl 2,3,2′,3′,4′-6′-hexa-*O*-acetyl-6-azido-6-deoxy-β-maltoside (**9**). This paper describes a convenient preparation of a homologous series of 6-substituted derivatives of **1** starting from methyl 4′,6′-*O*-benzylidene-β-maltoside[3] (**16**).

Selective *p*-toluenesulfonylation of **16** with 2 mol. equiv. of reagent in pyridine followed by acetylation gave a mixture composed of a major and a minor product



1 $R^1 = R^3 = R^4 = H, R^2 = OH$
2 $R^1 = R^3 = R^4 = Ac, R^2 = OTs$
3 $R^1 = R^3 = R^4 = H, R^2 = OTs$
4 $R^1 = R^3 = H, R^2 = OTs, R^4 = Ts$
5 $R^1 = R^3 = H, R^2 = OH, R^4 = Ts$
6 $R^1 = R^3 = R^4 = Ac, R^2 = I$
7 $R^1 = R^3 = R^4 = Ac, R^2 = H$
8 $R^1 = R^3 = R^4 = Ac, R^2 = OH$
9 $R^1 = R^3 = R^4 = Ac, R^2 = N_3$
10 $R^1 = R^3 = R^4 = Ac, R^2 = Br$
11 $R^1 = R^3 = R^4 = Ac, R^2 = Cl$
12 $R^1 = Ac, R^2 = OTs, R^3 = R^4 = Ms$
13 $R^1 = R^2 = R^3 = R^4 = H$
14 $R^1 = R^3 = R^4 = H, R^2 = Br$
15 $R^1 = R^3 = R^4 = H, R^2 = Cl$



16 R = H, R′ = OH
17 R = Ac, R′ = OTs
18 R = Ac, R′ = I
19 R = Ac, R′ = Br
20 R = Ac, R′ = Cl
21 R = Ac, R′ = N_3

(t.l.c.), from which methyl 2,3,2′,3′-tetra-*O*-acetyl-4′,6′-*O*-benzylidene-6-*O*-*p*-tolylsulfonyl-β-maltoside (**17**) was directly isolated in crystalline form in 66% yield. Displacement of the tosyloxy group in **17** with iodide ion in *N*,*N*-dimethylformamide gave crystalline methyl 2,3,2′,3′-tetra-*O*-acetyl-4′,6′-*O*-benzylidene-6-deoxy-6-iodo-β-maltoside (**18**). Removal of the benzylidene group of **18** with aqueous acetic acid followed by acetylation gave the known[1] compound **6**, which was reductively dehalogenated with Raney nickel in the presence of hydrazine[4] to afford the known[1] compound **7**, thus confirming the structure of **17**. It is of interest to note that a similar attempt of preferential *p*-toluenesulfonylation of benzyl 4′,6′-*O*-benzylidene-β-maltoside with a view to obtaining the 6-*O*-*p*-tolylsulfonyl derivative failed[5].

Similarly, treatment of **17** with sodium bromide in hexamethylphosphoric triamide gave crystalline methyl 2,3,2′,3′-tetra-*O*-acetyl-4′,6′-*O*-benzylidene-6-bromo-6-deoxy-β-maltoside (**19**), with lithium chloride in *N*,*N*-dimethylformamide, crystalline methyl 2,3,2′,3′-tetra-*O*-acetyl-4′,6′-*O*-benzylidene-6-chloro-6-deoxy-β-maltoside(**20**), and with sodium azide in *N*,*N*-dimethylformamide, crystalline methyl 2,3, 2′,3′-tetra-*O*-acetyl-6-azido-4′,6′-*O*-benzylidene-6-deoxy-β-maltoside (**21**). Sequential treatment of **19**, **20**, and **21** with aqueous acetic acid and pyridine–acetic anhydride produced crystalline methyl 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-6-bromo-6-deoxy-β-maltoside (**10**), crystalline methyl 2,3,2′,3′,4′,6′-hexa-*O*-acetyl-6-chloro-6-deoxy-β-maltoside (**11**), and the known[2] compound **9**, respectively. Treatment of **17** with aqueous acetic acid and subsequent methanesulfonylation gave methyl 2,3,2′,3′-tetra-*O*-acetyl-4′,6′-di-*O*-methylsulfonyl-6-*O*-*p*-tolylsulfonyl-β-maltoside (**12**).

O-Deacetylation of **7**, **10**, and **11** with methanolic sodium methoxide furnished methyl 6-deoxy-β-maltoside (**13**), methyl 6-bromo-6-deoxy-β-maltoside (**14**), and methyl 6-chloro-6-deoxy-β-maltoside (**15**), respectively, all the compounds being obtained as the crystalline monohydrate.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto hot-stage microscope and are uncorrected. Optical rotations were measured with an Ohyo Denki automatic polarimeter, Model MP-1T. N.m.r. spectra were recorded in

chloroform-*d* solution with a Varian A-60A spectrometer, and with tetramethylsilane as the internal standard. Solutions were concentrated at a temperature below 40° under reduced pressure.

*Methyl 2,3-di-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-6-*O*-p-tolylsulfonyl-β-*D*-glucopyranoside* (**17**). — To a stirred solution of **16** (6.4 g) in anhydrous pyridine (65 ml), cooled to −20°, was added portionwise *p*-toluenesulfonyl chloride (5.5 g, 2.0 mol. equiv.). The reaction mixture was further stirred for 30 min at −20°, stored for 5 h at 0°, treated with acetic anhydride (40 ml), and then kept overnight at room temperature. The solution was poured into ice–water, and the resulting precipitate was filtered off, washed extensively with water, and dried. Crystallization from ethanol and recrystallization from ethanol–chloroform gave **17** (7.3 g, 66%), m.p. 197–198° (dec.), $[\alpha]_D^{24}$ +20.3° (*c* 1.6, chloroform); n.m.r.: τ 4.48 (s, 1 H, benzylic-H), 6.62 (s, 3 H, OMe), 7.67 (s, 3 H, aryl-CH_3), 7.98 (s, 6 H, 2 OAc), and 8.02 (s, 6 H, 2 OAc).

Anal. Calc. for $C_{35}H_{42}O_{17}S$: C, 54.82; H, 5.52; S, 4.18. Found: C, 54.91; H, 5.47; S, 4.29.

*Methyl 2,3-di-*O*-acetyl-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-6-iodo-β-*D*-glucopyranoside* (**18**). — Sodium iodide (3 g) was added to a solution of **17** (2 g) in *N*,*N*-dimethylformamide (40 ml), and the mixture was heated for 3 h at 100°. The cooled mixture was poured into ice–water, and the precipitate formed was filtered off and dissolved in chloroform. The solution was washed with water, dried (sodium sulfate), and evaporated to a crystalline mass, which on recrystallization from ethanol–chloroform afforded **18** (1.65 g, 88%), m.p. 217–218.5°, $[\alpha]_D^{24}$ +20.5° (*c* 1.8, chloroform).

Anal. Calc. for $C_{28}H_{35}IO_{14}$: C, 46.55; H, 4.88; I, 17.56. Found: C, 46.71; H, 4.70; I, 17.72.

*Methyl 2,3-di-*O*-acetyl-6-deoxy-6-iodo-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**6**). — A solution of **18** (1.5 g) in acetic acid (15 ml) was heated at 100°, and water (9.4 ml) was added in small portions within a few min. After heating for 15 min, the solvents were removed by repeated codistillation with toluene to give an amorphous solid, which was treated with 1 : 1 (v/v) pyridine–acetic anhydride (14 ml), and kept overnight at room temperature. The mixture was poured into ice–water, and the precipitate was filtered off, washed with water, and dried. Crystallization from ethanol gave **6** (1.25 g, 84%), m.p. 129–130°, $[\alpha]_D^{24}$ +47.7° (*c* 1.8, chloroform); lit.[1] m.p. 129–130° (ethanol).

*Methyl 2,3-di-*O*-acetyl-6-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**7**). — A solution of **6** (880 mg) in ethanol (30 ml) was mixed with barium carbonate (3 g) and heated to boiling with stirring. A small amount of Raney nickel was then added to the mixture and, after 5 min, hydrazine hydrate (2 ml) was added dropwise during 5 min. The reaction mixture was boiled for 20 min under reflux, and then filtered through a Celite pad, and the filtrate was evaporated to dryness. The residue was dissolved in chloroform, and the solution was successively washed with water, 5% sodium thiosulfate, and water, dried (sodium sulfate), and

evaporated to give a solid, which was crystallized from ethanol to afford **7** (572 mg, 79%), m.p. 121–122°, $[\alpha]_D^{24}$ +46.6° (*c* 1.2, chloroform); lit.[1] m.p. 120–121° (ethanol).

*Methyl 2,3-di-*O*-acetyl-6-bromo-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**19**). — Compound **17** (1.1 g) was heated in hexamethylphosphoric triamide (7 ml) with sodium bromide (2 g) for 4 h at 100°. The cooled mixture was poured into ice–water, and the precipitate that separated was collected by centrifugation and dissolved in chloroform. The solution was washed with water, dried (sodium sulfate), and evaporated. Crystallization from ethanol–chloroform gave **19** (805 mg, 83%), m.p. 215–217°, $[\alpha]_D^{24}$ +13.6° (*c* 1.6, chloroform).

Anal. Calc. for $C_{28}H_{35}BrO_{14}$: C, 49.79; H, 5.22; Br, 11.83. Found: C, 49.96; H, 5.15; Br, 11.97.

*Methyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**20**). — A solution of **17** (1 g) in *N*,*N*-dimethylformamide (20 ml) containing lithium chloride (2 g) was heated for 3 h at 100°. The reaction mixture was processed as described for the preparation of **18**, and the residue was crystallized from ethanol to give **20** (690 mg, 84%), m.p. 218.5–220°, $[\alpha]_D^{24}$ +11.6° (*c* 1.7, chloroform).

Anal. Calc. for $C_{28}H_{35}ClO_{14}$: C, 53.30; H, 5.59; Cl, 5.62. Found: C, 53.44; H, 5.68; Cl, 5.47.

*Methyl 2,3-di-*O*-acetyl-6-azido-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**21**). — Compound **17** (500 mg) was heated in *N*,*N*-dimethylformamide (10 ml) with sodium azide (1 g) for 3.5 h at 100°. The reaction mixture was processed as described for **18** to give **21** (336 mg, 81%), m.p. 139–140° (ethanol), $[\alpha]_D^{24}$ +62.2° (*c* 1.8, chloroform); ν_{max}^{KBr} 2100 cm^{-1} (N_3).

Anal. Calc. for $C_{28}H_{35}N_3O_{14}$: C, 52.75; H, 5.53; N, 6.59. Found: C, 52.88: H, 5.46; N, 6.73.

*Methyl 2,3-di-*O*-acetyl-6-bromo-6-deoxy-4-*O*-(2,3,4,6,-tetra-*O*-acetyl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**10**). — Treatment of **19** (650 mg) in acetic acid (6.5 ml) with water (4 ml) at 100°, followed by acetylation with 1:1 (v/v) pyridine–acetic anhydride (6 ml) and isolation in the usual way, as described for the preparation of **6**, gave **10** (520 mg, 80%), m.p. 128–129.5° (ethanol–2-propanol), $[\alpha]_D^{24}$ +45.1° (*c* 1.2, chloroform).

Anal. Calc. for $C_{25}H_{35}BrO_{16}$: C, 44.72; H, 5.25; Br, 11.90. Found: C, 44.84; H, 5.32; Br, 12.11.

*Methyl 2,3-di-*O*-acetyl-6-chloro-6-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**11**). — Treatment of **20** (550 mg) in acetic acid (5.5 ml) with water (3.5 ml) at 100° and subsequent acetylation with 1:1 (v/v) pyridine–acetic anhydride (6 ml), as described for the preparation of **6**, gave **11** (454 mg, 83%), m.p. 126–127° (2-propanol), $[\alpha]_D^{24}$ +43.8° (*c* 1.6, chloroform).

Anal. Calc. for $C_{25}H_{35}ClO_{16}$: C, 47.89; H, 5.63; Cl, 5.65. Found: C, 47.79; H, 5.55.; Cl, 5.86.

*Methyl 2,3-di-*O*-acetyl-6-azido-6-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-gluco-*

pyranosyl)-β-D-glucopyranoside (**9**). — Sequential treatment of **21** (300 mg) in acetic acid (3 ml) with water (1.9 ml) and with 1:1 (v/v) pyridine–acetic anhydride (3 ml), as just described, gave **9** (229 mg, 77%), m.p. 100–102° (ether–petroleum ether), $[\alpha]_D^{24}$ +73.7° (*c* 1.5, chloroform); lit.[2] m.p. 107–110° (methanol), $[\alpha]_D^{24}$ +73° (*c* 0.5, chloroform).

Methyl 2,3-di-O-acetyl-4-O-(2,3-di-O-acetyl-4,6-di-O-methylsulfonyl-α-D-glucopyranosyl-6-O-p-tolylsulfonyl-β-D-glucopyranoside (**12**). — A solution of **17** (500 mg) in 60% acetic acid (8 ml) was heated for 15 min at 100°, and the solvents were removed by codistillation with toluene. The residue was dried and dissolved in pyridine (3 ml). The solution was treated with methanesulfonyl chloride (1 ml) at −10°, and then kept overnight at 0°. The mixture was processed as described for the preparation of **6**, and the resulting solid was crystallized from ethanol–acetone to give **12** (453 mg, 83%), m.p. 193–195° (dec.), $[\alpha]_D^{24}$ +48.7° (*c* 1.5, chloroform); n.m.r.: τ 6.88 (s, 6 H, 2 $MeSO_2$) and 7.53 (s, 3 H, aryl-CH_3).

Anal. Calc. for $C_{30}H_{42}O_{21}S_3$: C, 43.16; H, 5.07; S, 11.52. Found: C, 43.02; H, 5.15; S, 11.70.

Methyl 6-deoxy-4-O-α-D-glucopyranosyl-β-D-glucopyranoside (**13**), *methyl 6-bromo-6-deoxy-4-O-α-D-glucopyranosyl-β-D-glucopyranoside* (**14**), *and methyl 6-chloro-6-deoxy-4-O-α-D-glucopyranosyl-β-D-glucopyranoside* (**15**). — *O*-Deacetylation of **7** (350 mg), **10** (400 mg), and **11** (350 mg) with 0.5M sodium methoxide (0.1 ml) in anhydrous methanol (10 ml) for 1 h at room temperature, followed by neutralization with Amberlite IR-120 (H^+) ion-exchange resin, gave the corresponding 6-substituted methyl β-maltosides **13**, **14**, and **15**, respectively.

Compound **13** (190 mg, 90%), m.p. 194–195° (ethanol), $[\alpha]_D^{24}$ +74.6° (*c* 0.5, water).

Anal. Calc. for $C_{13}H_{24}O_{10} \cdot H_2O$: C, 43.57; H, 7.31. Found: C, 43.48; H, 7.27.

Compound **14** (225 mg, 87%), m.p. 166–167° (dec.) (ethanol), $[\alpha]_D^{24}$ +69.1° (*c* 1.6, water).

Anal. Calc. for $C_{13}H_{23}BrO_{10} \cdot H_2O$: C, 35.71; H, 5.76; Br, 18.26. Found: C, 35.63; H, 5.69; Br, 18.39.

Compound **15** (193 mg, 88%), m.p. 182–183° (ethanol), $[\alpha]_D^{24}$ +72.6° (*c* 1.2, water).

Anal. Calc. for $C_{13}H_{23}ClO_{10} \cdot H_2O$: C, 39.75; H, 6.42; Cl, 9.03. Found: C, 39.79; H, 6.56; Cl, 9.15.

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