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Note

Selective tritylation of phenyl α- and β-maltosides

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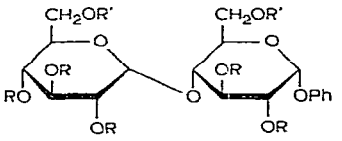
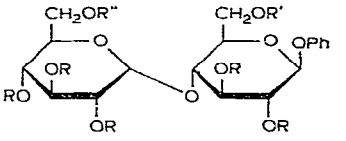
Although preferential reaction of trityl chloride[1–4], methanesulfonyl chloride[5], and *p*-toluenesulfonyl chloride[6–8] has been reported with the primary hydroxyl groups of maltose and its β-glycosides, there is no comparative study on the selective esterification and etherification of the α- and β-glycosides of maltose. We now report on the selective tritylation of phenyl α- and β-maltosides (**1** and **9**).





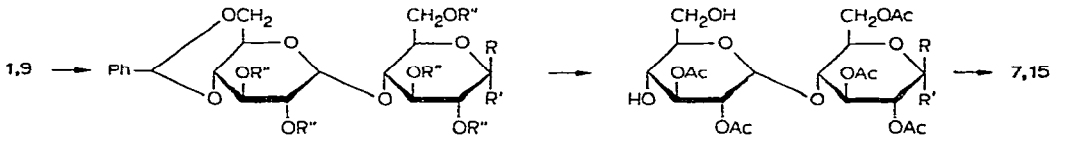
1	R = R' = R" = H	**9**	R = R' = R" = H
2	R = H, R' = R" = Tr	**10**	R = H, R' = R" = Tr
3	R = R' = H, R" = Tr	**11**	R = R' = H, R' = Tr
4	R = R" = H, R' = Tr	**12**	R = R' = H, R' = Tr
5	R = R' = R" = Ac	**13**	R = R' = R" = Ac
6	R = Ac, R' = R" = Tr	**14**	R = Ac, R' = R" = Tr
7	R = R' = Ac, R" = Tr	**15**	R = R' = Ac, R" = Tr
8	R = R" = Ac, R' = Tr	**16**	R = R" = Ac, R' = Tr

Tritylation of the α-anomer (**1**) with 2.2 mol. equiv. of reagent in pyridine gave three compounds, the 6,6'-di-*O*-trityl (**2**), the 6'-mono-*O*-trityl (**3**), and the 6-mono-*O*-trityl (**4**) derivatives in 75.1%, 17.0%, and 1.8% yield, respectively, with complete utilization of the starting sugar. Similar treatment of the β anomer (**9**) also gave the di- and mono-trityl ethers, **10**, **11**, and **12**, in 45.4%, 42.1%, and 2.6% yield, respectively. Treatment of **1** with 1.1 mol. equiv. of trityl chloride gave **2**, **3**, and **4** in 9.3%, 32.4%, and 25.2% yield, respectively, with a considerable amount of starting material, while **9** afforded **10**, **11**, and **12** in 2.4%, 30.7%, and 10.7% yield, respectively.

The structure of these tritylated products was elucidated by elemental analyses, u.v. spectral data, and p.m.r.[9,10]. U.v. molar extinction coefficients and chemical analyses indicated the presence of two trityl groups each in **2** and **10**, and one trityl group each in **3**, **4**, **11**, and **12**. Further, p.m.r. shifts of the methylene groups of the

peracetylated products showed that in all of the products tritylation had taken place at the primary hydroxyl groups.

In the unambiguous synthesis of phenyl 6′-*O*-trityl-α- (**3**) and β-maltosides (**11**), **1** and **9** were converted into 4′,6′-*O*-benzylidene derivatives (**17** and **18**, respectively), which were acetylated to yield **19** and **20**, respectively. Treatment with aqueous acetic acid removed the benzylidene groups to give **21** and **22**, respectively, which



17 R = R" = H, R' = OPh
18 R = OPh, R' = R" = H
19 R = H, R' = OPh, R" = Ac
20 R = OPh, R' = H, R" = Ac

21 R = H, R' = OPh
22 R = OPh, R' = H

with trityl chloride in pyridine, followed by acetylation, gave **7** and **15**, respectively. These two compounds proved to be identical with the peracetylated derivatives of **3** and **11**, respectively. Hence, the two other monoethers are phenyl 6-*O*-trityl-α- and β-maltosides (**4** and **12**, respectively).

The dimolar tritylation of the α-anomer (**1**) gave predominantly the 6,6′-ditritylether (**2**), whereas that of the β-anomer (**9**) gave the 6,6′-diether **10** and 6′-monoether **11** in almost identical yields. The monomolar tritylation of both anomers (**1** and **9**) gave the corresponding 6′-monoethers **3** and **11** as the major products in nearly the same quantity. This result indicates that substitution at C-6′ is not markedly influenced by the steric effects of the distantly located, bulky phenyl aglycon group, in agreement with the results of the partial tritylation of β-maltose[3] and benzyl β-maltoside[4], which led to the preponderant formation of the 6′-monoethers in almost identical yields (~30%). On the basis of the yields of the monomolar tritylation of **1** and **9**, the ratios of 6′- to 6-*O*-trityl substitution were found to be 1.3:1 for the α-anomer (ratio **3** to **4**) and 2.9:1 for the β-anomer (ratio **11** to **12**), demonstrating the great influence of the orientation of the aglycon on the reactivity of O-6, probably due to both steric and electronic effects[11].

EXPERIMENTAL

General. — 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. U.v. spectra were recorded with a Shimadzu UV-200 recording spectrophotometer. P.m.r. spectra were taken on a Hitachi–Perkin–Elmer 90-Hz instrument with tetramethylsilane as internal standard. T.l.c. was performed on silica Gel G (Merck) with the following solvent systems: (A) 45:5:3 ethyl acetate–ethanol–water and (B) 17:3 benzene–ethanol. The spots were

visualized by spraying the air-dried plates with 50% sulfuric acid, followed by heating on a hot plate. Column chromatography was performed on silica gel (Kanto Kagaku Co., 60–80 mesh) with 17:3 benzene-ethanol as eluent. Microanalyses were performed at the College of Pharmacy of Kyoto University.

Acetylation was performed in dry pyridine with an excess of acetic anhydride, overnight at room temperature, unless otherwise stated. Deacetylation was accomplished in dry methanol with 0.5M sodium methoxide, and the resulting solution was neutralized with dry Amberlite IR-120 (H^+) ion-exchange resin. The average yields (calculated on the basis of **1** and **9**) of three experiments of mono- and di-molar tritylations of **1** and **9** were recorded.

Phenyl α- and β-maltosides (**1** *and* **9**). — Phenyl α-maltoside heptaacetate (**5**) was prepared by the procedure reported by Helferich and Peterson[12] and had m.p. 185–186° (from ethanol–chloroform), $[\alpha]_D^{15}$ +171.5° (*c* 1.0, chloroform); lit.[12]: m.p. 184–184.5°, $[\alpha]_D^{24}$ +170.2° (*c* 1.0, chloroform); p.m.r. data (chloroform-*d*): δ 5.63 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.40 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1'), and 3.90–5.28 (m, 12 H, other ring and methylene protons).

Deacetylation of **5** followed by crystallization from ethanol afforded **1**, m.p. 212–213°, $[\alpha]_D^{15}$ +215.3° (*c* 1.86, water), λ_{max}^{MeOH} 260 nm (ε 770); lit.[13]: m.p. 202–204°, $[\alpha]_D^{14.5}$ +211° (*c* 1.3, water).

Phenyl β-maltoside heptaacetate (**13**) was obtained by the method described by Asp and Lindberg[14] and had m.p. 157–158° (from methanol), $[\alpha]_D^{15}$ +44.5° (*c* 1.0, chloroform); lit.[14]: m.p. 154–155.5°, $[\alpha]_D^{20}$ +42° (*c* 2, chloroform); p.m.r. data (chloroform-*d*): δ 3.80–5.40 (m, 14 H, ring and methylene protons).

Deacetylation of **13** gave **9** as a chromatographically homogeneous glass, softening at 97–99°, $[\alpha]_D^{15}$ +50.9° (*c* 1.93, water); λ_{max}^{MeOH} 260 nm (ε 790); t.l.c.: R_F 0.21, Solvent A; lit.[15]: m.p. 96°, $[\alpha]_D^{20}$ +34.0° (*c* 5.1, water).

Tritylation of phenyl α-maltoside (**1**). — To a solution of **1** (3.0 g, 7.17 mmoles) in dry pyridine (15 ml) was added trityl chloride (4.40 g, 15.78 mmoles) and the mixture was stirred at room temperature for 90 h. T.l.c. (Solvent B) showed the product to be composed of three tritylated derivatives having R_F values of 0.55 (**2**), 0.44 (**3**), and 0.30 (**4**), respectively. No starting material was detected. The solution was poured into ice–water and stirred overnight. The precipitate was collected by filtration, washed well with cold water, and dried to give a powder (7.13 g), which was dissolved in boiling methanol (40 ml). On being cooled, crystalline phenyl 6-*O*-trityl-4-*O*-(6-*O*-trityl-α-D-glucopyranosyl)-α-D-glucopyranoside (**2**) was deposited (4.610 g, 71.2%), m.p. 236–237°; $[\alpha]_D^{15}$ +106.8° (*c* 1.41, chloroform); λ_{max}^{MeOH} 259 nm (ε 2100).

Anal. Calc. for $C_{56}H_{54}O_{11}$: C, 74.48; H, 6.03. Found: C, 74.34; H, 6.04.

Acetylation of **2** gave phenyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-glucopyranosyl)-6-*O*-trityl-α-D-glucopyranoside (**6**), m.p. 140–141° (from methanol), $[\alpha]_D^{15}$ +134.4° (*c* 1.89, chloroform); p.m.r. data (chloroform-*d*): δ 5.64 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.37 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1'), 3.24–3.51 (m, 2 H, 6-methylene), and 2.28–3.20 (8-line mult., 2 H, 6'-methylene).

Anal. Calc. for $C_{66}H_{64}O_{16}$: C, 71.21; H, 5.80. Found: C, 71.33; H, 5.75.

The mother liquor from **2** was concentrated to dryness and chromatographed on a column of silica gel (200 g) to give an additional amount of crystalline **2** (250 mg, 3.9%).

Phenyl 4-*O*-(6-*O*-trityl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3**) was then eluted and crystallized from methanol (805 mg, 17.0%), m.p. 134–135°; $[\alpha]_D^{15}$ +116.6° (*c* 1.49, chloroform); λ_{max}^{MeOH} 259 nm (ε 1560).

Anal. Calc. for $C_{37}H_{40}O_{11}$: C, 67.26; H, 6.10. Found: C, 67.09; H, 6.07.

Acetylation of **3** gave the corresponding crystalline hexa-acetate (**7**), which was shown to be identical (m.p. and mixed m.p., p.m.r.) with the compound prepared by an unambiguous route, as described later.

Further elution of the column gave phenyl 4-*O*-α-D-glucopyranosyl-6-*O*-trityl-α-D-glucopyranoside (**4**) as a syrup that was crystallized from methanol (85 mg, 1.8%), m.p. 148–149°; $[\alpha]_D^{15}$ +142.5° (*c* 2.24, chloroform); λ_{max}^{MeOH} 259 nm (ε 1450).

Anal. Calc. for $C_{37}H_{40}O_{11}$: C, 67.26; H, 6.10. Found: C, 66.75; H, 6.08.

Acetylation of **4** afforded phenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-6-*O*-trityl-α-D-glucopyranoside (**8**), m.p. 202–203° (from methanol); $[\alpha]_D^{15}$ +133.1° (*c* 1.82, chloroform-*d*): δ 5.67 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.29 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1'), 3.71–5.18 (m, 10 H, other ring and 6'-methylene protons), and 3.29–3.69 (m, 2 H, 6-methylene).

Anal. Calc. for $C_{49}H_{52}O_{17}$: C, 64.47; H, 5.74. Found: C, 64.17; H, 5.68.

Treatment of **1** (3.0 g, 7.17 mmoles) with 2.20 g (7.89 mmoles) of trityl chloride under similar conditions gave **2** (602 mg, 9.3%), **3** (1.535 g, 32.4%), and **4** (1.194 g, 25.2%).

Tritylation of phenyl β-maltoside (**9**). — Compound **9** (3.0 g) in pyridine (15 ml) was treated with trityl chloride (4.40 g) as described for **1**. T.l.c. (Solvent B) indicated the presence of the three tritylated derivatives having R_F values of 0.55 (**10**), 0.44 (**11**), and 0.30 (**12**). No starting material was observed. Crystallization of the resulting mixture (6.97 g) from methanol (20 ml) gave crystalline phenyl 6-*O*-trityl-4-*O*-(6-*O*-trityl-α-D-glucopyranosyl)-β-D-glucopyranoside (**10**) (1.954 g, 30.2%), m.p. 140–141°; $[\alpha]_D^{15}$ +21.0° (*c* 1.81, chloroform); λ_{max}^{MeOH} 259 nm (ε 2150).

Anal. Calc. for $C_{56}H_{54}O_{11}$: C, 74.48; H, 6.03. Found: C, 74.42; H, 5.99.

Acetylation of **10** gave phenyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-glucopyranosyl)-6-*O*-trityl-β-D-glucopyranoside (**14**), m.p. 155–156° (from methanol); $[\alpha]_D^{15}$ +64.4° (*c* 1.74, chloroform); p.m.r. data (chloroform-*d*): δ 3.22–3.66 (m, 2 H, 6-methylene), and 2.33–3.20 (8-line mult., 2 H, 6'-methylene).

Anal. Calc. for $C_{66}H_{64}O_{16}$: C, 71.21; H, 5.80. Found: C, 70.94; H, 5.83.

Chromatographic fractionation on a column of silica gel (300 g) of the residue from the mother liquor of **10** led to the isolation of an additional amount of crystalline **10** (985 mg, 15.2%), of amorphous phenyl 4-*O*-(6-*O*-trityl-α-D-glucopyranosyl)-β-D-glucopyranoside (**11**) (1.995 g, 42.1%), and crystalline phenyl 4-*O*-α-D-glucopyranosyl-6-*O*-trityl-β-D-glucopyranoside (**12**) (123 mg, 2.6%).

Compound **11** was a single component, as shown by t.l.c. (Solvent B), but could not be crystallized, $[\alpha]_D^{15}$ +26.6° (*c* 1.66, chloroform); λ_{max}^{MeOH} 259 nm (ε 1610).

Anal. Calc. for $C_{37}H_{40}O_{11}$: C, 67.26; H, 6.10. Found: C, 67.26; H, 6.12.

Acetylation of **11** gave the corresponding crystalline hexa-acetate (**15**), which proved to be identical (m.p. and mixed m.p., p.m.r.) with the compound obtained by an unequivocal method, as described later.

Compound **12** had m.p. 183–184°; $[\alpha]_D^{15}$ +30.9° (*c* 1.05, chloroform); λ_{max}^{MeOH} 259 nm (ε 1440).

Anal. Calc. for $C_{37}H_{40}O_{11}$: C, 67.26; H, 6.10. Found: C, 67.19; H, 6.10.

Acetylation of **12** afforded phenyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-6-*O*-trityl-β-D-glucopyranoside (**16**) as a white solid, softening at 107–109°; $[\alpha]_D^{15}$ +32.3° (*c* 1.67, chloroform); p.m.r. data (chloroform-*d*): δ 3.78–5.33 (m, 14 H, ring and 6′-methylene protons), and 3.29–3.69 (m, 2 H, 6-methylene).

Anal. Calc. for $C_{49}H_{52}O_{17}$: C, 64.47; H, 5.74. Found: C, 64.43; H, 5.86.

Treatment of **9** (3.0 g) with 2.20 g (7.89 mmoles) of trityl chloride under similar conditions gave **10** (155 mg, 2.4%), **11** (1.455 g, 30.7%), and **12** (507 mg, 10.7%).

*Phenyl 4-*O*-(4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-α- and β-*D*-glucopyranosides* (**17** *and* **18**) *and phenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-*D*-glucopyranosyl)-α- and β-*D*-glucopyranosides* (**19** *and* **20**). — A suspension of **1** (10 g) and anhydrous zinc chloride (8 g) in freshly distilled benzaldehyde (50 ml) was stirred at room temperature for 72 h. The solution was poured into cold water–petroleum ether with vigorous stirring to give a viscous, syrupy product. This was dissolved in the minimum volume of ethanol, and the ethanol solution was again poured into ice–water. The precipitate was filtered off, washed with cold water, and then with cold petroleum ether, and dried to yield crude **17** as a powder (11.6 g, 95.5%). A portion of it (8 g) was dissolved in dry pyridine (25 ml), acetic anhydride (25 ml) was added, and the mixture was kept at room temperature for 24 h, and then heated on a boiling water-bath for 2 h under anhydrous conditions. The cooled reaction mixture was poured into ice–water, and the white precipitate was filtered off, washed well with water, and dried. Crystallization from methanol gave **19** (10.4 g, 91.9%), m.p. 187–188°; $[\alpha]_D^{15}$ +141.9° (*c* 1.83, chloroform); p.m.r. data (chloroform-*d*): δ 5.44 (s, 1 H, benzylic H).

Anal. Calc. for $C_{35}H_{40}O_{16}$: C, 58.66; H, 5.63. Found: C, 58.53; H, 5.69.

Deacetylation of **19** yielded the analytical sample of **17**, $[\alpha]_D^{15}$ +173.8° (*c* 1.54, methanol).

Anal. Calc. for $C_{25}H_{30}O_{11}$: C, 59.28; H, 5.97. Found: C, 59.25; H, 5.85.

Similar treatment of **9** with benzaldehyde and anhydrous zinc chloride gave crude **18** in 93% yield. Subsequent acetylation, as described for **17**, afforded **20** (92%), m.p. 217–218° (from methanol–chloroform), $[\alpha]_D^{15}$ +22.9° (*c* 1.57, chloroform); p.m.r. data (chloroform-*d*): δ 5.44 (s, 1 H, benzylic H).

Anal. Calc. for $C_{35}H_{40}O_{16}$: C, 58.66; H, 5.63. Found: C, 58.35; H, 5.69.

Deacetylation of **20** furnished the analytical sample of **18**, $[\alpha]_D^{15}$ +26.4° (*c* 1.96, methanol).

Anal. Calc. for $C_{25}H_{30}O_{11}$: C, 59.28; H, 5.97. Found: C, 59.38; H, 6.08.

*Phenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-α-*D*-glucopyranosyl)-α- and β-*D*-*

glucopyranosides (**21** *and* **22**). — A solution of **19** (5 g) in acetic acid (40 ml) was heated on a boiling water-bath, and water (25 ml) was added in small portions within a few min. After heating for 20 min, the solvents were evaporated under reduced pressure, and the last traces of volatile compounds were removed by repeated codistillation with toluene to give **21** (4.2 g, 96%) as an amorphous powder, $[\alpha]_D^{15}$ +170.4° (*c* 1.80, chloroform).

Anal. Calc. for $C_{28}H_{36}O_{16}$: C, 53.50; H, 5.77. Found: C, 53.65; H, 5.77.

Removal of the benzylidene group of **20** as just described gave **22** in 85% yield as an amorphous powder, $[\alpha]_D^{15}$ +35.4° (*c* 1.92, chloroform).

Anal. Calc. for $C_{28}H_{36}O_{16}$: C, 53.50; H, 5.77. Found: C, 53.75; H, 5.79.

*Phenyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-trityl-*α*-*D*-glucopyranosyl)-α- and β-*D*-glucopyranosides* (**7** *and* **15**). — To a solution of **21** (2 g) in dry pyridine (10 ml) was added trityl chloride (1.54 g) and the mixture was maintained at room temperature for 72 h. Acetic anhydride (7 ml) was added to the cooled solution, and the solution was again kept overnight at room temperature, and then poured into ice–water. The precipitate was filtered off and crystallized from ethanol to give **7** (2.44 g, 84%), m.p. and mixed m.p. 202–203°, $[\alpha]_D^{15}$ +133.1° (*c* 1.82, chloroform); p.m.r. data (chloroform-*d*): δ 5.62 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.44 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1'), 3.82–5.36 (m, 10 H, other ring and 6-methylene protons), and 2.87–3.36 (8-line mult., 2 H, 6'-methylene).

Anal. Calc. for $C_{49}H_{52}O_{17}$: C, 64.47; H, 5.74. Found: C, 64.33; H, 5.73.

In a similar manner, treatment of **22** with trityl chloride in pyridine and subsequent acetylation gave **15** (87%), m.p. and mixed m.p. 235–236° (from ethanol), $[\alpha]_D^{15}$ +64.4° (*c* 1.74, chloroform); p.m.r. data (chloroform-*d*): δ 3.73–5.51 (m, 14 H, ring and 6-methylene protons), and 2.33–2.88 (8-line mult., 6'-methylene).

Anal. Calc. for $C_{49}H_{52}O_{17}$: C, 64.47; H, 5.74. Found: C, 64.38; H, 5.78.

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