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Note

Syntheses of (1→3)-, (1→4)-, and (1→5)-linked disaccharides from tritylated monosaccharides

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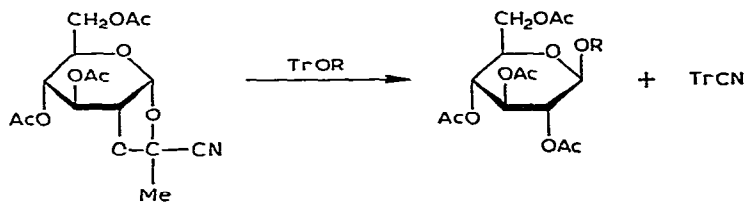
The synthesis of gentiobiose octa-acetate[1] *via* 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)-α-D-glucopyranose[2] (**1**) demonstrated the potential utility of this method of glycosylation. 6-*O*-Trityl sugar derivatives were used as the aglycons in this and Bredereck[3] syntheses of (1→6)-linked disaccharides. We now report on the reaction of secondary trityl ethers with **1**.



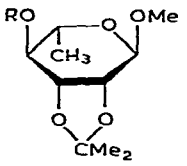
1

Such trityl ethers were synthesised by treatment[4] of the sugar derivatives **2**–**7** with triphenylmethylium perchlorate[5] in the presence of the sterically hindered base 2,6-di-*tert*-butyl-4-methylpyridine[6], which is more readily available than the 2,4,6-tri-*tert*-butylpyridine used previously[4]. Tritylation proceeded smoothly to yield the products **8**–**13**, which were isolated by column chromatography and characterised by p.m.r. spectroscopy. The location of the trityl group at O-5 in **10** was proved by conventional methylation analysis (deacetylation, Hakomori methylation[7], acid hydrolysis, borohydride reduction, and acetylation), which afforded 3,6-di-*O*-methylglucitol tetra-acetate identified by g.l.c.–m.s.

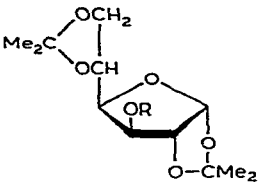
Tritylation of **7** gave rise to two monotrityl derivatives in the ratio ~1:7, and the major product (equatorial substitution) could be isolated by chromatography either before or after acetylation. The reaction of **21** with acetic anhydride–pyridine proceeded slowly and was incomplete after 20 h at 60°.

The trityl ethers **8**–**13** were glycosylated[1] with **1** in dichloromethane in the presence of triphenylmethylium perchlorate as catalyst at room temperature for 17–20 h; the yields were not optimised. The yield (86%) of the disaccharide derivative **14** from **8** exceeded that obtainable in the Helferich synthesis[8].

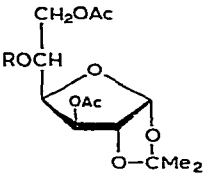
Glycosylation of **13** afforded 51% of **18**, and **13** is a convenient aglycon for the synthesis of oligosaccharides containing a 3-*O*-substituted galactose residue. The



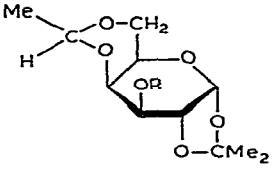
2 R = H
8 R = Tr
14 R = R'



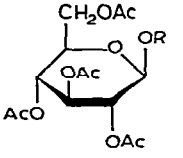
3 R = H
9 R = Tr
15 R = R'



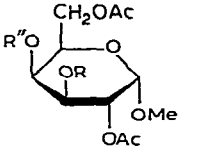
4 R = H
10 R = Tr
16 R = R'



5 R = H
11 R = Tr

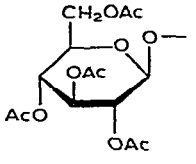


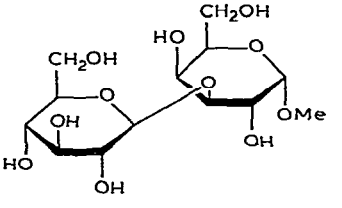
6 R = H
12 R = Tr
17 R = R'



7 R = H, R'' = H
13 R = Tr, R'' = Ac
18 R = R', R'' = Ac
21 R = Tr, R'' = H

R' =





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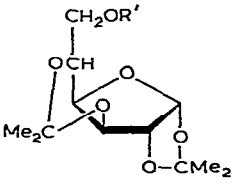

20

group. The structure of **20** was proved by its conversion into gentiobiose octa-acetate.

The attempted glycosylation of **11** failed, which may be due to the instability of the 4,6-*O*-ethylidene group under the reaction conditions. Triphenylmethylium perchlorate can abstract hydride ions from analogous systems, with the creation of cyclic acyloxonium ions[12].

Condensation of **10** with **1** gave 21.5% of the (1→5)-linked disaccharide derivative **16**, which has properties in accord with those of the product synthesised by the ortho-ester method[13].

Glycosylation of **12** yielded ~65% of trehalose derivatives, but was accompanied by a loss of stereospecificity, since the octa-acetates of β,β- and α,β-trehalose were subsequently isolated in yields of 11 and 9%, respectively. This result may be attributed to easy anomerisation of **12** under the reaction conditions.

The foregoing results demonstrate the utility of secondary trityl ethers of sugars as aglycons in oligosaccharide synthesis, which is limited only by the instability of certain protecting groups towards the glycosylating agent and/or the catalyst.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter for 1% solutions in chloroform, unless otherwise stated. T.l.c. was performed on silica gel LS 5/40 μm with detection by charring with sulphuric acid. Column chromatography was performed on alumina or silica gel L 100/160 μm. G.l.c.–m.s. was performed with a Varian MAT 111 "Gnom" instrument and a column of 3% of SE-30 on Diatomite CQ (100–200 mesh). P.m.r. spectra (internal Me_4Si) were recorded with a Tesla BS 497 (100-MHz) instrument, and ^{13}C-n.m.r. spectra [D_2O, internal Me_2SO (δ 39.45 p.p.m. relative to Me_4Si)] with a Bruker-Physik WP-60 instrument. Dichloromethane was distilled from calcium hydride before use. Solutions were concentrated *in vacuo* at 40°.

Tritylation reactions. — Dichloromethane (15 ml) was severally added to mixtures of **2–6** (3 mmol), 2,6-di-*tert*-butyl-4-methylpyridine[6] (615 mg, 3 mmol), and triphenylmethylium perchlorate[5] (1.04 g, 3 mmol), which were stored for 30 min at room temperature. Pyridine (0.1 ml) and methanol (0.1 ml) were then added, the mixture was concentrated, and the residue was eluted from alumina [light petroleum→light petroleum–ether (1 : 1) gradient] to give the following compounds.

Methyl 2,3-*O*-isopropylidene-4-*O*-trityl-α-L-rhamnopyranoside (**8**; 650 mg, 47%), R_F 0.21 (benzene), $[\alpha]_D$ −68.5° (*c* 2). P.m.r. data (CCl_4): δ 7.85–7.06 (m, 15 H, 3 Ph), 4.50 (s, 1 H, H-1), 3.32 (s, 3 H, OMe), 1.15, 1.04 (2 s, 6 H, CMe_2), and 0.92 (d, 3 H, *J* 6.4 Hz, Me of rhamnose).

Anal. Calc. for $C_{29}H_{32}O_5$: C, 75.62; H, 7.00. Found: C, 75.29; H, 7.50.

1,2 : 5,6-Di-*O*-isopropylidene-3-*O*-trityl-α-D-glucofuranose (**9**, 69%), m.p. 120–123°, $[\alpha]_D$ −23.5°; lit.[4] m.p. 120–122°, $[\alpha]_D$ −19.5°.

4,6-*O*-Ethylidene-1,2-*O*-isopropylidene-3-*O*-trityl-α-D-galactopyranose (**11**, 64%), m.p. 146–147° (from methanol), $[\alpha]_D$ +60°. P.m.r. data (CCl_4): δ 7.90–7.04 (m,

15 H, 3 Ph), 5.80 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1), 1.33, 1.17 (2 s, 6 H, CMe_2), and 1.26 (d, 3 H, *Me*CH).

Anal. Calc. for $C_{30}H_{32}O_6$: C, 73.74; H, 6.60. Found: C, 73.90; H, 6.77.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-trityl-β-D-glucopyranose (**12**, 51%), m.p. 145° (from benzene–light petroleum), R_F 0.57 (benzene–ether 3:2), $[\alpha]_D$ −21°. P.m.r. data (CCl_4): δ 7.78–7.41 (m, 15 H, 3 Ph), 4.45 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), and 2.32–2.14 (12 H, 4 OAc).

Anal. Calc. for $C_{33}H_{34}O_{10}$: C, 67.10; H, 5.80. Found: C, 67.25; H, 6.02.

3,6-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-trityl-α-D-glucofuranose (**10**, 70%). R_F 0.4 (ether–benzene 1:6), $[\alpha]_D$ −35°. P.m.r. data (CCl_4): δ 7.46–7.08 (m, 15 H, 3 Ph), 5.62 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 1.92, 1 72 (2 s, 6 H, 2 OAc), 1.37, and 1.22 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{33}H_{34}O_8$: C, 70.31; H, 6.13. Found: C, 70.88; H, 6.24.

*Methyl 2,4,6-tri-*O*-acetyl-3-O-trityl-α-D-galactopyranoside* (**13**). — Tritylation of **7** (835 mg, 3 mmol), with elution of the product from silica gel with a gradient benzene→ether, gave an uncharacterised product (90 mg; R_F 0.26, benzene–ether 1:3), and a main product (R_F 0.31) that was crystallised from ether to give methyl 2,6-di-*O*-acetyl-3-*O*-trityl-α-D-galactopyranoside (**21**: 750 mg, 47%), m.p. 165–166°, $[\alpha]_D$ +77°.

Anal. Calc. for $C_{30}H_{32}O_8$: C, 69.21; H, 6 20. Found: C, 69.62; H, 6.36.

A solution of **21** (300 mg) in pyridine (5 ml) and acetic anhydride (3 ml) was kept at 60° for 20 h, diluted with chloroform, washed with saturated, aqueous sodium hydrogen carbonate and water, and concentrated. The residue was crystallised from ether–light petroleum to give **13** (210 mg, 65%), m.p. 195–197°, $[\alpha]_D$ +112.5°, R_F 0.47 (benzene–ether 3:1). P.m.r. data ($CDCl_3$): δ 7.50–7.19 (m, 15 H, 3 Ph), 4.91 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 3.23 (s, 3 H, OMe), 2.22, 1.97, and 1.90 (3 s, 9 H, 3 OAc)

Anal. Calc. for $C_{32}H_{34}O_9$: C. 68.31; H, 6.09. Found: C, 67.91; H, 6.05.

In a separate tritylation of **7** (3 mmol), the reaction mixture was diluted with ether (20 ml), filtered, and evaporated. The residue was treated with acetic anhydride (5 ml) and pyridine (10 ml) at 60° for 20 h and at room temperature for 5 days. The product was processed in the usual manner, and chromatography on silica gel (benzene→ether gradient) then gave crystalline **13** in 32% yield.

Glycosylation reactions. — Condensation of **8**–**13** (0.52–0.55 mmol) severally with 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)-α-D-glucopyranose[2] (**1**; 187 mg, 0.52 mmol) in the presence of triphenylmethylium perchlorate (17 mg, 0.05 mmol) in dichloromethane (4 ml) for 17–20 h at room temperature was performed by a high-vacuum technique[1], and the following disaccharide derivatives were isolated by column chromatography on silica gel with a benzene→ether gradient.

Methyl 2,3-*O*-isopropylidene-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-L-rhamnopyranoside (**14**, 86%), m.p. 158–159° (from ethanol), $[\alpha]_D$ −28°, lit.[8] m.p. 158.5–159°, $[\omega]_D$ −30.6°.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucofuranose (**15**; 45 mg, 15%), R_F 0.37 (benzene–ether, 2:3), m.p. 132–134°

(from ether–light petroleum) $[\alpha]_D$ −20°; lit.[11] m.p. 132–134°, $[\alpha]_D$ −21°. Formed together with **15** was 1,2:3,5-di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucofuranose (**20**, 35%), R_F 0.43 (benzene–ether, 2:3), $[\alpha]_D$ +4°. P.m.r. data ($CDCl_3$): δ 5.95 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1 of glucofuranose), 2.10, 2.02, 2.00, 1.96 (4 s, 12 H, 4 OAc), 1.52, 1.48, and 1.36 (3 s, 12 H, 2 CMe_2).

Compound **20** (100 mg) was deacetylated with methanolic sodium methoxide, the solution was deionised with KU-2 (H^+) resin and concentrated, and the residue was treated with aqueous 90% trifluoroacetic acid (1 ml) for 1 h at room temperature. The solution was concentrated and the residue was treated conventionally with acetic anhydride–sodium acetate (2 h, 100°) to give β-gentiobiose octa-acetate (11 mg), m.p. 196–197° (from ethanol), $[\alpha]_D$ −5°; lit.[1] m.p. 193–196°, $[\alpha]_D$ −4.5°.

3,6-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-α-D-glucofuranose (**16**, 21.5%), m.p. 172–173° (from ether), $[\alpha]_D$ −23.5°; lit.[13] m.p. 173°, $[\alpha]_D$ −28°.

Column chromatography of the product obtained on glycosylation of **12** gave a mixture of isomeric trehalose octa-acetates (220 mg, 65%). Further chromatography on silica gel (elution with ether) gave β,β trehalose octa-acetate (**17**; 37 mg, 11%), m.p. 182°, $[\alpha]_D$ −13° (lit.[14] m.p. 181.5–182.5°, $[\alpha]_D$ −16.8°), and α,β-trehalose octa-acetate (31 mg, 9%), m.p. 139–140°, $[\alpha]_D$ +69.5° (lit.[14] m.p. 140–141°, $[\alpha]_D$ +79.6°).

Elution from silica gel (with a gradient benzene→ether→chloroform) of the product obtained on glycosylation of **13** gave methyl 2,4,6-tri-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (**18**; 200 mg, 51%), m.p. 163–165° (from ethanol), $[\alpha]_D$ +78°.

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.84; H, 5.88. Found: C, 49.88; H, 5.97.

Conventional deacetylation of **18**, with crystallisation of the product from ethanol, afforded methyl 3-*O*-β-D-glucopyranosyl-α-D-galactopyranoside (**19**), m.p. 210–211°, $[\alpha]_D$ +103° (*c* 1, water).

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