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PHASE-TRANSFER CATALYSED SYNTHESIS OF 4-*S*-β-D-GLUCOPYRANOSYL-4-THIO-D-GLUCOPYRANOSE (THIOCELLOBIOSE) AND 2-*S*-β-D-GLUCOPYRANOSYL-2-THIO-D-GLUCOPYRANOSE (THIOSOPHOROSE)

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ABSTRACT

Syntheses of the potential enzyme-inducers thiocellobiose (**7**) and thiosophorose (**11**) are described. The intermediates methyl 2,3,6-tri-*O*-benzoyl-4-*O*-trifluoromethylsulfonyl-α-D-galactopyranoside and 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethylsulfonyl-β-D-mannopyranose were obtained in good yield from methyl α-D-galactopyranoside or 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose. The stereoselective reaction of the triflates with the sodium salt of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose was performed under phase-transfer conditions. Transesterification of methyl 2,3,6-tri-*O*-benzoyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (after selective acetolysis) and 1,3,4,6-tetra-*O*-acetyl-2-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thio-β-D-glucopyranose afforded **7** and **11**.

INTRODUCTION

Thiocellobiose is an inducer of cellulose-degrading enzymes[1]. There are only a few reports on the synthesis of reducing thiodisaccharides[1-3], although several preparations of the corresponding methyl glycosides have been published[4]. Syntheses of thiocellobiose (**7**) and thiosophorose (**11**) are now reported.

RESULTS AND DISCUSSION

The syntheses were based on the S_N2 reaction of the sodium salt of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**4**) with methyl 2,3,6-tri-*O*-benzoyl-4-*O*-trifluoromethylsulfonyl-α-D-galactopyranoside[3] (**3**) or 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethylsulfonyl-β-D-mannopyranose (**9**) in the presence of a phase-transfer catalyst.

Selective benzoylation of methyl α-D-galactopyranoside (**1**) gave methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[5,6] (**2**), which, with trifluoromethylsul-

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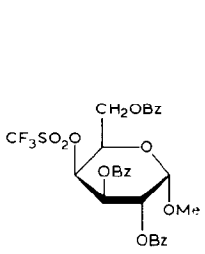

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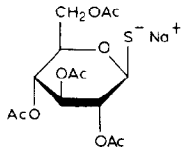

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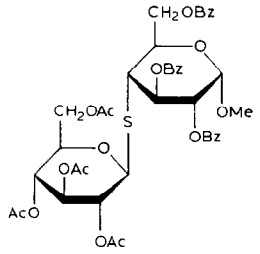

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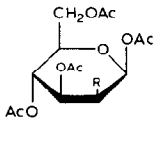
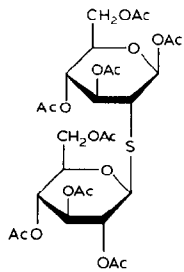
fonic anhydride, afforded crystalline **3**. Reaction of **3** with the sodium salt of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**4**) was carried out in anhydrous tetrahydrofuran in the presence of catalytic amounts of 1,7,10-trioxa-4,13-diazacyclopentadecane (Kryptofix® 21) and was complete at room temperature in less than 1 h. The crystalline product, methyl 2,3,6-tri-*O*-benzoyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-thio-α-D-glucopyranoside (**5**), was easily isolated (~75%). Benzene and dibenzo-18-crown-6 was a less effective reaction medium, and the product **5** was not so easily isolated.

Acetolysis of **5** at 40° with acetic anhydride–acetic acid containing 5% of sulfuric acid gave crystalline 1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-thio-α,β-D-glucopyranose (**6**, ~85%). Treatment of **6** with sodium methoxide in methanol afforded amorphous thiocellobiose (**7**).

The intermediate 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethylsulfonyl-β-D-mannopyranose (**9**), required for the synthesis of thiosophorose, was obtained by selective acetylation of D-mannose, to give 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose[7] (**8**), followed by triflation at −20° in dichlormethane. Phase-transfer catalysed glycosidation of **9** with the sodium salt of **4** was accomplished in anhydrous tetrahydrofuran, but using equimolar amounts of Kryptofix® 21 and **4** (the cryptate could be extracted from the reaction mixture and used again after purification). After reaction for 20 h, only ~30% of 1,3,4,6-tetra-*O*-acetyl-2-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thio-β-D-glucopyranose (**10**) was obtained. De-esterification of **10**, as described above, gave crystalline thiosophorose (**11**).



9 R = OSO_2CF_3



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The phase-transfer reaction of suitable sugar triflates with the sodium salt of thio sugar derivatives, using cryptates or crown ethers as catalysts, offers a general route to thiodisaccharides.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi 510 apparatus. N.m.r. spectra (^1H at 400 MHz, ^{13}C at 100 MHz) were recorded for solutions in $CDCl_3$ and D_2O (internal Me_4Si). I.r. spectra were recorded with a Pye Unicam SP 1000 spectrophotometer, using potassium bromide discs. Optical rotations were determined at 20° with a Perkin–Elmer polarimeter 241. T.l.c. was performed on silica gel 60 (Merck) with ether and detection by charring with sulfuric acid. The unblocked sugar derivatives were separated by using ethyl acetate–water–1-propanol (1:4:7) and detection with orcinol–sulfuric acid. Organic solvents were dried over 3 A molecular sieves. Tetrahydrofuran was dried with sodium, distilled, and stored over sodium hydride. Inert reaction environments were obtained by using deoxygenated (pyrogallol) nitrogen which was dried over 5 A molecular sieves. All organic solutions were concentrated under reduced pressure at <40°.

*Methyl 2,3,6-tri-*O*-benzoyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-4-thio-α-*D*-glucopyranoside* (**5**). — Sodium hydride (90 mg, 3 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (4.1 g, 2.75 mmol) in dry tetrahydrofuran (130 mL) at 20°. The suspension was stirred in an inert atmosphere until hydrogen formation had ceased. Kryptofix® 21 (0.12 g, 0.55 mmol) was then added followed dropwise by a solution of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-trifluoromethylsulfonyl-α-D-galactopyranoside (**3**; 1.6 g, 2.75 mmol) in dry tetrahydrofuran (20 mL). After being stirred for 1 h at room temperature, the mixture was filtered and concentrated, and the residue was crystallised from ethanol (40 mL), to give **5** (1.8 g, 75%), m.p. 194–195°, $[\alpha]_D^{20}$ +60° (*c* 1, chloroform), R_F 0.49 (ether); ν_{max}^{KBr} 1720 (Bz) and 1750 cm^{-1} (Ac). N.m.r. data: ^1H, δ 8.10–7.97 and 7.62–7.35 (m, 15 H, 3 Ph), 6.02 (dd, 1 H, $J_{2,3}$ 9.7, $J_{3,4}$ 11.2 Hz, H-3), 5.22 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 9.4 Hz, H-3'), 4.99 (d, 1 H, $J_{1',2'}$ 10.1, $J_{2',3'}$ 9.4 Hz, H-1'), 3.47 (s, 3 H, OMe), 3.33 (t, 1 H, $J_{3,4} = J_{4,5}$ = 11.2 Hz, H-4), 2.05–1.96 (3 s, 9 H, 3 OAc), and 1.60 (s, 3 H, OAc); ^{13}C, 97.3 (C-1), 81.4 (C-1'), 46.4 (C-4), 68.1 (C-4'), and 55.6 (OMe).

Anal. Calc. for $C_{42}H_{44}O_{17}S$: C, 59.15; H, 5.20; S, 3.76. Found: C, 58.97; H, 5.16; S, 3.48.

*1-*O*-Acetyl-2,3,6-tri-*O*-benzoyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-4-thio-α,β-*D*-glucopyranose* (**6**). — Compound **5** (2 g, 2.3 mmol) was added to a mixture of acetic anhydride (26 mL), glacial acetic acid (12 mL), and conc. sulfuric acid (5 mL). After the solid had dissolved, the mixture was heated for 10 min at 40°, and then added to a stirred mixture of crushed ice (100 mL) and pyridine (20 mL). The amorphous solid was collected, washed with water, and crystallised from

ethanol, to give **6** (1.7 g, 82.3%), m.p. 228° (dec.), $[\alpha]_D^{20}$ +55° (*c* 1, chloroform), R_F 0.36 and 0.39 (ether).

Anal. Calc for $C_{43}H_{44}O_{18}S$: C, 58.64; H, 5.03; S, 3.64. Found: C, 58.65; H, 5.02; S, 3.68.

Thiocellobiose (**7**). — Compound **6** (1.7 g, 1.93 mmol) was stirred with methanolic sodium methoxide (300 mL from ~350 mg of sodium) overnight at room temperature. The solution was neutralised with Bio-Rad AG 50W-X8 (H^+) resin, filtered, and concentrated. Water (100 mL) was added to the syrupy residue, and the mixture was extracted with chloroform (30 mL). The aqueous layer was concentrated under reduced pressure and the residue dried over phosphorus pentaoxide. A solution of the glassy product in methanol (15 mL) was added dropwise to ether (100 mL), to give **7** as a white, hygroscopic solid (0.53 g, 73%), m.p. 175°, $[\alpha]_D^{20}$ −16° (*c* 1, water), R_F 0.46 (ethyl acetate–water–1-propanol).

Anal. Calc for $C_{12}H_{22}O_{10}S$: C, 40.22; H, 6.19; S, 8.95. Found: C, 39.86; H, 6.41; S, 8.53.

1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethylsulfonyl-β-D-mannopyranose (**9**). — To a solution of 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose (3.14 g, 9 mmol) in dry dichloromethane (80 mL) and pyridine (1.7 mL) was added trifluoromethanesulfonic anhydride (3.4 mL, 2.1 mmol) dropwise at −20°. The yellow–green suspension was allowed to attain room temperature during 1 h, washed successively with cold water, saturated aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was crystallised twice from ethanol, to give **9** (2.6 g, 60%), m.p. 120°, $[\alpha]_D^{20}$ −16° (*c* 1, chloroform), R_F 0.38 (ether).

Anal. Calc. for $C_{15}H_{19}F_3O_{12}S$: C, 37.3; H, 3.96; S, 6.63. Found: C, 37.8; H, 4.07; S, 7.33.

1,3,4,6-Tetra-O-acetyl-2-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2-thio-β-D-glucopyranose (**10**). — Sodium hydride (33.5 mg, 1.1 mmol) was added at 20° to a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (0.37 g, 1 mmol) in dry tetrahydrofuran (50 mL) in an inert atmosphere. After the hydrogen formation had ceased, Kryptofix® 21 (0.21 g, 1 mmol) was added, followed dropwise by a solution of **9** (0.5 g, 1.05 mmol) in tetrahydrofuran (20 mL) within ~5 min. After 5 h at room temperature, the suspension was filtered and concentrated. The residue was treated with ether (50 mL), and the mixture was extracted with water (3 × 10 mL); the phase-transfer catalyst is recoverable from the aqueous phase. The ether extract was concentrated, and the residue was dried over phosphorus pentaoxide and crystallised from ether, to give **10** (0.16 g, 25%), m.p. 160–161°, $[\alpha]_D^{20}$ +4° (*c* 1, chloroform), R_F 0.21 (ether). N.m.r. data: ^1H, 5.69 (d, 1 H, $J_{1,2}$ 9 Hz, H-1), 4.70 (d, 1 H, $J_{1',2'}$ 10 Hz, H-1'), 3.10 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), and 1.99–2.15 (8 s, 24 H, 8 OAc).

Anal. Calc. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.51; S, 4.62. Found: C, 48.10; H, 5.73; S, 4.98.

Thiosophorose (**11**). — A solution of **10** (0.2 g, 0.3 mmol) in methanolic

sodium methoxide (15 mL, from 25 mg of sodium) was stirred for 1 h at 20°, neutralised with AG 50W-X8 (H^+) resin, and concentrated. The residue was dried over phosphorus pentaoxide, dissolved in dry methanol (3 mL), and added dropwise to ether (20 mL), to give **11** as a white, hygroscopic solid (90 mg, 87%), m.p. 102°, $[\alpha]_D^{20}$ −23° (*c* 1, water), R_F 0.62 (ethyl acetate–water–1-propanol).

Anal. Calc. for $C_{12}H_{22}O_{10}S$: C, 40.22; H, 6.19; S, 8.95. Found: C, 39.83; H, 6.24; S, 8.73.

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