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Note

8-Methoxycarbonyloctyl 2-*O*-α-D-glucopyranosyl-α-D-glucopyranoside

GERALD O. ASPINALL AND MUKUND K. GURJAR
Department of Chemistry, York University, Downsview, Toronto, Ontario M3J 1P3 (Canada)
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8-Methoxycarbonyloctyl glycosides of several oligosaccharides have been prepared to provide the linker arm for attachment of sugar sequences of defined structure and configuration to carrier proteins[1–3]. The majority of such substances have contained the *trans*-1,2-β-D-glycosidic linkage to the linker arm. We describe here experiments on the synthesis of 8-methoxycarbonyloctyl α-kojibioside with a high degree of anomeric purity. Insofar as few syntheses of kojibiose derivatives have been reported with high stereoselectivity (see ref. 4), the preparation of the title compound requires attention to anomeric purity at both glycosidic linkages. We have therefore re-examined the synthesis of kojibiose derivatives and then compared the formation of the title compound by stepwise synthesis and by direct glycosylation using the 2-*O*-glycosyl substituent as a non-participating group[5].

Igarashi *et al.*[4] have reported the stereoselective synthesis of α-kojibiose octaacetate by condensation of 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-β-D-glucopyranosyl chloride with 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose in the presence of silver perchlorate and *sym*-collidine in ether solution, followed by hydrogenation and acetylation. We have found that similar, or slightly improved, yields are obtained using the more accessible 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride[6] by performing the reaction with silver perchlorate and silver carbonate in dichloromethane solution in preference to ether. Alternatively, the same kojibiose derivative was obtained from condensation of the *O*-β-D-glycosyl imidiate, 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*N*-methylphenyl)diphenylacetamidyl-β-D-glucopyranose[7] with the same aglycon under the conditions described by Schmidt and Michel[7] in dichloromethane in the presence of *p*-toluenesulfonic acid and 4Å molecular sieves. In both cases, the resulting tetra-*O*-acetyl-tetra-*O*-benzyl derivative was converted into α-kojibiose octaacetate in essentially quantitative yield.

For the stepwise preparation of the disaccharide glycoside **5**, 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl chloride[8] was used as glycosylating agent for reaction with 8-methoxycarbonyloctanol in dichloromethane under the conditions already described. The anomeric purity of the syrupy product (**1**), as for other

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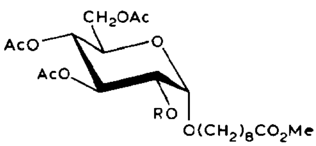
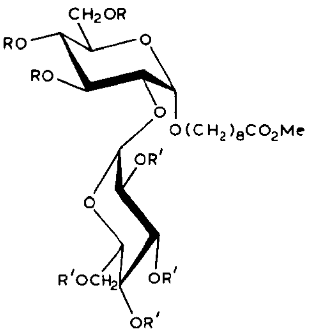


1 R = Bn
2 R = H



3 R = Ac, R' = Bn
4 R = H, R' = Bn
5 R = R' = H
6 R = R' = Ac

compounds in this series, was established by ^{13}C-n.m.r. spectroscopy. When the reaction was performed in ether solution, the ^{13}C-n.m.r. spectrum of the product showed signals for anomeric carbon atoms at δ 96.8 and 103.8 p.p.m. in the ratio of 81:19 for the α-D- and β-D-glycosides. The anomerically pure glycoside (**1**) was hydrogenolyzed to give 8-methoxycarbonyloctyl (MCO) 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (**2**). Reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride with the glycoside **2** as aglycon under the Igarashi conditions but using dichloromethane as solvent gave a mixture from which the anomerically pure (by ^{13}C-n.m.r.) 8-MCO 2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (**3**) was obtained by chromatography on silica gel. *O*-Deacetylation of this disaccharide derivative (**3**) gave the crystalline tetrabenzyl ether (**4**), which in turn furnished 8-methoxycarbonyloctyl α-kojibioside (**5**) on hydrogenolysis.

Direct glycosylation of 8-methoxycarbonyloctanol by reaction with hepta-*O*-acetyl-α-D-kojibiosyl bromide in dichloromethane in the presence of silver perchlorate and silver carbonate gave the hepta-*O*-acetyl derivative (**6**) from which 8-MCO α-kojibioside (**5a**) was obtained on *O*-deacetylation. This sample of the disaccharide glycoside was shown by ^{13}C-n.m.r. to contain traces (~5%) of the β-D anomer.

EXPERIMENTAL

General methods. — Evaporations were conducted under diminished pressure at 40° or less. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter at 20 ±2°. N.m.r. spectra were recorded at 60 MHz (for ^{1}H) with a Varian EM-360 spectrometer and at 20 MHz (for ^{13}C) with a Varian CFT-80A spectrometer for solutions in chloroform-*d* containing 1% of tetramethylsilane as the internal standard, unless otherwise stated. Light petroleum refers to the fraction of b.p. 30–60°.

α-Kojibiose octaacetate. — Freshly prepared 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride[6] (2.5 g) in dichloromethane (20 mL) was added to a stirred mixture of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose[9] (1.53 g), silver perchlorate (0.92 g), silver carbonate (3.5 g), and Drierite (5 g) in dichloromethane (40 mL) at 0°. The mixture was stirred for 4 h and kept overnight at 0°, and then filtered through Celite. The filtrate was washed with water, dried, and evaporated to a residue that was chromatographed on silica gel with elution with 2:1 ether–light petroleum to give syrupy 1,3,4,6-tetra-*O*-acetyl-2′,3′,4′,6′-tetra-*O*-benzyl-α-kojibiose (2.4 g, 62%), $[\alpha]_D$ +94° (*c* 1.0, chloroform): n.m.r.: δ 1.99, 2.06, 2.10, 2.16 (s, each 3 H, 4 OAc), 7.33 (m, 20 H, 4 Ph), 6.55 (d, 1 H, $J_{1,2}$ 4 Hz, H-1); δ_C 95.22 (C-1), 88.09 (C-1′).

Freshly prepared 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*N*-4-methylphenyl)diphenylacetimidyl-β-D-glucopyranose[7] (1.2 g) was added to a stirred mixture of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (0.51 g), anhydrous *p*-toluenesulfonic acid (0.4 g), and 4Å molecular sieves (4 g) in dichloromethane. The mixture was stirred for 48 h, at which time a further quantity of β-imidate (1.2 g) was added and the mixture was stirred for 48 h. The mixture was filtered, and the filtrate was evaporated to a residue that was chromatographed as before to give tetra-*O*-benzyl-α-kojibiose tetraacetate (0.88 g, 69%), which was indistinguishable from the previous sample.

The tetrabenzyl ether tetraacetate (0.55 g) in ethanol (20 mL) was hydrogenolyzed over 5% palladium-on-charcoal. The filtrate from the mixture was evaporated and the residue was acetylated with acetic anhydride (7 mL) in pyridine (15 mL) to give α-kojibiose octaacetate (0.42 g, 98%), m.p. 169° (ether); lit.[4] m.p. 171–172°; n.m.r.: δ_C 95.75 (C-1), 88.64 (C-1′).

*8-Methoxycarbonyloctyl 3,4,6-tri-O-acetyl-α-*D*-glucopyranoside* (**2**). — 3,4,6-Tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl chloride[8] was prepared from 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucose[10] (3.0 g) by treatment with dimethylchloroforminium chloride[6]. The anomerically pure product (2.8 g) had $[\alpha]_D$ +125° (*c* 1.0, chloroform); n.m.r.: δ 6.04 ($J_{1,2}$ 4 Hz, H-1). The freshly prepared chloride (2.0 g) in dichloromethane was added to a mixture of 8-methoxycarbonyloctanol[1] (0.8 g), silver perchlorate (1.0 g), silver carbonate (2.0 g), and Drierite (3.0 g) in dichloromethane (50 mL) at 0°, and the mixture was stirred for 2 h. The mixture was filtered through Celite, and the filtrate was washed with water, dried and evaporated. The residue was chromatographed on silica gel with 1:1 ether–light petroleum to yield 8-MCO 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranoside (**1**) (1.6 g, 68%), $[\alpha]_D$ +44.5° (*c* 1.0, chloroform); n.m.r.: δ_C 96.96.

The benzyl ether glycoside (**1**) (1.6 g) in ethanol (30 mL) was hydrogenolyzed over 5% palladium-on-charcoal (0.6 g) for 2 h. Evaporation of the filtrate afforded chromatographically homogeneous 8-MCO 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (**2**) (1.2 g).

8-Methoxycarbonyloctyl 3,4,6-tri-O-acetyl-2-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**3**). — 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride[6] (2.7 g) in dichloromethane (10 mL) was added to a mixture of glycoside **2** (1.2 g), silver perchlorate (1.0 g), and silver carbonate (3 g) in dichloromethane (10 mL) and the mixture was stirred for 4 h. The mixture was filtered through Celite and the filtrate was washed with water, dried and evaporated. The residue was chromatographed on silica gel with 1:1 ether–light petroleum to remove a small amount of anomeric (MCO α-sophoroside) derivative and then furnish anomerically pure disaccharide glycoside **3** (1.45 g), $[\alpha]_D$ +76.5° (*c* 1.0, chloroform); n.m.r.: δ_C 96.94 and 96.46 (C-1 and C-1′).

8-Methoxycarbonyloctyl α-kojibioside (**5**). — Methanolic sodium methoxide was added dropwise to disaccharide glycoside **3** (1.45 g) in methanol to maintain permanent alkalinity. After 4 h, the solution was treated with Amberlite IR-120 (H^+) resin to remove sodium ions. The resin was removed and the filtrate evaporated. The residue was crystallized from ether–light petroleum to give MCO 2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**4**) (1.13 g), m.p. 96–97°; n.m.r.: δ_C 97.18 and 96.52 (C-1 and C-1′).

Anal. Calc. for $C_{50}H_{64}O_{13}$: C, 68.80; H, 7.34. Found: C, 68.80; H, 7.44.

The tetrabenzyl ether **4** in methanol was hydrogenolyzed over 5% palladium-on-charcoal (0.5 g) overnight. The mixture was filtered and the filtrate evaporated to furnish MCO α-kojibioside (**5**) (0.66 g), $[\alpha]_D$ +90° (*c* 1.0, methanol); n.m.r. (methanol–water-d_2): δ_C 97.2 and 96.6 (C-1 and C-1′).

Anal. Calc. for $C_{22}H_{40}O_{13}$: C, 51.48; H, 7.81. Found: C, 51.56; H, 7.81.

8-Methoxycarbonyloctyl α-kojibioside (**5**) *from direct glycosylation.* — Hepta-*O*-acetyl-α-kojibiosyl bromide[11] (2.0 g) in dichloromethane (10 mL) was added to a mixture of 8-methoxycarbonyloctanol (0.5 g), silver perchlorate (0.6 g), silver carbonate (2 g) and Drierite (4 g) in dichloromethane (40 mL) at 0°. After 4 h, the mixture was filtered through Celite, and the filtrate was washed with water, dried, and evaporated to a syrup that was chromatographed on silica gel with 15:1 dichloromethane–acetone to give MCO hepta-*O*-acetyl-α-kojibioside (**6**) (1.2 g), $[\alpha]_D$ +97.5° (*c* 1.0, chloroform); n.m.r.: δ_C 95.98 and 94.87 (C-1 and C-1′ of α-kojibioside), 101.5 and 94.87 (C-1 and C-1′ of β-kojibioside, present as ~15% of the mixture). MCO hepta-*O*-acetyl-α-kojibioside (1.2 g) was deacetylated with methanolic sodium methoxide to give the syrupy glycoside **5a** (0.85 g) whose ^{13}C-n.m.r. spectrum showed the presence of ~10% of the contaminating β-glycoside.

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