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Note

A simple method for the synthesis of 2-acetamido-2-deoxy-β-D-galactopyranosides*

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INTRODUCTION

Oligosaccharides containing the 2-acetamido-2-deoxy-β-D-galactopyranosyl group are required in our laboratory to investigate the substrate specificity of multiple forms of the hexosaminidases present in ovarian tumors[1]. For the preparation of β-D-linked disaccharides, the Koenigs–Knorr or Helferich condensations of 2-acetamido-2-deoxy-α-D-galactopyranosyl halides have generally been employed[2,3]. Derivatives of 2-amino-2-deoxy-D-galactose have also been obtained by the inversion of configuration at C-4 of the corresponding 2-amino-2-deoxy-D-glucose derivatives[4–7]. Miyai and Jeanloz have applied this method for the synthesis of 6-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactose[8].

Recently 2-methyl-glyco[2′,1′:4,5]-2-oxazolines have been used for the synthesis of oligosaccharides containing 2-acetamido-2-deoxysugar residues[9,10]. In the present investigation, we report a simple method for the preparation of 2-methyl-(3,4,6-tri-*O*-acetyl-α-D-galactopyrano)-[2′,1′:4,5]-2-oxazoline, which can be employed for the synthesis of 2-acetamido-2-deoxy-β-D-galactopyranosides in good yields.

RESULTS AND DISCUSSION

The starting material, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose (**1**), prepared as described by Stacey[11], was treated with anhydrous ferric chloride in dichloromethane[12] to produce the desired 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyrano)-[2′,1′:4,5]-2-oxazoline (**2**) in 62% yield. The infrared spectrum and chromatographic properties of compound **2** were found identical with those of a sample obtained by reaction of 2-acetamido-2-deoxy-D-galactose with anhydrous zinc chloride in acetic anhydride, as described by Pravdić *et al.*[13].

The glycosylating capability of the oxazoline **2** was examined by heating it with benzyl alcohol in a 1:1 mixture of nitromethane and toluene in the presence of a small amount of *p*-toluenesulfonic acid. Benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-

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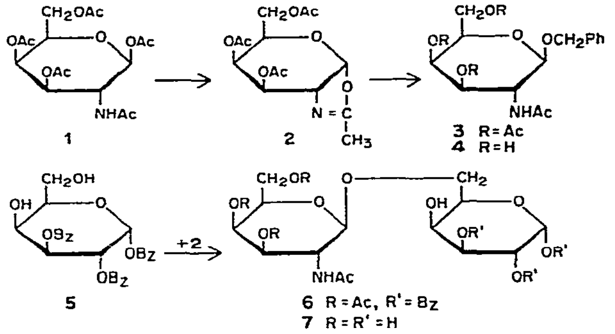
D-galactopyranoside (3) was obtained in 65% yield. Compound 3 was conventionally deacylated with sodium methoxide to give benzyl 2-acetamido-2-deoxy-β-D-galactopyranoside (4). The β-D configuration of compound 4 was confirmed by its optical rotation and infrared analyses.

Condensation of the oxazoline 2 with 1,2,3-tri-*O*-benzoyl-α-D-galactose[14] (5) under similar conditions afforded crystalline 6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-1,2,3-tri-*O*-benzoyl-α-D-galactose (6) in 44% yield. Compound 6, on treatment with barium methoxide in methanol gave 6-*O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactose (7). The properties of compound 7 were found identical with those of the disaccharide prepared by other methods[3,8].



EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer polarimeter Model 141. Infrared spectra were recorded for potassium bromide discs with a Perkin–Elmer Model 457 spectrophotometer. Ascending t.l.c. was performed on plates coated with a 0.25-mm layer of Silica Gel G (Merck, Darmstadt). Products were detected with potassium permanganate and sulfuric acid[15]. The solvent systems used were: A, benzene–methanol (9:1); B, propyl alcohol–ethyl acetate–water (7:5:2); C, butyl alcohol–acetone–water (4:5:1); D, benzene–methanol (2:3). Microanalyses were performed by Robertson Laboratory, Florham Park, New Jersey.

*2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyrano)-[2′,1′:4,5]-2-oxazoline* (2). — To a solution of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose (1, 1 g) in dichloromethane (400 ml) was added anhydrous ferric chloride (1 g). The reaction mixture was stirred for 3 h at room temperature, and then washed three times with cold water, dried (sodium sulfate), and evaporated to a syrup (0.55 g, 66%). The oxazoline 2 thus obtained was chromatographically identical with a sample prepared by the procedure of Pravdic *et al*[13]; $[\alpha]_D^{23}$ +25.8° (*c* 1, chloroform); ν_{max}^{KBr} 1770 (OAc) and 1675 cm^{-1} (C=N).

*Benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranoside* (3). — A solution of the oxazoline **2** (0.5 g) and freshly distilled benzyl alcohol (0.8 ml) in a 1:1 mixture of anhydrous toluene and nitromethane (10 ml) containing *p*-toluenesulfonic acid (8 mg) was heated for 50 min at 110°. The light-brown solution was cooled and the acid was neutralized with a drop of pyridine. Removal of the solvent under diminished pressure gave a syrup that was crystallized from chloroform–ether to give pure compound **3** (0.43 g, 65%); m.p. 180–182°, $[\alpha]_D^{23}$ $-55°$ (*c* 1, chloroform); t.l.c. R_1 1.25 (solvent A); ν_{max}^{KBr} 3430 (NH), 1750 (OAc), 1660, 1560 (CONH), 1600, 1500, 745, and 710 cm^{-1} (phenyl).

Anal. Calc. for $C_{21}H_{27}NO_9$: C, 57.66; H, 6.22; N, 3.20; Found: C, 57.38; H, 6.34; N, 3.17.

Benzyl 2-acetamido-2-deoxy-β-D-galactopyranoside (**4**). — Compound **3** (100 mg) was taken up in absolute methanol (10 ml) and treated with 0.3M sodium methoxide in methanol (0,5 ml) for 24 h at 4°. After the removal of sodium ions with Dowex 50W-x8 (H^+) ion-exchange resin, the solution was evaporated and the residue was crystallized from methanol–ether to give **4**; m.p. 210–212°, $[\alpha]_D^{23}$ $-3.4°$ (*c* 0.5, water); t.l.c. $R_{Lactose}$ 4.0 and $R_{Galactose}$ 1.73 (solvent B), $R_{Lactose}$ 1.67 and $R_{Galactose}$ 1.12 (solvent D); λ_{max}^{KBr} 3420–3320 (OH), 1625, 1560 (amide), 1590, 1500, 740, 730 (phenyl) 900 cm^{-1} (β-glycoside). There was no absorption at 830–860 cm^{-1}, indicating the absence of the α-glycoside.

Anal. Calc. for $C_{15}H_{21}NO_6 \cdot 0.5H_2O$: C, 56.24; H, 6.60; N, 4.37. Found: C, 56.25; H, 6.98; N, 4.60.

6-O-(2-Acetamido-3,4,6-tri-O-acetyl-β-D-galactopyranosyl)-1,2,3-tri-O-benzoyl-α-D-galactose (**6**). — A solution of oxazoline **2** (0.5 g) and 1,2,3-tri-*O*-benzoyl-α-D-galactose (**5**, 0.6 g) in 1:1 anhydrous toluene and nitromethane (10 ml) containing *p*-toluenesulfonic acid (10 mg) was heated for 30 min at 110–120°. The reaction mixture was treated as described for **3** and the residue was twice crystallized from chloroform ether to give colorless prisms of **6** (44%); m.p. 209–211°, $[\alpha]_D^{23}$ $+113.8°$ (*c* 1, chloroform); t.l.c. R_1 1.32 (solvent A); ν_{max}^{KBr} 3525 (OH), 3290 (NH), 1775–1740 (ester C=O), 1655, 1560 (amide), 1600, 1495, 720 (phenyl), 905 (β-glycoside), 870 cm^{-1} (galactopyranosyl ring).

Anal. Calc. for $C_{41}H_{43}NO_{17}$: C, 59.92; H, 5.27; N, 1.70. Found: C, 60.04; H, 5.42; N, 1.60.

6-O-(2-Acetamido-2-deoxy-β-D-galactopyranosyl)-D-galactose (**7**). — A cold solution of **6** (200 mg) in abs. methanol (15 ml) was treated with 0.5M barium methoxide (0.5 ml) and kept for 24 h at 4°. The solution was neutralized by stirring with Dowex 50W-x8 (H^+), and evaporation of the filtrate gave a residue that was crystallized from methanol–ether and recrystallized from water–methanol–ether to give pure **7** (80 mg, 78%); m.p. 182–184°, $[\alpha]_D^{23}$ $+37.9°$ (*c* 1, water) [Lit. Miyai and Jeanloz[8] m.p. 181–184°, $[\alpha]_D^{20}$ $+9°$; Acher and Shapiro[3] m.p. 204–205°, $[\alpha]_D^{18}$ $+38.5°$]; homogeneous by t.l.c. $R_{Lactose}$ 0.48, $R_{Galactose}$ 0.21 (Solvent B); $R_{Lactose}$ 0.49 $R_{Galactose}$ 0.27 (Solvent C); $R_{Lactose}$ 0.50, $R_{Galactose}$ 0.32 (Solvent D) [Lit.[3]: $R_{Lactose}$ 0.50, $R_{Galactose}$ 0.31 (Solvent D)]; ν_{max}^{KBr} 3500–3300 (OH), 1640 and 1560 (amide), 895 (β-glucoside) and 875 cm^{-1} (galactopyranose ring)[3].

Anal. Calc. for $C_{14}H_{25}NO_{11}$: C, 43.86; H, 6.57; N, 3.64. Found: C, 43.74; H, 6.71; N, 3.63.

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