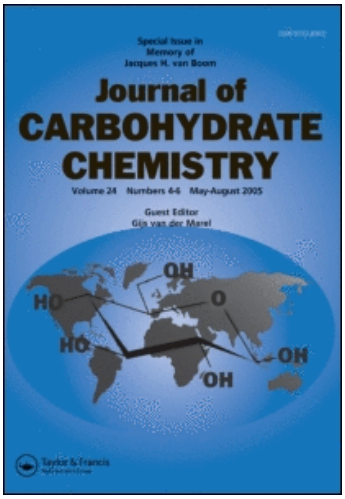

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SYNTHESIS OF 2-ACETAMIDO-2-DEOXY-5-THIO-α-D-GALACTOPYRANOSE*

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ABSTRACT

When treated with a large excess of 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid in 1,4-dioxane, 2-acetamido-2-deoxy-D-galactose gave methyl 2-acetamido-2-deoxy-5,6-O-isopropylidene-α- and -β-D-galactofuranosides, which were converted, via benzoylation and O-deisopropylidenation, into methyl 2-acetamido-3-O-benzoyl-2-deoxy-α- and -β-D-galactofuranosides (3,4). Selective benzoylation of 4, followed by mesylation, gave methyl 2-acetamido-3,6-di-O-benzoyl-2-deoxy-5-O-mesyl-β-D-galactofuranoside (6), which was treated with sodium methoxide to give the 5,6-anhydro derivative (7). Treatment of 7 with thiourea, followed by cleavage of the epithio ring in 8, afforded the 5-thio compound 9.

Alkaline treatment of 10, derived from 9 by hydrolysis, yielded the title compound.

INTRODUCTION

There has been a great deal of activity in recent years in the synthesis of hetero sugars, in which the ring-oxygen atom of aldoses has been replaced by sulfur, nitrogen, phosphorous, or selenium.

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* Studies on Hetero Sugars, Part VIII. For Part VII, see ref. 1.

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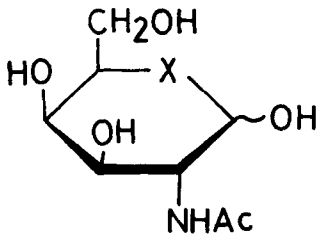
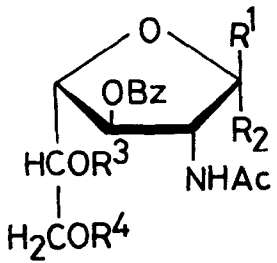
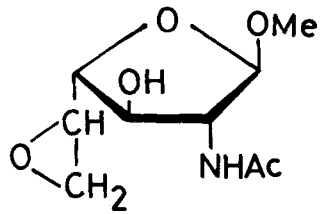


1 R = O
2 R = S

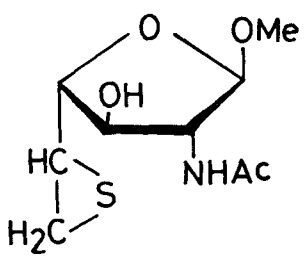


3 $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
4 $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
5 $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = Bz$
6 $R^1 = OMe$, $R^2 = H$, $R^3 = Ms$, $R^4 = Bz$



7

Bz = PhCO
Ms = $MeSO_2$



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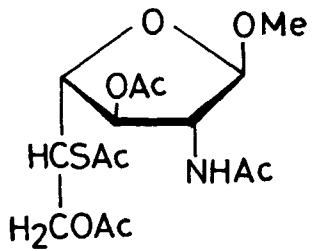

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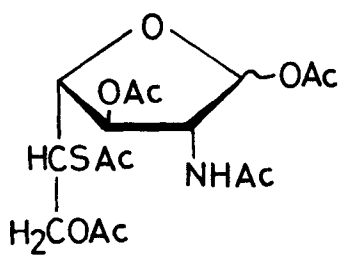

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These sugars are interesting, not only from the point of view of the chemistry involved, but also for their various, biological activities. We have been especially concerned with the synthesis[1-3] of 2-acetamido-2-deoxy-aldohexoses having sulfur in the ring, and with their biological activities.[4] The present report describes a synthesis of 2-acetamido-2-deoxy-5-thio-α-D-galactopyranose.

RESULTS AND DISCUSSION

Treatment[5] of 2-acetamido-2-deoxy-D-galactose (1) with a large excess of 2,2-dimethoxypropane in dry 1,4-dioxane in the presence of p-toluenesulfonic acid for 60 min at 80° gave an anomeric mixture of methyl 2-acetamido-2-deoxy-5,6-O-isopropylidene-D-galactofuranosides in good yield, which showed a single spot by TLC. Benzoylation of the 5,6-O-isopropylidene derivative, and subsequent removal of the isopropylidene group by a mild hydrolysis, afforded methyl 2-acetamido-3-O-benzoyl-2-deoxy-α-D-galactofuranoside (3; 25%) and the corresponding β-D-galactofuranoside (4; 44%). The NMR spectrum of 3 showed a benzoyl group and an O-methyl group, H-1 as a doublet (due to coupling with H-2) at δ 5.05 (5.4 Hz), and H-3 as a doublet of doublets at δ 5.62 ($J_{2,3}$ 7.8, $J_{3,4}$ 5.4 Hz), whereas significant signals in the NMR spectrum of 4 were an anomeric proton as a singlet at δ 4.90, H-2 as a doublet at δ 4.54 ($J_{1,2}$ = $J_{2,3}$ = 0, $J_{2,NH}$ 8.0 Hz), H-3 as a doublet at δ 5.30 ($J_{3,4}$ 3.0 Hz); these data were consistent with structures 3 and 4, respectively.

Selective benzoylation of the primary hydroxyl group on C-6 in 4 with benzoyl chloride in pyridine at -15° afforded the 3,6-dibenzoate (5) in good yield; 5 was mesylated with methanesulfonyl chloride in pyridine at 0° to give the 5-O-mesyl derivative (6) in 92% yield. Compound 6 in dry chloroform was treated with methanolic sodium methoxide to yield crystalline methyl 2-acetamido-5,6-anhydro-2-deoxy-α-L-altrofuranoside (7), which in turn was reated with thiourea for 6.5 h at 40° to afford crystalline 8 in 81% yield. Formation of 8 is patterned after work of Hough, et al.,[6] and involves inversion of configuration at C-5. This 5,6-anhydro to 5,6-epithio conversion was also used for the synthesis of 2-acetamido-2-deoxy-5-thio-D-glucopyranose.[2] Nucleophilic ring-opening of 8 with potassium acetate in acetic acid-acetic anhydride yielded methyl 2-acetamido-3,6-di-O-acetyl-5-S-acetyl-2-deoxy-β-D-galactofuranoside (9) in

good yield, whose IR spectrum showed characteristic absorption at 1700 cm^{-1} (S-acetyl), and whose NMR spectrum revealed the presence of an S-acetyl group at δ 2.42, and H-1 as a doublet at δ 4.81 (1.0 Hz); these data were consistent with structure 9. Selective hydrolysis in acetic acid-2M hydrochloric acid for 5 h at 40°, and acetylation of the product yielded 2-acetamido-1,3,6-tri-O-acetyl-5-thio-D-galactofuranose (10), whose IR and NMR data were consistent with structure 10. On treatment with sodium methoxide in methanol for 30 min at 0°, compound 10 gave crystalline 2-acetamido 2-deoxy-5-thio-α-D-galactopyranose (2); ^{1}H- and ^{13}C-NMR data (see the Experimental section) were well resolved.

EXPERIMENTAL

General methods. Melting points were determined with a Yanagimoto micro melting-point apparatus, and are uncorrected. Specific rotations were determined at 25° with a Union PM-201 polarimeter and IR spectra were recorded with a Jasco IRA-1 spectrophotometer. ^{1}H NMR data were recorded at 90 MHz with a Hitachi R-22 spectrometer, and were confirmed by use of decoupling techniques. ^{13}C NMR spectrum was recorded with a Jeol FX-100 spectrometer operated at 25.05 MHz. Preparative chromatography was performed on silica gel (Waco Co.; 200 mesh) with a solvent systems specified. Evaporations were conducted in vacuo.

Methyl 2-acetamido-3-O-benzoyl-2-deoxy-α-D-galactofuranoside (3) and methyl 2-acetamido-3-O-benzoyl-2-deoxy-β-D-galactofuranoside (4). A suspension of 2-acetamido-2-deoxy-D-galactose (1; 2.4 g) in 1,4-dioxane (24 mL) was heated at 80° and stirred, while 2,2-dimethoxypropane (7.2 mL) and p-toluenesulfonic acid monohydrate (720 mg) were added; stirring was continued for 1 h at 80°. The mixture was cooled and treated with Amberlite IRA-410 (OH^-) ion-exchange resin to remove the acid; the resin was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated to a syrup that was chromatographed on a column of silica gel (60 g) with chloroform and 50:1 chloroform-methanol. The latter eluate gave an anomeric mixture of methyl 2-acetamido-2-deoxy-5,6-O-isopropylidene-D-galactofuranosides (2.15 g, 72%), which showed a single spot in TLC. To a stirred solution of the

galactofuranosides in dry pyridine (20 mL) was added benzoyl chloride (1.3 g) at 0 °C. The mixture was stirred for 2 h at 0 °C, and was then extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. A solution of the 3-O-benzoate in 60% aqueous acetic acid (40 mL) was heated for 2 h at 45 °C, and evaporated to a syrup which was chromatographed on a column of silica gel (60 g) with (a) chloroform, (b) 30:1, and 20:1 chloroform-methanol. Eluant (b) gave methyl 2-acetamido-3-O-benzoyl-2-deoxy-α-D-galactofuranoside (3; 920 mg, 25%); mp 144-145 °C, $[\alpha]_D$ +63.8° (c 1.0, methanol); IR (Nujol) 3400-3100 (OH, NH), 1720, 1270 (ester), 1650, 1555 (amide), and 700 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.99 (s, 3 H, AcN), 3.48 (s, 3 H, MeO), 3.63-3.93 (m, 3 H H-5,6,6'), 4.26 (dd, 1 H, $J_{3,4}$ 5.4, $J_{4,5}$ 3.8 Hz, H-4), 4.82 (m, 1 H H-2), 5.05 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 5.62 (dd, 1 H, $J_{2,3}$ 7.8, $J_{3,4}$ 5.4 Hz, H-3), and 7.25-8.10 (m, 5 H, Ph).

Anal. Calcd for $C_{16}H_{21}NO_7$ (339.3): C, 56.63; H, 6.24; N, 4.13. Found: C, 56.59; H, 6.27; N, 4.15.

Eluant (c) afforded 4 (1.62 g, 44%) as a syrup; $[\alpha]_D$ -57.1° (c 1.3, methanol); IR (film) 3400-3100 (OH, NH), 1710, 1270 (ester) 1650, 1540 (amide), and 705 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.98 (s, 3 H, AcN), 3.34 (s, 3 H, MeO), 4.54 (d, 1 H, $J_{2,NH}$ 8.0 Hz, H-2), 4.90 (s, 1 H, H-1), 5.30 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 6.50 (d, 1 H, $J_{NH,2}$ 8.0 Hz, NH), and 7.20-8.05 (m, 5 H, Ph).

Anal. Calcd for $C_{16}H_{21}NO_7$ (339.3): C, 56.63; H, 6.24; N; 4.13. Found: C, 56.48; H, 6.38; N, 4.11.

Methyl 2-acetamido-3,6-di-O-benzoyl-2-deoxy-β-D-galactofuranoside (5). To a solution of 4 (2.1 g) in dry pyridine (10 mL) was added benzoyl chloride (1.05 g) at -15 °C. The mixture was stirred for 4 h at -10 – -5 °C, and was then extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a syrup which was chromatographed on a column of silica gel (80 g) with chloroform and 100:1 chloroform-methanol. The latter eluate gave 5 (2.1 g, 76.5%) as a syrup; $[\alpha]_D$ -26° (c 0.54, chloroform); IR (film) 3400-3200 (OH, NH), 1710, 1270 (ester), 1650, 1540 (amide), and 750 and 710 cm^{-1} (phenyl); NMR ($CDCl_3$): δ 1.98 (s, 3 H AcN), 3.35 (s, 3 H, MeO), 4.62 (d, $J_{2,NH}$ 8.4 Hz, H-2), 4.92 (s, 1 H

H-1), 5.32 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), and 7.23-8.15 (m, 10 H, 2Ph)

Anal. Calcd for $C_{23}H_{25}NO_8$ (443.4): C, 62.29; H, 5.68; N, 3.16. Found: C, 62.20; H, 6.73; N, 3.08.

Methyl 2-acetamido-3,6-di-O-benzoyl-2-deoxy-5-O-mesyl-β-D-galactofuranoside (6). To a solution of 5 (480 mg) in dry pyridine (5 mL) was added, with stirring, methanesulfonyl chloride (150 mg) at 0 °C, the mixture was kept overnight at 0 °C, and evaporated. The residue was extracted with chloroform, and the extract successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a syrup. The product was purified by chromatography on a column of silica gel (20 g) with chloroform and 150:1 chloroform-methanol. The latter eluate yielded 6 (520 mg, 92%) as a syrup, $[\alpha]_D$ -3.5° (c 1.1, chloroform); IR (film) 3240 (NH), 1720, 1270 (ester), 1650, 1530 (amide), 1360, 1175 (SO_2), and 710, 680 cm^{-1} (phenyl); NMR ($CDCl_3$): δ 2.00 (s, 3 H, AcN), 3.16 (s, 3 H, MeS), 3.40 (s, 3 H, MeO), 4.40 (dd, 1 H, $J_{3,4}$ 3.5, $J_{4,5}$ 2.5 Hz, H-4), 4.50-4.83 (m, 2 H, H-6,6'), 4.60 (dd, 1 H, $J_{2,3}$ 1.0, $J_{2,NH}$ 8.0 Hz, H-2), 5.00 (s, 1 H, H-1), 5.22 (dd, 1 H, $J_{2,3}$ 1.0, $J_{3,4}$ 3.5 Hz, H-3), 5.67 (m, 1 H, H-5), 6.59 (d, 1 H, $J_{NH,2}$ 8.0 Hz, NH), and 7.25-8.15 (m, 10 H, 2 Ph).

Anal. Calcd for $C_{24}H_{27}NO_{10}S$ (521.5): C, 55.27; H, 5.22; N, 2.69. Found: C, 55.39; H, 5.36; N, 2.53.

Methyl 2-acetamido-5,6-anhydro-2-deoxy-α-L-altrofuranoside (7) To a stirred solution of 6 (2.6 g) in dry chloroform (50 mL) was added sodium methoxide in methanol (250 mg of sodium in 10 mL of methanol) at -20 °C; stirring was continued for 5 h at -5 °C. Methanol (30 mL) was added to the mixture, which was then treated with Amberlite IR-120 (H^+) and Amberlite IR-45 (OH^-) resins; the resins were filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated to a syrup which was purified by chromatography on a column of silica gel (40 g) with 50:1 chloroform-methanol, to give 7. After recrystallization from ethanol-ether, the product was obtained as needles (780 mg, 72%), mp 119 °C, $[\alpha]_D$ -85.0° (c 0.5, methanol); IR (Nujol) 3280, 3100 (OH, NH), 1640, 1570 (amide), and 860 cm^{-1} (epoxide); NMR ($CDCl_3$): δ 2.00 (s, 3 H, AcN), 2.73-2.90 (m, 2 H, H-6,6'), 3.29 (m, 1 H, H-5), 3.42 (s, 3 H, MeO), 3.63 (m, 1 H, H-4), 4.14 (m, 1 H, H-2), 4.37 (dd, 1 H, $J_{2,3}$ 2.0, $J_{3,4}$ 4.0 Hz, H-3), 4.89 (d, 1 H,

$J_{1,2}$ 1.0 Hz, H-1), and 6.59 (d, 1 H, $J_{NH,2}$ 7.0 Hz, NH).

Anal. Calcd for $C_9H_{15}NO_5$ (217.2): C, 49.76; H, 6.96; N, 6.45. Found: C, 49.91; H, 6.93; N, 6.52.

Methyl 2-acetamido-2,5,6-trideoxy-5,6-epithio-β-D-galacto-furanoside (8). To a solution of 7 (450 mg) in methanol (15 mL) was added thiourea (472 mg), and the mixture was heated, with stirring, for 6.5 h at 40 °C, and evaporated. The residue was chromatographed on a column of silica gel (20 g) with 30:1 chloroform-methanol to give 8 (389 mg, 81%) as needles, mp 142 °C, $[\alpha]_D$ -122° (c 0.6, methanol); IR (Nujol) 3250, 3080 (OH, NH), and 1650, 1565 cm^{-1} (amide); NMR (1:1 $CDCl_3$-CD_3OD) δ 2.00 (s, 3 H, AcN), 2.47 (m, 2 H, H-6,6'), 3.09 (m, 1 H, H-5), 3.37 (s, 3 H, MeO), 3.60 (t, 1 H, $J_{3,4} = J_{4,5}$ = 6.0 Hz, H-4), 3.93 (dd, 1 H, $J_{2,3}$ 5.0, $J_{3,4}$ 6.0 Hz, H-3), 4.08 (dd, 1 H, $J_{1,2}$ 2.0, $J_{2,3}$ 5.0 Hz, H-2), and 4.80 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1).

Anal. Calcd for $C_9H_{15}NO_4S$ (233.3): C, 46.33; H, 6.48; N, 6.00. Found: C, 46.28; H, 6.50; N, 6.08.

Methyl 2-acetamido-3,6-di-O-acetyl-5-S-acetyl-2-deoxy-5-thio-β-D-galactofuranoside (9). To a solution of 8 (300 mg) in acetic acid (1.5 mL) and acetic anhydride (15 mL), was added potassium acetate (380 mg), and the mixture was heated, with stirring, for 5.5 h at 110 °C, and evaporated. The residue was extracted with chloroform, and the extract successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a syrup. The product was purified by chromatography on a column of silica gel (30 g) with (a) chloroform, (b) 200:1, and (c) 100:1 chloroform-methanol. Eluant (c) gave 9 (380 mg, 78.3%) as a syrup, $[\alpha]_D$ -96.0° (c 0.9, methanol); IR (film) 3250 (NH), 1750, 1240 (ester), 1700 (AcS), and 1660, 1540 cm^{-1} (amide); NMR ($CDCl_3$): δ 2.02, 2.09, 2.11 (3 s, 9 H, AcN, 2 AcO), 2.42 (s, 3 H, AcS), 3.37 (s, 3 H, MeO), 4.04-4.44 (m, 5 H, H-2,4-6'), 4.81 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 4.83 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 4.5 Hz, H-3), and 6.40 (d, 1 H, $J_{NH,2}$ 7.0 Hz, NH).

Anal. Calcd for $C_{15}H_{23}NO_8S$ (377.4): C, 47.73; H, 6.14; N, 3.71. Found: C, 47.59; H, 6.29; N, 3.66.

2-Acetamido-1,3,6-tri-O-acetyl-5-S-acetyl-2-deoxy-5-thio-D-galactofuranose (10). A solution of 9 (650 mg) in acetic acid (30 mL) and 2M hydrochloric acid (1.8 mL) was heated for 5 h at 40 °C,

and treated with Amberlite IR-45 (OH^{-1}) resin, and then evaporated. The residue was acetylated at room temperature with acetic anhydride (3 mL)-pyridine (10 mL). The product was purified by chromatography on a column of silica gel (30 g) with (a) chloroform (b) 150:1, and (c) 100:1 chloroform-methanol. Eluant (c) afforded 9 (400 mg, 57.3%) as a syrup; $[\alpha]_D$ -15° (c 0.5, chloroform); IR (film) 3300 (NH), 1760, 1230 (ester), 1700 (AcS), and 1660, 1540 cm^{-1} (amide); NMR ($CDCl_3$): δ 1.96, 2.00, 2.04, 2.09, 2.10, 2.15 (12 H, AcN, AcO), 2.38, 2.40 (2 s, 3 H, AcS), 6.00 (d, $J_{1,2}$ 1.0 Hz, H-1β), and 6.13 (d, $J_{1,2}$ 4.5 Hz, H-1α); anomeric ratio (α:β) was estimated at about 1:1 from the ratio of intensity of H-1α and H-1β, and two signals of AcS.

Anal. Calcd for $C_{15}H_{23}NO_9S$ (405.4): C, 47.40; H, 5.72; N, 3.71 Found: C, 47.21; H, 5.88; N, 3.35.

2-Acetamido-2-deoxy-5-thio-α-D-galactopyranose (2). To an ice-cooled solution of 10 (300 mg) in methanol (10 mL) was added sodium methoxide (100 mg), and the mixture was stirred for 30 min at 0 °C, and treated with Amberlite IR-120 (H^+) resin to remove the base; the resin was filtered off, and washed with methanol. The filtrate and washings were combined, evaporated to a crystalline mass. Recrystallization from ethanol gave needles (110 mg, 64%), mp 189 °C (dec.), $[\alpha]_D$ +173.8° (c 0.37, methanol; no mutarotation was observed after 24 h); IR (Nujol) 3400-3200 (OH, NH), and 1635, 1550 cm^{-1} (amide); ^1H NMR (1:1 CD_3OD-D_2O): δ 2.02 (s, 3 H, AcN), 3.40-3.90 (m, 4 H, H-4-6'), 4.15-4.37 (m, 2 H, H-2,3), and 4.91 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1); ^{13}C NMR (D_2O, TMS): δ 22.90 (Me), 44.39 (C-5), 54.19 (C-2), 62.06 (C-6), 69.22, 70.45 (C-3,4), and 72.86 (C-1)

Anal. Calcd. for $C_8H_{15}NO_5S$ (237.3): C, 40.49; H, 6.37; N, 5.90. Found: C, 40.63; H, 6.38; N, 5.86.

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