Carbohydrate Research, 122 (1983) 168–173
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Synthesis of 2-acetamido-2-deoxy-5-thio-α-D-mannopyranose*

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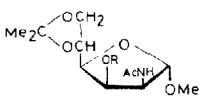
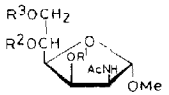
(Received March 25th, 1983; accepted for publication, May 3rd, 1983)

There has been a continuing interest in amino sugars containing sulfur instead of the ring-oxygen atom, because of their various, biological activities. In previous papers[1,2], we described the synthesis of 2-acetamido-2-deoxy-5-thio-α-D-glucopyranose and 2-acetamido-2-deoxy-5-thio-α-D-galactopyranose. The present report describes a synthesis of 2-acetamido-2-deoxy-5-thio-α-D-mannopyranose (**10**).

Benzoylation of methyl 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-α-D-mannofuranoside[3] (**1**), and *O*-deisopropylidenation of **2** by mild, acid hydrolysis, gave crystalline methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-α-D-mannofuranoside (**3**) in good yield. Selective benzoylation of the primary hydroxyl group on C-6 in **3** with benzoyl chloride in pyridine at −15° afforded the 3,6-dibenzoate (**4**) in 87% yield; **4** was mesylated with methanesulfonyl chloride in pyridine at 0°, to give the 5-*O*-mesyl derivative (**5**) in quantitative yield. When treated with methanolic sodium methoxide in dry chloroform at −5°, compound **5** afforded crystalline methyl 2-acetamido-5,6-anhydro-2-deoxy-β-L-gulofuranoside (**6**) in 72% yield, and **6** was treated with thiourea in methanol at 40° to afford the 5,6-epithio-D-man-

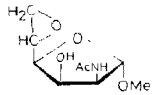


1 R = H
2 R = Bz
Bz = PhCO



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

Ms = $MeSO_2$



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

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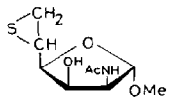
nofuranoside derivative **7** in 95% yield. Formation of **7** involving inversion at C-5 in **6** had been demonstrated by Hough *et al.*[4], and effectively used for the synthesis of 5-thio sugars[1,2,5]. Acetylation of **7** gave the 3-*O*-acetyl derivative; significant signals in the n.m.r. spectrum were a two-proton doublet of doublets at δ 2.32 and 2.56 ($J_{5,6}$ 5.0, $J_{5,6'}$ 6.0, and $J_{6,6'}$ 2.0 Hz, H-6,6'), a one-proton doublet of doublets at δ 3.63 ($J_{3,4}$ 4.0, $J_{4,5}$ 8.0 Hz, H-4), a one-proton doublet at δ 4.89 ($J_{1,2}$ 3.8 Hz, H-1), and a one-proton doublet of doublets at δ 5.66 ($J_{2,3}$ 5.0, $J_{3,4}$ 4.0 Hz, H-3). Other n.m.r. data are given in the Experimental section, and are consistent with the structure assigned.

Nucleophilic ring-opening of compound **7** with potassium acetate in acetic acid–acetic anhydride at 120° yielded methyl 2-acetamido-3,6-di-*O*-acetyl-5-*S*-acetyl-2-deoxy-5-thio-α-D-mannofuranoside (**8**) in 78% yield; its i.r. spectrum



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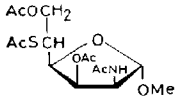

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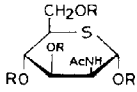

9 R = Ac
10 R = H

showed a characteristic absorption at 1680 cm^{-1} (*S*-acetyl), and its n.m.r. spectrum was consistent with structure **8**. Hydrolysis of compound **8** in 10:1 acetic acid–2M hydrochloric acid for 15 h at 40°, and acetylation of the product, yielded 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-5-thio-α-D-mannopyranose (**9**) in 54% yield. The i.r. spectrum of **9** did not exhibit *S*-acetyl absorption, and the n.m.r. signals (see Experimental section) were well resolved by use of decoupling techniques. On treatment with sodium methoxide for 30 min at 0°, compound **9** gave, in 92% yield, crystalline 2-acetamido-2-deoxy-5-thio-α-D-mannopyranose (**10**), whose n.m.r. spectrum was consistent with structure **10**.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Evaporations were conducted *in vacuo*. Specific rotations were determined with a Union PM-201 polarimeter, and i.r. spectra were recorded with a Jasco IRA-1 spectrophotometer. Preparative chromatography was performed on silica gel (Waco Co.; 300 mesh) with the solvent systems specified. N.m.r. data were recorded at 90 MHz with a Hitachi R-22 spectrometer, and were confirmed by use of decoupling techniques.

Methyl 2-acetamido-3-O-benzoyl-2-deoxy-5,6-O-isopropylidene-α*-*D*-mannofuranoside* (**2**). — To a solution of[3] **1** (1.0 g) in pyridine (10 mL) was added benzoyl chloride (600 mg) at 0°, and the mixture was kept overnight at 0°. Methanol

(1 mL) was added, and the solution was then evaporated to a syrup which was extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a column of silica gel (20 g) with chloroform and then 100:1 chloroform–methanol. The latter eluate gave **2** (1.3 g, 95% *c*); m.p. 105°, $[\alpha]_D^{25}$ +133.8° (*c* 0.5, methanol); ν_{max}^{Nujol} 3240 (NH), 1720 and 1260 (ester), 1640 and 1530 (amide), 850 (Me_3C), and 740 and 700 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.34, 1.47 (2 s, 6 H, Me_3C), 1.80 (s, 3 H, AcN), 3.37 (s, 3 H, MeO), 4.98 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 5.75 (dd, 1 H, $J_{2,3}$ 4.0, $J_{3,4}$ 2.5 Hz, H-3), 6.28 (d, 1 H, $J_{NH,2}$ 6.5 Hz, NH), and 7.34–8.05 (m, 5 H, Ph).

Anal. Calc. for $C_{19}H_{25}NO_7$: C, 60.14; H, 6.64; N, 3.69. Found: C, 60.20; H, 6.62; N, 3.51.

*Methyl 2-acetamido-3-O-benzoyl-2-deoxy-α-*D*-mannofuranoside* (**3**). — A solution of **2** (3.0 g) in 7:3 acetic–water acid (30 mL) was heated for 3 h at 45°, and then evaporated. The product crystallized from ether–hexane, to give **3** (2.2 g, 82%) as needles; m.p. 152°, $[\alpha]_D^{25}$ +177° (*c* 0.9, methanol); ν_{max}^{Nujol} 3350–3100 (OH, NH), 1720 and 1280 (ester), 1680 and 1530 (amide), and 720 cm^{-1} (phenyl); n.m.r. data (in 1:1 chloroform-*d*–methanol-d_4): δ 1.86 (s, 3 H, AcN), 3.39 (s, 3 H, MeO), 4.98 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.75 (dd, 1 H, $J_{2,3}$ 4.0, $J_{3,4}$ 2.5 Hz, H-3), and 7.20–8.12 (m, 5 H, Ph).

Anal. Calc. for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.59; H, 6.25; N, 4.08.

*Methyl 2-acetamido-3,6-di-O-benzoyl-2-deoxy-α-*D*-mannofuranoside* (**4**). To a stirred solution of **3** (1.8 g) in dry pyridine (25 mL) was added benzoyl chloride (800 mg) at −15°. The mixture was stirred for 11 h at −15°, methanol (1 mL) was added, and the solution was evaporated to a syrup. The residue was extracted with chloroform, and the extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to give a crystalline product. Recrystallization from ethanol–ether afforded **4** (2.05 g, 87%) as needles; m.p. 184°, $[\alpha]_D^{25}$ +124.8° (*c* 0.5, methanol); ν_{max}^{Nujol} 3280 (OH, NH), 1720, 1700, and 1280 (ester), 1640 and 1560 (amide), and 710 cm^{-1} (phenyl); n.m.r. data (in 1:1 chloroform-*d*–methanol-*d*): δ 1.85 (s, 3 H, AcN), 3.38 (s, 3 H, MeO), 4.98 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.82 (dd, 1 H, $J_{3,4}$ 3.5, $J_{3,4}$ 2.5 Hz, H-3), and 7.33–8.10 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{23}H_{25}NO_8$: C, 62.29; H, 5.68; N, 3.16. Found: C, 62.36; H, 5.72; N, 3.14.

*Methyl 2-acetamido-3,6-di-O-benzoyl-2-deoxy-5-O-mesyl-α-*D*-mannofuranoside* (**5**). — To an ice-cooled solution of **4** (1.9 g) in dry pyridine (20 mL) was added methanesulfonyl chloride (600 mg), and the mixture was kept overnight at 0°, and then 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 residue was purified by chromatography on a column of silica gel (40 g) with chloroform and then 200:1 chloro-

form–methanol. The latter eluate yielded **5** as a syrup (2.2 g, 99%); $[\alpha]_D^{25}$ +113° (*c* 0.6, methanol); ν_{max}^{film} 3250 (NH), 1720 and 1270 (ester),1650 and 1540 (amide), and 710 and 690 cm^{-1} (phenyl); n.m.r. data (in chloroform-*d*): δ 1.78 (s, 3 H, AcN), 2.96 (s, 3 H, MeS), 3.35 (s, 3 H, MeO), 4.56 (dd, 1 H, $J_{3,4}$ 4.0, $J_{4,5}$ 7.0 Hz, H-4), 4.56 (dd, 1 H, $J_{5,6}$ 6.0, $J_{6,6'}$ 12.2 Hz, H-6), 4.80 (m, 1 H, $J_{1,2}$ 3.0, $J_{2,3}$ 4.5, and $J_{2,NH}$ 9.0 Hz, H-2), 4.84 (dd, 1 H, $J_{5,6'}$ 3.0, $J_{6,6'}$ 12.2 Hz, H-6'), 4.98 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.31 (m, 1 H, $J_{4,5}$ 7.0, $J_{5,6}$ 6.0, $J_{5,6'}$ 3.0 Hz, H-5), 5.89 (dd, 1 H, $J_{2,3}$ 4.5, $J_{3,4}$ 4.0 Hz, H-3), 6.40 (d, 1 H, $J_{NH,2}$ 9.0 Hz, NH), and 7.21–8.08 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{24}H_{27}NO_{10}S$: C, 55.27; H, 5.22; N, 2.67. Found: C, 54.99; H, 5.38; N, 2.51.

*Methyl 2-acetamido-5,6-anhydro-2-deoxy-β-*L*-gulofuranoside* (**6**). — To a solution of **5** (2.58 g) in dry chloroform (10 mL), cooled to −15°, was added,with stirring, a solution of sodium methoxide (320 mg) in methanol (6.5 mL). The mixture was stirred for 3 h at −5°, methanol (10 mL) was added, and the mixture was then treated with Amberlite IR-120 (H^+) and Amberlite IR-45 (OH^-) ion-exchange resins. The product was purified by chromatography on a column of silica gel (50 g) with chloroform and then 50:1 chloroform–methanol. The latter eluate gave **6** (720 mg, 72%) as crystals; m.p. 178°, $[\alpha]_D^{25}$ +130° (*c* 0.5, methanol); ν_{max}^{Nujol} 3400 (OH), 3240 (NH), and 1640 and 1540 cm^{-1} (amide); n.m.r. data (in 1:1 chloroform-*d*–methanol-d_4): δ 2.00 (s, 3 H, AcN), 2.77 (dd, 1 H, $J_{5,6}$ 3.0, $J_{6,6'}$ 5.0 Hz, H-6), 2.84 (dd, 1 H, $J_{5,6'}$ 4.0, $J_{6,6'}$ 5.0 Hz, H-6'), 3.20 (m, 1 H, $J_{4,5}$ 5.0, $J_{5,6}$ 3.0, $J_{5,6'}$ 4.0 Hz, H-5), 3.30 (s, 3 H, MeO), 3.90 (dd, 1 H, $J_{3,4}$ 5.5, $J_{4,5}$ 5.0 Hz, H-4), 4.22 (dd, 1 H, $J_{1,2}$ 3.0, $J_{2,3}$ 5.5 Hz, H-2), 4.51 (t, $J_{2,3} = J_{3,4}$ = 5.5 Hz, H-3), and 4.78 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1).

Anal. Calc. for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.68; H, 6.91; N, 6.50.

*Methyl 2-acetamido-2,5,6-trideoxy-5,6-epithio-α-*D*-mannofuranoside* (**7**). — To a solution of **6** (570 mg) in methanol (40 mL) was added thiourea (600 mg), and the mixture was heated, with stirring, overnight at 40°, and evaporated. The residue was chromatographed on a column of silica gel (10 g) with chloroform and then 50:1 chloroform–methanol. The latter eluate gave **7** (600 mg, 95%) as needles; m.p. 189.5°, $[\alpha]_D^{25}$ +103.5° (*c* 0.5, methanol); ν_{max}^{Nujol} 3260 (OH, NH), and 1660 and 1560 cm^{-1} (amide).

Anal. Calc. for $C_9H_{15}NO_4S$: C, 46.33; H, 6.48; N, 6.00. Found: C, 46.35; H, 6.71; N, 6.12.

A sample of **7** (50 mg) was acetylated with acetic anhydride–pyridine, to give 51 mg (86%) of the 3-*O*-acetyl derivative; m.p. 167°, $[\alpha]_D^{25}$ +84° (*c* 0.5, methanol); ν_{max}^{Nujol} 3300 (NH), 1750 and 1240 (ester), and 1660 and 1550 cm^{-1} (amide); n.m.r. data (in chloroform-*d*): δ 2.00 (s, 3 H, AcN), 2.15 (s, 3 H, AcO), 2.32 (dd, 1 H, $J_{5,6}$ 5.0, $J_{6,6'}$ 2.0 Hz, H-6), 2.56 (dd, 1 H, $J_{5,6'}$ 6.0, $J_{6,6'}$ 2.0 Hz, H-6'), 2.90 (m, 1 H, $J_{4,5}$ 8.0, $J_{5,6}$ 5.0, $J_{5,6'}$ 6.0 Hz, H-5), 3.35 (s, 3 H, MeO), 3.63 (dd, 1 H, $J_{3,4}$ 4.0, $J_{4,5}$ 8.0 Hz, H-4), 4.89 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.56 (dd, 1 H, $J_{2,3}$ 5.0, $J_{3,4}$ 4.0 Hz, H-3), and 5.93 (d, 1 H, $J_{NH,2}$ 8.0 Hz, NH).

Anal. Calc. for $C_{11}H_{17}NO_5S$: C, 47.98; H, 6.22; N, 5.09. Found: C, 47.86; H, 6.17; N, 5.10.

Methyl 2-acetamido-3,6-di-O-acetyl-5-S-acetyl-2-deoxy-α-D-mannofuranoside (**8**). — A mixture of **7** (410 mg), potassium acetate (2.0 g), acetic anhydride (20 mL), and acetic acid (2 mL) was heated, with stirring, for 12 h at 120°, cooled, and evaporated. Chloroform (100 mL) was added to the residue, the precipitate was removed by filtration, and the filtrate was evaporated. The residue was chromatographed on a column of silica gel (10 g) with chloroform and then 100:1 chloroform–methanol. The latter eluate afforded **8** (510 mg, 78%) as needles; m.p. 170–171°, $[\alpha]_D^{25}$ +163° (*c* 0.5, methanol); ν_{max}^{Nujol} 3300 (NH), 1745, 1735, 1710, 1245, 1220, and 1210 (ester), 1680 (AcS), and 1660 and 1520 cm^{-1} (amide); n.m.r. data (in chloroform-*d*): δ 1.97 (s, 3 H, AcN), 2.06, 2.08 (2 s, 6 H, 2 AcO), 2.31 (s, 3 H, AcS), 3.33 (s, 3 H, MeO), 3.95–4.42 (m, 4 H, H-4–H-6'), 4.65 (m, 1 H, H-2), 4.87 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.50 (dd, 1 H, $J_{2,3}$ 4.5, $J_{3,4}$ 3.0 Hz, H-3), and 6.38 (d, 1 H, $J_{NH,2}$ 8.5 Hz, NH).

Anal. Calc. for $C_{15}H_{23}NO_8S$: C, 47.73; H, 6.14; N, 3.71. Found: C, 47.51; H, 6.14; N, 3.59.

2-Acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-5-thio-α-D-mannopyranose (**9**). — A solution of **8** (200 mg) in acetic acid (10 mL) and 2M hydrochloric acid (1.0 mL) was heated, with stirring, for 15 h at 40°. Water (10 mL) was added, and the mixture was treated with Amberlite IR-45 (OH^-) resin; the resin was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated to a syrup which was acetylated with acetic anhydride (2 mL)–pyridine (10 mL). The product was purified by chromatography on a column of silica gel (10 g) with chloroform and then 100:1 chloroform–methanol. The latter eluate gave compound **9** as an amorphous mass (115 mg, 54%); m.p. 64–66°, $[\alpha]_D^{25}$ +122.5° (*c* 0.5, methanol); ν_{max}^{Nujol} 3300 (NH), 1740 and 1220 (ester), and 1660 and 1530 cm^{-1} (amide); n.m.r. data (in chloroform-*d*): δ 1.98, 2.04, 2.06, and 2.17 (5 s, 15 H, 4 AcO, AcN), 3.50 (m, 1 H, H-5), 4.03 (dd, 1 H, $J_{5,6}$ 3.0, $J_{6,6'}$ 11.0 Hz, H-6), 4.32 (dd, 1 H, $J_{5,6'}$ 5.0, $J_{6,6'}$ 11.0 Hz, H-6'), 4.90 (m, 1 H, H-2), 5.27 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 6.0 Hz, H-3), 5.71 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), and 6.23 (d, 1 H, $J_{NH,2}$ 10.0 Hz, NH).

Anal. Calc. for $C_{16}H_{23}NO_9S$: C, 47.40; H, 5.72; N, 3.46. Found: C, 47.45; H, 5.83; N, 3.40.

2-Acetamido-2-deoxy-5-thio-α-D-mannopyranose (**10**). — To an ice-cooled solution of **9** (190 mg) in methanol (10 mL) was added sodium methoxide (50 mg), and the mixture was stirred for 30 min at 0°, and then 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, and evaporated to a crystalline mass. Recrystallization from ethanol–ether gave compound **10** as needles (103 mg, 92%); m.p. 189°, $[\alpha]_D^{25}$ +28.8° (*c* 0.4, methanol, no mutarotation observed during 24 h); ν_{max}^{Nujol} 3400–3300 (OH, NH), and 1630 and 1535 cm^{-1} (amide); n.m.r. data (in D_2O): δ 2.00 (s, 3 H, AcN), 3.20 (m, 1 H, H-5), 3.70 (t, 1 H, $J_{3,4} = J_{4,5}$

= 9.5 Hz, H-4), 3.92 (dd, 1 H, $J_{2,3}$ 3.8, $J_{3,4}$ 9.5 Hz, H-2), 4.51 (t, 1 H, $J_{1,2} = J_{2,3}$ = 3.8 Hz, H-2), and 4.80 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1).

Anal. Calc. for $C_8H_{15}NO_5S$: C, 40.49; H, 6.37; N, 5.90. Found: C, 40.58; H, 6.38; N, 5.93.

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