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5-THIO-L-RHAMNOSE*†

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ABSTRACT

Two routes for the synthesis of methyl 5-*S*-acetyl-6-deoxy-2,3-*O*-isopropylidene-5-thio-L-mannofuranoside (**8**) have been examined. Reaction of L-rhamnose with methanol in the presence of cation-exchange resin gives methyl 6-deoxy-α-L-mannofuranoside (**2**), which on conventional acetonation yields methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannofuranoside (**3**). Compound **3** is also obtained by acetonation of L-rhamnose followed by treatment with a mixture of methanol, acetone, and Amberlite IR-120(H^+) resin. Chlorination of **3** with triphenylphosphine–carbon tetrachloride gives methyl 5-chloro-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**7**), which reacts with potassium thioacetate to give **8**. Alternatively, **3** is oxidized with ruthenium tetraoxide to methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexofuranosid-5-ulose (**9**), which is reduced by sodium borohydride mainly to methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**10**). The *O*-tosyl derivative of **10** reacts with potassium thioacetate to produce **8**. Hydrolysis of **8** with 90% aqueous trifluoroacetic acid, followed by acetolysis with a solution of acetic acid, acetic anhydride, and sulfuric acid gives an anomeric mixture of 1,2,3,4-tetra-*O*-acetyl-6-deoxy-5-thio-L-mannopyranoses (**12**), together with a small proportion of 1,2,3-tri-*O*-acetyl-5-*S*-acetyl-6-deoxy-5-thio-β-L-mannofuranose (**13**). Deacetylation of **12** or **13** gives 5-thio-L-rhamnose (**6**), from which crystalline 1,2,3,4-tetra-*O*-(*p*-nitrobenzoyl)-5-thio-β-L-rhamnopyranose (**14**) is obtained.

INTRODUCTION

During the past few years this laboratory and others have been concerned with synthesis and biochemical characterization of sugar analogs containing sulfur in place of the ring oxygen-atom. These analogs possess interesting biological properties. Thus, 5-thio-D-glucose is an inhibitor of D-glucose transport in many tissues[1] and acts as a

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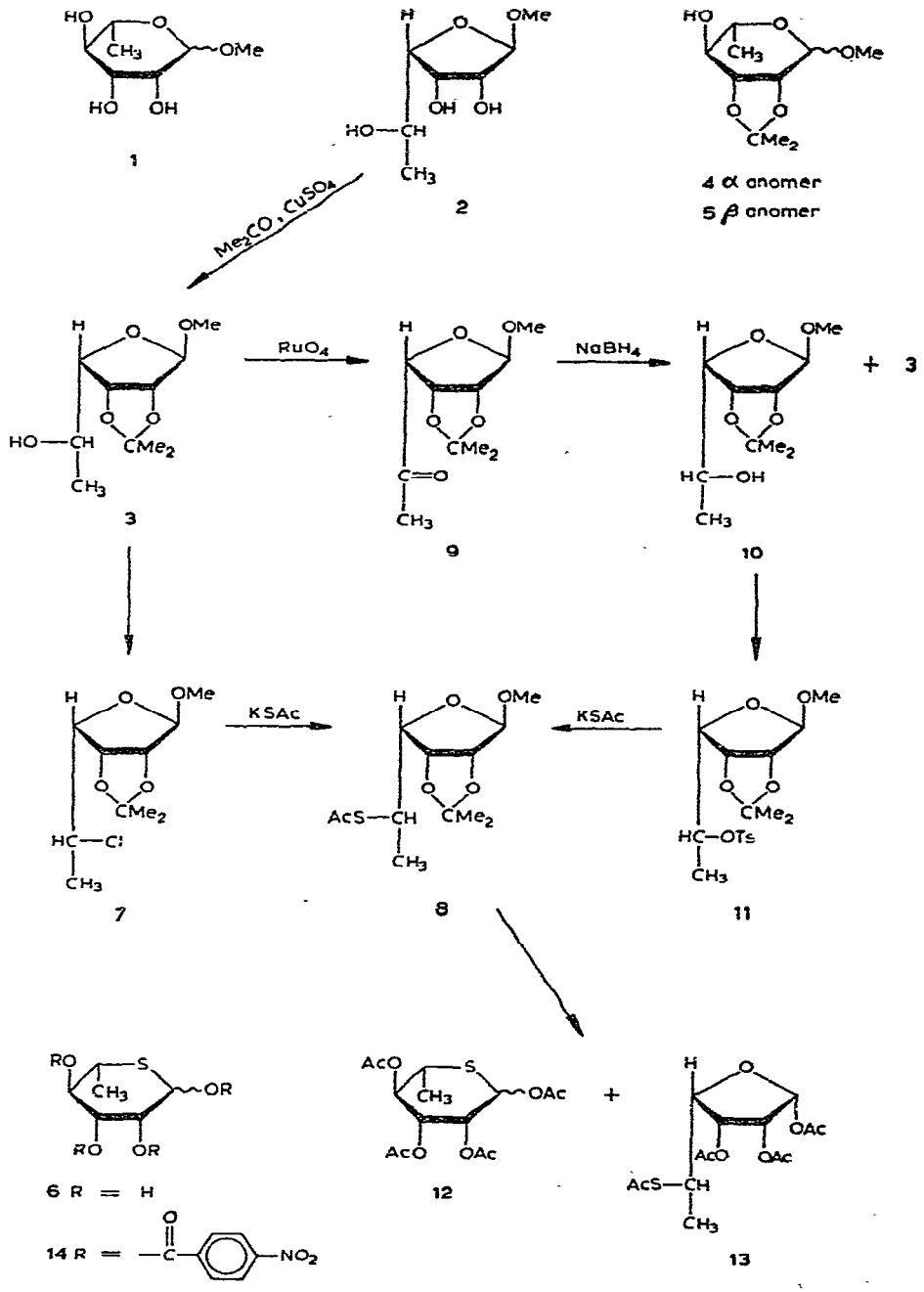
1
2
4 α anomer
5 β anomer
Me2CO, CuSO4
RuO4
NaBH4
+ 3
3
9
10
KSAc
KSAc
7
8
11
6 R = H
14 R =
12
13

male antifertility agent[2]. Analogs of nucleosides, nucleotides, antibiotics, and sugar phosphates made from 4-thio-D-ribose and 5-thio-D-glucose also have shown novel biochemical properties[3–6]. We are now engaged in the synthesis of 5′-thio analogs of the anthracycline antibiotics, daunorubicin and adriamycin, which have shown promise in the clinical treatment of cancers[7,8]. Here we report the synthesis of 5-thio-L-rhamnose (6-deoxy-5-thio-L-mannose), which might be converted into thio analogs of anthracycline antibiotics by reactions similar to those used for the synthesis of the foregoing antibiotics[9,10].

DISCUSSION

Although prolonged reaction[11] of 6-deoxy-L-mannose with methanolic hydrogen chloride gives exclusively methyl 6-deoxy-L-mannopyranoside (**1**), we found that brief treatment of L-rhamnose with a mixture of methanol and Amberlite IR-120(H^+) resin gave a 30% yield of methyl 6-deoxy-α-L-mannofuranoside (**2**), together with 70% of the pyranoside **1**. The furanoside **2** was separated from **1** by chromatography on a column of neutral silica gel, but if commercial silica gel was used, a portion of **2** was found to change into **1**. Common chromatographic-grade silica gel is considered to be an acidic catalyst[12], although complete information as to the nature of the acidic sites is not available. Conversion of **2** into **1** likely involves acid-catalyzed alteration in ring size.

The furanoside **2** was converted in quantitative yield into its 2,3-isopropylidene acetal **3** by refluxing **2** with a mixture of acetone and anhydrous copper sulfate; the use of an acidic catalyst for the isopropylidenation reaction was avoided because of the possibility of ring migration[13,14]. Another route to **3** was by treating L-rhamnose with acetone to give a 100% yield of crystalline 6-deoxy-2,3-*O*-isopropylidene-L-mannose, which on further treatment with a mixture of methanol, acetone, and IR-120(H^+) resin gave a 60% yield of **3**, together with 20% of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (**4**) and 5% of its β-L anomer **5**. The other possible isomer, methyl 6-deoxy-2,3-*O*-isopropylidene-β-L-mannofuranoside, was not formed. This is expected, because the β-L-rhamnofuranoside has all of the substituents *cis*-disposed on a five-membered ring, and the fusion of a cyclic isopropylidene ring would create considerable strain in producing the β-L-furanoid form.

Equilibrium in aqueous solution between furanoid and pyranoid forms of 6-deoxy-2,3-*O*-isopropylidene-L-mannose has been examined[15,16], and the equilibrium mixture shown[17] to contain 65% of α-L furanoid, 25% of α-L-pyranoid, and 10% of β-L-furanoid forms. The formation of different proportions of **3**, **4**, and **5** from the reaction of 6-deoxy-2,3-*O*-isopropylidene-L-mannose was probably the result of a similar equilibrium. The n.m.r. spectrum of **3** showed H-1 resonating as a singlet and H-2 as a doublet ($J_{2,3}$ 6 Hz); the data were compatible with the α-L-furanoid structure for **3**. The hydroxyl proton gave a broad signal at τ 7.4 that disappeared on exchange with D_2O. The other features of the n.m.r. spectrum resembled those recorded[17,18] for compounds possessing similar structures. The n.m.r.-spectral

parameters of **4** are similar to the recorded data*, and the negative optical rotation of **4** was consistent with the α-L-pyranoid structure. The n.m.r. spectrum of the β anomer (**5**) showed the H-1 resonance as a doublet ($J_{1,2}$ 2.5 Hz). The hydroxyl proton signal of **5** appeared at τ 7.1 and disappeared on exchange with D_2O.

As chloro sugars have proved valuable as intermediates in the preparation of amino sugars[19] and 5-thio-D-glucose[20], the conversion of **3** into 5-thio-L-rhamnose (**6**) via a chloro derivative was examined. Triphenylphosphine has been found to be a useful aid[20,21] in the direct replacement of primary and secondary hydroxyl groups by chlorine; in the absence of a participating group, this reagent effects chlorination with inversion of configuration at a carbon atom bearing a hydroxyl group. By treatment of **3** with a mixture of triphenylphosphine and carbon tetrachloride, methyl 5-chloro-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**7**) was obtained in 40% yield. The n.m.r. spectrum of **7** showed the H-1 signal as a singlet, H-4 as a doublet of doublets, and H-6 as a doublet at τ 8.45 ($J_{5,6}$ 6 Hz). The slight downfield shift of the H-6 signals as compared to those of **3** (at τ 8.65) was attributable to the presence of chlorine on C-5.

Previously, our laboratory effected[20] the displacement of both primary and secondary chlorine atoms of a dichloro sugar derivative by heating it with potassium thioacetate in boiling acetone. Under similar conditions, there was no reaction between **7** and potassium thioacetate, nor at 100°, even in a more-polar solvent such as *N*,*N*-dimethylformamide. By raising the temperature to 130°, a sluggish reaction started, but even after 10 days, the yield of methyl 5-*S*-acetyl-6-deoxy-2,3-*O*-isopropylidene-5-thio-α-L-mannofuranoside (**8**) was only 10%. Longer reaction-times and higher temperatures did not increase the yield of **8**, but resulted in decomposition of **7**.

Because of this extremely low yield of **8**, a second route for the preparation of **8** from **3** was developed. Compound **3** was converted in 100% yield into methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexofuranosid-5-ulose (**9**) by oxidation with ruthenium tetraoxide. The i.r. spectrum of **9** showed the expected carbonyl peak at 1718 cm^{-1}, and, in its n.m.r. spectrum, the H-1 signal was a singlet, H-2 a doublet ($J_{2,3}$ 6 Hz), H-4 a doublet ($J_{3,4}$ 4 Hz), and H-6 a singlet. Reduction of **9** with sodium borohydride yielded 80% of the known[17] methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranoside (**10**) and 20% of **3**. A molecular model of **9** showed that its favored conformation is one in which the carbonyl group at C-5 has the maximum distance from O-4 and O-3, and the stereoselectivity[22] of the reduction by sodium borohydride was therefore due to attack by the hydride ion from the less-hindered side of the carbonyl group. By modifying the literature procedure[17], through use of a higher temperature and longer reaction-time, the hydroxyl derivative **10** was converted into its tosyl derivative **11** with an increase in yield from 34 to 96%. The nucleophilic displacement of the *p*-tolylsulfonyloxy group of **11** with potassium thioacetate in *N*,*N*-dimethylformamide gave **8** in 60% yield. The i.r. spectrum of **8** showed the

*Angyal *et al.*[15] recorded the n.m.r. spectrum of a sample of **4** which might have contained some **5**.

S-acetyl peak at the expected 1685 cm^{-1} region, and the acetyl thio protons showed an n.m.r. signal at τ 7.72. The H-1 signal appeared as a singlet, whereas H-2 was a doublet ($J_{2,3}$ 6 Hz) and H-3 a quartet ($J_{3,4}$ 2.5 Hz). Hydrolysis of **8** with 90% aqueous trifluoroacetic acid, followed by treatment with a solution of acetic acid, acetic anhydride, and sulfuric acid yielded 1,2,3,4-tetra-*O*-acetyl-5-thio-L-rhamnopyranose (**12**) as a mixture of α and β anomers, together with a small proportion of 1,2,3-tri-*O*-acetyl-5-*S*-acetyl-5-thio-β-L-rhamnofuranose (**13**). The n.m.r. spectrum of **12** indicated the absence of *S*-acetyl and *O*-methyl groups, and its i.r. spectrum showed *O*-acetyl absorption at 1740 cm^{-1} but no absorption at 1685 cm^{-1} (*S*-acetyl). The infrared spectrum of **13** showed the *O*-acetyl peak at 1750 cm^{-1}, and the *S*-acetyl absorptions occurred at 1685 cm^{-1}. The H-1 signal of **13** appeared as a doublet ($J_{1,2}$ 3.7 Hz), suggesting the β-L configuration. The n.m.r. spectrum also showed signals characteristic of *O*-acetyl, *S*-acetyl, and *C*-methyl protons. Deacetylation of both **12** and **13** gave the same product, namely 5-thio-L-rhamnopyranose (**6**) and the thiopyranoid structure for **6** was confirmed by the absence of an i.r. peak at 2550 cm^{-1} (SH). The thio sugar **6** reacted with *p*-nitrobenzoyl chloride in pyridine to give an anomeric mixture of 1,2,3,4-tetra-*O*-(*p*-nitrobenzoyl)-5-thio-L-rhamnopyranose (**14**), from which the β anomer was separated by chromatography.

EXPERIMENTAL

General methods. — Purity of products was determined by thin-layer chromatography (t.l.c.) on glass plates coated with silica gel G (E. Merck, Darmstadt, Germany) and irrigated with *A*, 6:1 hexane–ethyl acetate, *B*, 2:1 hexane–ethyl acetate, *C*, 3:1 hexane–ethyl acetate, *D*, 9:2 chloroform–acetone, *E*, 6:1 chloroform–methanol, and *F*, 19:1 benzene–methanol. Components were located by spraying the plates with 5% sulfuric acid in ethanol and heating. Column chromatography was performed on silica gel powder (J. T. Baker Chemical Co.). Neutral silica gel was prepared by washing commercial silica gel with ammonium hydroxide solution and reactivated by heating. Columns were eluted with *G*, 15:1 chloroform–methanol, *H*, 15:1 hexane–ethyl acetate, *I*, 6:1 hexane–ethyl acetate, *J*, 15:1 chloroform–acetone, and *K*, 1:10 chloroform–hexane. Optical rotations were measured on a Perkin–Elmer model 141 polarimeter. N.m.r. spectra were determined with a Varian T-60A spectrometer in chloroform-*d* (Me_4Si as the internal standard) or deuterium oxide (DSS as internal standard). I.r. spectra were obtained with a Perkin–Elmer Model 337 spectrometer. Ruthenium dioxide hydrate was obtained from Ventron, Danver, MA. The source of this reagent is important, as some other suppliers produce material leading to low reaction-efficiencies. Evaporations were conducted under diminished pressure with a bath temperature below 40°.

Methyl α-L-*rhamnofuranoside* (**2**). — A solution of L-rhamnose (15 g) in methanol (500 ml) was boiled for 1.5 h under reflux with 20 g of Amberlite IR-120(H^+) resin. The mixture was cooled, filtered, and the filtrate evaporated to a syrup that was chromatographed on neutral silica gel. Elution with solvent (*G*) gave two

components, and the fractions containing the furanoside **2** (4.9 g, 30%) gave a crystalline solid. An analytical sample of **2** was obtained by crystallization from ether; m.p. 58°, $[\alpha]_D^{25}$ −92° (*c* 1.2, chloroform) [lit.[23] m.p. 62°, $[\alpha]_D^{18}$ −98.6° (*c* 2.2, water); n.m.r. ($CDCl_3$): τ 5.0 (s, H-1), 6.4 (s, OCH_3), 8.6 (d, $J_{5,6}$ 7 Hz, H-6), and 5.2–6.15 (m, 7 protons); ν_{max}^{KBr} 3440 cm^{-1} (OH).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.20; H, 7.87.

The fractions containing the component having a lower R_F value than **2** were evaporated to give methyl α,β-L-rhamnopyranoside (**1**, 11.2 g, 70%) as a syrup; $[\alpha]_D^{25}$ −31°; n.m.r. (D_2O): τ 6.65, 6.70 (pair of singlets, OMe of α and β anomers), and 8.75 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.32; H, 7.75.

2,3-O-Isopropylidene-L-rhamnose. — A mixture of L-rhamnose (18 g), acetone (400 ml), and anhydrous copper sulfate (30 g) was heated for 4.5 h at reflux. T.l.c. with solvent (*E*) indicated complete conversion of L-rhamnose into a single product. The mixture was filtered and the filtrate evaporated to a syrup (22 g) that crystallized on storing for 10 days at 0°. After crystallization from hexane, 2,3-*O*-isopropylidene-L-rhamnose had m.p. 93° (lit.[15] m.p. 92–93°).

Methyl 6-deoxy-2,3-O-isopropylidene-α-L-mannofuranoside (**3**). — *A. From* **2**. A mixture of **2** (1.8 g) in acetone (200 ml) and anhydrous copper sulfate (15 g) was heated for 4 h at reflux. T.l.c. with irrigant (*D*) indicated complete conversion of **2** into a single product. The mixture was filtered and the filtrate was evaporated to give **3** (2.2 g, 100%) as a colorless syrup. The acetal **3** had $[\alpha]_D^{25}$ −53.3° (*c* 0.9, chloroform); ν_{max}^{film} 3450 cm^{-1} (OH); n.m.r. ($CDCl_3$): τ 5.1 (s, H-1), 5.5 (d, $J_{2,3}$ 6 Hz, H-2), 5.95 (q, H-5), 6.35 (q, $J_{3,4}$ 4, $J_{4,5}$ 7 Hz, H-4), 6.7 (s, OMe), 7.4 (broad OH signal which disappeared on exchange with D_2O), 8.65 (d, $J_{5,6}$ 5 Hz, H-6), 8.55, and 8.75 (CMe_2).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.02; H, 8.31. Found: C, 55.00; H, 8.45.

B. From 2,3-O-isopropylidene-L-rhamnose. — A mixture of 2,3-*O*-isopropylidene-L-rhamnose (10 g), acetone (160 ml), methanol (120 ml), and 20 g of Amberlite IR-120 (H^+) resin was boiled for 1.5 h at reflux. The mixture was filtered and the filtrate evaporated to a syrup that was chromatographed on a column of silica gel. Elution with solvent (*J*) gave three components, the first containing 6.5 g (60%) of **3**, identical with a sample of **3** obtained from **2**.

The fractions of the component having slightly lower R_F value than **3** gave methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (**4**, 2.2 g, 20%) as an oil; $[\alpha]_D^{25}$ −23° (*c* 3, chloroform) (lit.[11] $[\alpha]_D^{21}$ −10.65°); ν_{max}^{film} 3440 cm^{-1} (OH); n.m.r. ($CDCl_3$): τ 5.22 (s, H-1) 6.65 (s, OMe), 8.45, 8.58 (CMe_2) and 8.8 (d, $J_{5,6}$ 5.8 Hz, H-6); n.m.r. (D_2O): τ 5.15 (s, H-1), 5.8 (d, $J_{2,3}$ 5.5 Hz, H-2), 6.05 (H-3), 6.67 (s, OMe, 8.5, 8.75 (CMe_2), and 8.8 ($J_{5,6}$ 5.8 Hz, H-6).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.02; H, 8.31. Found: C, 54.88; H, 8.52.

The fractions containing the component having the lowest R_F value were evaporated to give methyl 6-deoxy-2,3-*O*-isopropylidene-β-L-mannopyranoside (**5**) (0.5 g, 5%); $[\alpha]_D^{25}$ +98° (*c* 3, chloroform); ν_{max}^{film} 3450 cm^{-1} (OH); n.m.r. ($CDCl_3$):

τ 5.4 (d, $J_{1,2}$ 3 Hz, H-1), 6.0 (t, $J_{2,3} = J_{3,4}$ 6 Hz, H-3) 3.75 (q, H-2), 6.45 (s, OMe), 8.45, 8.6 (CMe_2), and 8.75 (d, $J_{5,6}$ 5.5 Hz, H-6).

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.02; H, 8.31. Found: C, 54.75; H, 8.60.

Methyl 6-chloro-5,6-dideoxy-2,3-O-isopropylidene-β-D-gulofuranoside (**7**). — A mixture of **3** (1.09 g) in carbon tetrachloride (100 ml) was boiled for 5 h under reflux with triphenylphosphine (6.0 g) and 10 g of molecular sieve (Matheson, Coleman and Bell). The mixture was filtered and the filtrate evaporated to a solid mass that was extracted with hexane. The extract was evaporated to a residue that was chromatographed on silica gel. Elution with solvent (*K*) removed the unreacted triphenylphosphine, and further elution with solvent (*H*) gave the crystalline chloro derivative **7** (470 mg, 40%). After crystallization from hexane, **7** had m.p. 54°, $[\alpha]_D^{25}$ −97.9, (*c* 1.3, chloroform); n.m.r. ($CDCl_3$): τ 5.18 (s, H-1), 5.3–6.05 (m, H-2, H-3, H-5), 6.2 (q, $J_{3,4}$ 3, $J_{4,5}$ 7 Hz, H-4), 6.7 (s, OMe), 8.45 (d, $J_{5,6}$ 6.5 Hz, H-6), 8.60, and 8.75 (CMe_2).

Anal. Calc. for $C_{10}H_{17}ClO_4$: C, 50.74; H, 7.24; Cl, 14.98. Found: C, 51.00; H, 7.35; Cl, 14.93.

Methyl 6-deoxy-2,3-O-isopropylidene-α-L-lyxo-hexofuranosid-5-ulose (**9**). — Ruthenium tetraoxide, prepared by treating ruthenium dioxide hydrate (1 g) with sodium periodate (18 g) in water (150 ml), was extracted with carbon tetrachloride. The extract was added to a solution of **3** (1.2 g) in dichloromethane (60 ml) at 0°. After keeping the mixture for 0.5 h at 0° and an additional 0.5 h at 25°, the excess of ruthenium tetraoxide was decomposed by the addition of 2-propanol. The mixture was filtered and the filtrate evaporated to give crystalline **9** (1.2 g, 100%), homogeneous by t.l.c. with irrigant (*F*). After crystallization from hexane, **9** had m.p. 56–57°, $[\alpha]_D^{25}$ 0°; ν_{max} 1718 cm^{-1} (C=O); n.m.r. ($CDCl_3$): τ 5.05 (s, H-1), 5.58 (d, $J_{2,3}$ 6 Hz, H-2), 5.65 (d, $J_{3,4}$ 4 Hz, H-4), 7.75 (s, OMe), 7.8 (s, H-6), 8.60, and 8.75 (CMe_2).

Anal. Calc. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.45. Found: C, 55.51; H, 7.51.

Reduction with **9** *with sodium borohydride.* — The carbonyl derivative **9** (5.0 g) was dissolved in methanol (200 ml) and sodium borohydride (2.5 g) was added to it at 0°. The mixture was stirred for 2 h at 0° and then evaporated to dryness. The residue was extracted with ether and the extract was washed with water, dried, and evaporated to a crystalline mass (5.0 g). Recrystallization from hexane gave **10** (3.0 g, 60%); m.p. 78°, $[\alpha]_D^{25}$ −85° (*c* 0.8, methanol) [lit.[17] m.p. 78–78.5°, $[\alpha]_D^{23}$ −85.3°]. The mother liquor was evaporated to a syrup which, on chromatography with solvent (*C*), gave an additional amount of **10** (1 g, 20%) and **3** (1 g, 20%). Compound **9** had a slightly lower R_F value than **3** with solvent (*B*),

Methyl 6-deoxy-2,3-O-isopropylidene-5-O-(p-tolylsulfonyl)-β-D-gulofuranoside (**11**). — The hydroxy derivative **10** (4.36 g) was dissolved in pyridine (100 ml) and the solution was stirred with *p*-toluenesulfonyl chloride (10 g) for 4 days at 40°. Pyridine was removed by evaporation, and the residue was stirred with saturated aqueous sodium hydrogencarbonate. The mixture was then extracted with chloroform. The extract was washed with water, dried, and evaporated to a crystalline solid

that crystallized from ether–hexane to give **11** (7.2, 96%); m.p. 71°, $[\alpha]_D^{25}$ −70° (*c* 0.9, methanol) (lit.[17] m.p. 70–71°, $[\alpha]_D^{24}$ −73.1°).

Methyl 5-S-acetyl-6-deoxy-2,3-O-isopropylidene-5-thio-α-L-mannofuranoside (**8**). — *A. From* **7**. A mixture of **7** (400 mg), dry *N,N*-dimethylformamide (20 ml) and potassium thioacetate (600 mg) was heated under nitrogen for 10 days at 130°. The mixture was then diluted with xylene (100 ml) and evaporated to dryness. The residue was stirred with water and extracted with ether. Evaporation of the dried extract gave an oil that was purified by chromatography on silica gel with solvent (*H*) as the eluent. The fractions containing **8** were evaporated to give 40 mg (10%) of **8** which, after crystallization from hexane, had m.p. 48°, $[\alpha]_D^{25}$ −69.9 (*c* 1, chloroform); ν_{max} 1685 cm^{-1} (SAc); n.m.r. ($CDCl_3$): τ 5.2 (s, H-1), 5.38 (q, $J_{2,3}$ 6, $J_{3,4}$ 2.5 Hz, H-3), 5.9–6.3 (m, H-4, H-5), 6.75 (s, OMe), 7.75 (SAc), 8.55 (CMe_2), and 8.65 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{12}H_{20}O_5S$: C, 52.15; H, 7.29; S, 11.60. Found: C, 52.22; H, 7.14; S, 11.55.

There was no reaction between **7** and potassium thioacetate either in boiling acetone or in *N,N*-dimethylformamide at 100°.

B. From **11**. A mixture of **11** (1.8 g), *N,N*-dimethylformamide (100 ml), and potassium thioacetate (2 g) was heated for 2 days at 115° under nitrogen. Processing of the mixture and chromatography as before gave **8** (0.83 g, 60%).

1,2,3-Tri-O-acetyl-5-S-acetyl-6-deoxy-5-thio-β-L-mannofuranose (**13**) *and 1,2,3,5-tetra-O-acetyl-6-deoxy-5-thio-L-mannopyranose* (**12**). — Compound **8** (1.1 g) was dissolved in 15 ml of 90% aqueous trifluoroacetic acid and, after keeping for 0.5 h at 25°, the solution was evaporated to a syrup that was dried by the addition and evaporation of benzene. The residue was dissolved at 0° in a solution containing 8 ml of acetic acid, 8 ml of acetic acid, 8 ml of acetic anhydride, and 0.4 ml of sulfuric acid. After 2 days at 0°, sodium acetate (4 g) was added and the mixture was diluted with toluene (50 ml). The residue left after evaporation was treated with water at 0° and extracted with ether. The extract was washed with saturated aqueous sodium hydrogencarbonate and water, and then dried. Evaporation gave a syrup (1.2 g) that was chromatographed on silica gel with solvent (**1**). Compound **13** (40 mg) was eluted first and, after crystallization from ether–hexane, it had m.p. 98°, $[\alpha]_D^{25}$ −128° (*c* 0.8, chloroform); ν_{max}^{Nujol} 1750 (*O*-acetyl) and 1685 cm^{-1} (*S*-acetyl); n.m.r. ($CDCl_3$): τ 3.85 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.45–4.75 (m, H-2, H-3), 5.80 (q, $J_{3,4}$ 3, $J_{4,5}$ 10 Hz, H-4), 6.6 (m, H-5), 7.75 (*S*-acetyl), 7.85, 7.95, 8.0 (*O*-acetyl), and 8.62 (d, $J_{5,6}$ 6 Hz, H-6).

Anal. Calc. for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.45; H, 5.98; S, 9.29.

The fractions containing **12** (having slightly lower R_F values than **13** with irrigant *C*) were concentrated to a syrup (0.9 g) that was homogeneous by t.l.c. Compound **12** had $[\alpha]_D^{25}$ −134° (*c* 1, chloroform); ν_{max}^{film} 1750 cm^{-1} (OAc); n.m.r. ($CDCl_3$): τ 6.22, 6.35 (pd, H-1), 7.8–8.05 (m, *O*-acetyl), 8.7, and 8.8 (pd, $J_{5,6}$ 6 Hz, H-6 of α,β anomers).

Anal. Calc. for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.54; H, 6.01; S, 8.94.

5-Thio-D-rhamnopyranose (**6**). — To a solution of **12** (570 mg) in methanol (21 ml) saturated with nitrogen, was added at 0° a 0.2M solution of sodium methoxide in methanol until the mixture became alkaline. After 0.5 h at 0°, compound **12** had been converted into a single product having R_F 0.28 (solvent *E*). The mixture was treated with Amberlite IR-120(H^+) resin to remove sodium ions, filtered, and the filtrate evaporated to give **6** as a colorless syrup (290 mg, 100%); $[\alpha]_D^{25}$ −55.6° (*c* 1, methanol); ν_{max}^{film} 3440 cm^{-1} (OH), but no peak at 2550 cm^{-1}.

Anal. Calc. for $C_6H_{12}O_4S$: C, 39.98; H, 6.71; S, 17.79. Found: C, 40.03; H, 6.80; S, 17.92.

Similar deacetylation of **13** also gave **6** in quantitative yield.

1,2,3,4-Tetra-O-(p-nitrobenzoyl)-5-thio-L-rhamnopyranose (**14**). — A solution of 0.1 g of **6** in 5 ml of pyridine was treated with 1 g of *p*-nitrobenzoyl chloride for 3 days. Pyridine was removed by evaporation and the residue was stirred with 100 ml of saturated aqueous sodium hydrogencarbonate. The insoluble solid was filtered off, washed with water, dried, and crystallized from ethyl acetate–hexane to yield **14** (380 mg, 88%) as an anomeric mixture; m.p. 135–145°, $[\alpha]_D^{25}$ −5° (*c* 1, chloroform).

Anal. Calc. for $C_{34}H_{24}N_4O_{16}S$: C, 52.58; H, 3.11. Found: C, 52.72; H, 3.06.

Chromatography of the foregoing mixture on silica gel with solvent (*I*) as the eluent gave the pure β-L anomer of **14**; m.p. 202°, $[\alpha]_D^{25}$ +62.9° (*c* 2, chloroform); ν_{max}^{Nujol} 1730 cm^{-1} (C=O); n.m.r. ($CDCl_3$): τ 3.75 (d, $J_{1,2}$ 3.7 Hz, H-1), 4–4.25 (m, H-2, H-3, H-4), 6.4 (m, H-5), and 8.65 (d, $J_{5,6}$ 7 Hz, H-6).

Anal. Calc. for $C_{34}H_{24}N_4O_{16}S$: C, 52.58; H, 3.11; N, 7.21; S, 4.13. Found: C, 52.61; H, 3.09; N, 7.34; S, 4.00.

REFERENCES

1 D. J. Hoffman and R. L. Whistler, *Biochemistry*, 7 (1968) 4479–4483; R. L. Whistler and W. C. Lake, *Biochem. J.*, 130 (1972) 919–925.
2 J. Zysk, A. Bushway, R. L. Whistler, and W. W. Carlton, *J. Reprod. Fert.*, 45 (1975) 69–72.
3 M. Bobek, R. L. Whistler, and A. Bloch, *J. Med. Chem.*, 13 (1970) 411–413; N. Otofani and R. L. Whistler, *ibid.*, 17 (1974) 535–537.
4 A. K. M. Anisuzzaman, W. C. Lake, and R. L. Whistler, *Biochemistry*, 12 (1973) 2041–2045; T. L. Graham and R. L. Whistler, *ibid.*, 15 (1976) 1189–1194.
5 M. Bobek, R. L. Whistler, and A. Bloch, *J. Med. Chem.*, 15 (1972) 168–171.
6 M. Chen and R. L. Whistler, *Arch. Biochem. Biophys.*, 169 (1975) 392–396.
7 R. H. Blum and S. K. Carter, *Ann. Intern. Med.*, 80 (1974) 249–259.
8 G. Bonadonna, M. DeLena, and G. Beretta, *Eur. J. Cancer*, 7 (1971) 365–367.
9 J. P. Marsh, Jr., C. M. Mosher, R. M. Acton, and L. Goodman, *Chem. Commun.*, (1967) 973–974.
10 E. M. Acton, A. N. Fujiwara, and D. W. Henry, *J. Med. Chem.*, 17 (1974) 659–660; F. Arcamone, G. Franceschi, and S. Penco, U. S. Patent 3803,124 (April 9, 1974).
11 J. Jarý, K. Čapek, and J. Kovař, *Collect. Czech. Chem. Commun.*, 28 (1963) 2171–2180.
12 C. Walling, *J. Am. Chem. Soc.*, 72 (1950) 1164–1168.
13 C. R. Barker, T. M. Noone, D. C. C. Smith, and J. W. Spoors, *J. Chem. Soc.*, (1955) 1327–1332.
14 G. R. Barker and J. W. Spoors, *J. Chem. Soc.*, (1956) 2556–2658.
15 S. J. Angyal, V. A. Pickles, and R. Ahluwalia, *Carbohydr. Res.*, 3 (1967) 300–307.
16 A. S. Perlin, *Can. J. Chem.*, 42 (1964) 1365–1372.

17 K. J. RYAN, H. ARZOUMANIAN, E. M. ACTON, AND L. GOODMAN, *J. Am. Chem. Soc.*, 86 (1964) 74–77.
18 K. KEFURT AND J. JARÝ, *Chem. Commun.*, (1969) 213–214.
19 B. T. LAWTON, W. A. SZAREK, AND J. K. N. JONES, *J. Chem. Soc., D*, (1969) 787–788.
20 C-W. CHIU AND R. L. WHISTLER, *J. Org. Chem.*, 38 (1973) 832–834.
21 J. B. LEE AND T. J. NOLAN, *Can. J. Chem.*, 44 (1966) 1331–1334; J. B. LEE AND T. J. NOLAN, *Tetrahedron*, 23 (1967) 2789–2794.
22 C. L. STEVENS AND K. K. BALASUBRAMANIAN, *Carbohydr. Res.*, 21 (1972) 166–168; K. JAMES, A. R. TATCHELL, AND P. K. RAY, *J. Chem. Soc.*, (1967) 2681–2886.
23 I. AUGESTAD AND E. BERNER, *Acta Chem. Scand.*, 10 (1956) 911–916.