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REACTIONS OF ETHYL 3,5,6-TRI-*O*-ACETYL-2-*S*-ETHYL-1,2-DITHIO-α-D-MANNOFURANOSIDE WITH HALOGENS*

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ABSTRACT

Ethyl 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-1,2-dithio-α-D-mannofuranoside (**5**) reacted with bromine to give the very unstable glycosyl bromide **4**, which with water gave a mixture of the 1-hydroxyl analogue (**8**) and the nonreducing α-D-(1→1)-linked disaccharide derivative **9**. When the bromide **4** was treated with mercuric acetate or potassium acetate, 1,3,5,6-tetra-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannofuranose (**7**) was obtained, but silver acetate in carbon tetrachloride gave **7** in admixture with its β-anomer (**10**). Methanol reacted with **4** to give an anomeric mixture of the glycofuranosides (**11** and **12**). An excess of chlorine converted the dithio derivative **5** into a 3,5,6-tri-*O*-acetyl-2-chloro-2-*S*-ethyl-2-thio-D-manno(or gluco)furanosyl chloride (**13**), whereas a lower proportion of chlorine appeared to give the 1-chloro analogue of **4**. Treatment of the dichloro derivative **13** with methanol led to a mixture of three methyl glycosides, one (**14**) retaining the chlorine atom at C-2, and the other two (**15** and **16**) resulting from exchange of both chlorine atoms by methoxyl groups.

INTRODUCTION

Ethyl 2-*S*-ethyl-1,2-dithio-α-D-mannofuranoside (**2**) is obtainable from a 2-*S*-ethyl-2-thio-D-hexose diethyl dithioacetal[2] having the D-*manno* stereochemistry[3,4] by the action of mercuric chloride[3,5] and also by the nitrous acid deamination of 2-amino-2-deoxy-D-glucose diethyl dithioacetal in acetic acid containing sodium acetate[6]. The furanoside structure of **2** was established by periodate oxidation[5], and its total stereochemistry by chemical[6] and X-ray crystallographic[7] methods. This paper reports studies on the reaction of the derived triacetate **5** with bromine and chlorine, designed to evaluate the utility of **5** as a starting material for syntheses based on replacement of the glycosidic ethylthio group by other groups, and for subsequent transformations involving the ethylthio group at C-2, with a route to 2-deoxyaldofuranosyl nucleosides being a particular objective[8]. The replacement of the alkylthio group in acetylated alkyl 1-thioglycosides by bromine[9] is a well established route to

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acetylated glycosyl bromides[10], and related chlorination reactions have been described[11]; furthermore, acylated dialkyl dithioacetals have been halogenated to give acyclic monohalo monothio derivatives useful in synthesis[12,13]. Thus far, the synthetic possibilities of this type of reaction with such cyclic dithio derivatives as **5** have not been explored.

RESULTS AND DISCUSSION

Treatment of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal[2] (**1**) with one molecular proportion of mercuric chloride in aqueous solution in the presence of barium carbonate, essentially as already described[3], gave a 70% yield of crystalline ethyl 2-*S*-ethyl-1,2-dithio-α-D-mannofuranoside[6,7] (**2**), $[\alpha]_D^{25}$ +106° in chloroform. This compound had previously been purified by recrystallization from benzene–petroleum ether[5] or chloroform–petroleum ether[6], but, in the present work, water was found the most satisfactory recrystallization solvent for obtaining **2** free from inorganic contaminants. The mother liquors from the reaction contained a second product, isolated crystalline in 1.5% yield after chromatography. Its analysis showed it to be isomeric with **2**, and it was formulated as the β-anomer (**3**) of **2** from its levorotation ($[\alpha]_D$ −183° in ethanol), from its mass spectrum (which was practically identical with that[6] of **2**), and from the similarity of its n.m.r. spectrum (see Table I) with that[6] of **2**; the high $J_{1,2}$ coupling (7.5 Hz) is incompatible with a pyranoid structure having the α- or β-D-*manno* configuration.

Acetylation of **2** gave the triacetate **5** as a crystalline, low-melting (43°) solid having m.p. and specific rotation (+105° in chloroform) in agreement with the product (of then-undetermined stereochemistry) isolated by Wolfrom *et al.*[5]; this product was reported[6] as a solidified oil in work that established its stereochemistry. To obtain the crystalline triacetate **5**, it was found important to keep the quantities of pyridine and acetic anhydride to the minimum in the acetylation reaction; use of an excess of pyridine impeded the crystallization of **5**. The syrupy triacetate (**6**) of the β-anomer **3** had an n.m.r. spectrum very similar to that of the α-anomer **5**, except that the H-1 and H-2 signals resonated at lower field in **6** than in **5**; the $J_{1,2}$ couplings were essentially the same (~8 Hz) for the two anomers. The H-3 signal of **3** appeared as a triplet ($J_{3,4}$ 4.0 Hz), whereas this signal was a doublet of doublets for **5** ($J_{3,4}$ 3.0 Hz). The mass spectrum of **6** was essentially identical with that[6] of **5**.

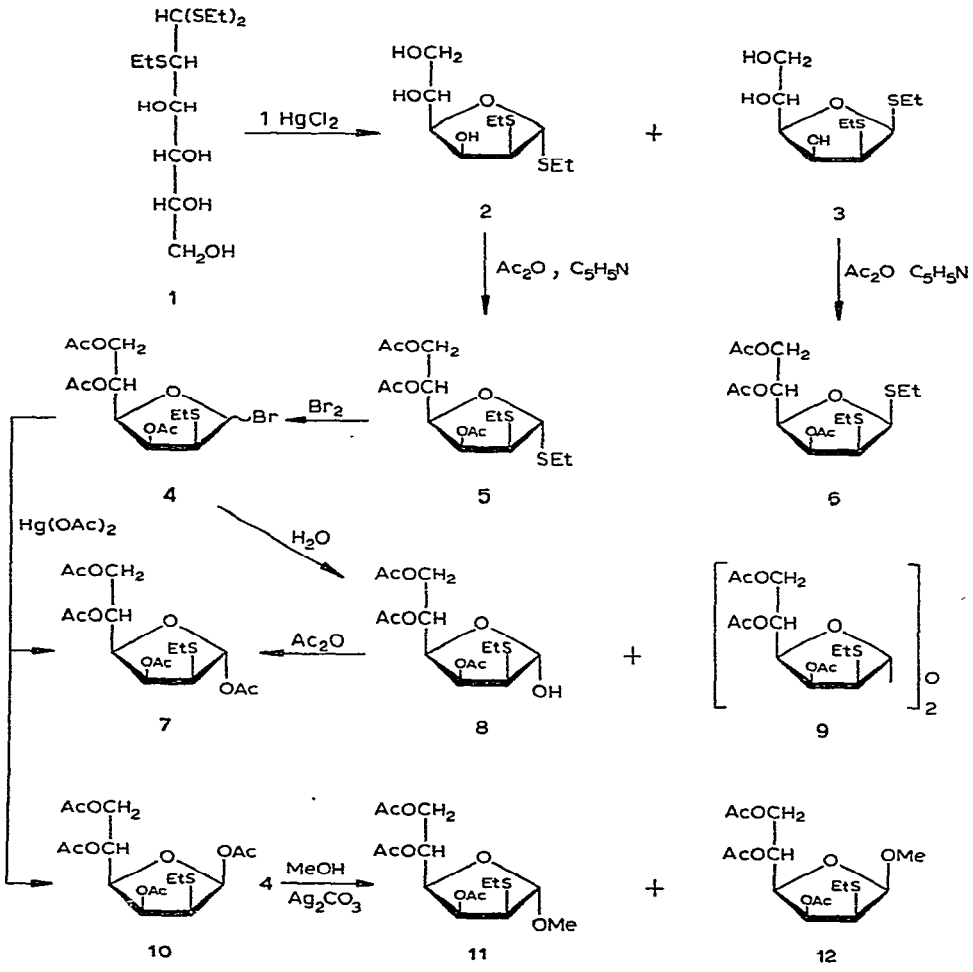
Treatment of the acetylated dithioglycoside **5** with a slight excess of bromine in carbon tetrachloride for 5 min at ~25° gave the syrupy, unstable bromide **4** through replacement of the glycosidic ethylthio group by bromine, with retention of the 2-ethylthio group. The n.m.r. spectrum of **4** resembled that of the precursor **5**, except that the H-1 and H-2 signals had been shifted downfield by about 1.2 and 0.8 p.p.m., respectively, in the solvent (carbon tetrachloride) used. Compound **4** was a single anomer, as only one anomeric-proton signal (a doublet of $J_{1,2}$ 3.0 Hz) was observed in the n.m.r. spectrum. The configuration of **4** is most probably α, as indicated by the $J_{3,4}$ coupling of 3.5 Hz (see later discussion for compound **9**). The product decomposed extensively on attempted storage or on gentle warming.

Treatment of the bromide **4** with mercuric acetate in acetic acid[14], or with potassium acetate in methanol, gave one major product, 1,3,5,6-tetra-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannofuranose (**7**), isolated crystalline. In contrast, use of silver acetate in carbon tetrachloride converted **4** into a mixture of **7** and its β-anomer (**10**), obtained as a levorotatory oil that showed a mass-spectral peak at *m/e* 392 for the molecular ion, together with the anticipated fragment-ions (see Experimental section). The n.m.r. spectra of **7** and **10** showed little difference, except that H-1 of the β-anomer **10** resonated 0.23 p.p.m. to lower field than for the α-anomer **7**; the $J_{1,2}$ couplings were practically the same (~5 Hz) although the $J_{3,4}$ values were characteristically different, being 3.5 Hz for **7** (H-3 resonating as a doublet of doublets) and 5.0 Hz for **10** (H-3 resonating as a triplet). The n.m.r. data for **7** and **10** stand in distinct contrast to those observed for the pyranoid analogue, 1,2,4,6-tetra-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannopyranose[6]; most noteworthy is the wide separation (~1.2 p.p.m.) of the H-3 and H-4 signals for the furanoid derivatives, in contrast to the α-pyranoid analogue, for which these signals are practically coincident. Thus, the presumed retention of the furanoid ring-structure in the conversion of **4** into the 1-acetates **7** and **10** is clearly confirmed.

The α-acetate **7** had previously been reported as an oil[6], but its anomeric configuration was not then assigned; it was obtained by treating the dithio precursor **5** with mercuric chloride and cadmium carbonate in aqueous acetone, to give crystalline 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannofuranose (**8**), which was subsequently acetylated. The α-D configuration for **7** and **8** can now be assigned definitively from the present results.

When the bromide **4** in carbon tetrachloride was treated with aqueous sodium hydrogen carbonate, there resulted a mixture of two compounds, one of which proved to be the product (**8**) of replacement of bromine by a hydroxyl group; it was isolated in 17% yield. A second product, isolated crystalline in 28% yield, was formulated as the disaccharide derivative 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannofuranosyl 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannofuranoside (**9**). The compound gave an acceptable elemental analysis, contained no free hydroxyl group, gave mass-spectral fragments resulting from cleavage of the glycosidic linkage with retention of charge on either the glycosyl or the glycosyloxy fragment, and had an n.m.r. spectrum concordant with a symmetrical structure as there was no additional signal multiplicity beyond that observed with other compounds in this study. The spectrum very closely resembled that of the α-tetraacetate **7**, except that the H-1 signal resonated at higher field, and there were only three acetate signals per sugar residue. From the high dextrorotation of the compound (+119.5° in chloroform) and from the $J_{3,4}$ coupling of 3.0 Hz, the anomeric configuration was assigned as α,α. (The $J_{1,2}$ values for compounds in this series showed little difference between anomers, but all of the α anomers showed $J_{3,4}$ couplings of 3.0–3.5 Hz, whereas the β anomers showed $J_{3,4}$ couplings of ~5 Hz.) The disaccharide **9** presumably arises through attack of **8**, formed by hydrolysis of bromide **4**, upon unreacted **4**.

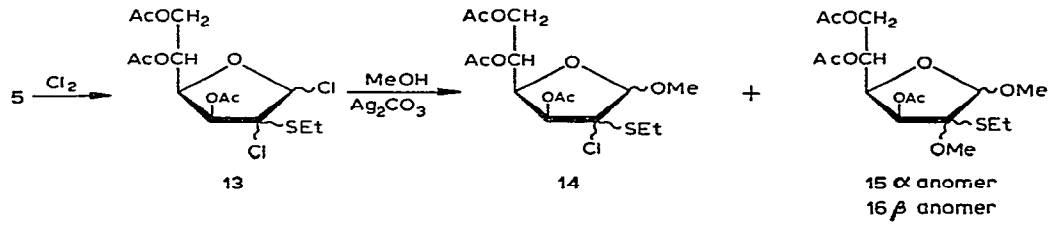
Reaction of the bromide **4** with methanol under Koenigs–Knorr conditions

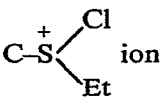


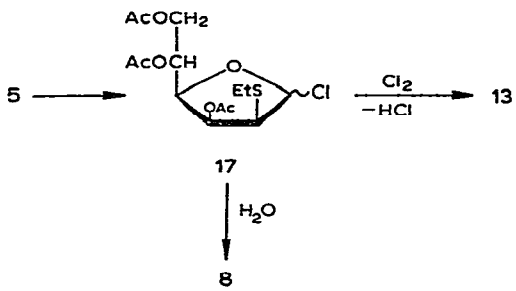
gave a mixture of the syrupy methyl glycofuranosides, separable by chromatography to give 11% of the dextrorotatory ($[\alpha]_D$ +79° in chloroform) α-glycoside **11** and 38% of the levorotatory ($[\alpha]_D$ −17° in chloroform) β-glycoside **12**; the products were homogeneous by the evidence of n.m.r. spectroscopy, and they showed essentially identical mass spectra, giving M^+ (*m/e* 364) and $M^+ - \cdot OMe$ peaks (*m/e* 333). Except for minor chemical-shift differences, the spectra of the anomers were extremely similar, displaying identical $J_{1,2}$ couplings (5.0 Hz). The notable difference, characteristic throughout this series, was again observed in the appearance of the H-3 signal as a result of the $J_{3,4}$ coupling. For the α-anomer **11**, $J_{3,4}$ is 3.5 Hz, and the H-3 signal appears as a doublet of doublets because $J_{2,3}$ is larger (~5.0 Hz). In contrast, $J_{3,4}$ for the β-anomer **12** is 5.0 Hz, so that the H-3 signal appears as a triplet. This behavior is exactly analogous to that observed for the anomeric 1-acetates **7** and **10**.

The dithioglycoside **5** reacted rapidly with an excess of chlorine (8% of chlorine in carbon tetrachloride) at room temperature to give a product, isolated crystalline in

70% yield, whose elemental analysis indicated replacement of one ethylthio group by chlorine, together with incorporation of a second atom of chlorine. From its n.m.r. and mass spectra, the structure of 3,5,6-tri-*O*-acetyl-2-chloro-2-(ethylthio)-D-manno-(or gluco)furanosyl chloride (**13**) was assigned to this product. The H-1 signal resonated as a singlet, there was no proton on C-2, and the H-3 resonance appeared as a doublet showing $J_{3,4}$ 5.0 Hz. The remaining signals and couplings were closely similar to those observed for the other compounds of related structure in this study (see Table I). The mass spectrum (see Experimental section) showed, in addition to the molecular ion containing two chlorine atoms, fragments corresponding to loss of one chlorine atom and of both chlorine atoms.



When the chlorination of **5** was conducted with a diluted (1%) solution of chlorine in carbon tetrachloride and the product was resolved by chromatography on silica gel, there was obtained a low yield of the dichloro derivative **13**, together with 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannopyranose (**8**). The formation of **8** suggests that the 1-ethylthio group of **5** had been replaced by chlorine to give the chloro analogue of **4**, which was subsequently hydrolyzed during the chromatographic separation. Presumably, the monochloro derivative **17** undergoes further chlorination by an excess of chlorine to give **13**, possibly by way of an intermediate  ion formed by attack of electrophilic chlorine on S-2, with subsequent loss of HCl through attack at C-2 by Cl^-.



The dichloro derivative **13** reacted with methanol in the presence of silver carbonate to give a mixture of three syrupy products. All three had n.m.r. spectra that

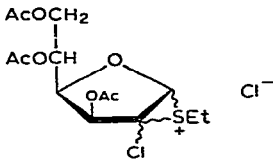
TABLE I

100-MHz N.M.R. SPECTRAL DATA FOR COMPOUNDS 3–7 AND 9–16

Compound	*Solvent*	*Chemical shifts in τ values[a] (first-order couplings, Hz, in parentheses)*									
		H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{3,4}$)	*H-4* ($J_{4,5}$)	*H-5* ($J_{5,6}$)	*H-6* ($J_{6,6'}$)	*H-6'* ($J_{5,6'}$)	$-CH_2S-$	CH_2CH_3	*OAc (and OMe)*
3	C_5D_5N, D_2O	4.36d (7.5)	6.17q (4.0)	5.31t (4.0)	5.67q (8.5)	5.41sp (3.0)	5.76q (11.5)	5.93q (5.5)	7.35q, 7.47q	8.83t, 8.85t	
4	CCl_4	3.55d (3.0)	5.90q (6.5)	4.38q (3.5)	5.50q (9)	4.26o (2.5)	5.51q (12.9)	5.98q (5.5)			
5[b,c]	$CDCl_3$	4.83d (8.0)	6.78q (4.5)	4.46q (3.0)	5.66q (9.0)	4.78o (2.5)	5.50q (12)	5.88q (6)	7.10–7.68, two q	8.57–8.88 two t	7.92s, 7.98s, 8.03s
6	$CDCl_3$	4.52d (7.5)	6.36q (4.5)	4.44t (4.5)	5.73q (9.5)	4.70o (2.5)	5.45q (12)	5.89q (4.5)	7.39q, 7.60q	8.72t, 8.80t	7.91s, 7.97s, 8.04s
7[b]	$CDCl_3$	3.86d (5.5)	6.49t (5.0)	4.37q (3.5)	5.57q (9.5)	4.80o (3.0)	5.47q (12.5)	5.95 (5.5)	7.40q	8.77t	7.91s, 7.93s, 7.97s, 8.03s
9	$CDCl_3$	4.61d (5.0)	6.61t (5.0)	4.36q (3.0)	5.60q (9.0)	4.72o (2.5)	5.40 (12.0)	5.86 (5.0)	7.35q	8.71t	7.90s, 7.93s, 8.00s
10	$CDCl_3$	3.63d (5.0)	6.61t (5.0)	4.34t (5.0)	5.64q (9.0)	4.77o (2.5)	5.40q (12.0)	5.95q (5.0)	7.44q	8.78t	7.91s (×2), 7.97s, 8.01s
11	$CDCl_3$	5.04d (5.0)	6.71t (5.0)	4.42q (3.0)	5.69q (9.5)	4.77o (2.5)	5.43q (12.5)	5.86q (5.5)	7.40q	8.75t	7.90s, 7.92s, 8.00s; 6.60s (OMe)
12	$CDCl_3$	4.96d (5.0)	6.68t (5.0)	4.33t (5.0)	5.64q (9.5)	4.73o (2.5)	5.32q (12.5)	5.82q (5.0)	7.43q	8.77t	7.92s, 7.95s, 8.02s; 6.59s (OMe)
13	$CDCl_3$	3.72s		4.32d (5.0)	5.20q (9.0)	4.66o (2.5)	5.42q (12.5)	5.93q (5.0)	7.12q	8.68t	7.90s, 7.95s, 8.01s
14	$CDCl_3$	5.17s		4.40d (5.0)	5.31q (10.0)	4.72o (2.5)	5.33q (12.5)	5.87q (5.0)	7.05q	8.65t	7.93s (×2), 8.02s; 6.52s (OMe)
15	$CDCl_3$	5.30s		4.43d (5.0)	5.37q (9.5)	4.73o (2.5)	5.32q (12.5)	5.87q (5.0)	7.31q	8.70t	7.95s (×2), 8.02s; 6.57s, 6.61s (OMe)
16	$CDCl_3$	5.08s		4.56d (5.0)	5.64q (9.5)	4.97o (2.5)	5.32q (12.5)	5.87q (5.0)	7.52q	8.81t	7.91s, 7.95s, 8.03s; 6.55s, 6.58s (OMe)

[a]Signal multiplicities: d, doublet; m, multiplet; o, octet; q, quartet or doublet of doublets; s, singlet; sp, septet; t, triplet. [b]Partial data also given in ref. 6. [c]Spectrum also recorded at 220 MHz in pyridine-d_5 to confirm all assignments.

indicated the same general structure as that of the parent dichloro derivative **13**, with disubstitution at C-2 and monosubstitution at C-1, and all showed $M^{\ddagger}$ and $M^{\ddagger} - \cdot OCH_3$ peaks in their mass spectra, indicating that they were methyl glycosides. One product, isolated in 12% yield, retained one atom of chlorine (as demonstrated by analysis and by the isotopic pattern in the $M^{\ddagger}$, $M^{\ddagger} - \cdot OMe$, and $M^{\ddagger} - AcOH$ peaks) and was formulated as a methyl 3,5,6-tri-*O*-acetyl-2-chloro-2-*S*-ethyl-2-thio-D-manno(gluco)furanoside (**14**), whereas the other two products contained no chlorine but contained two methoxyl groups. One of these latter two products, isolated in 37% yield, was dextrorotatory and was assigned the structure of a methyl 3,5,6-tri-*O*-acetyl-2-(ethylthio)-2-*O*-methyl-α-D-manno(gluco)furanoside (**15**). The other one, obtained in 7% yield, was levorotatory and was most probably the β-anomer (**16**) of **15**. No firm evidence for the stereochemistry at C-2 of these products **13**–**16** was obtained. It is possible that **14**–**16** arise from **13** by way of an ionic inter-



13a

mediate of the type **13a**. It was established by experiment that compound **14** was not transformed into **15** or **16** under conditions of the Koenigs–Knorr reaction, indicating that **15** and **16** probably arise by initial replacement of the 2-chloro substituent by methoxyl, followed by replacement of the chlorine atom at C-1, whereas a competing reaction involving initial replacement at C-1 of **13** gives **14**, a product in which replacement of the second chlorine atom does not occur readily.

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. A Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r. spectra were recorded with a Perkin–Elmer "Infracord" spectrophotometer. N.m.r. spectra were recorded at 100 MHz with Varian HA-100 or JEOL MH-100 spectrometers; chemical shifts refer to an internal standard of tetramethylsilane ($\tau = 10.00$), and are recorded, together with spin-coupling values (Hz) in Table I. T.l.c. was performed with Silica Gel G (E. Merck, Darmstadt, Germany) activated at 120°, 9:1 or 7:3 (v/v) benzene–ether as the developer, and sulfuric acid as the indicator. Column chromatography was performed with silica gel Merck No. 7734 (0.05–0.2 mm). Columns were packed by allowing a slurry of the adsorbent in benzene to settle under gravity, and elution with 9:1 to 9:3 benzene–ether was effected without application of pressure or suction. Microanalyses

were made by W. N. Rond. Mass spectra were recorded by C. R. Weisenberger with an AEI MS-9 double-focusing, high-resolution spectrometer. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

Ethyl 2-S-ethyl-1,2-dithio-α-D-mannofuranoside (**2**) *and its β-D anomer* (**3**). — The procedure employed was a slightly modified and scaled-up version of that already described[3]. A solution of 2-*S*-ethyl-2-thio-D-mannose diethyl dithioacetal[2,3] (**1**, 14.00 g, 42.4 mmoles) in hot (50°) water (700 ml) was stirred with barium carbonate (16.7 g, 85 mmoles), and a solution of mercuric chloride (12.0 g, 44.3 mmoles) in hot (50°) water (250 ml) was poured into the mixture with thorough stirring. After 20 min, the mixture was filtered and the filtrate evaporated. The resulting solid was extracted with chloroform (100 ml), and the extract was evaporated to yield a crystalline solid which was dissolved in warm water (50 ml), and the clear solution concentrated and left to crystallize. Recrystallization of the product from a small amount of water gave pure **2**; yield 8.0 g (70%), m.p. 93–94°, $[\alpha]_D^{25}$ +106° (*c* 1.1, chloroform) (lit.[5] m.p. 88–90°, $[\alpha]_D$ +139°; lit.[6] m.p. 92–93°, $[\alpha]_D$ +108.2°). The product was identical with authentic[6] **2** by i.r. spectrum and mixed m.p.

T.l.c. of the mother liquor showed, in addition to **2**, traces of starting material **1** and a third component. This mixture was resolved by chromatography on a column of silica gel, to afford the third component, the β-anomer **3**; yield 150 mg (1.5%), m.p. 112–113°, $[\alpha]_D^{25}$ −183° (*c* 1.5, ethanol); *m/e* 268 (M^+), 207 ($M^+ - \cdot SEt$); X-ray powder diffraction data: 13.82 vs (2,2), 7.90 vs (1), 5.09 vs (2,2), 4.57 s (3,3), 4.44 w, 4.23 w, 4.08 s (3,3), 3.85 m, 3.53 vw, 3.32 vw, 3.23 vw, 3.15 w, 3.04 w, 2.91 w, 2.78 m, 2.61 m, and 2.46 m.

Anal. Calc. for $C_{10}H_{20}O_4S_2$: C, 44.75; H, 7.51; S, 23.89. Found: C, 45.18; H, 7.65; S, 23.68.

Ethyl 3,5,6-tri-O-acetyl-2-S-ethyl-1,2-dithio-α-D-mannofuranoside (**5**). — A solution of **2** (10.0 g, 37.5 mmoles) in pyridine (10 ml) and acetic anhydride (30 ml) was kept overnight at ~25°, and the mixture was then poured with stirring into ice–water (1 liter). The syrup that separated solidified gradually; the solid was crushed into a fine powder with a glass rod, filtered off, and washed with water. A solution of this product in ethanol (40 ml) was cooled to 10°, and water was added until the solution became slightly turbid. After the mixture had been kept for several h in a refrigerator, pure crystalline **5** (9.0 g) was obtained. By further addition of water to the filtrate, there was obtained additional **5**; total yield 12.0 g (82%), m.p. 43°, $[\alpha]_D^{25}$ +105° (*c* 2.0, chloroform) (lit.[5] m.p. 43°, $[\alpha]_D$ +107.5°; lit.[6] syrup, $[\alpha]_D^{23}$ +74.2°); X-ray powder diffraction data: 9.76 vs (1), 7.96 vw, 7.06 w, 6.25 vw, 5.37 m, 5.01 s (2), 4.74 m, 4.47 s (3), 3.93 m, 3.77 m, 3.41 m, and 2.96 w.

Anal. Calc. for $C_{16}H_{26}O_7S_2$: C, 48.73; H, 6.59; S, 16.24. Found: C, 48.66; H, 6.87; S, 16.23.

The use of larger proportions of pyridine in this preparation impeded the crystallization of the product.

*Ethyl 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-1,2-dithio-β-*D*-mannofuranoside* (**6**). — Conventional acetylation of **3** (300 mg) in pyridine (2 ml) and acetic anhydride (6 ml) gave **6** as a thick oil; *m/e* 394 ($M^{\ddagger}$), 333 ($M^{\ddagger} - \cdot SEt$).

*3,5,6-Tri-*O*-acetyl-2-*S*-ethyl-2-thio-*D*-mannofuranosyl bromide* (**4**). — To a solution of **5** (2.0 g, 5.08 mmoles) in carbon tetrachloride (20 ml) was added a solution of bromine (0.9 g, 5.62 mmoles) in carbon tetrachloride (20 ml) with stirring at ~25°. After 3 min, t.l.c. showed that the starting material had disappeared, and a single spot, presumably that of the bromide **4**, was observed. After 5 min, the mixture was concentrated under diminished pressure to 5–10 ml, and then carbon tetrachloride (20 ml) was added and the mixture was evaporated to remove the excess of bromine and the (volatile) ethylsulfenyl bromide. This evaporation procedure was repeated four times. The resulting syrupy bromide **4** was unstable, and was used directly in the next step. The n.m.r. spectrum of the reaction mixture at 3 min after the addition of bromine is recorded in Table I. Additional scans of the spectrum during a 10-min period showed changes in the appearance of the H-1 and H-2 signals, which became multiplets; after these scans had been completed, the solution at the probe temperature of the spectrometer (~35°) had become black.

*3,5,6-Tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-*D*-mannofuranose* (**8**) *and 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-*D*-mannofuranosyl 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-*D*-mannofuranoside* (**9**). — Compound **5** (2.00 g, 5.08 mmoles) in carbon tetrachloride (20 ml) was treated as in the preceding experiment with a solution of bromine (0.9 g, 5.62 mmoles) in carbon tetrachloride (20 ml). After 5 min at ~25°, the mixture was successively washed with saturated, aqueous sodium hydrogen carbonate and water, dried (sodium sulfate), evaporated to dryness, and a little ether added to the residue, whereupon the disaccharide derivative **9** crystallized, yield 0.50 g (28%). Recrystallization from ethanol gave pure **9**; m.p. 176–177°, $[\alpha]_D^{25}$ +119.5° (*c* 1.1, chloroform); *m/e* 349 ($M^{\ddagger}$ – glycosyloxy), 333 ($M^{\ddagger}$ – glycosyl).

Anal. Calc. for $C_{28}H_{42}O_{15}S_2$: C, 49.25; H, 6.20; S, 9.39. Found: C, 48.96; H, 6.23; S, 9.63.

Addition of petroleum ether to the filtrate from crystallization of **9** until slight turbidity appeared, followed by refrigeration overnight, gave crystalline **8**; yield 0.3 g (17%). Recrystallization from ether–petroleum ether gave pure **8**; m.p. 86–87°, $[\alpha]_D^{25}$ +52.3° (*c* 1.5, chloroform) (lit.[6] m.p. 87°, $[\alpha]_D$ +51.5° in chloroform). This compound was identical with authentic material[6] by mixed m.p., and i.r. spectrum.

*1,3,5,6-Tetra-*O*-acetyl-2-*S*-ethyl-2-thio-α-*D*-mannofuranose* (**7**). — *A. By acetylation of* **8**. A solution of **8** (3.00 g, 8.58 mmoles) in pyridine (6 ml) and acetic anhydride (6 ml) was kept overnight at ~25° and then poured with stirring into ice–water (200 ml). A syrup separated that subsequently crystallized, and the solid mass was finely crushed, filtered off, washed with water, and dried in the air; yield 2.8 g (94%). Recrystallization from aqueous ethanol gave pure **7**; m.p. 73–74°, $[\alpha]_D^{25}$ +77.6° (*c* 1, chloroform) (lit.[6], syrup, $[\alpha]_D$ +59.3° in chloroform); X-ray powder diffraction

data: 10.06 s (3), 8.58 m, 7.77 m, 5.71 vw, 5.41 s, 4.82 vs (1), 4.47 s (2), 3.99 m, 3.84 m, 3.72 vw, 3.62 w, 3.49 m, 3.39 w, and 2.95 w.

Anal. Calc. for $C_{16}H_{24}O_9S$: C, 48.99; H, 6.16; S, 8.17. Found: C, 49.13; H, 6.15; S, 8.19.

B. From the bromide **4** *by action of mercuric acetate.* Mercuric acetate (405 mg, 1.27 mmoles) in acetic acid (20 ml) was added to **4** that had been prepared from **5** (500 mg, 1.27 mmoles). The mixture was stirred for 1 h at ~25°, and then evaporated under diminished pressure. The residue was dissolved in chloroform, and the solution was successively washed with aqueous sodium hydrogen carbonate and water, dried (sodium sulfate), and evaporated to a syrup that showed one major component by t.l.c. After column-chromatographic resolution, there was obtained 250 mg (50%) of pure **7**, m.p. 73–74°.

The use of potassium acetate (2 molar equivs.) in place of mercuric acetate led to a similar result.

Reaction of the bromide **4** *with silver acetate to give* **7** *and its β anomer* **10.** — To a solution of **4** prepared from **5** (1.00 g, 2.54 mmoles), in carbon tetrachloride (30 ml), was added silver acetate (0.63 g, 3.77 mmoles), and the mixture was stirred for 30 min at ~25°. The mixture was filtered through Celite, and the filtrate was evaporated to dryness. T.l.c. showed two principal products that were barely resolved (1:1 benzene–ether, double development). The mixture was resolved on a column (40 × 3 cm) of silica gel, with 9:1 benzene–ether as the eluant, to give initially the α anomer **7** (125 mg) identical by i.r. spectrum and mixed m.p. with the product already described. Fractions containing both anomers in admixture were then eluted, followed by the pure β anomer **10**; yield 86 mg (8.5%); total yield of **7** and **10**, 642 mg (64%). The β-acetate **10** was an oil, $[\alpha]_D^{24}$ −17.7° (*c* 1, chloroform); *m/e* 392 (M^+), 333 ($M^+ - \cdot OAc$), 332 ($M^+ - AcOH$), 272 ($M^+ - 2AcOH$), 230 ($M^+ - 2AcOH - CH_2CO$), 208, and 166.

*Methyl 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-*D*-mannofuranoside* (**11**) *and its β anomer* (**12**). — Anhydrous methanol (50 ml) was shaken with anhydrous calcium sulfate (2.0 g) plus fresh silver carbonate (2.0 g) for 20 min. The mixture was then added to the bromide **4** prepared from the dithioglycoside **5** (2.00 g, 5.08 mmoles), and the mixture was shaken for 1 h at ~25°, filtered through Celite, and the filtrate evaporated to a syrup. The residue was extracted with chloroform, a brown residue was filtered off, and the extract was successively washed with 2% aqueous ammonia (twice) and water, dried (sodium sulfate), evaporated, and the product resolved on a column of silica gel, with 9:1 benzene–ether as the eluant, to give **11** and **12** as the principal products. Compound **11** was a syrup; yield 200 mg (11%), $[\alpha]_D^{24}$ +79° (*c* 1.25, chloroform); *m/e* 364 (M^+), 333 ($M^+ - \cdot OMe$). The β anomer **12** was also a syrup; yield 710 mg (38%), $[\alpha]_D^{25}$ −17° (*c* 1.1, chloroform); *m/e* 364 (M^+), 333 ($M^+ - \cdot OMe$).

Anal. Calc. for $C_{15}H_{24}O_8S$: C, 49.44; H, 6.64; S, 8.80. Found (for **11**): C, 49.92; H, 6.87; S, 8.99; (for **12**): C, 49.69; H, 6.58; S, 8.56.

*3,5,6-Tri-*O*-acetyl-2-chloro-2-*S*-ethyl-2-thio-*D*-manno(or gluco)furanosyl chloride* (**13**). — Carbon tetrachloride (5 ml) saturated at 25° with chlorine was added to a

solution of the dithioglycoside **5** (1.00 g, 2.54 mmoles) in carbon tetrachloride. After 5 min, the mixture was evaporated to dryness, and the residue was dissolved in petroleum ether (b.p. 30–60°). Refrigeration gave crystalline **13**; yield 0.72 g (70%). Recrystallization from ether–petroleum ether gave pure **13**, m.p. 84°, $[\alpha]_D^{24}$ +102° (*c* 1.1, chloroform); *m/e* 402, 404 (406) (M^+), 367, 369 ($M^+ - Cl$), 332 ($M^+ - 2Cl$), 307, 309 ($M^+ - \cdot Cl - AcOH$), and 289 ($M^+ - HCl - AcCl$).

Anal. Calc. for $C_{14}H_{20}Cl_2O_7S$: C, 41.70; H, 5.00; Cl, 17.58; S, 7.95. Found: C, 41.70; H, 4.99; Cl, 17.21; S, 7.66.

Repetition of this experiment, but with a diluted (1%) solution of chlorine in carbon tetrachloride, and resolution of the product on a column of silica gel, led to the isolation, in low yield, of the crystalline dichloro derivative **13**, together with crystalline 3,5,6-tri-*O*-acetyl-2-*S*-ethyl-2-thio-α-D-mannofuranose (**8**).

*Methyl 3,5,6-tri-*O*-acetyl-2-chloro-2-*S*-ethyl-2-thio-*D*-manno(gluco)furanoside* (**14**), *methyl 3,5,6-tri-*O*-acetyl-2-(ethylthio)-2-*O*-methyl-α-*D*-manno(gluco)furanoside* (**15**), *and methyl 3,5,6-tri-*O*-acetyl-2-(ethylthio)-2-*O*-methyl-β-*D*-manno(gluco)furanoside* (**16**). — A mixture of anhydrous methanol (25 ml), anhydrous calcium sulfate (1.0 g), and freshly prepared silver carbonate (2.0 g) was shaken with the dichloro derivative **13** (1.0 g, 2.49 mmoles), and processed as described for the glycosides **11** and **12**. Three major components were isolated as syrups by chromatography on silica gel. Compound **14** (120 mg, 12%) had $[\alpha]_D^{22}$ +15° (*c* 1.6, chloroform); *m/e* 398, 400 (M^+), 367, 369 ($M^+ - \cdot OMe$) 338, 340 ($M^+ - AcOH$); compound **15** (360 mg, 37%) had $[\alpha]_D^{22}$ +28° (*c* 1.5, chloroform); *m/e* 394 (M^+), 363 ($M^+ - \cdot OMe$), 334 ($M^+ - AcOH$); and compound **16** (70 mg, 7%) had $[\alpha]_D^{23}$ −33° (*c* 1.1, chloroform); *m/e* 394 (M^+), 363 ($M^+ - \cdot OMe$), 334 ($M^+ - AcOH$).

Anal. Calc. for compound **14**, $C_{15}H_{23}ClO_8S$: Cl, 8.89. Found: Cl, 8.65. Calc. for compound **15**. $C_{16}H_{26}O_9S$: C, 48.72; H, 6.64; S, 8.13. Found: C, 48.70; H, 6.67; S, 8.77.

Treatment of **14** with methanol and silver carbonate, under the conditions used in the preparation of this compound, did not lead to its conversion into **15** or **16** (t.l.c.).

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