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SYNTHESIS OF 5-THIO-D-GALACTOSE*

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ABSTRACT

A synthesis of 5-thio-D-galactose, in the form of its crystalline, anomeric methyl glycopyranosides, is described. Compounds prepared as intermediates included ethyl 2,3-di-*O*-(*tert*-butyldimethylsilyl)-5,6-*O*-carbonyl-β-D-galactofuranoside, the corresponding 5,6-dideoxy-5,6-epithio derivative, and ethyl 2,3,6-tri-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-galactofuranoside. On methanolysis, the latter afforded methyl 5-thio-α-D-galactopyranoside which, in turn, was transformed into methyl 5-thio-β-D-galactopyranoside. Acetolysis proved to be less satisfactory for incorporation of the sulfur atom into a pyranose ring-form. Characteristics of the ^{13}C-n.m.r. spectra of derivatives of 5-thio-D-galactose are described, including the fact that $^{1}J_{C,H}$ values for the anomeric pyranosides differ by only 1–3 Hz, as compared with ~10 Hz for their oxygen analogs.

INTRODUCTION

A substantial number of thio sugars and derivatives containing sulfur as a ring heteroatom have been synthesized[1–3], largely because of interest in their potential as biologically active compounds. Among these are 4′-thiopentofuranosyl nucleosides[4], and 5-thiopyranoses of the D-*gluco*, D-*ribo*, and D-*xylo* configuration[3,5–7]. Studies in this laboratory on the substrate specificity of D-galactose oxidase[8] and of α- and β-D-galactosidases[9] prompted an interest in examining possible influences of a ring-sulfur atom on the reactivity of these enzymes. As 5-thio-D-galactose was unknown, a synthesis of it was undertaken, and we now report a method for preparation of the sugar in the form of its methyl α- and β-pyranosides (**13** and **14**, respectively).

RESULTS AND DISCUSSION

The route devised, which incorporates several reactions used in the synthesis of other thio sugars[1–3], is illustrated in Scheme 1. It entails the preparation of suitably protected D-galactofuranose intermediates (**1**–**4**), formation of a 5,6-epoxide (**8**) having the L-*altro* configuration, conversion of epoxide **8** into the corresponding

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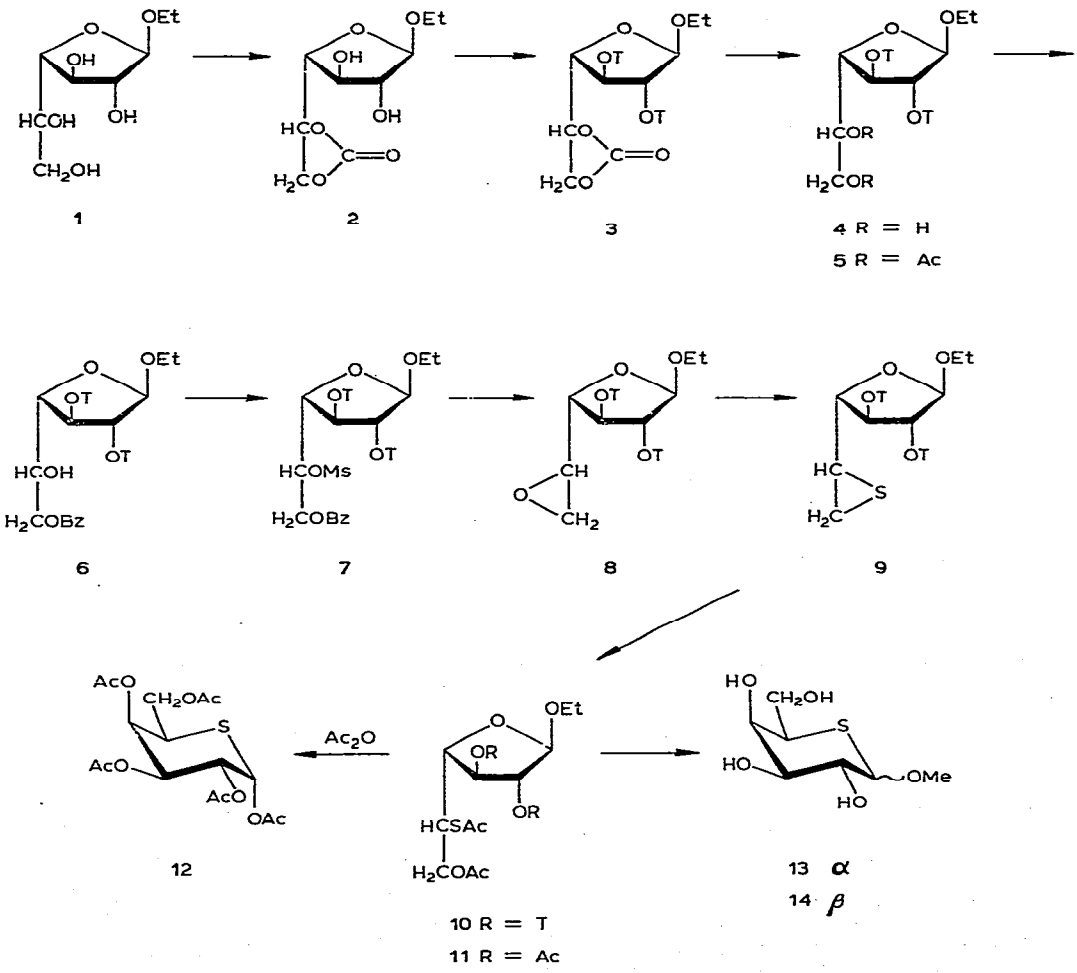
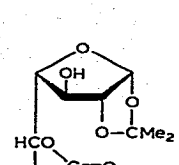
D-*galacto* 5,6-episulfide (**9**), and ring opening of the latter to yield a 5-thio-D-galactofuranoside (**10**). Finally, a pyranose derivative (**12** or **13**) is produced under conditions that promote incorporation of the sulfur atom into the ring.

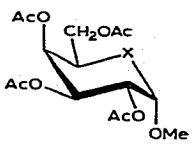
*Synthesis of 5-thio-*D*-galactofuranose derivatives.* — Ethyl β-D-galactofuranoside (**1**), prepared from D-galactose diethyl dithioacetal[10], was transformed into the 5,6-cyclic carbonate (**2**). This step was achieved with high selectivity, in 70–80% yield, by trans-esterification between **1** and ethylene carbonate during[11] 1 h at 150–155°. The use of phosgene in pyridine, or of *N,N'*-carbonyldiimidazole, proved to be less satisfactory; both reactions were less selective, and gave a lower yield of **2**. Chlorocarbonyl substituents were prominent in the product obtained with phosgene, as indicated[12] by a strong absorption band at 1740 cm^{-1} in its i.r. spectrum. Treatment



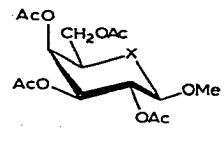
Scheme 1. Synthesis of derivatives of 5-thio-D-galactose (T = *tert*-butyldimethylsilyl; Ms = methylsulfonyl; Bz = benzoyl).



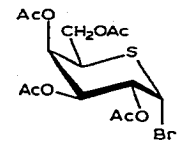
15



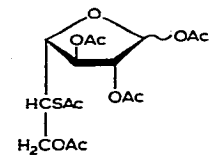
16 X = S
19 X = O



17 X = S
20 X = O



18



21 β
22 α

of **2** with acetone and sulfuric acid afforded crystalline 5,6-*O*-carbonyl-1,2-*O*-isopropylidene-α-D-galactofuranose (**15**), prepared while we were examining an alternative pathway to 5-thio-D-galactose which was not, however, completed.

The 2,3-di-*O*-(*tert*-butyldimethylsilyl) ($BuMe_2Si$) ether[13] (**3**) of **2** was prepared as a distillable oil in quantitative yield. Removal of the carbonate group of **3** with barium methoxide afforded **4**, a low-melting solid that was further characterized as its crystalline diacetate (**5**). High regioselectivity was observed on treating **4** with 1.2 molar equivalents of benzoyl chloride, which gave the 6-benzoate **6** in 85% yield. A methylsulfonyl group was then introduced onto O-5, to give **7**, and reaction of **7** with sodium methoxide produced the 5,6-epoxide **8** in 90% yield. Evidence for formation of the epoxide was readily furnished by the characteristically upfield[14] position of the H-5 and H-6,6′ signals of **8** (at δ 3.10 and 2.76, respectively) as compared with

TABLE I

^{13}C-CHEMICAL SHIFTS OF DERIVATIVES OF 5-THIOALDOFURANOSES AND THEIR 5-OXA ANALOGS[a]

Compound	*C-1*	*C-2, C-3, C-4*	*C-5*	*C-6*	*O-CH₂* | (*CH₃*)	*O-CO* | (*CH₃*)	*S-CO* | (*CH₃*)	*SiC-* | (*CH₃*)	*Δ (CO−CS)*
8	108.7	84.7, 83.6, 81.2	52.0	45.4	62.9 (17.9)			15.1 (25.7)	
									16.6(C-5) 23.6(C-6)
9	109.9	85.4, 84.5, 82.8	35.4	21.8	63.3 (18.0)			15.2 (25.7)	
b	104.9	81.1, 79.3, 76.1	68.9	62.1	62.8 (14.4)	169.8–169.0 (20.1)			
									25.2(C-5)
11	105.1	81.8, 78.9, 77.7	43.7	63.8	63.1 (14.8)	170.2–169.6 (20.5)	193.4 (30.4)		
c	99.3	82.2, 80.7, 76.4	69.4	62.6		170.5–169.1 (20.7–20.0)			
									25.4(C-5)
21	99.1	81.8, 81.1, 77.6	44.0	64.0		170.5–169.1 (21.0–20.7)	193.6 (30.6)		

[a]Solvent, $CDCl_3$. [b]Ethyl 2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranoside. [c]1,2,3,5,6-penta-*O*-acetyl-β-D-galactofuranose.

those of **7** (at δ 5.17 and 4.70, 4.50, respectively). As the transformation of **7** into **8** must involve an inversion at C-5, **8** was assigned the L-*altro* configuration. By treating epoxide **8** with thiourea, ethyl 2,3-di-*O*-(*tert*-butyldimethylsilyl)-5,6-dideoxy-5,6-epithio-α-D-galactofuranoside (**9**) was obtained as the sole product. Introduction of the sulfur atom resulted in a characteristically large, upfield shift for C-5 and C-6 of **9** as compared with those of **8** (see Table I). However, the carbon atoms of the furanose ring and of its substituent groups were affected relatively little by this replacement of the oxygen atom and the accompanying inversion of configuration.

Ring opening of an unsymmetrical thiirane with a base is known[15] to proceed by SN2 attack on the less-hindered carbon atom. Accordingly, 5,6-episulfides of D-*gluco*[3] and L-*ido*[16] derivatives yield products in which the sulfur atom remains on C-5. Opening of the thiirane ring of **9** with acetate ion was found, similarly, to take place with a high degree of regioselectivity. Although four products were obtained, all appeared to be derivatives of 5-thio-D-galactose, differing only in the number and position of the *O*-$BuMe_2Si$ and *O*-acetyl substituents. Two of these products, isolated in crystalline form, were the 6-*O*-acetyl-5-*S*-acetyl derivative (**10**) (30% yield) and the tetraacetate (**11**) (12% yield); each of the other two, obtained as an oily mixture in 30% yield, bore a $BuMe_2Si$ ether group at either O-2 or O-3. In another experiment, when the *O*-$BuMe_2Si$ substituents of episulfide **9** were first removed with tetrabutylammonium fluoride[13,17] and the product was then subjected to basic acetolysis, the tetraacetate (**11**) was obtained exclusively. However, its overall yield under these conditions was only 33%, possibly because the fluoride ion had also caused partial attack on the thiirane ring.

That **10** and **11** each contained an *S*-acetyl group was shown by the 3-proton methyl singlet at δ 2.4, a $^{13}C{=}S$ signal at δ 193, and a strong, i.r. absorption band at 1700 cm^{-1}. Furthermore, the assignment of this group to C-5 of **11** was clear[18] from the upfield location of the signal of C-5 at δ 43.7, as compared with δ 68.9 for C-5 of its oxygen analog **5** (see Table I).

*Formation of pyranose derivatives of 5-thio-*D*-galactose.* — In order to obtain pyranoid forms of 5-thio-D-galactose, the furanose products obtained after opening of the thiirane ring were subjected to methanolysis, or to acid-catalyzed acetolysis. When heated under reflux in 5% methanolic hydrogen chloride for 10 h, **10** gave a mixture of at least four products. Following acetylation of the mixture, methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-galactopyranoside (**16**) was isolated in 40% yield. Evidence had been obtained[9] that a minor proportion of the β anomer (**17**) is also formed, and that two other compounds in the mixture are novel, anhydro derivatives.

Methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-β-D-galactopyranoside (**17**) was obtained by conversion of the α-glycoside (**16**) into 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-galactopyranosyl bromide (**18**), followed by treatment with methanol and silver carbonate. However, there were several other products in the overall reaction-mixture[9], including the α anomer (**16**), and crystalline **17** was isolated in only 6% yield.

The pyranoside structures assigned to **16** and **17** find support in a comparison of their ^1H- and ^{13}C-n.m.r. spectra with those of their oxygen analogs, *viz.*, methyl

TABLE II

A COMPARISON OF ^{1}H- AND ^{13}C-N.M.R. PARAMETERS OF METHYL 2,3,4,6-TETRA-*O*-ACETYL-5-THIO-α- AND -β-D-GALACTOPYRANOSIDES (**16** AND **17**) WITH THOSE OF METHYL 2,3,4,6-TETRA-*O*-ACETYL-α- AND -β-D-GALACTOPYRANOSIDES (**19** AND **20**)[a]

Atom or group	^1H (δ)				*Atom or group*	^{13}C			
	16	**19**	**17**	**20**		**16**	**19**	**17**	**20**
H-1	4.70	4.98	4.50	4.42	C-1	81.6	97.0	82.7	101.5
H-2	5.35	5.36	5.44	5.22	C-2	71.2	68.0	71.1	70.2
H-3	5.35	5.25	4.95	5.02	C-3	68.3	67.3	71.0	68.5
H-4	5.64	5.42	5.58	5.41	C-4	68.3	66.1	67.7	66.8
H-5	3.64	~4.1	3.35	3.92	C-5	38.1	68.0	40.2	70.6
H-6	4.14	~4.1	4.28	4.25	C-6	60.9	61.5	62.2	51.0
H-6′	3.94	~4.1	4.14	4.13	OCH_3	56.5	55.2	57.9	56.6
OCH_3	3.42	3.40	3.42	3.52					

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{C-1,H-1}$
16	2.5	11.0	1.5	1.8	160
19	3.2	11.0	3.0	2.8	171
17	7.2	8.2	3.0	3.0	157
20	7.8	10.3	3.4	3.4	161

[a]Generally, the solvent was $CDCl_3$, although C_6D_6 was used for measuring $J_{H,H}$ of **17** (at 220 MHz) and of **19** (at 100 MHz); values of *J* given are observed spacings, in Hz.

2,3,4,6-tetra-*O*-acetyl-α- and -β-D-galactopyranoside (**19** and **20**) (see Table II). Of particular note are several large differences between the two series involving nuclei at atoms 1 and 5. Thus, there is an upfield displacement of the C-1 signals of **16** and **17** by 15–18 p.p.m., and of their H-5 signals by ~0.5 p.p.m., relative to the corresponding signals in the spectra of* **19** and **20**. As the direction of these shielding changes is consistent[18] with the lower electronegativity of sulfur, it is clear that this element constitutes the ring heteroatom in **16** and **17**. In addition, the patterns of vicinal coupling between protons of the ring in **16** and **17** are closely similar to those of **19** and **20** (see Table II). This shows, moreover, that 5-thio-D-galactopyranosides favor the $^4C_1$(D) conformation, as depicted for **16** and **17**.

Incorporated into the ring, the sulfur atom also has a marked effect on the magnitude of direct ^{13}C–^1H coupling (^1J) at the anomeric center. Although ^1J of an axial anomer is commonly ~10 Hz larger than that of the equatorial anomer[19,20], as typified by **19** and **20** (see Table II), only a 3-Hz difference is found between **16**

*Although H-1 of **16** also experiences an increase in shielding, as compared to that of **18**, H-1 of **17** is exceptional in exhibiting a slight downfield shift relative to that of **20**.

and **17**. As the sulfur atom lowers only the coupling value of the α anomer, these results suggest that a ring–oxygen atom stereoselectively enhances the ^1J values of α-pyranosides.

On *O*-deacetylation, **16** and **17** afforded methyl 5-thio-α-D-galactopyranoside (**13**) and methyl 5-thio-β-D-galactopyranoside (**14**), respectively, both in crystalline form.

As noted for the tetraacetates (**16** and **17**), strong inductive influences attributable to the sulfur heteroatom are also observed in the n.m.r. spectra of **13** and **14**, as compared with the spectra of methyl α- and β-D-galactopyranoside. For example, the anomeric carbon atoms of **13** and **14** resonate at 85.1 and 85.9 p.p.m., respectively, whereas the C-1 chemical-shifts of the corresponding oxygen analogs are 100.5 and 104.9 p.p.m., respectively. Similarly, C-1–H-1 coupling is lowered for **13** to only 160 Hz, and is 159 Hz for **14**; again, the effect on the anomeric center of the α-glycoside is pronounced, so that the two $^1J_{C,H}$ values for **13** and **14** are almost the same.

For the preparation of pyranose derivatives, acetolysis of furanosides **10** and **11** proved to be less effective than methanolysis. By employing acetic anhydride–acetic acid–sulfuric acid under a variety of conditions, at least four compounds were invariably produced. In one of these experiments, the major product was isolated in crystalline form, and shown to be 1,2,3,6-tetra-*O*-acetyl-5-*S*-acetyl-5-thio-β-D-galactofuranose (**21**). ^{1}H- and ^{13}C-N.m.r. spectra of the product mixtures indicated that the α-furanose (**22**) was also formed, whereas the α-pyranose **12**, the desired product, constituted only one-third or less of these mixtures.

Under the acid-catalyzed conditions of acetolysis or methanolysis, a 4- or 5-thio sugar might be expected[1–4] to favor formation of the sulfur-containing ring-structure, because of the greater nucleophilicity of a thiol than of a hydroxyl group. Nevertheless, the relative stabilities of the pyranose and furanose forms should determine the equilibrium compositions. Hence, it is noteworthy that higher yields of 5-thiopyranose products have been obtained from the acetolysis of derivatives of 5-thio-D-glucose[21] (69%) or -L-rhamnose[22] (64%) than of 5-thio-L-idose[16] (44%). Similarly, in the methanolysis of 1,2-*O*-isopropylidene-5-thio-aldopentoses, the yield of pyranosides was greater from the xylose derivative[23] (54%) than from either its *arabino*[24] (27%) or *ribo*[25] (12%) isomer. By contrast, ring contraction during acetolysis of methyl 4-thio-aldopyranosides is favored much more in the *ribo* series[26] (97%) than in the *xylo* series[27] (45%). Although equilibrium conditions may not have been attained in these various reactions, it appears that those configurations (*arabino, ribo, ido*) associated with stable furanose forms (in their oxygen counterparts) give rise to low yields of 5-thiopyranoses, or high yields of 4-thiofuranoses.

By analogy, it is not surprising that only relatively low yields of pyranose products have been obtained in the current experiments with a 5-thio sugar having the *galacto* configuration. However, another factor contributing to lowered yields of pyranose derivatives **12–14** is the marked acid-lability of 5-thio-D-galactose. As already noted, under the conditions employed for acetolysis or methanolysis, a number of side products are formed[9].

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Optical rotations were determined at room temperature, for solutions in 1-dm tubes, with a Carl Zeiss polarimeter (Model 367732). I.r. spectra were recorded for films on AgCl or NaCl discs, or for KBr pellets, with a Unicam SP-200 G grating spectrophotometer. Microanalyses were performed by C. Daessle, Montreal, or by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Plates of Silica Gel G were used for t.l.c., and the developing solvents were as specified. Silica Gel for column chromatography (0.08 mm particle size) was obtained from Macherey Nagel and Co. Gas–liquid chromatography was performed with a Hewlett–Packard F and M 402 gas chromatograph, using an OV-101 or an OV-225 column. Proton magnetic resonance spectra were recorded with a Varian HA-100 or a Bruker WH-90 spectrometer. ^{13}C-N.m.r. spectra were recorded at 22.6 MHz with a Bruker WH-90 spectrometer. Chemical shifts (δ) are reported with reference to tetramethylsilane.

Ethyl β-D-galactofuranoside (**1**). — Compound **1** was prepared by the method of Green and Pacsu[10] in 73% yield; m.p. 83–85°, $[\alpha]_D$ −103° (*c* 1.0, water); ^{1}H-n.m.r. data (D_2O): δ 4.70 (d, 1 H, H-1), 4.1–3.4 (m, 8 H), and 1.16 (t, 3 H, CH_3); $J_{1,2}$ 2.1 Hz.

Ethyl 5,6-O-carbonyl-β-D-galactofuranoside (**2**). — A mixture of **1** (16.7 g, 0.1 mol) and ethylene carbonate (28.1 g, 0.35 mol) was heated at 148–155°/30–40 mm Hg, the course of the reaction being monitored by t.l.c. (solvent, 1 : 1 chloroform–acetone). After 40 min, the mixture was cooled, washed with chloroform, and then extracted with water; the chloroform wash was extracted with water, and the aqueous extracts were combined and evaporated. The residue was chromatographed on a column (2.5 × 40 cm) of Silica Gel with 9 : 1 ether–ethanol as the eluant, giving first, residual ethylene carbonate, followed by syrupy **2** (14.3 g, 79%); ^{1}H-n.m.r. data (acetone-d_6): δ 5.1 (m, 1 H, H-5), 4.89 (d, 1 H, H-1), 4.7–4.3 (m, 5 H), 3.9–3.3 (m, 2 H, CH_2), and 1.16 (t, 3 H, CH_3); $J_{1,2}$ ~1 Hz; ^{13}C-n.m.r. data: δ 155.8 (CO_3), 108.4 (C-1), 83.1 (C-4), 77.5 (C-2), 75.6 (C-3), 66.9 (C-5), 63.8 (C-6), 55.1 (CH_2), and 15.3 (CH_3).

Ethyl 2,3-di-O-(tert-butyldimethylsilyl)-5,6-O-carbonyl-β-D-galactofuranoside (**3**). — A solution of **2** (14 g), imidazole (20.4 g), and *tert*-butylchlorodimethylsilane (21.7 g) in dry *N*,*N*-dimethylformamide (40 mL) was stirred for 18 h at room temperature. Ice–water was introduced, the mixture was extracted with chloroform, and the extract was washed successively with water, 2M hydrochloric acid, water, saturated sodium hydrogencarbonate, and water, dried (anhydrous sodium sulfate), and evaporated, to give a yellow syrup (28 g) that was purified by distillation at 110°/20 μm Hg; $[\alpha]_D$ −55.2° (*c* 6.0, chloroform); ν_{max} 1800 cm^{-1} (C=O, cyclic carbonate); ^{1}H-n.m.r. data ($CDCl_3$): δ 4.8 (s, 1 H, H-1), ~4.7 (m, 1 H, H-5), 4.56 (s, 1 H, H-6), 4.40 (d, 1 H, H-6′), 4.4–3.9 (3 H, H-2,3,4), 3.9–3.3 (m, 2 H, CH_2), 1.2 (t, 3 H, CH_3), and 0.92–0.89 [m, 9 H, $(CH_3)_3$].

Anal. Calc. for $C_{21}H_{42}O_7Si_2$: mol. wt., 462. Found: M − 45, *m/e* 417 (M − OCH_2CH_3); M − 57, *m/e* 405 [M − $C(CH_3)_3$].

5,6-O-Carbonyl-1,2-O-isopropylidene-α-D-galactofuranose (**15**). — Anhydrous copper(II) sulfate (2 g) and conc. sulfuric acid (3 drops) were added to a solution of **3** (0.56 g) in acetone (25 mL) with vigorous stirring. After being stirred for 72 h, the suspension was filtered, the filtrate was made neutral with calcium hydroxide, and treated with charcoal, the suspension filtered, and the filtrate evaporated. The residue was chromatographed on a column of Silica Gel with 10:1 chloroform–acetone as the eluant, giving crystalline **15** (0.4 g, 67%); m.p., after recrystallization from acetone–hexane, 178–180°; ν_{max} 3400 (OH) and 1800 cm^{-1} (C=O, cyclic carbonate); ^{1}H-n.m.r. data (acetone-d_6): δ 5.86 (d, 1 H, H-1), 5.15–4.93 (o, 1 H, H-5), 4.67 (t, 1 H, H-6), 4.58 (t, 1 H, H-2), 4.40 (q, 1 H, H-6'), 4.21 (m, 1 H, H-3), 3.96 (t, 1 H, H-4), 1.5 (s, 3 H, CH_3), and 1.31 (s, 3 H, CH_3); $J_{1,2}$ 4.0, $J_{2,3}$ 1.6, $J_{3,4}$ 5.0, $J_{4,5}$ 5.0, $J_{5,6}$ 8.0, $J_{5,6'}$ 6.0, and $J_{6,6'}$ 8.0 Hz.

Anal. Calc. for $C_{10}H_{14}O_7$: C, 48.8; H, 5.7. Found: C, 48.9; H, 5.7.

Ethyl 2,3-di-O-(tert-butyldimethylsilyl)-β-D-galactofuranoside (**4**). — M Barium methoxide (10 mL) was added to a solution of **3** (27 g) in dry methanol (100 mL) at −15°, and, 5 h later, the solution was made neutral with solid carbon dioxide. Evaporation of part of the methanol afforded a thin syrup (30 mL) that was applied to a column (2.5 × 40 cm) of Silica Gel. A minor product was eluted with 50:1 chloroform–hexane, and elution with 25:1 chloroform–ethanol gave **4** (21 g, 82%); m.p. 58–60°, $[\alpha]_D$ −44.3° (*c* 3.0, chloroform); ν_{max} 3500 cm^{-1} (OH).

Anal. Calc. for $C_{20}H_{44}O_6Si_{12}$: C, 55.0; H, 10.2. Found: C, 55.4; H, 10.5.

Ethyl 5,6-di-O-acetyl-2,3-di-O-(tert-butyldimethylsilyl)-β-D-galactofuranoside (**5**). — A solution of glycoside **4** (0.31 g) in 2:1 pyridine–acetic anhydride was kept for 18 h at room temperature, and then evaporated, benzene being introduced to aid in removal of the pyridine. A solution of the residual syrup in dichloromethane was washed successively with M hydrochloric acid, water, saturated sodium hydrogencarbonate, and water, dried (anhydrous sodium sulfate), and evaporated, to give a crystalline product (0.35 g, 94%) which, after recrystallization from ethanol, had m.p. 88–89°, $[\alpha]_D$ −20.0° (*c* 2.2, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 5.31 (o, 1 H, H-5), 4.83 (d, 1 H, H-1), 4.37 (q, 1 H, H-6), 4.19 (q, 1 H, H-6'), 4.19–3.85 (m, 3 H, H-2,3,4), 3.90–3.60 (m, 2 H, CH_2), 2.12 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), and 1.20 (t, 3 H, CH_3); $J_{1,2}$ 2.0, $J_{4,5}$ 3.0, $J_{5,6}$ 5.0, $J_{5,6'}$ 7.0, and $J_{6,6'}$ 11.5 Hz.

Anal. Calc. for $C_{24}H_{48}O_8Si_2$: C, 55.4; H, 9.3. Found: C, 55.3; H, 9.3.

Ethyl 6-O-benzoyl-2,3-di-O-(tert-butyldimethylsilyl)-β-D-galactofuranoside (**6**). — A solution of **4** (21 g) in dry pyridine (170 mL) was cooled to −15°, and benzoyl chloride (7.0 mL, 1.2 eq.) in ethanol-free chloroform (20 mL) was added dropwise during 1 h, with stirring. The mixture was kept for 6 h below −12° and then overnight at 0°. T.l.c. (100:1 chloroform–acetone) then showed the presence of a major product (**6**) (R_F 0.47) and a minor product (R_F 0.56); for **4**, R_F = 0.12. Ice–water was now introduced slowly, with stirring, the mixture was thrice extracted with dichloromethane, and the extracts were combined, washed successively with 2M hydrochloric acid, water,

saturated sodium hydrogencarbonate, and water, dried (anhydrous sodium sulfate), and evaporated to a syrup (29 g) which was redissolved in dichloromethane, and transferred to a column (3.5 × 40 cm) of Silica Gel. Elution with 7:3 petroleum ether–dichloromethane afforded the 5,6-dibenzoate (6 g, 17%). Further elution, with 9:1 dichloromethane–petroleum ether gave the monobenzoate (**6**) (21.6 g, 83%); ν_{max} 3500 (sharp, OH), 1750 (C=O), and 1650–1550 cm^{-1} (aromatic C=C); ^{1}H-n.m.r. data ($CDCl_3$ + D_2O): δ 8.16–8.04 and 7.68–7.38 (5 H, C_6H_5), 4.88 (d, 1 H, H-1), 4.67–4.37 (o, 2 H, H-6,6'), 4.32–3.97 (4 H, H-2,3,4,5), 3.9–3.3 (m, 2 H, CH_2), and 1.20 (t, 3 H, CH_3). For the dibenzoate: δ 8.2–8.0 (10 H, 2 C_6H_5CO), 5.75 (m, 1 H, H-5), 4.95 (s, 1 H, H-1), 4.72 and 4.66 (2 s, 2 H, H-6,6'), 4.28 (q, 1 H, H-4), 4.14–4.06 (m, 2 H, H-2,3), 3.88–3.38 (m, 2 H, CH_2), and 1.20 (t, 3 H, CH_3).

Ethyl 6-O-benzoyl-2,3-di-O-(tert-*butyldimethylsilyl*)-*5*-O-(*methylsulfonyl*)-β-D-*galactofuranoside* (**7**). — To a solution of monobenzoate **6** (21 g) in pyridine (35 mL) at 0° was added, dropwise, methanesulfonyl chloride (3 mL, 1.2 eq.) in dry dichloromethane (10 mL). After 18 h at room temperature, the mixture was thrice extracted with dichloromethane, and the extracts were combined, washed successively with 2M hydrochloric acid, water, saturated sodium hydrogencarbonate, and water, dried (anhydrous sodium sulfate), treated with charcoal (Darco G-60), and evaporated, to give **7** as a clear syrup (23.5 g, 97%); ν_{max} 1750 (C=O), 1650–1550 (aromatic C=C), and 1350 cm^{-1} (S=O); ^{1}H-n.m.r. data: δ 8.2–8.0 and 7.5–7.3 (2 H, 3 H, C_6H_5C=O), 5.25–5.08 (m, 1 H, H-5), 4.8–4.4 (o, 2 H, H-6,6'), 4.30–4.06 (3 H, H-2,3,4), 4.06–3.38 (m, 2 H, CH_2), 2.96 (s, 3 H, SO_2CH_3), and 1.2 (t, 3 H, CH_3).

Ethyl 5,6-anhydro-2,3-di-O-(tert-*butyldimethylsilyl*)-α-L-*altrofuranoside* (**8**). — Sodium methoxide (4.6 g) in methanol (100 mL) was added dropwise to a solution of **7** (20.0 g) in dry chloroform (50 mL) at −10°. After 18 h at −10°, when the reaction was complete according to t.l.c. in 100:1 chloroform–acetone (R_F 0.61 for **8**, as compared with R_F 0.50 for **7**), the base was neutralized with Amberlite IR-120 (H^+) resin, and the solution was evaporated. Compound **8** was obtained as an oil (12.8 g, 94%), which tended to co-evaporate with methyl benzoate and was purified by distillation (75°/20 μm Hg); $[\alpha]_D$ −43.5° (*c* 3.1, chloroform); its infrared spectrum confirmed the disappearance of the methylsulfonyl and benzoyl groups; ^{1}H-n.m.r. data ($CDCl_3$): δ 4.84 (d, 1 H, H-1), 3.84–3.79 (3 H, H-2,3,4), 3.79–3.30 (m, 2 H, CH_2), 3.16–3.0 (m, 1 H, H-5), 2.84–2.66 (m, 2 H, H-6,6'), and 1.20 (t, 3 H, CH_3); $J_{1,2}$ ~1 Hz; for the ^{13}C-n.m.r. data, see Table I.

Anal. Calc. for $C_{20}H_{42}O_5Si_2$: C, 57.4; H, 10.1. Found: C, 57.2; H, 10.0.

Ethyl 2,3-di-O-(tert-*butyldimethylsilyl*)-*5,6-dideoxy-5,6-epithio-β*-D-*galactofuranoside* (**9**). — A solution of anhydride **8** (11.1 g) and thiourea (5.4 g) in dry methanol (120 mL) was kept for 3 days at room temperature and then evaporated. A solution of the residue in chloroform was washed with water, dried (anhydrous sodium sulfate), and evaporated, and the residual oil (11.1 g, 96%) was purified by distillation (70°/20 μm Hg); $[\alpha]_D$ −56.7° (*c* 1.2, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 4.80 (d, 1 H, H-1), 4.09–3.25 (3 H, H-2,3,4), 3.8–3.25 (m, 2 H, CH_2), 3.0 (q, 1 H, H-5),

2.4 (o, 2 H, H-6,6'), and 1.20 (t, 3 H, CH_3); $J_{1,2}$ ~2 Hz; for the ^{13}C-n.m.r. data, see Table I.

Anal. Calc. for $C_{20}H_{42}O_4SSi_2$: S, 7.4; mol. wt., 434. Found: S, 7.7; *m/e* 389 (M — OCH_2CH_3), *m/e* 377 (M — CMe_3).

Ethyl 6-O-acetyl-5-S-acetyl-2,3-di-O-(tert-butyldimethylsilyl)-5-thio-β-D-galactofuranoside (**10**). — A solution of episulfide **9** (13.5 g) and anhydrous potassium acetate (2 g) in acetic acid (10 mL) and acetic anhydride (100 mL) was heated under nitrogen for 30 h at 136–140°. T.l.c. in 100:1 dichloromethane–petroleum ether then showed the presence of four products (R_F 0.33, 0.25, 0.15, and 0.06, as compared with 0.56 for **9**). The mixture was poured onto ice, dichloromethane was added, and the organic layer was successively washed with saturated sodium hydrogencarbonate, and water, dried (anhydrous sodium sulfate), and evaporated. The residue, a dark tar (14.5 g), was chromatographed on a column (3.5 × 40 cm) of Silica Gel, with dichloromethane as the eluant, affording **10** as a low-melting solid (4.0 g); m.p. ~10°, $[\alpha]_D$ −28.0° (*c* 1.4, chloroform); ν_{max} 1740 (OAc) and 1700 cm^{-1} (SAc); ^{1}H-n.m.r. data ($CDCl_3$): δ 4.75 (d, 1 H, H-1), 4.36–4.09 (3 H, H-5,6,6'), 4.06–3.92 (3 H, H-2,3,4), 3.9–3.2 (m, 2 H, CH_2), 2.37 (s, 3 H, $SCOCH_3$), 2.05 (s, 3 H, $OCOCH_3$), and 1.20 (t, 3 H, CH_3); $J_{1,2}$ ~2 Hz.

Ethyl 2,3,6-tri-O-acetyl-5-S-acetyl-5-thio-β-D-galactofuranoside (**11**). — (*A*) On continued elution of the column (see preceding section) with dichloromethane, a syrupy mixture of **10** and two other products was obtained (yield, 4.5 g). With 9:1 dichloromethane–acetone, crystalline **11** was eluted (1.5 g, 12%); after recrystallization from methanol, m.p. 61°, $[\alpha]_D$ −69.7° (*c* 1.3, chloroform); ν_{max} 1740 (OAc) and 1700 cm^{-1} (SAc); ^{1}H-n.m.r. data ($CDCl_3$): δ 5.11–4.98 (3 H, H-1,2,3), 4.42 (q, 1 H, H-4), 4.20 (q, 1 H, H-6), 4.14 (o, 1 H, H-5), 3.9–3.2 (m, 2 H, CH_2), 2.39 (s, 3 H, $SCOCH_3$), 2.1–2.0 (9 H, 3 $OCOCH_3$), and 1.17 (t, 3 H, CH_3); $J_{3,4}$ 5.4, $J_{4,5}$ 2.5, $J_{5,6}$ 8.0, $J_{5,6'}$ 5.4, and $J_{6,6'}$ 10.8 Hz; for the ^{13}C-n.m.r. data, see Table I.

(*B*) A solution of episulfide **9** (0.7 g) and tetrabutylammonium fluoride (0.94 g) in dry oxolane (30 mL) was kept for 18 h at room temperature, and then evaporated; the resulting brown syrup was chromatographed on a column (1.3 × 30 cm) of Silica Gel with 17:2 dichloromethane–ethyl acetate as the eluant. The syrupy product, together with potassium acetate (2 g), was dissolved in acetic anhydride (10 mL) and acetic acid (6 mL), and the solution was heated for 4 h at 140° under nitrogen, and then evaporated. Water and dichloromethane were added to the residue, and the organic layer was dried (anhydrous sodium sulfate), decolorized (Darco G-60), and evaporated, giving crystalline **11** (0.16 g, 33%); after recrystallization from ethanol, m.p. 58°.

Anal. Calc. for $C_{16}H_{24}O_9S$: S, 8.2. Found: S, 8.1.

1,2,3,6-Tetra-O-acetyl-5-S-acetyl-5-thio-β-D-galactofuranose (**21**). — A portion (1.2 g) of the crude material obtained from the ring opening of **9** was dissolved in 19:19:1 acetic anhydride–acetic acid–sulfuric acid, and the solution was kept under nitrogen for one day at 0° and then for two days at 10°. Sodium acetate (2.4 g) was added, and the suspension was concentrated, diluted with water, and extracted with

dichloromethane. The extract was washed with water, dried (anhydrous sodium sulfate), and evaporated, affording a crystalline product (1.0 g). Recrystallization from ethanol gave **19** (0.4 g), m.p. 112°, $[\alpha]_D$ −67.4° (*c* 1.7, chloroform); ^{1}H-n.m.r. data ($CDCl_3$): δ 6.10 (d, 1 H, H-1), 5.16 (q, 1 H, H-2), 5.09 (q, 1 H, H-3), 4.62–4.07 (m, 3 H, H-5,6,6'), 4.50 (q, 1 H, H-4), 2.37 (s, 3 H, $SCOCH_3$), and 2.12–2.03 (12 H, 4 $OCOCH_3$); $J_{1,2}$ 0.9, $J_{2,3}$ 2.5, $J_{3,4}$ 6.0, and $J_{4,5}$ 2.7 Hz; for the ^{13}C-n.m.r. data, see Table I.

Anal. Calc. for $C_{16}H_{12}O_{10}S$: S, 7.9. Found: S, 8.1.

*Methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-α-*D*-galactopyranoside* (**16**). — A solution of **10** (4.0 g) in dry methanol (50 mL) and acetyl chloride (2.5 mL) was heated under reflux in a nitrogen atmosphere for 10 h, and then made neutral with silver carbonate and the suspension filtered. The filtrate was clarified with charcoal (Darco G-60), and evaporated to a syrup which was acetylated with 2:1 acetic anhydride–pyridine. Chromatography of the acetylation product (2.7 g) on a column (1.8 × 30 cm) of Silica Gel with 50:1 dichloromethane–acetone afforded a syrup (0.43 g) consisting of at least three components. Elution with 25:1 dichloromethane–acetone, and evaporation, then gave crystalline **16**; after recrystallization from ethyl acetate–hexane, yield 1.2 g, m.p. 95°, $[\alpha]_D$ +216° (*c* 1.2, chloroform); recrystallized from ethanol, m.p. 96–98°, $[\alpha]_D$ +225.5° (*c*, 1.4 chloroform); for the ^{1}H- and ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{15}H_{22}O_9S$: C, 47.6; H, 5.8; S, 8.5. Found: C, 47.4; H, 6.0; S, 8.3.

*Methyl 5-thio-α-*D*-galactopyranoside* (**13**). — A solution of **16** (0.30 g) in dry methanol (25 mL) containing sodium methoxide (20 mg) was kept for 10 h at −10°, made neutral with Amberlite IR-120 (H^+) ion-exchange resin, the suspension filtered, and the filtrate evaporated. The solid residue was recrystallized from hot ethyl acetate, giving **13** (35 mg, 21%), m.p. 91–93°, $[\alpha]_D$ +347.7° (*c* 0.72, methanol).

*2,3,4,6-Tetra-*O*-acetyl-5-thio-α-*D*-galactopyranosyl bromide* (**18**). — Crystalline glycoside **16** (35 mg) was dissolved in a solution of hydrogen bromide in acetic acid (30%, 0.3 mL). After 2 h, chloroform and ice–water were added, and the aqueous layer was separated, and extracted twice with dichloromethane. The extracts were combined, washed successively with saturated sodium hydrogencarbonate and water, dried (anhydrous sodium sulfate), and evaporated, affording a dark syrup (30 mg); ^{1}H-n.m.r. data ($CDCl_3$): δ 5.69 (q, 1 H, H-4), 5.61 (d, 1 H, H-1), 5.42 (q, 1 H, H-3), 5.09 (q, 1 H, H-2), 4.3–3.8 (m, 2 H, H-6,6'), 3.6–3.3 (m, 1 H, H-5), and 2.10, 2.06, 2.02 (12 H, OCO-CH_3); $J_{1,2}$ 3.5, $J_{2,3}$ 10.0, $J_{3,4}$ 3.0, and $J_{4,5}$ ~2 Hz.

*Methyl 2,3,4,6-tetra-*O*-acetyl-5-thio-β-*D*-galactopyranoside* (**17**). — The crude bromide **18** obtained by treatment of 1.7 g of α-glycoside **16** with hydrogen bromide was dissolved in methanol (100 mL) containing silver carbonate (3 g), the suspension was stirred for 1 day, the solids were filtered off, and the filtrate was evaporated. G.l.c. of the residual syrup indicated that it consisted of four products, including some of the α-glycoside **16**. By chromatography of the syrup on a column (2 × 3.5 cm) of Silica Gel with 25:1 benzene–ethyl ether, a fraction consisting of crystalline **17** was

isolated (yield, 0.1 g); after recrystallization from methanol, m.p. 102–103°, $[\alpha]_D$ +9.5° (*c* 4.2, chloroform); for the ^{1}H- and ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{15}H_{22}O_9S$: mol. wt., 378. Found: *m/e* 318 (M — CH_3CO_2H), *m/e* 258 (M — 2 CH_3CO_2H).

Methyl 5-thio-β-D-galactopyranoside (**14**). — *O*-Deacetylation of **17** (52 mg) with sodium methoxide afforded crystalline **14** (28 mg), m.p. 142–145°, $[\alpha]_D$ −12.2° (*c* 2.8, water).

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