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# *O*-BENZYLATED THIO SUGARS. DERIVATIVES OF 2,3,6-TRI-*O*-BENZYL-1-THIO-D-GALACTOPYRANOSE SUITABLE FOR USE IN OLIGOSACCHARIDE SYNTHESIS

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ABSTRACT

The 4-*O*-benzoyl (**15a**) and 4-*O*-*p*-nitrobenzoyl (**15b**) derivatives of 2,3,6-tri-*O*-benzyl-1-thio-D-galactopyranose were synthesized from allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**1**). In the first stage of the synthesis, the 3-position of **1** was benzylated by an indirect route, and also by the direct reaction (preferred) of benzyl bromide with the 3,4-*O*-dibutylstannylene intermediate **7**. The product **6** was sequentially isomerized (allyl → 1-propenyl), acylated at the 4-position, and hydrolyzed. The free sugars **11a** and **11b** were converted into the thio sugars by a standard sequence involving formation of the glycosyl halides **13a** and **13b** and the reaction of these with appropriate sulfur nucleophiles. A third derivative (**29**) of 2,3,6-tri-*O*-benzyl-1-thio-D-galactopyranose, having a 4-*O*-allyl protecting group, was similarly made from the corresponding normal sugar **25**. The key intermediate **22**, precursor to **25**, was prepared by two routes from methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**17**).

## INTRODUCTION

In a previous paper[1], and in a note[2] in this issue, syntheses of 2,3,4- and 2,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranose have been reported. These benzylated 1-thio sugars have free hydroxyl groups at positions 6 and 3, respectively, and are designed for use as the first sugar in oligosaccharide syntheses by the thioglycoside scheme[3,4] on solid supports.

To complete the series, we wished to prepare benzylated 1-thio-D-galactopyranose derivatives having position 4 available for coupling. These compounds pose a special problem in that, if the usual synthetic routes are employed, there are two points at which isomerization to unwanted furanose forms can occur. This may happen at the stage of the free (1-OH) sugar[5] **9** if it is an intermediate, and again at

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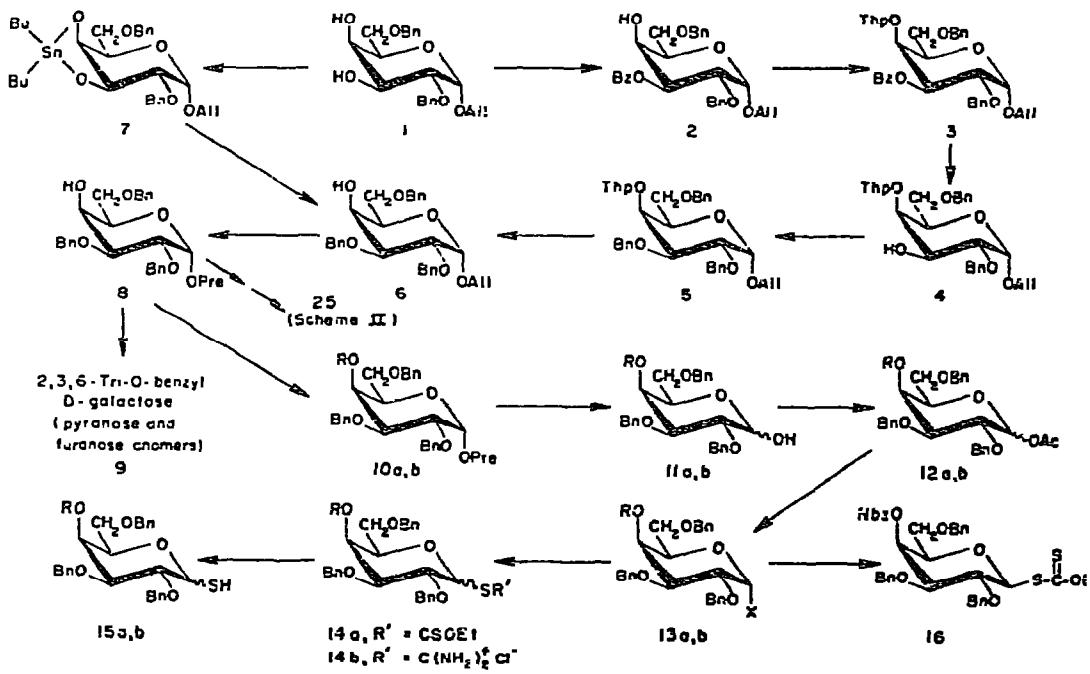
the stage of the free 1-thio sugar. To avoid this complication, it is necessary to keep OH-4 blocked with a temporary protecting group at all times until the thioglycosidic link to the support is established. The present paper describes the preparation, by unequivocal pathways, of three derivatives of 2,3,6-tri-*O*-benzyl-1-thio-D-galactopyranose having temporary blocking groups at position 4.

## RESULTS AND DISCUSSION

In our previous work, we found that allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**1**) could be selectively benzoylated at position 3, and we used the resulting monobenzoate **2** as the precursor of 2,4,6-tri-*O*-benzyl-D-galactopyranose[1]. The transformation of the 3-benzoate **2** into the known[6] 2,3,6-tri-*O*-benzyl-D-galactose **9** was accomplished by blocking position 4 with a tetrahydropyranyl group, exchanging the benzoyl group at position 3 for benzyl, then removing the tetrahydropyranyl and allyl groups (Scheme I). These operations proceeded smoothly and the intermediates **3**, **4**, and **5** were obtained as pure syrups by chromatography on silica gel columns. As mentioned previously[1], compound **2** prepared by the low-temperature benzoylation of **1** in pyridine is contaminated with several percent of the 3,4-dibenzoate. Nevertheless it proved feasible to convert **1** into the key intermediate,




Scheme I

allyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**6**), without purifying **2**, **3**, **4**, and **5**. The crude **6** was readily purified by chromatography on silica gel.

In search of an improved synthesis of **6**, we investigated the reactions of the 3,4-*O*-dibutylstannylene derivative (**7**) of **1**. The monoacylation and monoalkylation of the 2',3'-*O*-dibutylstannyleneribonucleosides had earlier been demonstrated by Wagner, Verheyden, and Moffatt[7]. Our work[8] with **7** and some related stannylene derivatives of axial–equatorial, vicinal diols in the carbohydrate series showed that, on treatment with benzoyl chloride or reactive alkyl halides, these compounds give essentially exclusively monosubstitution products, with very high selectivity for reaction at the equatorial oxygen. This conclusion was adumbrated independently by Augé, David, and Veyrières[9] from experiments on an analog of **7**. Thus, a "clean" preparation of **2**, for conversion into **6** via the tetrahydropyranyl route, could be obtained by the benzoylation[2,8] of **7**. This reaction was not further exploited, however, as the benzylation[8] of **7** with benzyl bromide furnished a direct, high-yielding pathway to **6**. The crude product was suitable for use in the next synthetic step after passage through a short column of silica gel to remove tin compounds.

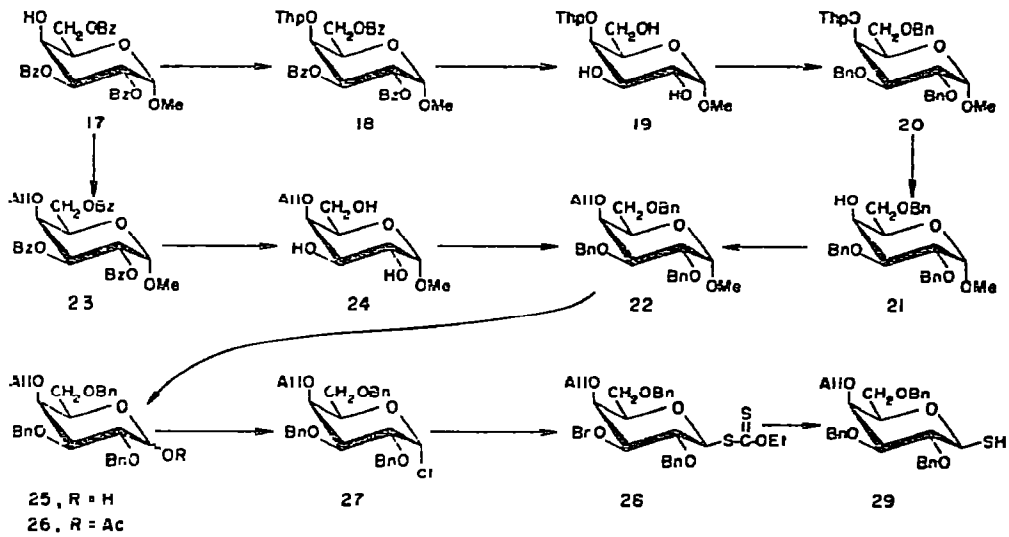
For the protection of the 4-position our attention turned first to the benzoyl and *p*-nitrobenzoyl groups. The *p*-nitrobenzoyl group has some advantage in that it is more easily removed, and the amount removed can be quantitated by spectrophotometry[10]. In this way the "degree of loading" of a solid support with the nitrobenzoylated thio sugar may be determined. In order to be able to set the anomeric position free after the benzoylation of O-4, it was necessary first to isomerize[11] the allyl glycoside **6** to the 1-propenyl glycoside **8**. After the acylation of **8**, the products **10a** and **10b** were hydrolyzed with mild acid[11] to give the free sugars **11a** and **11b**. These were converted into the glycosyl halides (chlorides and bromides) **13a** and **13b** via the 1-acetates **12a** and **12b**.

In the case of the 4-*O*-benzoyl glycosyl bromide **13a**, further transformation to the 4-*O*-benzoyl thio sugar **15a** was accomplished via the 1-ethylxanthate (**14a**), as in our previous syntheses of *O*-benzylated-1-thio sugars[1,12,13]. Care was required to effect the selective saponification of the ethylxanthate group in **14a**, but conditions were found that gave the final product **15a** in 72% yield. In the saponification of the ethylxanthate **16**, the *p*-nitrobenzoyl group was removed preferentially, and hence **16** could not be used to make the 4-*O*-*p*-nitrobenzoyl thio sugar **15b**. This product was successfully obtained, however, via the pseudothouronium salt **14b**.

We also considered the allyl group as a possible protecting group for position 4, as it appeared that the route to the requisite thio sugar, 4-*O*-allyl-2,3,6-tri-*O*-benzyl-1-thio-β-D-galactopyranose (**29**), would be shorter than the route to the acyl protected compounds **15a** and **15b**. (The complete synthesis of **15a** and **15b** is not shown in Scheme I; five additional steps are required to convert D-galactose into the starting compound **1**.) After the attachment of **29** to the support, the isomerization of the allyl ether group to the readily hydrolyzable 1-propenyl ether could be accomplished with potassium *tert*-butoxide in the usual way if the support is alkali-stable. If it is not

(porous glass), isomerization with tris(triphenylphosphine)rhodium(I) chloride[14,15] should be feasible.

The synthesis of **29** is shown in Scheme II. As the starting material we chose methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**17**), readily available by the partial benzoylation of methyl α-D-galactopyranoside[16]. Protection of the 4-position by a tetrahydropyranyl group, and then replacement of the benzoyl groups by benzyl, removal of the tetrahydropyranyl group, and allylation at position 4 gave the key intermediate, methyl 4-*O*-allyl-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**22**). This sequence parallels the conversion **2**→**10** in Scheme I, but is one step shorter, since isomerization of the anomeric substituent is not required. Alternatively, **17** was directly allylated with allyl bromide under Purdie conditions, and the benzoyl groups were replaced by benzyl to give **22**. The identity of the products obtained by the two routes showed that the Purdie allylation proceeded without benzoyl migration.




Scheme II

In the final stage, the methyl glycoside **22** was hydrolyzed to the free sugar **25**, which could also be prepared by a third pathway starting with compound **1**. In this latter synthesis, the propenyl galactoside **8** was allylated at position 4 and then subjected to mild acid hydrolysis. Compound **25** was converted into the thio sugar **29** via the 1-ethylxanthate **28**.

The stereochemistry of the last two steps of the thio sugar synthesis is of interest. In accord with our previous results[1,12,13], the reactions of the *O*-benzylated α-glycosyl bromides **13a** (X = Br) and **13b** (X = Br) with potassium ethylxanthate gave β-glycosyl ethylxanthates. The 4-*O*-benzoyl ethylxanthate (**14a**), when saponified in the normal way, yielded a 1-thio-β sugar. However, when thiourea was used as the sulfur nucleophile in reactions with the 4-*O*-*p*-nitrobenzoylglycosyl halides (**13b**,

X = Br, and the corresponding chloride) the resulting pseudothiouronium salts were α,β-mixtures, with the α anomer as the major component. Although the anomeric configuration of the glycosyl chloride (preferred for the preparation of the pseudothiouronium salt) was not determined, it appears from our experience with the bromide that the displacement of halide ion by thiourea proceeds in these cases with preponderant retention of configuration. The hydrolysis of the α,β-pseudothiouronium salt **14b** gave, of course, a 1-thio-α,β sugar (**15b**). The 4-*O*-allyl-1-thio-sugar **29** was also obtained as an α,β-mixture when the conditions for its production from **28** were more vigorous than usual. Evidently, 1-thio sugars are subject to anomerization under basic conditions, in spite of an earlier suggestion[17] to the contrary.

## EXPERIMENTAL

*General methods.* — Instrumental and chromatographic procedures were as described in earlier papers of this series[3,12,13]. The following solvent combinations (v/v) were utilized for thin-layer and column chromatography: A, 19:1 chloroform–acetone; B, 97:3 chloroform–ethyl acetate; C, 19:1 chloroform–ethyl acetate; D, 9:1 chloroform–ethyl acetate; E, 4:1 benzene–ethyl acetate; F, 49:1 chloroform–methanol; G, 17:3 chloroform–methanol. P.m.r. spectra at 270 MHz (specifically noted) were recorded with a Bruker WH-270 instrument.

*Allyl 3-O-benzoyl-2,6-di-O-benzyl-4-O-(tetrahydro-2-pyranyl)-α-D-galacto-pyranoside* (**3**). — Pure allyl 3-*O*-benzoyl-2,6-di-*O*-benzyl-α-D-galactopyranoside[1] (**2**, 2.9 g, 5.75 mmol) was dissolved in chloroform (25 ml). 2,3-Dihydro-4*H*-pyran (2.1 ml) and *p*-toluenesulfonic acid (~30 mg) were added to the solution. T.l.c. in solvent A indicated that the reaction was complete in 10–15 min. After 30 min the solution was washed successively with 5% sodium hydrogencarbonate and water, dried over anhydrous magnesium sulfate, and evaporated to dryness under diminished pressure. Chromatography of the residue on silica gel (solvent A) gave 2.58 g (76%) of syrupy **3**, $[\alpha]_D^{25}$ +63° (*c* 0.5, chloroform); p.m.r. ($CDCl_3$) similar to that[1] of **2**, with the addition of an envelope at δ 2.0–1.0, due to the protons at C-3,4, and 5 of the tetrahydropyranyl group. Found: C, 71.76; H, 6.86. $C_{35}H_{40}O_8$ (588.67) requires C, 71.41; H, 6.85.

*Allyl 2,6-di-O-benzyl-4-O-(tetrahydro-2-pyranyl)-α-D-galactopyranoside* (**4**). — Pure **3** (2.64 g, 4.5 mmol) was dissolved in methanol (70 ml), ~20 mg of sodium metal was added, and the solution was boiled under reflux. The debenzoylation was monitored by t.l.c. (solvent E), which indicated disappearance of the starting material after 1 h. Water was added to the cooled solution, and the product was isolated by conventional chloroform extraction. Chromatography on silica gel (solvent E) afforded 1.7 g (78%) of the syrupy title compound, $[\alpha]_D^{25}$ +47.4° (*c* 0.7, chloroform). In the p.m.r. spectrum, the signal at δ 8.3–7.9 (2 H of PhCO) was now absent, δ 7.63–7.13 (Ph–H) now 10 H, 2.73–2.23 (bs, 1, $D_2O$ exchangeable, O*H*). Found: C, 69.09, H, 7.59. $C_{28}H_{36}O_7$ (484.57) requires C, 69.40; H, 7.49.

*Allyl 2,3,6-tri-O-benzyl-4-O-(tetrahydro-2-pyranyl)-α-D-galactopyranoside* (**5**). — Pure **4** (1.1 g, 2.3 mmol) was stirred with benzyl chloride (10 ml) and powdered potassium hydroxide (15 g) for 5 h at 100°. After the mixture had cooled to room temperature, 25 ml of ice water was added, and stirring was continued until the salts dissolved. The product was recovered by conventional chloroform extraction. Chromatography on silica gel (solvent A) afforded 0.9 g (70%) of syrupy **5**, $[\alpha]_D^{25}$ +62°, $[\alpha]_{436}^{25}$ +120° (*c* 1, chloroform); p.m.r. ($CDCl_3$): $\delta$ 7.68–7.05 (Ph–H) now 15 H. Found: C, 73.67; H, 7.06. $C_{35}H_{42}O_7$ (574.69) requires C, 73.14; H, 7.37.

*Allyl 2,3,6-tri-O-benzyl-α-D-galactopyranoside* (**6**). — *A. From* **5**. A stirred solution of **5** (10.2 g, 17.7 mmol) in methanol (40 ml), and 60% acetic acid (100 ml) was kept for 1 h at 95–100°. At this time, t.l.c. (solvent A) showed disappearance of the starting material. Water was added to the cooled solution, and the product was isolated by conventional chloroform extraction. Chromatography on silica gel (solvent A) afforded 5.42 g (62%) of the syrupy title compound **6**, $[\alpha]_D^{25}$ +52.8°, $[\alpha]_{436}^{25}$ +99.7° (*c* 1, chloroform). In the p.m.r. spectrum, the envelope at $\delta$ 2.0–1.0 (protons at C-2, 3, and 4 of the tetrahydropyranyl group) was now absent; $\delta$ 2.57–2.05 (bs, 1, $D_2O$ exchangeable, O*H*-4). Found: C, 73.74; H, 7.19. $C_{30}H_{34}O_6$ (490.57) requires C, 73.44; H, 6.99.

*B. From allyl 2,6-di-O-benzyl-α-D-galactopyranoside* (**1**) *via the stannylene derivative.* A suspension of allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[11,18] (**1**) (0.8 g, 2 mmol) and dibutyltin oxide (0.5 g, 2 mmol) in methanol (100 ml) was heated for ~1 h under reflux to give a clear solution, then the solvent was removed under diminished pressure. The resulting *allyl 2,6-di-O-benzyl-3,4-O-dibutylstannylene-α-D-galactopyranoside* (**7**) was dried under oil-pump vacuum, taken up in *N,N*-dimethylformamide (5 ml), and treated with benzyl bromide (0.7 ml, 6 mmol). The mixture was heated for ~1.5 h at 100°, at which point t.l.c. (solvent A) showed a major spot corresponding to **6**, along with a few percent of **1** (unreacted **7** decomposes on silica gel). Following evaporation of the solvent, the material was chromatographed on a column of silica gel (solvent A) to afford 0.7 g (72%) of the syrupy title compound indistinguishable in chromatographic mobility, p.m.r. spectrum, and specific rotation from a sample prepared by method A.

*2,3,6-Tri-O-benzyl-D-galactose* (**9**). — Allyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**6**, 7.0 g, 14.3 mmol) and potassium *tert*-butoxide (2.7 g, 24 mmol) in dry methyl sulfoxide (50 ml) were heated for ~30 min at 100°. At this time t.l.c. (solvent C) showed complete conversion of the starting material into a product having slightly higher mobility. The solution was cooled and extracted with ether, and the ether extract dried over sodium sulfate. The syrupy *1-propenyl 2,3,6-tri-O-benzyl-α-D-galactopyranoside* (**8**) obtained by evaporation of the ether was dissolved in acetone (180 ml) and M hydrochloric acid (20 ml), and the solution was refluxed for 15 min. Neutralization of the cooled mixture with 5% sodium hydrogencarbonate caused the product to oil out. It was isolated by conventional chloroform extraction. Chromatography on silica gel (solvent D) afforded 3.8 g (59%) of the syrupy title compound (**9**), $[\alpha]_D^{25}$ +11.9 to +13.2° in chloroform (varied from batch to batch),

lit.[6] $[\alpha_D^{25}]$ +13.5°; p.m.r. ($CDCl_3$): $\delta$ 5.57–5.18 (m, 0.9, H-1 of α-pyranose and furanoses) and 2.83 (bs, $D_2O$ exchangeable, O*H*-4), no -C*H*=C$H_2$ signals.

**4-O-*Benzoyl*-2,3,6-*tri*-O-*benzyl*-α,β-D-*galactopyranose* (11a).** — The 1-propenyl galactoside (**8**) from 3.0 g (6.1 mmol) of **6** was treated with benzoyl chloride (4 ml, 35 mmol) in pyridine (20 ml) for ~5 h at room temperature. The reaction mixture was stirred into 100 ml of cold water and the product, *1-propenyl 4-O-benzoyl-2,3,6-tri-O-benzyl-α-D-galactopyranoside* (**10a**), was recovered by conventional chloroform extraction. The hydrolysis of **10a** was conducted as for the conversion of **8** into **9**. Chromatography of the crude hydrolysis product on a silica-gel column (250 g, 2.7-cm diameter, solvent A) afforded 2.12 g (62.5%) of syrupy **11a**, $[\alpha]_D^{25}$ +59.3 (initial) → +55.9° (24 h), $[\alpha]_{436}^{25}$ +118 → +114° (*c* 0.6, chloroform); p.m.r. ($CDCl_3$): $\delta$ 8.32–7.82 (m, ~2, PhCO), 7.63–6.93 (Ph-H) now ~18 H, 5.82 (m, 1, H-4), 5.42 (d, ~0.9, *J* 3.5 Hz, H-1α), and 5.18 (bs, 1, $D_2O$ exchangeable, O*H*-1), no signals for vinyl-H. Found: C, 73.46; H, 6.18. $C_{34}H_{34}O_7$ (554.61) requires C, 73.63; H, 6.18.

*2,3,6-Tri-O-benzyl-4-O-p-nitrobenzoyl-α,β-D-galactopyranose* (**11b**). — The 1-propenyl galactoside (**8**) from 1.3 g (2.6 mmol) of **6** was acylated with *p*-nitrobenzoyl chloride (1.6 g, 8.6 mmol) in pyridine (10 ml) for ~10 h at room temperature. Further treatment as described for the preparation of **11a** gave first *1-propenyl 2,3,6-tri-O-benzyl-4-O-p-nitrobenzoyl-α-D-galactopyranoside* (**10b**), and then crude **11b**. Chromatography on a column of silica gel (100 g, solvent A) afforded 1.21 g (76%) of pure syrupy **11b**, $[\alpha]_D^{25}$ +53.8°, $[\alpha]_{436}^{25}$ +117.6° (24 h, slight downward mutarotation) (*c* 1, chloroform); p.m.r. ($CDCl_3$): $\delta$ 8.38–8.05 (m, ~4, $O_2NPhCO$) and 5.35 (d after $D_2O$ exchange, ~0.5, H-1α). Found: C, 68.16; H, 5.55; N, 2.33. $C_{34}H_{33}NO_9$ (599.61) requires C, 68.10; H, 5.55; N, 2.34.

*1-O-Acetyl-4-O-benzoyl-2,3,6-tri-O-benzyl-α,β-D-galactopyranose* (**12a**). — A solution of **11a** (2.12 g, 3.8 mmol) in dry pyridine (10 ml) was treated with acetic anhydride (1.5 ml) for ~8 h at room temperature, and the mixture was then poured into 100 ml of cold water. Recovery of the product by conventional chloroform extraction gave 2.15 g (94%) of **12a** as a colorless syrup. For analysis, a portion was chromatographed on silica gel (solvent B). The sample had $[\alpha]_D^{25}$ +49.0°, $[\alpha]_{436}^{25}$ +105.2° (*c* 1.15, chloroform); p.m.r. ($CDCl_3$) similar to that of **11a**, but showing signals at $\delta$ 6.50 and 5.40 (H-1α, H-1β), and singlets at 2.13 (COC$H_3$-α)[19] and 2.07 (COC$H_3$-β)[19]. Found: C, 72.29; H, 6.00. $C_{36}H_{36}O_8$ (596.65) requires C, 72.46; H, 6.08.

*1-O-Acetyl-2,3,6-tri-O-benzyl-4-O-p-nitrobenzoyl-α,β-D-galactopyranose* (**12b**). — Compound **11b** (1 g, 1.7 mmol) was acetylated as described for **11a**. The yield of colorless, syrupy **12b** was 0.91 g (85%). A portion chromatographed on silica gel (solvent B) had $[\alpha]_D^{25}$ +58.6°, $[\alpha]_{436}^{25}$ +131.3° (*c* 0.54, chloroform); p.m.r. ($CDCl_3$) similar to that of **11b**, but showing signals at $\delta$ 6.43 and 5.68 (H-1α, H-1β), and singlets at 2.13 (COC$H_3$-α)[19] and 2.10 (COC$H_3$-β)[19]. Found: C, 67.57; H, 5.33; N, 2.22. $C_{36}H_{35}NO_{10}$ (641.65) requires C, 67.38; H, 5.50; N, 2.18.

*4-O-Benzoyl-2,3,6-tri-O-benzyl-β-D-galactopyranosyl ethylxanthate* (**14a**). — Compound **12a** (1 g, 1.67 mmol) was dissolved in 15 ml of dry dichloromethane

saturated with hydrogen bromide, and the solution was kept for ~3 h at room temperature. The solvent was evaporated under diminished pressure, and residual hydrogen bromide was removed by the addition and evaporation of several portions of dry dichloromethane. Further drying of the residue under oil-pump vacuum gave crude *4-O-benzoyl-2,3,6-tri-O-benzyl-α-D-galactopyranosyl bromide* (**13a**, X = Br), p.m.r. ($CDCl_3$): $\delta$ 6.5 (d, ~1, $J_{1,2}$ 3.5 Hz, H-1α), no signals for $COCH_3$.

The dried glycosyl bromide was dissolved in 25 ml of dry benzene, and potassium ethylxanthate (0.35 g, 2.2 mmol) in 25 ml of abs. ethanol was added. The solution was stirred for 5 h at room temperature and then washed with water. Evaporation of the dried benzene layer left a yellow syrup, which was crystallized from methanol and recrystallized from chloroform–methanol. The yield was 0.84 g (75% based on **12a**) of needles, m.p. 124.5–125°, $[\alpha]_D^{25}$ +34.9°, $[\alpha]_{436}^{25}$ +106.4° (*c* 1, chloroform); p.m.r. ($CDCl_3$) at 270 MHz: $\delta$ 5.43 (d, 1, $J_{1,2}$ 9.6 Hz, H-1) and 1.39 (t, 3, *J* 7.0 Hz, $CH_2CH_3$). Found: C, 67.85; H, 5.88; S, 9.89. $C_{37}H_{38}O_7S_2$ (658.81) requires C, 67.45; H, 5.81; S, 9.73.

*2,3,6-Tri-O-benzyl-4-O-p-nitrobenzoyl-β-D-galactopyranosyl ethylxanthate* (**16**). — The treatment of **12b** (0.8 g, 1.2 mmol) with hydrogen bromide in dichloromethane as described for **12a** gave crude *2,3,6-tri-O-benzyl-4-O-p-nitrobenzoyl-α-D-galactopyranosyl bromide* (**13b**, X = Br), p.m.r. ($CDCl_3$): $\delta$ 6.57 (d, ~1, $J_{1,2}$ 3.5 Hz, H-1α), no signals for $COCH_3$. The conversion of this bromide into the ethylxanthate was accomplished as described for **13a**. Crystallization of the product from ether–Skellysolve B and recrystallization from ethanol yielded 0.53 g (60% based on **12b**) of needles, m.p. 102–103°, $[\alpha]_D^{25}$ +33.8°, $[\alpha]_{436}^{25}$ +109.7° (*c* 0.8, chloroform); p.m.r. ($CDCl_3$): $\delta$ 5.43 (d, ~1, $J_{1,2}$ 10.0 Hz, H-1) and 1.38 (t, 3, *J* 7.0 Hz, $CH_2CH_3$) Found: C, 62.75; H, 5.30; N, 1.93; S, 9.05. $C_{37}H_{37}NO_9S_2$ (703.81) requires C, 63.14; H, 5.30; N, 1.99; S, 9.11.

*4-O-Benzoyl-2,3,6-tri-O-benzyl-1-thio-β-D-galactopyranose* (**15a**). — Compound **14a** (1.2 g, 1.8 mmol) was dissolved in 150 ml of abs. methanol by heating, then the solution was brought to ~25° and 15 ml of M methanolic sodium methoxide was added. The mixture was gently stirred until t.l.c. (solvent F) showed the reaction to be complete (40 min). Conventional extraction with chloroform and chromatography of the crude product on silica gel (100 g, column diameter 1.7 cm, solvent F) afforded 0.75 g (72%) of the syrupy title compound, $[\alpha]_D^{25}$ +40.0°, $[\alpha]_{436}^{25}$ +88.1° (*c* 0.5, chloroform); p.m.r. ($CDCl_3$) at 270 MHz: $\delta$ 4.59 (dd, 1, H-1, collapses to d, $J_{1,2}$ 9.2 Hz on irradiation of S*H*) and 2.39 (d, 1, $J_{1,SH}$ 8.0 Hz, $D_2O$ exchangeable, S*H*), no signal for $CH_2CH_3$. Found: C, 71.31; H, 5.83; S, 5.66. $C_{34}H_{34}O_6S$ (570.68) requires C, 71.55; H, 6.01; S, 5.62.

*2,3,6-Tri-O-benzyl-4-O-p-nitrobenzoyl-1-thio-α,β-D-galactopyranose* (**15b**). — Compound **12b** (0.31 g, 0.48 mmol) was dissolved in 7 ml of dry dichloromethane saturated with hydrogen chloride, and the solution was kept for 4 h at room temperature. T.l.c. in solvent A showed that the **12b** had been converted into a product of slightly higher mobility. Isolation as described for the bromide **13a** gave crude *2,3,6-tri-O-benzyl-4-O-p-nitrobenzoyl-D-galactopyranosyl chloride* (**13b**, X = Cl).

A solution of the dried, syrupy **13b** and thiourea (0.06 g, 0.8 mmol) in anhydrous acetone (3 ml) was boiled for 15 min under reflux[20]. T.l.c. (solvent A) indicated complete conversion into a very polar product. Evaporation of the acetone yielded crude *S-(2,3,6-tri-O-benzyl-4-O-p-nitrobenzoyl-α,β-D-galactopyranosyl)pseudothiouronium chloride* (**14b**), p.m.r. ($CDCl_3$) at 270 MHz; $\delta$ 6.53 (d, $J_{1,2}$ 5.2 Hz, H-1α) and 4.67 (d, $J_{1,2}$ 9.4 Hz, H-1β).

The dried **14b** in 0.5 ml of carbon tetrachloride was added to 0.1 g of sodium metabisulfite in 0.4 ml of water at 85°. The mixture was boiled for 15 min under reflux with constant stirring, whereupon t.l.c. (solvent C) showed complete conversion of the starting material into a less-polar product. The solution was cooled, and the organic layer was separated, washed with water, dried, and evaporated. Chromatography of the residue on silica gel (10 g, column diameter 0.6 cm, solvent A) afforded 0.21 g (71% based on **12b**) of the syrupy thio sugar **15b**, $[\alpha]_D^{25}$ +121.4°, $[\alpha]_{436}^{25}$ +260.6° (*c* 0.4, chloroform); p.m.r. ($CDCl_3$) at 90 MHz: $\delta$ 2.39 (d, $D_2O$ exchangeable, *J* 7.92 Hz, S*H*-β) and 1.91 (d, $D_2O$ exchangeable, *J* 4.12 Hz, S*H*-α). Found: C, 66.46; H, 5.43; S, 5.51. $C_{34}H_{33}NO_8S$ (615.68) requires C, 66.32; H, 5.40; S, 5.21.

*Methyl 2,3,6-tri-O-benzoyl-4-O-(tetrahydro-2-pyranyl)-α-D-galactopyranoside* (**18**). — Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**17**) was prepared as described by Williams and Richardson[16], p.m.r. ($CDCl_3$) at 270 MHz: $\delta$ 8.10–7.95 and 7.62–7.26 (2 m, 15, PhCO), 5.76 and 5.69 [q of d, 2, H-3 (5.76) and H-2 (5.69, collapses to d on irradiation of H-1), $J_{1,2}$ 3.3, $J_{2,3}$ 10.7, and $J_{3,4}$ 2.9 Hz], 5.21 (d, 1, $J_{1,2}$ 3.3 Hz, H-1), 4.71–4.32 (m, 4, H-4,5,6,6'), 3.45 (s, 3, $OCH_3$) and 2.63 (bs, 1, $D_2O$ exchangeable, O*H*). The compound (10.5 g, 20.7 mmol) was treated with 2,3-dihydro-4*H*-pyran (7.0 ml, 80 mmol) and *p*-toluenesulfonic acid (100 mg) by the procedure already given for the pyranylation of **2**. This procedure gave, after chromatography on silica gel (solvent C), 8.25 g (67%) of glassy compound **18**, $[\alpha]_D^{25}$ +100° (*c* 2.8, chloroform); p.m.r. ($CDCl_3$) similar to that of **17**, except for the loss of O*H* and the addition of an envelope at $\delta$ 2.05–1.07 due to the protons at C-3,4, and 5 of the tetrahydropyranyl group. There were two $OCH_3$ sigals (3.46, 3.42), indicative of the presence in **18** of two components epimeric at C-2 of the tetrahydropyranyl group. Found: C, 66.97; H, 5.85. $C_{33}H_{34}O_{10}$ (590.60) requires C, 67.11; H, 5.80.

*Methyl 4-O-(tetrahydro-2-pyranyl)-α-D-galactopyranoside* (**19**). — The debenzoylation of compound **18** (5.0 g, 8.5 mmol) was accomplished by boiling it for 3 h under reflux in 40 ml of 0.5M methanolic sodium methoxide. After evaporation of the methanol the product was dissolved in chloroform, then extracted into water (three 20-ml portions). The residue obtained by evaporating the water was purified on silica gel (150 g, column diameter 1.8 cm, solvent G) to afford 1.9 g (78%) of syrupy **19**, $[\alpha]_D^{25}$ +124.5°, $[\alpha]_{436}^{25}$ +221.5° (*c* 1, chloroform); p.m.r. ($CDCl_3$): no signals below $\delta$ 4.8 (loss of PhCO, with upfield shift of H-2 and H-3). Found: C, 49.76; H, 7.62. $C_{12}H_{22}O_7 \cdot 0.5\,H_2O$ (287.30) requires C, 50.16; H, 8.07.

*Methyl 2,3,6-tri-O-benzyl-4-O-(tetrahydro-2-pyranyl)-α-D-galactopyranoside* (**20**). — Pure compound **19** (2.0 g, 7.0 mmol) was benzylated with benzyl chloride and potassium hydroxide as already described for compound **4**. The yield of syrupy **20**

after chromatography on silica gel (solvent C) was 3.55 g (93%), $[\alpha]_D^{25}$ +34° (*c* 1.4, chloroform); p.m.r. ($CDCl_3$): δ 7.62–7.12 (m, 15, Ph–H). Found: C, 72.43; H, 7.27. $C_{33}H_{40}O_7$ (548.65) requires C, 72.24; H, 7.35.

*Methyl 2,3,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**21**). — The depyranylation of 0.70 g (1.28 mmol) of **20** by the procedure used for compound **5** gave, after chromatography of the product on silica gel (solvent A), 0.45 g (76%) of syrupy **21**, $[\alpha]_D^{25}$ +39.3° (*c* 2.8, chloroform), lit.[6] $[\alpha]_D^{25}$ +39.5°; p.m.r. ($CDCl_3$): loss of δ 2.05–1.07 (tetrahydropyranyl-H), and appearance of δ 2.68 (bs, 1, $D_2O$ exchangeable, O*H*-4).

*Methyl 4-*O*-allyl-2,3,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**22**). — *A. From* **21**. Compound (**21**) (3 g, 6.5 mmol), allyl bromide (1 ml, 11.5 mmol), and sodium hydride (0.6 g) in dry benzene (25 ml) were refluxed[18] for 3 h. T.l.c. (solvent C) showed the allylation to be complete. After the mixture was cooled, the excess of sodium hydride was decomposed by the cautions addition of methanol, and water was added. The organic layer was separated, washed with water, dried, and evaporated. Chromatography of the crude product on silica gel (solvent C) gave 2.86 g (88%) of pure **22**, $[\alpha]_D^{25}$ +60.8°, $[\alpha]_{436}^{25}$ +117.6°, (*c* 1.14, chloroform); p.m.r. ($CDCl_3$): similar to that of **21** but showing δ 6.20–5.63 (m, 1, –C*H*=) and 5.55–4.88 (m, 2, =C$H_2$), 4.98–3.98 now 15 H (addition of OC$H_2$CH=). Found: C, 73.88; H, 7.03. $C_{31}H_{36}O_6$ (504.60) requires C, 73.78; H, 7.19.

*B. From methyl 4-*O*-allyl-α-*D*-galactopyranoside* (**24**). Compound **24** (50 mg, 0.2 mmol), 10 ml of dry benzene, 1 ml of benzyl chloride, and 2 g of powdered potassium hydroxide were stirred for 5 h under reflux[21]. T.l.c. in solvent C showed the benzylation to be complete. The solution was cooled, water was added, and the organic layer was separated, washed, dried, and evaporated under diminished pressure. The residual yellow syrup was purified on silica gel (5 g, solvent C) to afford 80 mg (74%) of pure **22**, indistinguishable in chromatographic mobility, p.m.r. spectrum, and specific rotation from a sample prepared by method A.

*Methyl 4-*O*-allyl-2,3,6-tri-*O*-benzoyl-α-*D*-galactopyranoside* (**23**). — Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**17**, 0.8 g, 1.6 mmol), freshly prepared, powdered, silver oxide (0.9 g, washed extensively and then dried with acetone and ether), and ground Drierite (0.7 g) were stirred in dry benzene (5 ml) for 30 min in the dark at room temperature with exclusion of moisture[22]. The mixture was then cooled to ~15°, allyl bromide (0.3 ml, 3.5 mmol) was added, and stirring was continued for ~18 h at room temperature. T.l.c. (solvent A) indicated that the reaction was almost complete. The mixture was filtered, the salts were washed with benzene, and the filtrate and washings combined and evaporated. Chromatography of the residue on silica gel (solvent A) gave 0.55 g (64%) of syrupy **23**, $[\alpha]_D^{25}$ +93.7°, $[\alpha]_{436}^{25}$ +189.7° (*c* 0.71, chloroform); p.m.r. ($CDCl_3$): similar to that of **17**, but with loss of O*H*, the addition of signals at δ 6.17–5.50 (–C*H*=) and 5.40–4.87 (=C$H_2$), and the addition of 2 H (OC$H_2$CH=) to δ 4.71–4.32. Found: C, 68.22; H, 5.63. $C_{31}H_{30}O_9$ (546.55) requires C, 68.12; H, 5.53.

*Methyl 4-*O*-allyl-α-*D*-galactopyranoside* (**24**). — Compound **23** (0.226 g, 0.41 mmol) was debenzoylated by refluxing it for 30 min in 5.5 ml of 0.1M methanolic

sodium methoxide. Evaporation of the solvent, extraction of the residue thrice with 10 ml of hot chloroform, and evaporation of the chloroform gave the crude, crystalline product. Recrystallization from dichloromethane yielded 0.075 g (77%) of **24** as needles, m.p. 133–134°, $[\alpha]_D^{25}$ +154°, $[\alpha]_{436}^{25}$ +298° (*c* 0.5, methanol); p.m.r. ($CD_3COCD_3$): no signals below $\delta$ 6.25 (loss of PhCO). Found: C, 50.90; H, 7.75. $C_{10}H_{18}O_6$ (234.24) requires C, 51.27; H, 7.75.

*4-O-Allyl-2,3,6-tri-O-benzyl-D-galactopyranose* (**25**). — *A. From* **22**. Compound **22** (1.65 g, 3.3 mmol) in 1,4-dioxane (30 ml) and 6M hydrochloric acid (6 ml) were stirred and kept for 30 h at ~100°, when t.l.c. (solvent A) showed the hydrolysis to be nearly complete. Aqueous, 5% sodium hydrogencarbonate was added to the cooled solution, and the product was isolated by conventional chloroform extraction. Evaporation of the dried chloroform extract left a yellow syrup, which was crystallized and recrystallized from ether–Skellysolve B. The yield of pure **25** was 1.15 g (72%), needles, m.p. 95–96°, $[\alpha]_D^{25}$ +19.3 (5 min) → +21.4° (12 h), $[\alpha]_{436}^{25}$ +36.0 (7 min) → +37.5° (12 h) (*c* 0.6, chloroform); p.m.r. ($CDCl_3$): $\delta$ 3.20 (bs, ~1, $D_2O$ exchangeable, O*H*-1), no signal for O$CH_3$. Found: C, 73.68; H, 7.04. $C_{30}H_{34}O_6$ (490.57) requires C, 73.44; H, 6.99.

*B. From compound* **8**. The propenyl galactoside (**8**) from 1 g (2 mmol) of **6** was allylated by the procedure used for the preparation of **22** from **21**. The crude product was hydrolyzed by heating it in 9:1 acetone–M hydrochloric acid for 15 min under reflux. Conventional chloroform extraction of the hydrolyzate gave a syrup, which was crystallized and recrystallized from ether–Skellysolve B. The yield was 0.67 g (67% based on **6**) of material indistinguishable in chromatographic mobility, p.m.r., and m.p. from a sample prepared by method A.

*1-O-Acetyl-4-O-allyl-2,3,6-tri-O-benzyl-α,β-D-galactopyranose* (**26**). — Compound **25** (0.36 g, 0.73 mmol) was acetylated as already described for compound **11a** to give 0.38 g (97%) of nearly colorless, syrupy **26**. A portion chromatographed on silica gel (solvent A) had $[\alpha]_D^{25}$ +43.4°, $[\alpha]_{436}^{25}$ +110.5° (*c* 0.84, chloroform); p.m.r. ($CDCl_3$): $\delta$ 6.35 (d, ~0.7, H-1$\alpha$), 2.09 (s, COC$H_3$-$\alpha$)[19], and 2.00 (s, COC$H_3$-$\beta$)[19]. Found: C, 72.72; H, 6.75. $C_{32}H_{36}O_7$ (532.61) requires C, 72.16; H, 6.81.

*4-O-Allyl-2,3,6-tri-O-benzyl-β-D-galactopyranosyl ethylxanthate* (**28**). — Compound **26** (0.3 g, 0.56 mmol) was dissolved in 10 ml of dry dichloromethane saturated with hydrogen chloride, and the solution was kept ~5 h at room temperature. The solvent was evaporated under diminished pressure, and residual hydrogen chloride was removed by the addition and evaporation of several portions of dry dichloromethane. Further drying of the residue under oil-pump vacuum gave crude *4-O-allyl-2,3,6-tri-O-benzyl-D-galactopyranosyl chloride* (**27**), p.m.r. ($CDCl_3$): no signals for COC$H_3$.

The dried glycosyl chloride was treated with potassium ethylxanthate as already described for the conversion **13a** → **14a**. The resulting yellow syrup was crystallized and recrystallized from methanol. The yield of **28** was 0.21 g (63% based on **26**), needles, m.p. 91–92°, $[\alpha]_D^{25}$ +36.4°, $[\alpha]_{436}^{25}$ +124° (*c* 1, chloroform); p.m.r. ($CDCl_3$) at 270 MHz: $\delta$ 5.32 (d, 1, $J_{1,2}$ 9.9 Hz, H-1) and 1.37 (t, 3, *J* 7.2 Hz, $CH_2CH_3$).

Found: C, 66.64; H, 6.35; S, 10.77. $C_{33}H_{38}O_6S_2$ (594.77) requires C, 66.64; H, 6.44; S, 10.78.

*4-O-Allyl-2,3,6-tri-O-benzyl-1-thio-β-D-galactopyranose* (**29**) was prepared by the saponification[1] of 0.23 g (0.4 mmol) of **28**. The compound crystallized from methanol once seed crystals had been obtained from a portion purified on a small column of silica gel (solvent B). The yield of material melting at 78.5–79° was 0.158 g (81%), $[\alpha]_D^{25}$ +13.5°, $[\alpha]_{436}^{25}$ +29.5° (*c* 0.8, chloroform); p.m.r. ($CDCl_3$) at 270 MHz: $\delta$ 4.44 (dd, 1, collapses to d, $J_{1,2}$ 9.2 Hz on irradiation of S*H*, H-1) and 2.30 (d, 1, $J_{1,SH}$ 8.1 Hz, S*H*), no signal for $CH_2CH_3$. Found: C, 70.73; H, 6.69; S, 6.19. $C_{30}H_{34}O_5S$ (506.64) requires C, 71.12; H, 6.76; S, 6.33.

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