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"STANDARDIZED INTERMEDIATES" FOR OLIGOSACCHARIDE SYNTHESIS. PRECURSORS OF D-GALACTOPYRANOSE RESIDUES HAVING CHAIN EXTENSION AT POSITION 3, OR POSITIONS 3 AND 2

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ABSTRACT

A series of 2-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-galactopyranosyl halides carrying either a second benzoyl group (**8a**, **12a**) or a selectively removable, temporary protecting group (**8b–d**, **12b**) at position 3 was synthesized from allyl α-D-galactopyranoside (**1**). The key intermediate was 1-propenyl 4,6-di-*O*-benzyl-α-D-galactopyranoside (**5**), prepared from **1** via the 4,6-*O*-benzylidene-2,3-di-*O*-crotyl derivative **2**. The successive incorporation of the 2-*O*-benzoyl group, by selective acylation at low temperature, and of various 3-substituents gave fully substituted 1-propenyl α-D-galactopyranosides **6a–d**. These were converted into the glycosyl halides by published methods. An improved preparation of allyl 2,6-di-*O*-benzyl-(**15**) and 2,4,6-tri-*O*-benzyl-(**19**) α-D-galactopyranoside was achieved. The direct acetonation of **1** to the 3,4-*O*-isopropylidene derivative **13**, followed by benzylation and mild acid hydrolysis, gave **15** in 56% yield. The transient protection of O-3 in **15** was accomplished by the alkylation of the dibutylstannylene derivative **16** with (2-methoxyethoxy)methyl chloride. Successive benzylation and mild acid hydrolysis of the product **17** efficiently furnished **19**.

INTRODUCTION

As part of a continuing project on chemical oligosaccharide synthesis from "standard building blocks", we recently prepared groups of intermediates suitable for use as precursors of β-linked, internal D-galactopyranose residues. The preceeding paper[1] described one set of these galactose derivatives, which we designate the 4(2)-Gal-β series because their protecting groups are arranged to provide for chain extension at position 4, with the option of branching at position 2. In the present article, we deal with the corresponding compounds of the 3(2)-Gal-β series, designed for chain extension at position 3, with branching at position 2 if desired. We also

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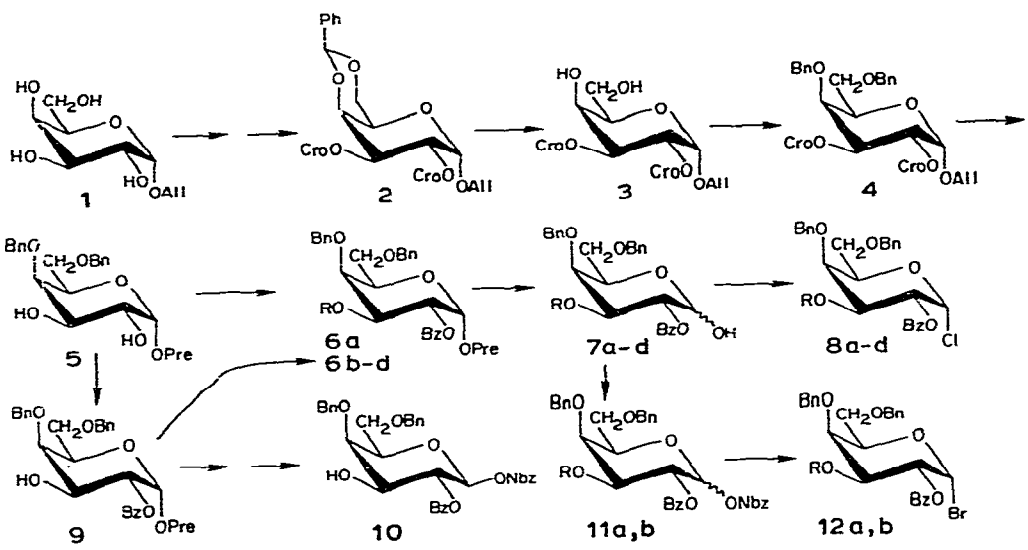
report a convenient preparation of the previously known allyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**19**), which has its 3-position open for coupling. Compound **19** is a useful precursor of reducing end-groups, or of α-linked interior residues in a blockwise synthesis.

RESULTS AND DISCUSSION

The considerations discussed in the previous paper led to the conclusion that suitable precursors of 3(2)-Gal-β residues would be D-galactopyranosyl halides (**8, 12**) carrying *O*-benzyl persistent protecting groups at positions 4 and 6, a β-directing, *O*-benzoyl group at position 2, and a selectively removable, temporary protecting-group at position 3. Our strategy for the synthesis of these halides was the same as the one initially used for the halides of the 4(2)-Gal-β series. A di-*O*-benzyl D-galactopyranoside was first prepared, and the benzoyl group and the temporary protecting group were successively emplaced. Then each fully substituted galactoside was hydrolyzed to the free sugar (1-hydroxy compound) and this was converted into the galactosyl chloride or bromide.

1-Propenyl 4,6-di-*O*-benzyl-α-D-galactopyranoside (**5**) was made by converting



All = allyl
Bn = benzyl
Bz = benzoyl
Cro = crotyl
Nbz = *p*-nitrobenzoyl
Ph = phenyl
Pre = 1-propenyl

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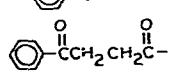
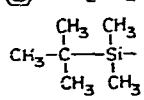
b	
c	
d	

SCHEME 1.

allyl α-D-galactopyranoside (**1**) into its 4,6-*O*-benzylidene derivative[2], and blocking positions 2 and 3 of the benzylidene compound with crotyl groups. After cleavage of the benzylidene group from the blocked galactoside **2** the intermediate **3** could be smoothly benzylated to **4** by treatment with sodium hydride and benzyl bromide. Removal of the crotyl groups from **4** was accomplished with potassium *tert*-butoxide[3], which also caused isomerization of the aglyconic allyl group to a 1-propenyl group.

For the selective benzoylation of OH-2, we first tried the reaction of the 2,3-*O*-dibutylstannylene derivative of **5** with benzoyl chloride. This procedure is reported[4] to give 2-substitution exclusively when applied to methyl 4,6-*O*-benzylidene-α-hexopyranosides of the 1,2-*cis* series, but in the present example it yielded a mixture of the two possible monobenzoates. On the other hand, the partial benzoylation of **5** itself in pyridine at low temperature gave a single, crystalline monobenzoate in 65% yield, together with some 2,3-dibenzoate (**6a**). The monosubstituted product was readily characterized as the desired 2-benzoate (**9**) by its ^{1}H-n.m.r. spectrum, which showed a downshifted C*H* multiplet at δ 5.32, identified by decoupling as the signal for H-2. The regioselectivity of this benzoylation is in contrast to that we observed with allyl 4,6-*O*-benzylidene-α-D-galactopyranoside, in which OH-3 reacted preferentially. As 4,6-*O*-benzylidene β-galactopyranosides show the same behavior[5], selectivity for OH-3 appears to be conditioned by the bicyclic structure of the benzylidene derivatives.

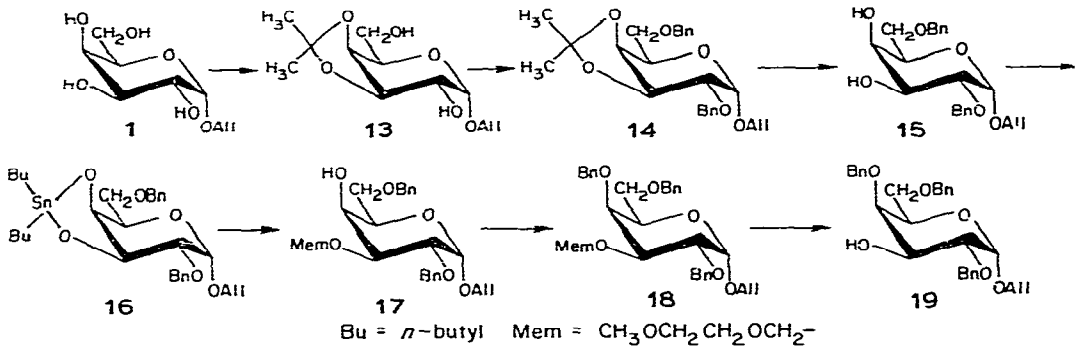
To perform the function of temporary protection in the present series of galactose derivatives, we chose to investigate the 3-benzoylpropanoyl group[6,7], the *tert*-butyldimethylsilyl group[8], and the tetrahydro-2-pyranyl group. The attachment of these groups to O-3 of **9** by standard procedures furnished the fully substituted 1-propenyl α-D-galactopyranosides **6b–d**. The 2,3-dibenzoate **6a**, obtained directly from **5** by acylation with excess benzoyl chloride, was prepared as a model compound for use in exploring the remaining steps of the synthesis. Hydrolysis of the 1-propenyl glycosides was accomplished by mild treatment with acid (**6a**), or by treatment with mercuric chloride–mercuric oxide[2] (**6b–d**), which provided the neutral conditions required to avoid cleavage of the acid labile *tert*-butyldimethylsilyl (**6c**) and tetrahydro-2-pyranyl (**6d**) substituents. Finally, the galactopyranosyl chlorides **8a–d** were made by reaction of the 1-hydroxy compounds **7a–d** with carbon tetrachloride and tris(dimethylamino)phosphine[1,9]. This method of generating glycosyl chlorides has the virtues of directness and compatibility with acid-labile substituents.

Intending to investigate the *p*-nitrobenzoyl group as a differentially removable substituent at position 3, we cleaved the 1-propenyl group from **9**, and treated the resulting 1,3-diol with an excess of *p*-nitrobenzoyl chloride in pyridine. The major product of the reaction was a nicely crystalline, monosubstituted derivative, the β-1-*p*-nitrobenzoate **10**. This compound might be used for the preparation of fully substituted derivatives in the same way as **9**, but we did not explore this possibility.

Compounds **7a** and **b**, having acid stable 3-substituents, were converted into the 1-*p*-nitrobenzoate derivatives **11a** and **b**, and thence into the glycosyl bromides

12a and **b** by reaction of the 1-*p*-nitrobenzoates with hydrogen bromide in dichloromethane.

One of the product galactosyl chlorides, the 2,3-di-*O*-benzoyl compound **8a**, is crystalline, and readily isolable in analytically pure state. It is stable during extended periods of storage in a freezer. The other galactosyl halides (**8b–d**, **12a,b**) have thus far been obtained only as syrups, which were characterized by their ^{1}H-n.m.r. spectra. These halides undergo some decomposition on being kept, and hence are best used when freshly prepared.



SCHEME 2.

Allyl 2,4,6-tri-O-benzyl-α-D-galactopyranoside (**19**). — Nashed and Anderson six years ago reported[10] the synthesis of this compound in three steps from allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**15**). Intermediate **15** was in turn made from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose by the five-step procedure of Gigg and coworkers[3,11]. As this synthesis was somewhat tedious, we sought an improved route, and were able to obtain **15** from allyl α-D-galactopyranoside (**1**) by the three-step sequence shown in Scheme 2. The first intermediate was generated by the acetonation of **1** with a mixture of acetone, 2,2-dimethoxypropane, and a catalytic amount of *p*-toluenesulfonic acid. As expected from the results of Gent, Gigg, and Conant[3], who used acetone–*p*-toluenesulfonic acid, the preponderant product was the 3,4-*O*-isopropylidene derivative* **13**. This was established by acetylation of the product and characterization of the diacetate by its ^{1}H-n.m.r. spectrum. Benzylation of **13** followed by mild acid hydrolysis furnished first allyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside* (**14**), and then allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[3] (**15**). Compound **15**, previously isolated only as a syrup, was obtained crystalline.

The benzylation of axial O-4 in **15** requires the prior protection of O-3. In the earlier work[10], we employed partial benzoylation for this purpose, but the results were not fully satisfactory[12]. Therefore, in the present synthesis, we turned to the (2-methoxyethoxy)methyl (Mem) group of Corey *et al.*[13], thus far little used in sugar

*This compound was obtained by Gent, Gigg, and Conant[3], but not characterized.

chemistry. The selective alkylation of equatorial O-3 was accomplished by the "stannylene procedure", previously explored in our laboratory[12,14]. Treatment of the 3,4-*O*-dibutylstannylene derivative (**16**) of **15** with (2-methoxyethoxy)methyl chloride in *N*,*N*-dimethylformamide furnished the 3-*O*-Mem compound **17** almost exclusively. Benzylation (benzyl bromide, sodium hydride) of the Mem-protected intermediate then gave the fully substituted galactoside **18**.

In an attempt to cleave the Mem group from O-3, compound **18** in dichloromethane solution was treated with zinc bromide, as recommended by Corey *et al.*[13]. Unfortunately, the reagent was completely ineffective, and other Lewis acids[13] were either ineffective or nonselective, causing cleavage of the glycosidic function as well as the Mem ether linkage. However, the selective hydrolysis of the Mem group was readily accomplished with methanolic hydrochloric acid, and by this means the desired product **19** was obtained in good yield.

In both parts of the present work, allyl α-D-galactopyranoside (**1**) was shown to be a convenient starting material for the synthesis of *O*-benzylated derivatives of D-galactose. Although the preparation[15] of **1** from D-galactose and allyl alcohol proceeds in rather poor yield (~30% in our hands), the low cost of the reactants, the simplicity of the manipulations, and the fact that the operation can be done on a moderately large scale make the compound readily available.

The second stage of the conversion of **1** into **19** was made more convenient and efficient through the use of the Mem group as a transient blocking group. The Mem group may also be desirable as a selectively removable blocking-group in galactosyl halides which could be prepared from the intermediate **18** and which would serve as precursors of 3-Gal-α units. However, the failure of specific catalysts to remove the Mem group as expected raises questions about one of its proposed uses[13], namely in situations requiring the selective cleavage of the group in the presence of other acid-labile groups.

Oligosaccharide synthesis. — The galactosyl halides **8a–d** and **12a,b** have all been successfully coupled to other substituted sugars, and in all instances the expected β-linked products were obtained. The details will be reported in separate publications. Efforts at the selective removal of the benzoylpropionyl group from the coupling products of **8b** and **12b** have not been successful, but selective deprotection of the coupling products of **8c** and **8d** (removal of a *tert*-butyldimethylsilyl and a tetrahydro-2-pyranyl group, respectively) proceeded smoothly. Chloride **8d** appears to be the most versatile of the 3(2)-Gal-β building blocks described in this paper, because either of its non-permanent protecting groups (2-*O*-benzoyl, 3-*O*-tetrahydropyranyl) may be removed from its coupling products without causing loss or migration of the other.

EXPERIMENTAL

Instrumental and chromatographic procedures. — These were described in a previous paper in this series[16]. In recording ^{1}H-n.m.r. data (270 MHz), decoupling

was performed as required. Line assignments, except those that could be made unambiguously by inspection, are based on decoupling experiments. Chromatography on silica gel was accomplished with mixtures of ethyl acetate and chloroform or acetone and chloroform. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL, and by Galbraith Labs, Inc., Knoxville, TN.

Most of the compounds described in this paper were chromatographically purified for purposes of characterization. However, in the normal preparation of glycosyl chlorides **8a–d** from **1**, only intermediates **4** and **9**, possibly **5** (see later), and the final products, required chromatography. Similarly, in the preparation of **19**, it sufficed to chromatograph intermediate **15**, and the final product.

General procedure for alkylation[17]. — A solution of sugar derivative (1 g) in *N,N*-dimethylformamide (15 mL) was cooled to 0°. Sodium hydride (0.25 g) was added, and then the chosen alkyl bromide (1.5–2 molar portions per hydroxyl group to be alkylated). The mixture was brought to room temperature slowly and kept for ~0.5 h, whereupon t.l.c. showed complete reaction. The excess of sodium hydride was decomposed by the addition of methanol, and the bulk of the *N,N*-dimethylformamide was removed in a rotary evaporator. The syrupy residue was taken up in water, and the product was extracted into chloroform (two portions). The organic layer was then washed with water and dried over sodium sulfate. Evaporation of the chloroform and traces of *N,N*-dimethylformamide gave the alkylated derivative in near-quantitative yield.

Allyl 4,6-O-benzylidene-2,3-di-O-(2-butenyl)-α-D-galactopyranoside (**2**). — Compound **1** was prepared as described by Lee and Lee[15] and then converted into allyl 4,6-*O*-benzylidene-α-D-galactopyranoside[2], ^{1}H-n.m.r. ($CDCl_3$): δ 7.50–7.35 (m, 5 H, Ph-H), 6.01–5.83 (m, 1 H, -C*H*=), 5.54 (s, 1 H, PhC*H*), 5.35–5.21 (m, 2 H, -CH=CH_2), 5.08 (d, 1 H, $J_{1,2}$ 2.2 Hz, H-1), 4.29–3.72 (m, 6 H, OCH_2CH= and sugar C*H*), and 2.62 and 2.33 (2 bs, 2 H, D_2O exchangeable, 2 O*H*). The benzylidene derivative (1.0 g, 3.24 mmol) was treated with 1-bromo-2-butene according to the general procedure already given, and the product purified on a column of silica gel. The yield of **2** was 1.2 g (89%). The compound crystallized from dichloromethane–hexane as fine needles, m.p. 64–65°, $[\alpha]_D^{25}$ +137°, $[\alpha]_{436}^{25}$ +269° (*c* 1.16, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of the benzylidene compound except for new signals at δ 5.77–5.58 (m, 4 H, C*H*=C*H*-CH_3), additional signals at 4.30–3.68 (m, 4 H, OCH_2CH=), new signals at 1.70–1.64 (m, 6 H, =CH-CH_3), and loss of the two exchangeable signals (O*H*). Two doublets were observed for H-1, at δ 5.09 and 5.08 ($J_{1,2}$ 2.9 Hz), attributed to *cis–trans* isomerism in the crotyl groups.

Anal. Calc. for $C_{24}H_{32}O_6$ (416.51): C, 69.21; H, 7.74. Found: C, 69.21; H, 7.73.

Allyl 4,6-di-O-benzyl-2,3-di-O-(2-butenyl)-α-D-galactopyranoside (**4**). — Compound **2** was hydrolyzed with M hydrochloric acid in methanol and the crude product (**3**) was isolated by conventional extraction with chloroform. After purification on a column of silica gel **3** was a colorless syrup, ^{1}H-n.m.r. ($CDCl_3$) similar to that of **2** except for loss of the aromatic signals, loss of the methine proton signal, and the appearance of new signals at δ 2.89 (bs, 1 H, D_2O-exchangeable, O*H*), and 2.78

(bs, 1 H, D_2O-exchangeable, O*H*). Benzylation of **3** by the general procedure, and then purification of the product by chromatography on a column of silica gel, gave **4** in 90% yield, colorless syrup, $[\alpha]_D^{25}$ +58.4°, $[\alpha]_{436}^{25}$ +110° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **3** except: new signals at δ 7.37–7.16 (m, 10 H, Ph-H), 4.75 (AB, 2 H, *J* 11.8 Hz, PhCH_2), and 4.43 (AB, 2 H, *J* 11.4 Hz, PhCH_2); no signals for O*H*.

Anal. Calc. for $C_{31}H_{40}O_6$ (508.66): C, 73.20; H, 7.93. Found: C, 73.58; H, 8.00.

*1-Propenyl 4,6-di-*O*-benzyl-α-*D*-galactopyranoside* (**5**). — Compound **4** (1.32 g, 2.60 mmol) was dissolved in dry *N*,*N*-dimethylformamide (15 mL) containing potassium *tert*-butoxide (1 g). The mixture was stirred for 2 h at 85° under dry nitrogen, and then poured into water. The product was isolated by conventional extraction with chloroform, dried, and purified by chromatography on a column of silica gel. This gave 0.83 g (80%) of **5**, syrup, $[\alpha]_D^{25}$ +30.1°, $[\alpha]_{436}^{25}$ +47.9° (*c* 2.6, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **4** except: new signals at δ 6.14–6.07 (m, 1 H, OC*H*=), 4.64–4.56 (m, 1 H, =C*H*-), 2.53 and 2.26 (2 bs, 2 H, D_2O-exchangeable, 2 O*H*), and 1.59 (dd, 3 H, *J* 1.9 and 7.0 Hz, =CHCH_3), and loss of the two 2-butenyl residues.

Anal. Calc. for $C_{23}H_{28}O_6$ (400.47): C, 68.98, H, 7.05. Found: C, 69.13, H, 6.93.

The decrotylation–isomerization of **4** by potassium *tert*-butoxide also proceeds smoothly in boiling toluene (compare Srivastava *et al.*[18]), if prolonged refluxing is avoided. When this solvent is used, the mixture is more readily processed, and the product does not require chromatographic purification.

*1-Propenyl 2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-α-*D*-galactopyranoside* (**6a**). — Compound **5** (4 g, 10 mmol) was benzoylated with benzoyl chloride in pyridine, and then the product was recovered by conventional extraction with chloroform and purified on a column of silica gel. The yield of **6a** was 5.6 g (92%). Crystallization from abs. ethanol produced fine needles, m.p. 64–65°, $[\alpha]_D^{25}$ +152°, $[\alpha]_{436}^{25}$ +325° (*c* 1.03, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **5** except: additional signals at δ 8.17–7.10 (2 C_6H_5CO), downfield shift of H-2 and H-3 to δ 5.90–5.75 (m, 2 H), and loss of the O*H* signals.

Anal. Calc. for $C_{37}H_{36}O_8$ (608.69): C, 73.01; H, 5.96. Found: C, 72.53; H, 5.91.

*1-Propenyl 2-*O*-benzoyl-3-*O*-(3-benzoylpropionyl)-4,6-di-*O*-benzyl-α-*D*-galactopyranoside* (**6b**). — To a stirred solution of **9** (2 g, 3.96 mmol) in *N*,*N*-dimethylformamide (10 mL) at ~100° was added 3-benzoylpropanoic anhydride[7] (1.5 g, 4.43 mmol) and 4-dimethylaminopyridine (0.04 g). After 2 h, t.l.c. of the mixture showed complete conversion of the starting material. The mixture was cooled and poured into cold water, and the product was recovered by conventional extraction with chloroform. Purification on a column of silica gel gave 2.1 g (80%) of the syrupy title compound, $[\alpha]_D^{25}$ +114°, $[\alpha]_{436}^{25}$ +236° (*c* 1.05, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **9** except: 5 additional Ph-H at low field and δ 5.54 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.73 (dd, 1 H, $J_{2,3}$ 9.9 Hz, H-2), 5.84 (dd, 1 H, $J_{3,4}$ 2.5 Hz, H-3), and 3.13–3.30 and 2.64–2.71 (2 m, 4 H, COCH_2 and CH_2COO).

Anal. Calc. for $C_{40}H_{40}O_9$ (664.75): C, 72.27; H, 6.07. Found: C, 71.89; H, 6.11.

1-Propenyl-2-O-benzoyl 4,6-di-O-benzyl-3-O-tert-butyldimethylsilyl-α-D-galactopyranoside (**6c**). — Compound **9** (1.5 g, 2.97 mmol) was dissolved in 1:1 dichloromethane–*N*,*N*-dimethylformamide (10 mL), and *tert*-butylchlorodimethylsilane (1.5 g, 9.9 mmol), triethylamine (1.5 mL), and 4-dimethylaminopyridine (0.3 g) were added[19]. The mixture was heated for 20 h on a steam bath, at which time t.l.c. showed complete reaction. Conventional extractive isolation with ether as the organic solvent, and purification of the crude compound on a column of silica gel, gave 1.65 g (90%) of the title compound as a syrup, $[\alpha]_D^{25}$ +130°, $[\alpha]_{436}^{25}$ +272° (*c* 1.0, chloroform), ^{1}H-n.m.r. ($CDCl_3$) similar to that of **9** except δ 5.38 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 5.75 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 0.94 (s, 9 H, CCH_3), and 0.17 and 0.3 (2 s, 6 H, $SiCH_3$).

Anal. Calc. for $C_{36}H_{46}O_7Si$ (618.84): C, 69.87; H, 7.49. Found: C, 69.71; H, 7.27.

1-Propenyl 2-O-benzoyl-4,6-di-O-benzyl-3-O-(tetrahydro-2-pyranyl)-α-D-galactopyranoside (**6d**). — To a stirred solution of **9** (1 g, 1.98 mmol) in chloroform (20 mL), was added *p*-toluenesulfonic acid (0.15 g) and an excess of 2,3-dihydro-4*H*-pyran (1 mL). After proceeding for 30 min at room temperature, the reaction was complete (t.l.c.). Conventional aqueous isolation gave a residue, which was purified on a column of silica gel to yield 0.95 g (81%) of the title compound as a syrup, $[\alpha]_D^{25}$ +99.0°, $[\alpha]_{436}^{25}$ +204° (*c* 1.0, chloroform). The ^{1}H-n.m.r. ($CDCl_3$) spectrum was complex because of stereoisomerism in the tetrahydropyranyl group, but a multiplet characteristic of this group appeared at δ 1.35–1.98 (9 H).

Anal. Calc. for $C_{35}H_{40}O_8$ (588.70): C, 71.41; H, 6.85. Found: C, 71.60; H, 6.81.

2,3-Di-O-benzoyl-4,6-di-O-benzyl-α,β-D-galactopyranose (**7a**). — The propenyl glycoside **6a** (2 g) was dissolved in methanol (25 mL), and 10 mL of 5% hydrochloric acid was added. The solution was boiled for 1 h under reflux, and then evaporated to dryness in a rotary evaporator. Chromatography of the crude hydrolysis product on a column of silica gel gave syrupy **7a** in quantitative yield, $[\alpha]_D^{25}$ +92.7°, $[\alpha]_{436}^{25}$ +198° (*c* 2.4, chloroform). The ^{1}H-n.m.r. ($CDCl_3$) spectrum was complex, suggesting the presence of α- and β-anomers. Signals for the propenyl group were absent.

Anal. Calc. for $C_{34}H_{32}O_8$ (568.62): C, 71.82; H, 5.67. Found: C, 71.42; H, 5.64.

2-O-Benzoyl-3-O-(3-benzoylpropanoyl)-4,6-di-O-benzyl-α,β-D-galactopyranose (**7b**). — Compound **6b** was hydrolyzed by treatment with mercuric oxide (yellow) and mercuric chloride in a mixture of acetone and water[2] to give the title compound in quantitative yield as a syrup, $[\alpha]_D^{25}$ +72.2°, $[\alpha]_{436}^{25}$ +150° (*c* 0.95, chloroform); ^{1}H-n.m.r. ($CDCl_3$): complex, no propenyl signals.

Anal. Calc. for $C_{37}H_{36}O_9$ (624.69): C, 71.14; H, 5.81. Found: C, 70.87; H, 5.85.

2-O-Benzoyl-4,6-di-O-benzyl-3-O-tert-butyldimethylsilyl-α,β-D-galactopyranose (**7c**). — Compound **6c** was hydrolyzed as described for **6b** to give the title compound in quantitative yield as a syrup, $[\alpha]_D^{25}$ +85.5°, $[\alpha]_{436}^{25}$ +176° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): complex, no propenyl signals.

Anal. Calc. for $C_{33}H_{42}O_7Si$ (578.78): C, 68.48; H, 7.31. Found: C, 68.95; H, 7.10.

2-O-Benzoyl-4,6-di-O-benzyl-3-O-(tetrahydro-2-pyranyl)-α,β-D-galactopyranose (**7d**). — The propenyl group was removed from compound **6d** in the same way as

from **6b**. This furnished **7d** in quantitative yield as a syrup, $[\alpha]_D^{25}$ +54.3°, $[\alpha]_{436}^{25}$ +114°. (*c* 0.83, chloroform); ^{1}H-n.m.r. ($CDCl_3$): complex, no propenyl signals.

Anal. Calc. for $C_{32}H_{36}O_8$ (548.63): C, 70.06; H, 6.61. Found: C, 69.87; H, 6.64.

*Preparation of 2,3,4,6-tetra-*O*-substituted* α-D-*galactopyranosyl chlorides.* — The procedure was that described in the previous paper of this series[1]. Because of their instability, the syrupy chlorides **8b–d** were characterized only by ^{1}H-n.m.r. spectroscopy. The expected low-field doublet for H-1α appeared in all of the spectra, which were otherwise similar to the spectra of the propenyl glycosides **6a–d**, respectively.

Application of the procedure to **7a** gave crystalline *2,3-di-*O*-benzoyl-4,6-di-*O-benzyl-α-D-*galactopyranosyl chloride* (**8a**) in quantitative yield, m.p. 103–104°, $[\alpha]_D^{25}$ +145°, $[\alpha]_{436}^{25}$ +334° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.70 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1).

Anal. Calc. for $C_{34}H_{31}ClO_7$ (587.07): C, 69.56; H, 5.32; Cl, 6.04. Found: C, 69.50; H, 5.28; Cl, 5.97.

The 3-*O*-(3-benzoylpropanoyl)-D-galactopyranose **7b** furnished *2-*O*-benzoyl-3-*O*-(3-benzoylpropanoyl)-4,6-di-*O*-benzyl-α-D-galactopyranosyl chloride* (**8b**) as a syrup in 80% yield; ^{1}H-n.m.r. ($CDCl_3$): δ 6.60 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1).

The 4-*O*-*tert*-butyldimethylsilyl-D-galactopyranose **7c** provided *2-*O*-benzoyl-4,6-di-*O*-benzyl-3-*O*-tert-butyldimethylsilyl-α-D-galactopyranosyl chloride* (**8b**) in 90% yield as a syrup, ^{1}H-n.m.r. ($CDCl_3$): δ 6.52 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1).

The 4-*O*-(tetrahydro-2-pyranyl)-D-galactopyranose **7c** gave *2-*O*-benzoyl-4,6-di-*O*-benzyl-3-*O*-(tetrahydro-2-pyranyl)-α-D-galactopyranosyl chloride* (**8d**) in 84% yield as a syrupy mixture of diastereoisomers (epimeric at C-2 of the tetrahydropyranyl group), ^{1}H-n.m.r. ($CDCl_3$): δ 6.56 and 6.52 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1).

*1-Propenyl 2-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-galactopyranoside* (**9**). — To a solution of compound **5** (0.65 g, 1.62 mmol) in anhydrous pyridine (10 mL), benzoyl chloride (0.3 mL, 2.59 mmol) was added dropwise over a 10-min period, while the temperature was maintained at −35°. The mixture was kept for an additional h below −30°, and then allowed to warm slowly to 25°. Conventional isolation by chloroform extraction gave a syrup that was purified on a column of silica gel. Crystallization and recrystallization of the syrup from benzene–hexane gave 0.56 g (68%) of **9** as needles, m.p. 77–77.5°, $[\alpha]_D^{25}$ +121°; $[\alpha]_{436}^{25}$ +252° (*c* 1.7, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **5** except: additional signals at δ 8.02–7.29 (C_6H_5CO), downfield shift of H-2 to δ 5.32 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.2 Hz, H-2), and loss of one exchangeable H. The signal for O*H*-3 was at δ 2.23 (d, *J* 9.2 Hz).

Anal. Calc. for $C_{30}H_{32}O_7$ (504.56): C, 71.41; H, 6.39. Found: C, 71.66; H, 6.35.

*2-*O*-Benzoyl-4,6-di-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-galactopyranose* (**10**). — Compound **9** (1.8 g, 3.57 mmol) was hydrolyzed with methanolic hydrochloric acid as already described for compound **6a** (conversion into **7a**). The resulting 1,3-diol was treated with *p*-nitrobenzoyl chloride (1.8 g, 9.7 mmol) in pyridine (80 mL), the mixture was stirred overnight at room temperature, and the product recovered by conventional extraction with chloroform. Crystallization and recrystallization of the product from methanol gave 1.6 g (73%) of the title compound **10**, m.p. 165–166°,

$[\alpha]_D^{25}$ −31.2°, $[\alpha]_{436}^{25}$ −82.5° (*c* 0.65, chloroform); ^{1}H-n.m.r. similar to that of **9** except: additional signals at δ 8.22–7.30 (C_6H_4), downfield shift of H-1 to δ 5.98 (d, 1 H, $J_{1,2}$ 8.1 Hz), and loss of signals for the propenyl moiety.

Anal. Calc. for $C_{34}H_{31}NO_{10}$ (613.62): C, 66.55; H, 5.09; N, 2.28. Found: C, 66.45; H, 5.25; N, 2.07.

*2,3-Di-*O*-benzoyl-4,6-di-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-*D*-galactopyranose* (**11a**) *and its conversion into the bromide* **12a**. — Conventional acylation of **7a** with *p*-nitrobenzoyl chloride in pyridine afforded **11a** as a solid. Crystallization from hot methanol gave the pure compound in 92% yield as needles, m.p. 176–179°, $[\alpha]_D^{25}$ +100°, $[\alpha]_{436}^{25}$ +221° (*c* 0.78, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **7a** except for additional signals at δ 8.43–8.10 (C_6H_4), and a downfield shift of H-1 to δ 6.80 (d, 1 H, $J_{1,2}$ 3.5 Hz).

Anal. Calc. for $C_{41}H_{35}NO_{11}$ (717.73): C, 68.61; H, 4.92; N, 1.95. Found: C, 68.63; H, 4.83; N, 1.94.

Compound **11a** (1 g, 1.39 mmol) was dissolved in dry dichloromethane saturated with hydrogen bromide (30 mL), and the mixture was stirred for 30 min in a tightly stoppered vessel. The precipitated *p*-nitrobenzoic acid was removed by filtration and the solvent was evaporated. The syrupy *2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-α-*D*-galactopyranosyl bromide* (**12a**) had a ^{1}H-n.m.r. spectrum ($CDCl_3$) similar to that of **11a** except for the absence of signals for the *p*-nitrobenzoyl moiety. The signal for H-1 appeared at δ 6.77 (d, 1 H, $J_{1,2}$ ~3 Hz).

*2-*O*-Benzoyl-3-*O*-(3-benzoylpropanoyl)-4,6-di-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α,β-*D*-galactopyranose* (**11b**) *and its conversion into the bromide* **12b**. — Compound **6b** was hydrolyzed by acid as already mentioned, and the product **7b** was isolated by conventional extraction with chloroform. The acylation of **7b** with *p*-nitrobenzoyl chloride in pyridine afforded the title compound. Purification on a column of silica gel furnished **11b** as an amorphous solid, $[\alpha]_D^{25}$ +78.2°, $[\alpha]_{436}^{25}$ +168° (*c* 0.62, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **6a** except: additional signals at δ 8.27–7.00 (C_6H_4), downfield shift of H-1 to δ 6.77 (d, <1 H, $J_{1,2}$ 3.7 Hz, H-1α) and 6.05 (d, <1 H, $J_{1,2}$ ~8 Hz, H-1β), and disappearance of the signals for the propenyl group.

Anal. Calc. for $C_{44}H_{39}NO_{12}$ (773.79): C, 68.30; H, 5.08; N, 1.81. Found: C, 68.74; H, 5.20; N, 1.74.

Compound **11b** was converted into *2-*O*-benzoyl-3-*O*-(3-benzoylpropanoyl)-4,6-di-*O*-benzyl-α-*D*-galactopyranosyl bromide* (**12b**) by treatment with hydrogen bromide in dichloromethane as described for the conversion **11a**→**12a**. The ^{1}H-n.m.r. spectrum ($CDCl_3$) was similar to that of **11b** except that only one signal for H-1 was present (δ 6.82, d, 1 H, $J_{1,2}$ 3.7 Hz); signals for the *p*-nitrobenzoyl moiety were absent.

*Allyl 3,4-*O*-isopropylidene-α-*D*-galactopyranoside* (**13**). — Allyl α-D-galactopyranoside **1** (5 g, 22.7 mmol) was dissolved in 1:1 acetone–dimethoxypropane (40 mL) and *p*-toluenesulfonic acid (0.2 g) was added. The solution was boiled under reflux for ~1.5 h, when t.l.c. showed the absence of the starting material and the presence of one major, faster-moving compound. The mixture was cooled, pyridine

(2 mL) was added to neutralize the acid, and the solvents were evaporated off. Fractionation of the residue on a column of silica gel gave 4 g (68%) of the title compound as a syrup, $[\alpha]_D^{25}$ +131°, $[\alpha]_{436}^{25}$ +256° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.14–5.95 (m, 1 H, -C*H*=), 5.46–5.28 (m, 2 H, =CH_2), 5.01 (d, $J_{1,2}$ 4.2 Hz, H-1), 4.39–3.83 (m, 8 H, OCH_2CH= and sugar C*H*, CH_2), 3.20 and 2.96 (2 bs, 2 O*H*), and 1.53 and 1.32 (2 s, 6 H, CCH_3).

Anal. Calc. for $C_{12}H_{20}O_6$ (260.29): C, 55.37; H, 7.75. Found: C, 55.54; H, 7.35.

Acetylation of **13** with acetic anhydride in pyridine gave *allyl 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-α-*D*-galactopyranoside*, ^{1}H-n.m.r. ($CDCl_3$) similar to that of **13** except δ 4.93 (dd, 1 H, $J_{1,2}$ 4.2, $J_{2,3}$ 7.5 Hz, H-2), 4.03–4.23 (m, 2 H, H-6, H-6′), 2.12 and 2.13 (2 s, 6 H, CH_3CO), and the absence of O*H* signals.

*Allyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-α-*D*-galactopyranoside* (**14**). — Compound **13** was treated with benzyl bromide according to the general procedure for alkylation to give the syrupy title compound in 92% yield, $[\alpha]_D^{25}$ +112°, $[\alpha]_{436}^{25}$ +215° (*c* 0.35, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **13** except δ 7.57–7.39 (m, 10 H, Ph-*H*), 4.85 (AB, *J* 13.2 Hz, 2 H, PhCH_2), and 4.65 (AB, *J* 12.5 Hz, PhCH_2); no O*H* signals.

Anal. Calc. for $C_{26}H_{32}O_6$ (440.54): C, 70.89; H, 7.32. Found: C, 71.08; H, 7.68.

*Allyl 2,6-di-*O*-benzyl-3-*O*-(2-methoxyethoxy)methyl-α-*D*-galactopyranoside* (**17**). — Compound **14** was treated with M hydrochloric acid in methanol to give the known allyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**15**). The compound was crystallized from chloroform–hexane, yield 90%, m.p. 49–51°; $[\alpha]_D^{25}$ +95.5°, $[\alpha]_{436}^{25}$ +187° (*c* 1.0, chloroform) (lit.[3] $[\alpha]_D$ +95.8°); ^{1}H-n.m.r. ($CDCl_3$) as previously described by Nashed and Anderson[10].

A solution of compound **15** (0.8 g, 2 mmol) in methanol (25 mL) was heated for 1 h under reflux with dibutyltin oxide (0.5 g). The methanol was evaporated off and the residual syrup was dried with a vacuum pump for ~0.5 h. A solution of the syrup in *N,N*-dimethylformamide (15 mL) was then warmed to 35°, and methoxyethoxymethyl chloride[13] (0.68 mL, 5.96 mmol) was added dropwise with constant stirring. After reaction for 1.5 h at 35°, t.l.c. showed complete conversion of the starting material into a product having higher mobility*. The mixture was cooled and sodium methoxide (5 mL, M) was added to decompose the excess of methoxyethoxymethylene chloride. Volatile materials were removed by evaporation under diminished pressure, and the residue was chromatographed on a column of silica gel to give 0.79 g (81%) of the title compound as a syrup, $[\alpha]_D^{25}$ +35.6°, $[\alpha]_{436}^{25}$ +67.4° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **15** except δ 3.35 (s, 3 H, OCH_3), and additional signal intensity (6 H) in the range 5.00–3.50 (OCH_2OCH_2CH_2O).

Anal. Calc. for $C_{27}H_{36}O_8$ (488.58): C, 66.38; H, 7.43. Found: C, 66.33; H, 7.58.

Compound **17** was converted into *allyl 4-*O*-benzoyl-2,6-di-*O*-benzyl-3-*O*-(2-methoxyethoxy)methyl-α-*D*-galactopyranoside* by treatment with benzoyl chloride in pyridine. The ^{1}H-n.m.r. spectrum was similar to that of **17** except for the appearance

*In subsequent preparations we have found it preferable to use 1 molar portion of Mem chloride, and conduct the reaction at 25°.

of a degenerate doublet at δ 5.89 (1 H, $J_{3,4}$ 3.0 Hz, H-4), and additional complexity and intensity in the range 8.26–7.42 (m, 15 H, Ph-H).

*Allyl 2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**19**). — The benzylation of **17** with benzyl bromide as described in the general procedure for alkylation gave *allyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-methoxyethoxy)methyl-α-*D*-galactopyranoside* (**18**). A portion (4 g, 6.92 mmol) of the **18** was dissolved in methanol (50 mL), hydrochloric acid (2M, 3 mL) was added, and the mixture was boiled for 3 h under reflux. T.l.c. showed one major spot, having an R_F value lower than that of the starting material. The mixture was cooled and made neutral with sodium hydrogencarbonate. The solvent was evaporated off, the residue was taken up in chloroform, and the mixture was filtered. The filtrate was evaporated to give the title compound, which was crystallized from dichloromethane–hexane. The yield was quantitative, m.p. 64–65°, $[\alpha]_D^{25}$ +61.5°, $[\alpha]_{436}^{25}$ +122° (*c* 1.0 chloroform) (reported[10] m.p. 67–68°, $[\alpha]_D^{25}$ +62.3°, $[\alpha]_{436}^{25}$ +122.5°).

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