Carbohydrate Research, 93 (1981) 219–230
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

"STANDARDIZED INTERMEDIATES" FOR OLIGOSACCHARIDE SYNTHESIS. PRECURSORS OF β-LINKED, INTERIOR D-GALACTOPYRANOSE UNITS HAVING CHAIN EXTENSION AT POSITION 4, OR POSITIONS 4 AND 2

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(Received November 26th, 1980; accepted for publication, December 28th, 1980)

ABSTRACT

Allyl 6-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (**1**) was used to prepare a series of 2-*O*-benzoyl-3,6-di-*O*-benzyl-α-D-galactopyranosyl halides carrying either a second benzoyl group (**11**, **17a**) or a selectively removable, temporary protecting group (**17b–d**) at position 4. In one synthetic scheme, the 2-butenyl (crotyl) group was used for the transient protection of position 2, and the 2-*O*-benzoyl group was incorporated by selective acylation of a 2,4-diol (**6**). In a more direct scheme, the 2-*O*-benzoyl group was introduced at the first step (**1**→**12**). Selective benzylation of O-3 was accomplished by the action of α-bromotoluene on 3,4-*O*-dibutylstannylene derivatives (**4** and **14**). Benzoyl, allyl, *tert*-butyldimethylsilyl, and tetrahydro-2-pyranyl groups, respectively, were incorporated at position 4 by derivatization of the otherwise fully substituted 1-propenyl glycoside **7**, or its precursor **15**. The fully substituted propenyl glycosides (**8a–d**) were converted into the 1-hydroxy compounds (**9a–d**) by mercuric ion-catalyzed hydrolysis, and thence directly into the chlorides (**17a–d**) by rection with hexamethylphosphorous triamide–carbon tetrachloride. The 2,4-di-*O*-benzoylated bromide **11** was made from **8a** by a conventional sequence. On coupling to the 2-amino-2-deoxyglucoside **18**, it gave the disaccharide β-D-Gal*p*-(1→4)-D-GlcNAc in fully substituted form (**19**).

INTRODUCTION

Derivatives of the common sugars suitable for use as "standard building-blocks" in chemical oligosaccharide synthesis are of continuing interest in this laboratory. Previously, we have described preparation of the position-isomeric tri-*O*-benzyl-1-thio-D-galactopyranoses[1–3], their corresponding benzyl thioglycosides[4],

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0008-6215/81/0000–0000/$ 02.50,

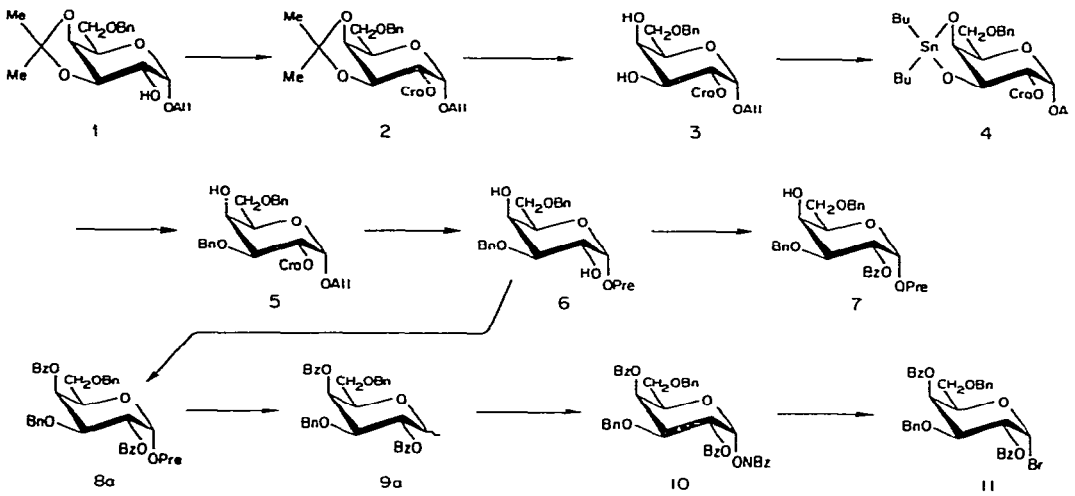
and *O*-benzylated oxazolines related to 2-acetamido-2-deoxy-D-glucopyranose[5,6]. We now report the synthesis of an additional group of *O*-benzylated D-galactose derivatives. These compounds were designed to serve as precursors of β-linked, interior D-galactopyranose units having chain extension at position 4, with branching at position 2, if desired.

RESULTS AND DISCUSSION

The incorporation of a D-galactopyranose residue into an interior position in an oligosaccharide may be accomplished by coupling an appropriately substituted galactopyranosyl halide to the partially protected, reducing moiety of the oligosaccharide, removing a temporary protecting group to unmask a hydroxyl group on the newly attached galactose unit, and then coupling an additional sugar to the exposed hydroxyl group. Thus, for the purpose specified in the Introduction, we proposed to make D-galactopyranosyl halides carrying persistent blocking groups (benzyl ether) at positions 3 and 6, and a temporary blocking group at position 4. The substituent at position 2 would be an *O*-acyl group, which is necessary to assure the formation of β linkages when currently available coupling methods are used. This requirement restricted the choice of groups to be used at position 4, as the 4-substituent had to be selectively removable.

In planning the syntheses, it was early necessary to pick the 2-*O*-acyl group to be employed. As evidenced in the long-known chemistry of the poly-*O*-acetylglycosyl halides, as well as in recent studies[7], the acetyl group is able to perform satisfactorily as a participating neighboring-group in glycosylation reactions. However, we considered that selective substitution at the 2-position (a feature of our original scheme) would be more readily achieved with a benzoylating agent. In addition, the benzoyl group is more stable to premature cleavage than the acetyl group, less prone to migration, and less likely to cause "anomalous" coupling reactions leading to orthoester products[8]. For these reasons, we chose the benzoyl group as the 2-substituent.

Allyl 6-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside[9] (**1**) was selected as the starting material for the preparation of the proposed galactosyl halides. In our first approach (Scheme I), the base-stable crotyl group was used as a transient protecting group at position 2. Alkylation of **1** with 1-bromo-2-butene furnished **2**, which was converted into the diol **3** by hydrolysis of the isopropylidene group. Compounds **2** and **3** were previously prepared by Gent and Gigg[10], but not fully characterized. Selective benzylation of the equatorial O-3 was accomplished by conversion of **3** into its dibutylstannylene derivative, and treatment of this with benzyl bromide in *N*,*N*-dimethylformamide[2,11,12]. The structure of the product **5** was confirmed by examination of the ^{1}H-n.m.r. spectrum of its benzoyl derivative, in which a signal characteristic of H-4 of galactose derivatives appeared at low field. Treatment of **5** with potassium *tert*-butoxide caused removal of the crotyl group, and thus furnished the propenyl derivative **6**, having free hydroxy groups at positions



All = allyl Bn = benzyl Bz = benzoyl Bu = *n*-butyl
Cro = crotyl (2-butenyl) NBz = *p*-nitrobenzoyl Pre = 1-propenyl

SCHEME I

2 and 4. Selective benzoylation of **6** with one molar proportion of benzoyl chloride at low temperature (−35°) yielded chiefly a monobenzoate. The 270-MHz n.m.r. spectrum of this product showed a doublet of doublets at δ 5.51 with spacings of 3.3 and 10.3 Hz, identifiable by decoupling as the signal for H-2. The downfield shift of H-2 established the structure of the product as **7**, in which position 4 is ready for substitution by any desired temporary protecting-group.

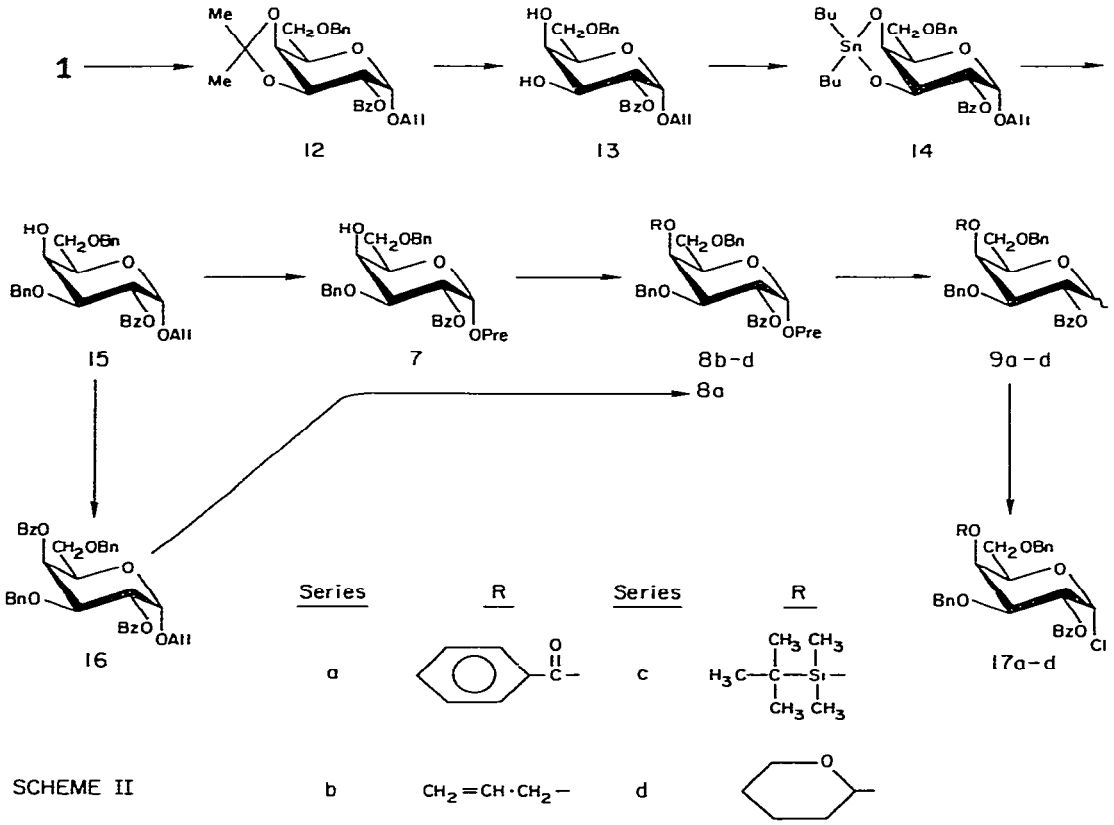
As candidates for the protection of position 4, we first considered the *p*-nitrobenzoyl and chloroacetyl groups. However, when a sample of the 4-*p*-nitrobenzoate of **7** was prepared and kept in methanolic sodium methoxide, the removal of the *p*-nitrobenzoyl group was not highly selective. A substantial proportion of the sample lost its 2-*O*-benzoyl group as well. When the 4-chloroacetate of **6** was treated with thiourea[13], cleavage of the chloroacetyl group was incomplete, even after prolonged reaction. Hence, we turned to other protecting groups and, by alkylation of **7** with allyl bromide in the presence of silver oxide, were able to obtain the fully substituted, 4-*O*-allyl propenyl galactoside **8b** in good yield (Scheme II).

Complete benzoylation of **6** with an excess of benzoyl chloride furnished the 2,4-dibenzoate **8a**, which served as a model compound for testing the remaining steps of the sequential synthesis. Mild acid-hydrolysis removed the anomeric propenyl group[9] to furnish **9a**, and acylation of this with *p*-nitrobenzoyl chloride gave the crystalline 2,4-di-*O*-benzoyl-3,6-di-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-galactopyranose **10** in 95% yield. Compound **10** was readily converted into the galactosyl bromide **11** by treatment with hydrogen bromide in dichloromethane[14].

A more-convenient route from **1** to the key intermediate **7** was established (Scheme II) when it was found that the 2-*O*-benzoyl group could be put in place

at the first step, to give **12**. The benzoyl group was stable to the conditions used for the removal of the 3,4-*O*-isopropylidene group (**12**→**13**) and the selective benzylation of position 3 *via* the stannylene procedure (**13**→**15**). Rearrangement of the allyl group, under neutral conditions, with tris(triphenylphosphine)rhodium(I) chloride[15,16] in ethanol provided **7** in good yield.

Three intermediates were prepared by the substitution of various groups onto O-4 of compound **7**. Alkylation with allyl bromide in the presence of freshly prepared silver oxide gave the already mentioned 4-*O*-allyl derivative **8b**, and silylation with *tert*-butylchlorodimethylsilane–imidazole[17] gave the 4-*tert*-butyldimethylsilyl ether **8c**. The addition of 2,3-dihydro-4*H*-pyran under catalysis by *p*-toluenesulfonic acid proceeded smoothly, without effect on the anomeric 1-propenyl group, to yield the 4-tetrahydropyranyl derivative **8d**.

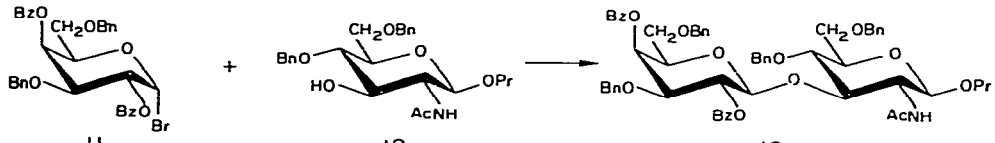


SCHEME II

Conversion of the fully substituted 1-propenyl glycosides **8a–d** into 1-hydroxy compounds and thence to glycosyl halides now had to be accomplished under neutral conditions, at least with **8c** and **8d**, because of the acid-labile groups at position 4 of these derivatives. Consequently, mercuric chloride–mercuric oxide in aqueous acetone was used[18] to effect the hydrolysis of **8c** and **d** to **9c** and **d**. The 1-hydroxy

compounds (**9a–d**) were then treated with hexamethylphosphorous triamide in carbon tetrachloride[19,20] to give the galactosyl chlorides **17a–d**. This method of obtaining the chlorides avoids the use of acidic reagents, and also eliminates the intermediate step of preparing the 1-*p*-nitrobenzoate or other 1-ester. Because of their greater stability, we preferred the chlorides over the bromides as building-block derivatives and, as we expected to use the silver triflate procedure[21,22] for coupling the halides to acceptors, the lower reactivity of the chlorides was not expected to be disadvantageous. As will be described in a separate publication, all of the galactosyl chlorides **17a–d** showed normal activity as glycosylating agents, and two of them (**17b, 17d**) were found satisfactory as precursors of β-linked, interior galactopyranose residues.

In a preliminary experiment, the galactosyl bromide **11** was coupled under modified Koenigs–Knorr conditions to propyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**18**) (Scheme III). This acceptor was prepared by reduction of the corresponding 1-propenyl glycoside[6]. The product was the substituted disaccharide glycoside **19**, obtained in 69% yield.



11 18 19

SCHEME III

Pr = *n* – propyl

EXPERIMENTAL

Instrumental and chromatographic procedures. — These were described in a previous paper in this series[6]. 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, for compounds of low polarity, or acetone and chloroform, for the more-polar compounds.

Allyl 6-O-benzyl-2-O-(2-butenyl)-3,4-O-isopropylidene-α-D-galactopyranoside (**2**). — Acetonation of allyl 6-*O*-benzyl-α-D-galactopyranoside[9] gave allyl 6-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside[9] (**1**); ^{1}H-n.m.r. ($CDCl_3$): δ 7.51–7.15 (m, 5 H, Ph-H), 6.04–5.83 (m, 1 H, -C*H*=), 5.24 (m, 2 H, -CH=CH_2), 4.91 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.59 (q, 2 H, *J* 11.8 Hz, PhCH_2), 4.27–4.18 (m, 3 H, sugar C*H*), 4.14 (dq, 2 H, *J* 6.2 and 11.1 Hz, OCH_2CH=), 3.73–3.65 (m, 3 H, sugar C*H*), 2.69 (d, 1 H, *J* 6.6 Hz, D_2O exchangeable, O*H*), 1.50 (s, 3 H, CCH_3), and 1.33 (s, 3 H, CCH_3). Compound **1** was then treated with sodium hydride and 1-bromo-2-butene in benzene as described by Gent and Gigg[10]. The product **2** was a colorless syrup, $[\alpha]_D^{25}$ +94.2°, $[\alpha]_{436}^{25}$ +184° (*c* 1.3, chloroform; ^{1}H-n.m.r. ($CDCl_3$) similar to that of **1** except for new signals at δ 5.77–5.52 (m, 2 H, C*H*=C*H*CH_3), additional signals at δ 4.99–3.52 (2 H, OCH_2CH=), and new signals at δ 1.71–1.61 (m, 3 H,

$=CHCH_3$). Two signals were observed for H-1, at δ 4.97 (d, $J_{1,2}$ 3.7 Hz, minor) and 4.94 (d, $J_{1,2}$ 3.7 Hz, major), indicative of *cis,trans* isomerism in the crotyl group.

Anal. Calc. for $C_{23}H_{32}O_6$ (404.50): C, 68.29; H, 7.97. Found: C, 68.27; H, 7.96.

Allyl 3,6-di-O-benzyl-2-O-(2-butenyl)-α-D-galactopyranoside (**5**). — Compound **2** was hydrolyzed with 0.5M hydrochloric acid is methanol[10], and the crude product was isolated by conventional chloroform extraction. Purification on a column of silica gel gave **3** as a colorless syrup, ^{1}H-n.m.r. ($CDCl_3$) similar to that of **2**, with loss of the two *C*-methyl signals and the appearance of new signals at δ 2.91 (bs, 1 H, D_2O-exchangeable, O*H*), and 2.68 (bs, 1 H, D_2O-exchangeable, O*H*). Compound **3** (4.82 g, 13.2 mmol) was dissolved in methanol (260 mL) containing dibutyltin oxide (3.38 g, 13.6 mmol). The mixture was heated until a clear solution was obtained (~1 h), and then evaporated to dryness under diminished pressure. The dried syrup (**4**) was dissolved in *N,N*-dimethylformamide containing benzyl bromide (4.6 mL). The solution was stirred for 30 min at 100° after which time the solvent was removed by evaporation and the product purified by chromatography on a column of silica gel. The yield of **5** was 4.91 g (82%), syrup, $[\alpha]_D^{25}$ +72.0°, $[\alpha]_{436}^{25}$ +135.5° (*c* 2.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **3** except: δ 7.36–7.21 now 10 H (Ph-H), 5.02 (d, $J_{1,2}$ 2.6 Hz, minor signal for H-1), 4.99 (d, <1 H, $J_{1,2}$ 2.6 Hz, major signal for H-1), 4.74 (AB, 2 H, *J* 11.7 Hz, $PhCH_2$), and loss of one exchangeable signal (O*H*).

Anal. Calc. for $C_{27}H_{34}O_6$ (454.56): C, 71.34; H, 7.54. Found: C, 71.14; H, 7.73.

1-Propenyl 3,6-di-O-benzyl-α-D-galactopyranoside (**6**). — Pure **5** (1.83 g, 4.03 mmol) was dissolved in dry *N,N*-dimethylformamide (36 mL) containing potassium *tert*-butoxide (1.83 g, 16.3 mmol). The mixture was stirred for 2 h at 80–85° under dry nitrogen, and then poured into water. Conventional chloroform extraction, followed by evaporation of the solvent, gave a dried syrup that was purified on a column of silica gel. The yield of **6** was 1.31 g (81%), $[\alpha]_D^{25}$ +69.4°, $[\alpha]_{436}^{25}$ +133° (*c* 0.8, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **5** except: δ 6.15–6.07 (m, 1 H, $OCH=$), 5.17 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.76–4.58 (m, 1 H, $=CH-$), 2.05 (s, 1 H, D_2O-exchangeable, O*H*), and 1.60 (dd, 3 H, *J* 1.8 and 7.0 Hz, $=CHCH_3$).

Anal. Calc. for $C_{23}H_{28}O_6$ (400.47): C, 68.98; H, 7.05. Found: C, 68.71; H, 7.06.

1-Propenyl 2-O-benzoyl-3,6-di-O-benzyl-α-D-galactopyranoside (**7**). — *A. From* **6**. Compound **6** (0.50 g, 1.25 mmol) was dissolved in dry pyridine (10 mL) and the solution was cooled to −35°. Benzoyl chloride (0.19 mL, 1.63 mmol) was added dropwise with stirring while the mixture was maintained at −35°. After 45 min, a few drops of water were added to the cooled solution. The mixture was allowed to warm to room temperature and then poured into chloroform. The chloroform solution was washed successively with 5% hydrochloric acid, saturated sodium hydrogencarbonate, and water, and then dried with magnesium sulfate. After purification on a column of silica gel, the yield of **7** was 0.53 g (84%), $[\alpha]_D^{25}$ +136°, $[\alpha]_{436}^{25}$ +277° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **6** except for new signals at δ 8.05–7.23 (C_6H_5CO), δ 5.51 (dd, 1 H, $J_{1,2}$ 3.3 Hz, $J_{2,3}$ 10.3 Hz, H-2), and loss of one O*H* signal.

Anal. Calc. for $C_{30}H_{32}O_7$ (504.58): C, 71.41; H, 6.39. Found: C, 71.05; H, 6.17.

B. From **15**. To a solution of compound **15** (4.1 g, 8.13 mmol) in ethanol (30 mL) were added diazabicyclo[2.2.2]octane (0.15 g, 1.34 mmol) and tris(triphenylphosphine)rhodium(I) chloride (0.5 g, 0.54 mmol). The mixture was stirred for ~2 h under reflux, at which time t.l.c. showed almost complete rearrangement of the allyl group to the propenyl group. Water was added and the cooled solution was extracted with ether, and the ether layer was washed with saturated potassium chloride, dilute hydrochloric acid, saturated potassium chloride, water, sodium hydrogencarbonate, and water. The dried ethereal layer was evaporated to give 3.8 g (93%) of the title compound 7, which had the same chromatographic mobility and ^{1}H-n.m.r. spectrum as the product obtained by method *A*.

1-Propenyl 2,4-di-O-benzoyl-3,6-di-O-benzyl-α-D-galactopyranoside (**8a**). — *A. From* **6**. Benzoylation of **6** with benzoyl chloride in pyridine, and then recovery of the product by conventional extraction with chloroform and purification on a column of silica gel gave **8a**, syrup, $[\alpha]_D^{25}$ +160°, $[\alpha]_{436}^{25}$ +335° (*c* 1.8, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **7** except for additional signals at δ 8.10–7.08 (C_6H_5CO), downfield shift of H-4 to δ 6.04 (dd, 1 H, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ ~1 Hz), and loss of the O*H* signal.

Anal. Calc. for $C_{37}H_{36}O_8$ (608.69): C, 73.01; H, 5.96. Found: C, 73.22; H, 6.07.

B. From **16**. The rearrangement of the allyl group in compound **16** was achieved by the procedure just described for the conversion of **15** into **7**. Thus, 3.3 g of **16** gave 3.1 g (94%) of product having the same physical constants and ^{1}H-n.m.r. spectrum as **8a** prepared by method *A*.

General procedure for the hydrolysis of 1-propenyl glycosides[18]. — A weighed portion of the 1-propenyl 2,3,4,6-tetra-*O*-substituted α-D-galactopyranoside was placed in an Erlenmeyer flask, and the following additions were made, per g of glycoside: 5:1 (v/v) acetone–water (30 mL) to dissolve the compound, and then mercuric oxide (1.16 g), and then (dropwise) mercuric chloride (1.46 g) in acetone–water (10 mL). The suspension was stirred for 5 min at room temperature and then filtered through Celite. The filtrate was evaporated to dryness, and the residue dissolved in chloroform. The chloroform solution was washed first with saturated potassium iodide and then water, dried, and evaporated to dryness. T.l.c. was used to check the crude product for completeness of removal of the propenyl group.

2,4-Di-O-benzoyl-3,6-di-O-benzyl-1-O-p-nitrobenzoyl-α-D-galactopyranose (**10**). Compound **8a** (1.77 g, 2.91 mmol) was hydrolyzed by the foregoing general procedure to *2,4-di-O-benzoyl-3,6-di-O-benzyl-D-galactopyranose* (**9a**) in almost quantitative yield. Conventional *p*-nitrobenzoylation of **9a** with *p*-nitrobenzoyl chloride in pyridine yielded 1.99 g (95.5%) of the title compound **10**. Crystallization from abs. ethanol produced fine needles, m.p. 127–129°, $[\alpha]_D^{25}$ +133°, $[\alpha]_{436}^{25}$ +278° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **8a** except for additional signal at δ 8.27–7.04 (C_6H_4), a downfield shift of H-1 to δ 6.81 (d, 1 H, $J_{1,2}$ 3.3 Hz), and disappearance of signals for the propenyl group.

Anal. Calc. for $C_{41}H_{35}NO_{11}$ (717.73): C, 68.61; H, 4.92; N, 1.95. Found: C, 68.38; H, 4.78; N, 1.88.

*2,4-Di-*O*-benzoyl-3,6-di-*O*-benzyl-α-*D*-galactopyranosyl bromide* (**11**). — Compound **10** (0.36 g, 0.50 mmol) was dissolved in dry dichloromethane saturated with hydrogen bromide (14.5 mL) and the mixture was stirred for 30 min in a tightly stoppered vessel. The solution was evaporated to dryness, and then a small amount of dry dichloromethane was added to the syrup and the solid *p*-nitrobenzoic acid was removed by filtration. The ^{1}H-n.m.r. spectrum of the dried syrup showed the complete absence of *p*-nitrobenzoyl groups, and a signal for the anomeric proton at δ 6.90 (d, ~1 H, $J_{1,2}$ 3.7 Hz). This syrup was used directly for coupling reactions.

*Allyl 2-*O*-benzoyl-6-*O*-benzyl-α-galactopyranoside* (**13**). — Compound **1** was prepared[9] from 45 g (145 mmol) of allyl 6-*O*-benzyl-α-D-galactopyranoside[9], and benzoylated conventionally (benzoyl chloride–pyridine). The resulting *allyl* 2-O-*benzoyl-6-*O*-benzyl-3,4-*O*-isopropylidene-α-*D*-galactopyranoside* (**12**) had a ^{1}H-n.m.r. spectrum ($CDCl_3$) similar to that of **1** (see under **2**, preceding) except for new signals at δ 8.33–7.55 (C_6H_5CO), a downfield shift of H-2, and loss of the O*H* signal. Hydrolysis of the crude **12** with 0.5M hydrochloric acid in methanol[10] gave **13**, which was recovered as a syrup by conventional chloroform extraction. The compound crystallized from ether–hexane as fine needles, yield 47 g (78% overall) m.p. 91–92°, $[\alpha]_D^{25}$ +116°, $[\alpha]_{436}^{25}$ +230° (*c* 0.78, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **12** except for loss of the two *C*-methyl signals, appearance of signals at δ 3.22 (d, 1 H, *J* 2.4 Hz, D_2O-exchangeable, O*H*), and 2.76 (d, 1 H, *J* 7.3 Hz, D_2O-exchangeable, O*H*), and a change in the signal for H-1 (δ 4.62, d, 1 H, $J_{1,2}$ 3.1 Hz).

Anal. Calc. for $C_{23}H_{26}O_7$ (414.45): C, 66.65; H, 6.32. Found: C, 66.25; H, 6.08.

*Allyl 2-*O*-benzoyl-3,6-di-*O*-benzyl-α-*D*-galactopyranoside* (**15**). — Compound **13** (27 g, 65.2 mmol) was dissolved in methanol (400 mL) containing dibutyltin oxide (18 g, 72.3 mmol). The mixture was heated until a clear solution was obtained (<1 h), and then was evaporated to dryness under diminished pressure to give **14**. The syrupy **14** was dried in a vacuum and then dissolved in *N,N*-dimethylformamide (100 mL) containing benzyl bromide (25 mL). The solution was stirred for ~30 min at 100°. Evaporation of the solvent and purification of the residue on silica gel yielded 29.5 g (90%) of the pure title compound, syrup, $[\alpha]_D^{25}$ +118°, $[\alpha]_{436}^{25}$ +238° (*c* 1.9, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **13** except for a downfield shift of H-2 (δ 5.53, dd, 1 H, $J_{1,2}$ 3.8 and $J_{2,3}$ 10.5 Hz), a downfield shift of H-1 (δ 5.28, d, 1 H, $J_{1,2}$ 3.8 Hz), and a new signal at δ 4.73 (AB, 2 H, $PhCH_2$).

Anal. Calc. for $C_{30}H_{32}O_7$ (504.58): C, 71.41; H, 6.39. Found: C, 71.32; H, 6.69.

*Allyl 2,4-di-*O*-benzoyl-3,6-di-*O*-benzyl-α-*D*-galactopyranoside* (**16**). — Compound **15** was benzoylated with benzoyl chloride in pyridine to provide **16** in quantitative yield. A pure sample obtained by chromatography on silica gel was a syrup, $[\alpha]_D^{25}$ +137°, $[\alpha]_{436}^{25}$ +286° (*c* 1.91, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **5a** except for additional signals at δ 8.31–7.55 (C_6H_5CO), a downfield shift of H-4 (δ 6.06, bd, 1 H, $J_{3,4}$ ~3 Hz), and loss of the O*H* signal.

Anal. Calc. for $C_{37}H_{36}O_8$ (608.69): C, 73.01; H, 5.96. Found: C, 73.04; H, 6.11.

1-Propenyl 4-O-allyl-2-O-benzoyl-3,6-di-O-benzyl-α-D-galactopyranoside (**8b**).— Compound **7** (357 mg, 0.71 mmol) was dissolved in benzene (3.2 mL) containing freshly prepared silver oxide (400 mg, 1.73 mmol) and freshly powdered Drierite (320 mg). The solution was stirred in the dark for 30 min at room temperature, and then allyl bromide (0.14 mL, 1.6 mmol) was added. Stirring was continued for 22 h at 50°. The mixture was filtered through Celite, and the solids were washed thoroughly with benzene. The benzene solution was washed with water, dried with magnesium sulfate, and evaporated to dryness. Purification of the syrup by column chromatography on silica gel gave 308 mg (80%) of **8b**, syrup, $[\alpha]_D^{25}$ +137°, $[\alpha]_{436}^{25}$ +277° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **7**, except for new signals at δ 5.98–5.83 (m, 1 H, -C*H*=), 5.26–5.11 (m, 2 H, CH_2=), and 4.58–3.57 (OCH_2), and loss of the O*H* signal.

Anal. Calc. for $C_{33}H_{36}O_7$ (544.64): C, 72.77; H, 6.66. Found: C, 72.63; H, 6.72.

2-O-Benzoyl-3,6-di-O-benzyl-4-O-tert-*butyldimethylsilyl-D-galactopyranose* (**9c**). — To compound **7** (1 g, 2 mmol) in *N,N*-dimethylformamide (5 mL), imidazole (0.54 g, 7.9 mmol) and *tert*-butylchlorodimethylsilane (0.6 g, 4.0 mmol) were added. The mixture was stirred overnight at 70°, an additional 4 mmol of the reagents were added, and stirring was continued for 2 more days. Chloroform was added to the cooled solution, which was then extracted with 5% hydrochloric acid (twice), water, 5% sodium hydrogencarbonate, and water. Evaporation of the solvent gave syrupy *1-propenyl 2-O-benzoyl-3,6-di-O-benzyl-4-O*-tert-*butyldimethylsilyl-α-D-galactopyranoside* (**8c**).

Hydrolysis of the propenyl glycoside by the general procedure gave the free sugar **9c**. Purification on a column of silica gel furnished 0.8 g (70%) of colorless syrup, $[\alpha]_D^{25}$ +28.7°, $[\alpha]_{436}^{25}$ +59.5° (*c* 0.74, chloroform); ^{1}H-n.m.r. similar to that of **7** except for loss of the signals for -C*H*=C*H*CH_3, the appearance of δ 0.93 [m, 9 H, SiC(CH_3)$_3$] and 0.06 (m, 6 H, SiCH_3), and changes in the signals for H-1 and H-2 because of partial anomerization: δ 5.56 (d, <1 H, $J_{1,2}$ 4.2 Hz, H-1α), 5.50 (dd, <1 H, $J_{1,2}$ 4.2 and $J_{2,3}$ 10.5 Hz, H-2α), and 5.39 (dd, <1 H, $J_{1,2}$ 7.5 and $J_{2,3}$ 9.8 Hz, H-2β).

Anal. Calc. for $C_{33}H_{42}O_7Si$ (578.78): C, 68.48; H, 7.31. Found: C, 68.42; H, 7.33.

2-O-Benzoyl-3,6-di-O-benzyl-4-O-(tetrahydro-2-pyranyl)-D-galactopyranose (**9d**). — To **7** (3.7 g, 7.33 mmol) in chloroform (50 mL) were added 2,3-dihydro-4*H*-pyran (2 mL) and *p*-toluenesulfonic acid (50 mg). After 30 min, the solution was washed successively with 5% sodium hydrogencarbonate and water, and then dried and evaporated to yield *1-propenyl 2-O-benzoyl-3,6-di-O-benzyl-4-O-(tetrahydro-2-pyranyl)-α-D-galactopyranoside* (**8d**). This was converted by the general procedure for hydrolysis into the title compound **9d**. Purification on a column of silica gel yielded 2.9 g (72%) of material having $[\alpha]_D^{25}$ +142°, $[\alpha]_{436}^{25}$ +287° (*c* 0.68, chloroform); ^{1}H-n.m.r. ($CDCl_3$) similar to that of **7** except for loss of the signals for the propenyl group, the appearance of δ 2.04–1.20 (m, tetrahydropyranyl-H), and changes in the signals for H-1 and H-2 because of partial anomerization: δ 5.59 (dd,

<1 H, $J_{1,2}$ 3.3 Hz, H-1α), 5.45 (dd, <1 H, $J_{1,2}$ 3.3 and $J_{2,3}$ 10.7 Hz, H-2α), 5.34 (dd, <1 H, $J_{1,2}$ 7.7 and $J_{2,3}$ 9.9 Hz, H-2β).

Anal. Calc. for $C_{32}H_{36}O_8$ (548.63): C, 70.06; H, 6.61. Found: C, 69.83; H, 6.80.

Substituted α-D-galactopyranosyl chlorides. — The 2,3,4,6-tetra-*O*-substituted D-galactopyranose (1 g) was dissolved in dry dichloromethane (7 mL) and dry carbon tetrachloride (1 mL), the solution was cooled to −45°, and then hexamethylphosphorous triamide (0.3 mL) was added dropwise, with stirring. Stirring was continued for 1 h at −45°, and then overnight at room temperature. The solvents were evaporated off, and the crude glycosyl chloride was rapidly chromatographed on a short column of silica gel, with dry dichloromethane as the eluant. The ^{1}H-n.m.r. spectra of the chlorides were similar to those of the 1-propenyl glycosides from which they were ultimately derived, except that the anomeric doublets were at the low field characteristic of H-1 in glycosyl halides, and signals for the aglycon were absent.

Application of the foregoing procedure to the 4-*O*-benzoyl-D-galactopyranose derivative **9a** gave *2,4-di-O-benzoyl-3,6-di-O-benzyl-α-D-galactopyranosyl chloride* (**17a**), having ^{1}H-n.m.r. ($CDCl_3$) δ 6.65 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1α).

The 1-propenyl 4-*O*-allyl-D-galactopyranoside **8b**, on treatment with mercuric chloride–mercuric oxide (see general procedure) gave *4-O-allyl-2-O-benzoyl-3,6-di-O-benzyl-D-galactopyranose* (**9b**). Crude **9b** was converted into *4-O-allyl-2-O-benzoyl-3,6-di-O-benzyl-α-D-galactopyranosyl chloride* (**17b**), ^{1}H-n.m.r. ($CDCl_3$) δ 6.57 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1α).

The 4-*O*-*tert*-butyldimethylsilyl-D-galactopyranose **9c** furnished *2-O-benzoyl-3,6-di-O-benzyl-4-O-tert-butyldimethylsilyl-α-D-galactopyranosyl chloride* (**17c**), ^{1}H-n.m.r. ($CDCl_3$) δ 6.61 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1α).

The 4-*O*-(tetrahydro-2-pyranyl)-D-galactopyranose derivative **9d** yielded *2-O-benzoyl-3,4-di-O-benzyl-4-O-(tetrahydro-2-pyranyl)-α-D-galactopyranosyl chloride* (**17d**) as a mixture of diastereoisomers (epimeric at C-2 of the tetrahydropyranyl group); ^{1}H-n.m.r. ($CDCl_3$) δ 6.53 and 6.50 (doublets, total 1 H, $J_{1,2}$ 2.8 Hz, H-1α).

Propyl 2-acetamido-4,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**18**). — Pure 1-propenyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside[6] (3.0 g, 6.8 mmol) was dissolved in methanol (150 mL) containing 10% palladium-on-carbon (0.30 g). After hydrogenation at 1 atmosphere for 1 h, the suspension was filtered through Celite and evaporated to dryness. Chromatography on a column of silica gel yielded 2.89 g (96%) of pure **18**. Crystallization from ethanol gave large, fibrous needles, m.p. 119.5–120.5°, $[\alpha]_D^{25}$ −24.1°, $[\alpha]_{436}^{25}$ −54.1° (*c* 1.2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.36–7.20 (m, 10 H, Ph-H), 5.80 (bd, 1 H, $J_{NH,2}$ 4.9 Hz, N*H*), 4.94 and 4.61 (AB, 2 H, *J* 11.0 Hz, PhCH_2), 4.61 and 4.56 (AB, 2 H, *J* 12.1 Hz, PhCH_2), 4.45 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 3.93–3.35 (m, 8 H, sugar C*H* and -OCH_2CH_2), 2.05 (s, 3 H, CH_3CO), 1.69–1.53 (m, 2 H, CH_2CH$_3$), and 0.94 (t, 3 H, *J* 7.4 Hz, CH$_2$CH_3).

Anal. Calc. for $C_{25}H_{33}NO_6$ (443.54): C, 67.70; H, 7.50; N, 3.16. Found: C, 67.90; H, 7.42; N, 3.00.

Propyl 2-acetamido-4,6-di-O-benzyl-2-deoxy-3-O-(2,4-di-O-benzoyl-3,6-di-O-

benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**19**). — The galactosyl bromide **11** (455 mg, 0.72 mmol) was dissolved in 8 mL of 1:1 (v/v) toluene–nitromethane containing the propyl 2-amino-2-deoxy-β-glucoside **18** (177 mg, 0.40 mmol) and mercuric cyanide (200 mg, 0.80 mmol). The solution was stirred at room temperature under anhydrous conditions. After 3 h, the mixture was diluted with benzene and washed with saturated sodium hydrogencarbonate, and then with water. The benzene phase was dried with magnesium sulfate and evaporated to a syrup under diminished pressure. Column chromatography (silica gel) yielded 275 mg (69%) of syrupy (**19**), $[\alpha]_D^{25}$ +40.2°, $[\alpha]_{436}^{25}$ +91.5° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 8.09–7.04 (m, 30 H, Ph-H), 5.90 (d, 1 H, *J* 3.1 Hz, H-4′), 5.49 (dd, 1 H, $J_{1',2'}$ 8.2, and $J_{2',3'}$ 9.8 Hz, H-2′), 5.05 (d, 1 H, $J_{NH,2}$ 7.4 Hz, D_2O-exchangeable, N*H*), 4.77 (d, 1 H, $J_{1',2'}$ 8.2 Hz, H-1′, identified by decoupling H-2′), 4.81–4.24 (m, 9 H, PhCH_2, H-1), 3.87–2.96 (m, 14 H, sugar C*H* and CH_2, OCH_2CH_2), 1.75 (s, 3 H, CH_3CO), 1.41 (m, 2 H, CH_2CH_3), and 0.75 (t, 3 H, CH_2CH_3).

Anal. Calc. for $C_{59}H_{63}NO_{13}$ (994.15): C, 71.28; H, 6.39; N, 1.41. Found: C, 71.03; H, 6.44; N, 1.36.

ACKNOWLEDGMENTS

This work was supported by the College of Agricultural and Life Sciences, University of Wisconsin–Madison, and by Grant No. AM-10588 from the National Institute of Arthritis, Metabolism, and Digestive Diseases, N.I.H. High-resolution (270 MHz) n.m.r. spectra were provided by the Biochemistry NMR Facility, established by grants from the Graduate School and the National Science Foundation (No. BMS74-23826), and directed by Prof. W. A. Gibbons. C.W.S. received support from a training grant (GM-00236 BCH) provided by the National Institute of General Medical Sciences.

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