Carbohydrate Research, 150 (1986) 173–185
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

THE ASSEMBLY OF OLIGOSACCHARIDES FROM "STANDARDIZED INTERMEDIATES": β-(1→3)-LINKED OLIGOMERS OF D-GALACTOSE*

MANJIT S. CHOWDHARY, JUAN L. NAVIA, AND LAURENS ANDERSON**
Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin, Madison, WI 53706 (U.S.A.)

(Received October 15th, 1985; accepted for publication, December 9th, 1985)

ABSTRACT

Several 2-*O*-benzoyl-4,6-di-*O*-benzyl-3-*O*-R-α-D-galactopyranosyl chlorides, designed as general precursors of β-linked, interior D-galactopyranosyl residues in oligosaccharides, were tested in a sequential synthesis of the galactotriose β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-D-Gal (**19**). The chlorides having R = tetrahydro-2-pyranyl and *tert*-butyldimethylsilyl gave excellent results, whereas those having R = 3-benzoylpropionyl and chloroacetyl were unsatisfactory. An activated disaccharide block (**17**), having R = 2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-galactopyranosyl, was also prepared and tested as a glycosyl donor. The coupling of **17** to 1-propenyl 2-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-galactopyranoside (**14**), in the molar ratio 1.13:1, gave 64% of a trisaccharide derivative (**18**) that could be converted into **19**. This latter synthesis of **19** is efficient because all three galactose units are derived from **14** or its immediate precursor.

INTRODUCTION

We previously described a number of D-galactose derivatives designed as standardized reagents ("building blocks") for use in chemical oligosaccharide synthesis[1–3]. The efficiency of one group of these compounds, designated the "4(2)-Gal-β" series[3,†], was demonstrated by syntheses of branched tetrasaccharide isomers of the human blood-group B determinant[4,5]. The present work was then undertaken to test the utility of the "3(2)-Gal-β" series[3], comprising candidate precursors of 3- and 2,3-di-substituted, interior β-D-galactopyranose residues.

The test involved the synthesis of the trisaccharide β-D-Gal*p*-(1→3)-β-D-

*Dedicated to Professor N. K. Kochetkov.

**Please address correspondence to this author.

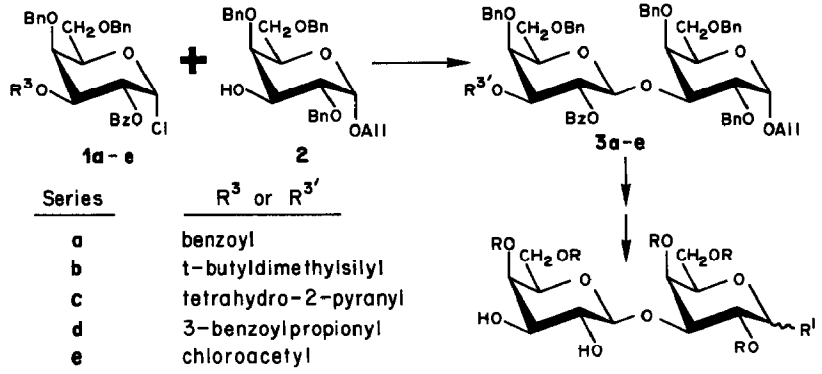
†Abbreviations such as 4(2)-Gal-β were suggested for glycosyl donors and acceptors as a shorthand means of indicating the parent sugar (Gal), the position(s) [4 and (2)] carrying temporary protecting groups, and (for donors) the expected anomeric configuration (β) after coupling to an acceptor. When there are two temporarily protected positions, the one normally deprotected for chain extension after coupling is listed first.

0008-6215/86/$ 03.50

Gal*p*-(1→3)-D-Gal (**19**), which embodies the characteristic linkage sequence of many naturally occurring galactans[6]. The assembly of **19** was investigated both by the usual sequential approach and by the coupling of an activated disaccharide block to monosaccharide acceptors, and the 3(2)-Gal-β intermediates were found to be suitable for both types of synthesis. An alternative route to **19** and its homologs has recently been proposed[7] and simple derivatives of β-D-Gal*p*-(1→3)-D-Gal*p* for use as glycosyl donors have been prepared[8].

RESULTS AND DISCUSSION

Sequential assembly from the reducing end. — In the first stage of this synthesis, namely, preparation of a disaccharide having a selectively removable protecting-group at position 3′, the effect of varying the substituent on O-3 of the galactosyl donor was examined. This was of interest for comparison with the donors of the 4(2)-Gal-β series, where the nature of the temporary protecting group at position 4 can be an important determinant of the stereoselectivity (β/α) of the coupling reaction[4,5]. The chlorides[3] **1a–d** of the 3(2)-Gal-β group proved to be excellent galactosyl donors when coupled to allyl 2,4,6-tri-*O*-benzyl-α-D-galacto-pyranoside[3] (**2**) under the conditions of Hanessian and Banoub[9] as elaborated by Nashed and Anderson[4]. When a slight excess (20%, molar basis) of the chloride was used, the yields of chromatographically isolated disaccharide products (**3a–d**) ranged from 85 to over 95%. The 3-*O*-chloroacetylgalactosyl chloride **1e**, prepared as an additional member of the donor series, also furnished a disaccharide product (**3e**), but in poorer yield because the compound was difficult to purify (details not given).



Scheme I

The β configuration of the newly formed glycosidic linkage in **3a–e** was evidenced by the ^{1}H-n.m.r. data (δ ~5.2, d, J ~8 Hz, H-1′). For further characterization, **3a**, which cannot be selectively deblocked and therefore served only as a model, was *O*-debenzoylated to give the diol **4**. This, on treatment with Wilkinson's catalyst and then mercuric chloride–mercuric oxide, was deallylated to **5**. Hydrogenolysis of **5** then gave a crystalline sugar having the physical constants of *O*-β-D-galactopyranosyl-(1→3)-D-galactopyranose[10] (**6**). The complete deprotection of **3b** and **3c**, *via* intermediate **8**, also yielded **6**. N.m.r. spectroscopy[11] of the alditol obtained by the borohydride reduction of **6** showed the anomeric purity of the inter-sugar linkage to be >98%.

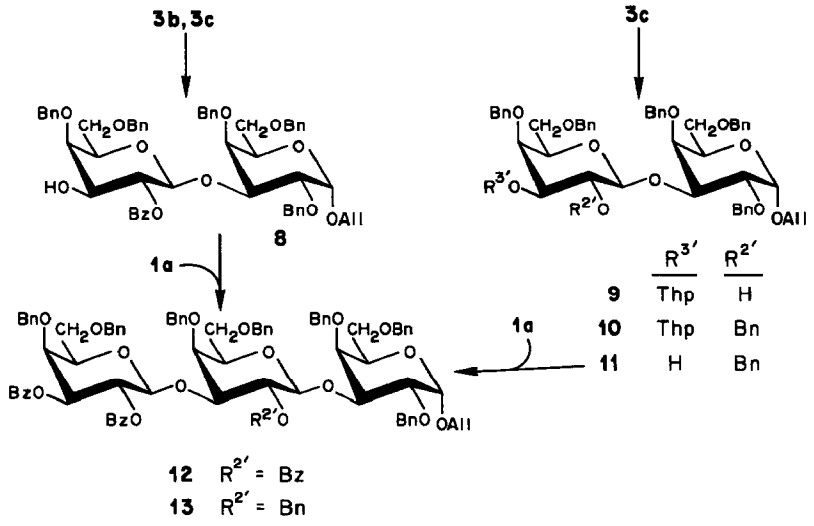
To confirm the (1→3) linkage of the initial coupling products, the crystalline propyl glycoside **7** was prepared by treating **4** with hydrogen over Pd/C. Periodate oxidation of **7** and mild acid hydrolysis of the product gave propyl α-D-galactopyranoside, showing that only the non-reducing residue was susceptible to attack by the reagent.

The removal of the *tert*-butyldimethylsilyl group from O-3′ of the disaccharide derivative **3b**, to give the glycosyl acceptor **8**, was accomplished by treatment with boron trifluoride etherate at low temperature[12]. Similarly, **8** was obtained in good yield from **3c** by mild acid hydrolysis of the tetrahydropyranyl group, and from **3e** (details not given) by *O*-dechloroacetylation with thiourea. Attempts to remove the benzoylpropionyl group from **3d** by treatment with hydrazine–acetic acid were unproductive, even though the reaction proceeded smoothly on the monomeric precursor (the 1-propenyl galactoside[3] corresponding to **1d**).

For the second stage of coupling, in addition to the selectively deprotected disaccharide derivative **8**, the alternative glycosyl acceptor **11** was prepared. Compound **11** has a benzyl ether group at position 2′, adjacent to the site of coupling*, in place of the benzoic ester group of **8**. The preparation of **11** required the debenzoylation of **3c** at O-2 to give **9**, then benzylation to give **10**, and the hydrolysis of the tetrahydropyranyl group. The di-*O*-benzoylgalactosyl chloride **1a** was then used as the glycosyl donor, primarily because of its ready availability. On treatment with 1.5–1.9 mol of **1a** under the conditions described for the first-stage coupling, **8** and **11** gave the trisaccharide derivatives **12** and **13**, respectively (65–85%); **11** appeared to be a slightly better glycosyl acceptor. The deprotection of **12** and **13** gave the target trisaccharide **19**, and its propyl glycoside **20**, which were characterized as described below.

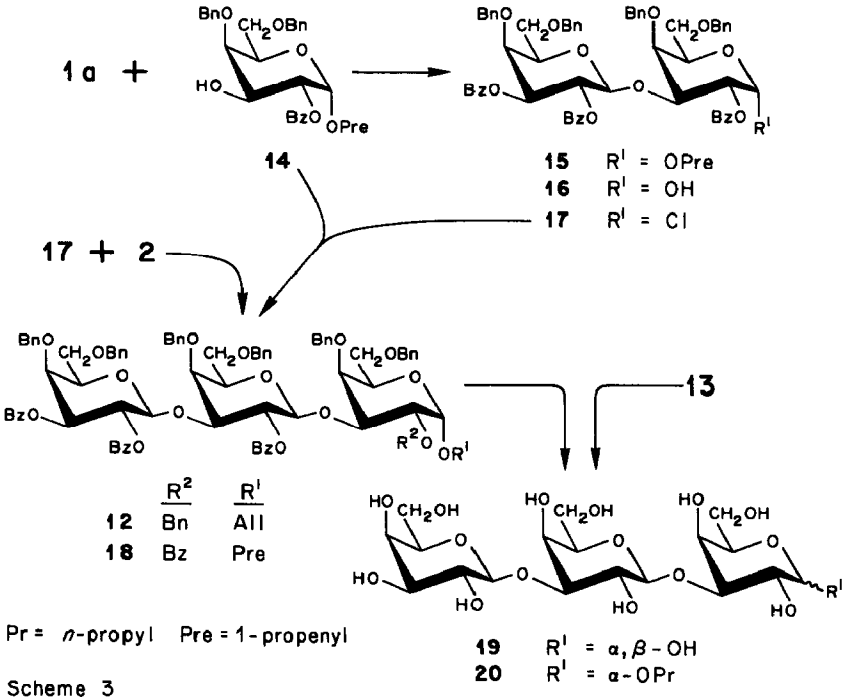
Synthesis via *an activated disaccharide block.* — For the assembly of tetra- and higher oligo-saccharides, a blockwise approach is often the most economical in terms of effort and material. To test the utility of the 3(2)-Gal-β compounds in this synthetic mode, the propenyl galactoside **14** was used as the acceptor in the initial stage. Compound **14** is an intermediate in the preparation[3] of **1b, 1c,** *etc.* When

*Observations in this and other laboratories[13] suggest that neighboring benzyl ether substituents facilitate the glycosylation of a hydroxyl group.



Thp = tetrahydro-2-pyranyl

Scheme 2



Pr = *n*-propyl Pre = 1-propenyl

Scheme 3

2,6-dimethylpyridine was added to the mixture to forestall acid-catalyzed cleavage of the propenyl group, the reaction of **1a** with **14** gave 88% of a crystalline product, expected to have the structure **15**. This expectation was supported by the ^{1}H-n.m.r. spectrum of the compound (see Experimental), and confirmed by its deprotection to the disaccharide **6**. The conversion of **15** through the 1-hydroxy compound **16** into the glycosyl chloride **17** then provided an activated disaccharide block.

The coupling, by the procedure mentioned above, of **17** in 50% excess to the allyl galactoside **2** gave the expected product **12**, but the yield was modest (45%). This figure could no doubt be improved, but for optimization experiments **14** was used as the acceptor reactant. In the process, the donor–acceptor ratio was reduced until only a 10–15% excess of donor (**17**) was used. With careful adjustment of the other reaction parameters, these proportions consistently gave 60–70% yields of the trisaccharide derivative **18**.

Deprotection and characterization of the trisaccharide products. — *O*-Debenzoylation of **18** proceeded smoothly in methanolic sodium methoxide. However, further processing was hampered by the tendency of HO-2 to add to the glycosidic propenyl group, forming a 1,2-*O*-propylidene structure. This rearrangement was catalyzed by an acidic ion-exchange resin and by iodine in aqueous oxolane[14,*]. In order to avoid the rearrangement, the product of debenzoylation was isolated by extraction, and aqueous trifluoroacetic acid was employed for the hydrolysis of the propenyl group. The trifluoroacetic acid cleaved any propylidene acetal that may have arisen.

Hydrogenolysis of the *O*-benzyl groups from the product of the acid hydrolysis gave an amorphous sugar corresponding in specific rotation to the known trisaccharide[15,16] β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→3)-D-Gal (**19**). The ^{13}C-n.m.r. spectrum of **19** showed the expected signals at δ 104.32 and 104.09 for C-1′β and C-1″β, respectively, and signals at δ 96.32 and 92.31 (together accounting for one C atom) attributable to C-1αβ.

The deprotection of the trisaccharide derivatives **12** and **13** was accomplished essentially as described for **18**, with the addition of a step employing Wilkinson's catalyst for the isomerization of the allyl group of the *O*-debenzoylated products. The presence of a 2-*O*-benzyl group in these propenyl glycosides prevented cyclic acetal formation.

Hydrogenation (Pd/C) of the *O*-debenzoylated allyl glycoside derived from **12** afforded the propyl glycoside (**20**) of the trisaccharide. Periodate attacked only the non-reducing galactosyl group of **20**, confirming the intersugar linkages in **19** and **20** as (1→3).

Conclusions. — Two compounds of the 3(2)-Gal-β series, **1b** and **1c**, served

*The latter reagent might be expected to give a (2-iodo)propylidene acetal, but the ^{1}H-n.m.r. spectrum of the product showed that it was the simple 1,2-*O*-propylidene compound. Perhaps hydriodic acid generated in the depropenylation of a portion of the material was the catalyst for the cyclization of the remainder.

well as precursors of the interior residue of the β-(1→3)-linked galactotriose **19**. In the sequential synthesis, these reagents underwent coupling with high stereoselectivity, and gave excellent yields of disaccharide products suitable for partial deprotection and chain extension. Replacement of the temporary protecting group at position 3 of **1b/1c** by a substituted β-D-galactopyranosyl unit gave the activated disaccharide block **17**, which also showed high selectivity for the formation of β linkages with acceptors. The yield (65%) of protected trisaccharide from the coupling of **17** and **14** is comparatively good, since the ratio of glycosyl donor to glycosyl acceptor was kept near to 1:1, as is desirable in blockwise syntheses. In many published examples, yields of <50% have been obtained, even though a substantial excess of one or the other of the oligosaccharide blocks was used.

Overall, the results suggest that **1b** and **1c** will be useful synthons for oligosaccharides containing 3-substituted, interior β-D-galactopyranose residues. The related derivatives **1a** and **14** can serve, as shown here, as convenient reagents for the synthesis of β-(1→3)-linked galacto-oligosaccharides. However, when the oligosaccharides of this series are the specifically desired end-products, the scheme of Kováč *et al.*[7] is probably more convenient.

EXPERIMENTAL

General methods. — The instrumental and chromatographic procedures listed in a previous paper[17] were employed, with some modifications. ^{1}H-N.m.r. spectra were routinely determined at either 200 or 270 MHz, on solutions in $CDCl_3$ (internal Me_4Si) unless otherwise noted, with decoupling as required for the identification of signals that could not be assigned unambigously by inspection. T.l.c. and column chromatography were done on silica gel, using mixtures of chloroform with hexane, acetone, or methanol, or of toluene with acetone (specifically noted). Elemental analyses were done at the Galbraith Laboratories, Inc. (Knoxville, TN 37821).

Coupling reactions. — The two-armed reaction vessels used for the coupling steps and the essential features of the procedure have been described[4]. The molar ratios of glycosyl donor–acceptor–silver trifluoromethanesulfonate ("triflate")–tetramethylurea were usually 1:0.8:2:1. Reaction volumes were kept to a minimum by the use of as little as 3 mL of solvent (dichloromethane) per g of glycosyl chloride. Reaction mixtures were neutralized with pyridine, diluted with methanol, filtered, and concentrated to dryness under reduced pressure. Toluene was repeatedly evaporated from the residue, which was then subjected to column chromatography. Deviations from this protocol are mentioned at the relevant points.

Allyl O-(2,3-di-O-benzoyl-4,6-di-O-benzyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-O-benzyl-α-D-galactopyranoside (**3a**). — 2,3-Di-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-galactopyranosyl chloride[3] (**1a**; 704 mg, 1.2 mmol) was coupled to **2** (ref. 3; 491 mg, 1.0 mmol), using the above procedure, to give **3a** (1.02 g, 98%), isolated

as a syrup, $[\alpha]_D^{25}$ +21°, $[\alpha]_{436}^{25}$ +39° (*c* 0.9, chloroform). ^{1}H-N.m.r. data: δ 8.1–7.5 (m, 4 H, PhCO), 7.5–6.9 (m, 31 H, Ph), 6.07–5.80 (m, 1 H, -C*H*=), 5.98 (dd, 1 H, $J_{2',3'}$ 10.5 Hz, H-2'), 5.42 (dd, 1 H, $J_{3',4'}$ 3.0 Hz, H-3'), 5.18 (d, 1 H, $J_{1',2'}$ 8.3 Hz, H-1'), 4.28 (bd, 1 H, H-4').

Anal. Calc. for $C_{64}H_{64}O_{13}$ (1041.20): C, 73.83; H, 6.20. Found: C, 73.57; H, 6.25.

Allyl O-*(2-*O*-benzoyl-4,6-di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-β-*D*-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**3b**). — Compound **1b** (ref. 3; 438 mg, 0.73 mmol), on coupling by the general procedure to **2** (300 mg, 0.61 mmol), gave **3b** (620 mg, 96%), isolated as a syrup, $[\alpha]_D^{25}$ −1°, $[\alpha]_{436}^{25}$ −4° (*c* 1.2, chloroform). The ^{1}H-n.m.r. spectrum was similar to that of **3a**, and also contained signals at δ 0.90 (s, $SiCMe_3$) and 0.35–0.05 (m, $SiMe_2$).

Anal. Calc. for $C_{63}H_{74}O_{12}Si$ (1051.36): C, 71.97; H, 7.09. Found: C, 71.77; H, 7.27.

Allyl O-[*2-*O*-benzoyl-4,6-di-*O*-benzyl-3-*O*-(tetrahydro-2-pyranyl)-β-*D*-galactopyranosyl]-(1→3)-2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**3c**). — Compound **1c** (470 mg, 0.83 mmol) was coupled to **2** (340 mg, 0.69 mmol) by the general procedure, with the addition to the reaction mixture of 2,6-dimethylpyridine (0.164 mL, 1.4 mmol), to give **3c** (650 mg, 92%), isolated as a syrup, $[\alpha]_D^{25}$ −25°, $[\alpha]_{436}^{25}$ −56° (*c* 0.7, chloroform). ^{1}H-N.m.r. data (complex spectrum because of stereoisomerism in the tetrahydropyranyl group): δ 5.92–5.78 (m, 1 H, -C*H*=) and 1.8–1.2 (m, 6 H, tetrahydropyranyl H).

Anal. Calc. for $C_{62}H_{68}O_{13}$ (1021.21): C, 72.92; H, 6.71. Found: C, 72.57; H, 6.52.

Coupling of **1d** *to* **2**. — The reaction of **1d** (ref. 3; 364 mg, 0.6 mmol) with **2** (245 mg, 0.5 mmol), according to the general procedure, gave a syrupy product (460 mg, 84%) having a ^{1}H-n.m.r. spectrum similar to that of **3a**, with additional signals at δ 3.18–2.48 (m, 4 H, $COCH_2CH_2CO$). The product was thus allyl *O*-[2-*O*-benzoyl-3-*O*-(3-benzoylpropionyl)-4,6-di-*O*-benzyl-β-D-galactopyranosyl]-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**3d**). A solution of a portion (55 mg) of **3d** in pyridine (0.8 mL) and acetic acid (0.2 mL) was treated with hydrazine hydrate (0.1 mL) at 70°. A second addition of hydrazine hydrate was made after 48 h. T.l.c. after 60 h showed that <25% of **3d** had been converted into a slowly moving product (presumably **8**).

*O-(4,6-Di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-*D*-galactopyranose* (**5**). — A solution of **3a** (1.0 g, 0.96 mmol) in methanolic 0.13M sodium methoxide (23 mL) was kept 2 h at room temperature, then neutralized with Rexyn 101 (H^+) resin, filtered, and concentrated to give allyl *O*-(4,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**4**, 800 mg) as a syrup. The ^{1}H-n.m.r. spectrum of **4** was similar to that of **3a**, except that the signals for H-2' and H-3' were no longer discernible.

To a solution of **4** in 9:1 ethanol–water (50 mL) were added 1,4-diazabicyclo[2.2.2]octane (200 mg) and tris(triphenylphosphine)rhodium(I) chloride

(Wilkinson's catalyst) (60 mg), and the mixture was heated for 6 h under reflux, then cooled, filtered, diluted with water, and extracted with chloroform. The organic layer was washed successively with saturated aq. NaCl, aq. 5% HCl, and water, dried (Na_2SO_4), and concentrated to give 1-propenyl *O*-(4,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (700 mg). The ^{1}H-n.m.r. spectrum was similar to that of **4**, but with new signals at δ 6.15 (bd, 1 H, OC*H*=) and 1.63 (d, 3 H, CH_3).

For hydrolysis[2], equal weights (700 mg) of glycoside, HgO, and $HgCl_2$ were stirred with 9:1 acetone–water (70 mL). After 30 min, the mixture was filtered, diluted with water, and extracted with chloroform. Further work-up[2], including column chromatography, gave **5** as a syrup (660 mg, 87% from **3a**), $[\alpha]_D^{25}$ −0.2°, $[\alpha]_{436}^{25}$ −0.9° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: complex spectrum because of α,β isomerism; no signals for the propenyl group.

Anal. Calc. for $C_{47}H_{52}O_{11}$ (792.92): C, 71.19; H, 6.61. Found: C, 70.95; H, 6.48.

O-β-D-*Galactopyranosyl-(1→3)*-D-*galactopyranose* (**6**). — A solution of **5** (300 mg, 0.38 mmol) in aq. 95% ethanol (30 mL) was stirred with 10% Pd/C (50 mg) for 24 h at room temperature under hydrogen at 1 atm., then filtered, and concentrated to give **6** (120 mg, 93%), which, after crystallization from water–ethanol, had m.p. 166–169°; $[\alpha]_D^{25}$ +62° (initial), +60° (final); $[\alpha]_{436}^{25}$ +125° (final) (*c* 0.5, water); lit.[10] m.p. 165–168°, $[\alpha]_D^{26}$ +71°→+62° (*c* 1, water).

A portion of **6** (20 mg) was reduced with sodium borohydride (40 mg) in water (2 mL), and the disaccharide-alditol was obtained as a salt-free residue[12]. ^{1}H-N.m.r. data (D_2O, internal sodium 4,4-dimethyl-4-silapentanoate): δ 4.54 (d, 1 H, $J_{1',2'}$ 8.3 Hz, H-1'), but no discernible anomeric signal at lower field.

Propyl O-β-D-*galactopyranosyl-(1→3)*-α-D-*galactopyranoside* (**7**). — Hydrogenolysis of **4** (200 mg), as described for **5**, gave **7** (85 mg, 88%), m.p. 176–177° (from ethanol), $[\alpha]_D^{25}$ +118°, $[\alpha]_{436}^{25}$ +202° (*c* 0.4, water). ^{1}H-N.m.r. data (D_2O): δ 4.61 (d, 1 H, $J_{1',2'}$ 7.5 Hz, H-1'), 1.59 (m, 2 H, $OCH_2CH_2CH_3$), and 0.89 (t, 3 H, CH_2CH_3).

Anal. Calc. for $C_{15}H_{28}O_{11} \cdot H_2O$ (402.29): C, 44.77; H, 7.52. Found: C, 44.61; H, 7.46.

A sample of **7** (20 mg) in water (2 mL) was stirred with sodium metaperiodate (40 mg) for 8 h at room temperature. The mixture was acidified (5M HCl, pH paper) and then stirred for another 3 h. T.l.c. (2:1:1 ethyl acetate–ethanol–water) showed a major spot with R_F the same as that of propyl α-D-galactopyranoside.

Allyl O-*(2-O-benzoyl-4,6-di-O-benzyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-O-benzyl-α-D-galactopyranoside* (**8**). — (*a*) *From* **3c**. Compound **3c** (85 mg, 0.083 mmol) in 8:1:1 acetic acid–methanol–water (2.0 mL) was completely converted into a slower moving substance when the solution was stirred for 1 h at 100°. The mixture was concentrated, and a solution of the residue in toluene was concentrated to remove traces of acetic acid. Column chromatography of the residue then gave **8** (76 mg, 97%), isolated as a syrup.

(*b*) *From* **3b**. A solution of **3b** (500 mg, 0.48 mmol) in chloroform (25 mL) at −10° was treated with boron trifluoride etherate (48%, 10 mL). After 0.5 h at <0°, **3b** was no longer present (t.l.c.). Triethylamine (10 mL) was added and, after brief stirring, the mixture was extracted with water. The organic layer, plus chloroform-washes of the water layer, were washed with water, dried (Na_2SO_4), and concentrated. Column chromatography of the residue gave **8** (435 mg, 97.5%), $[\alpha]_D^{25}$ −8.4°, $[\alpha]_{436}^{25}$ −14.3° (*c* 0.75, chloroform). The ^{1}H-n.m.r. spectrum was similar to those of **3c** and **3b**, but it lacked signals for tetrahydropyranyl or *tert*-butyldimethylsilyl groups.

Anal. Calc. for $C_{57}H_{60}O_{12}$ (937.10): C, 73.06; H, 6.45. Found: C, 73.33; H, 6.30.

Preparation of the 2'-O-benzyl analog (**11**) *of* **8**. — A solution of **3c** (200 mg, 0.20 mmol) was boiled in methanolic sodium methoxide for ~6 h under reflux, then neutralized with Rexyn 101 (H^+) resin, filtered, and concentrated. Column chromatography of the residue gave allyl *O*-[4,6-di-*O*-benzyl-3-*O*-(tetrahydro-2-pyranyl)-β-D-galactopyranosyl]-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**9**; 175 mg, 97%), as a syrup. The ^{1}H-n.m.r. spectrum of **9** was similar to that of **3c**, but it lacked signals for the benzoate group at δ 8.0–7.5 and a low-field signal for H-2'.

Treatment[11] of **9** (230 mg, 0.25 mmol) with benzyl bromide and sodium hydride in *N,N*-dimethylformamide gave syrupy allyl *O*-[2,4,6-tri-*O*-benzyl-3-*O*-(tetrahydro-2-pyranyl)-β-D-galactopyranosyl]-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**10**; 245 mg, 97%). The ^{1}H-n.m.r. spectrum of chromatographically pure **10** was similar to that of **9**, but showed increased signal intensity in the aromatic region, and added complexity in the range δ 5.0–4.5 (PhCH_2).

Cleavage of the tetrahydropyranyl group from **10**, by the procedure used on **3c**, gave 225 mg (quantitative) of syrupy allyl *O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**11**), which was homogeneous by t.l.c. The ^{1}H-n.m.r. spectrum closely resembled those of **9** and **10**, but lacked the characteristic signal of the tetrahydropyranyl CH_2 groups at δ 1.3–1.2.

Allyl O-*(2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→3)-*O*-(2-*O*-benzoyl-4,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**12**). — (*a*) Galactosyl chloride **1a** (220 mg, 0.375 mmol), silver triflate (193 mg, 0.75 mmol), and **8** (234 mg, 0.25 mmol) were processed according to the general procedure for coupling reactions. Chromatography of the products furnished syrupy **12** (260 mg, 70%).

(*b*) The general procedure was also used for the coupling of the disaccharide chloride **17** (450 mg, 0.44 mmol) to allyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**2**; 150 mg, 0.31 mmol). Fractionation of the products yielded **12** (210 mg, 46%).

Trisaccharide **12**, prepared by either method, had $[\alpha]_D^{25}$ ~0°, $[\alpha]_{436}^{25}$ +1.7° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 8.00–7.60 (m, 6 H, PhCO), 7.50–6.90 (m, 44 H, Ph), 5.86 (t, 1 H, $J_{1',2'} = J_{2',3'} = 7.5$ Hz, H-2'), 5.80–5.60 (m, 1 H, -C*H*=), 5.66

(t, 1 H, $J_{1'',2''} = J_{2'',3''} = 7.5$ Hz, H-2''), 5.30–3.20 (m, 37 H, sugar C*H* and CH_2, PhCH_2, and OCH_2CH=CH_2).

Anal. Calc. for $C_{91}H_{90}O_{19}$ (1487.70): C, 73.47; H, 6.10. Found: C, 72.99; H, 6.44.

Allyl O-*(2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→3)-*O*-(2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-*D*-galactopyranoside* (**13**). — The coupling of **1a** (134 mg, 0.23 mmol) to disaccharide acceptor **11** (140 mg, 0.15 mmol), under the conditions of the general procedure, and column chromatography of the products gave syrupy **13** (190 mg, 85%), $[\alpha]_D^{25}$ +26°, $[\alpha]_{436}^{25}$ +56° (*c* 1.5, chloroform). ^{1}H-N.m.r. data: δ 7.96–7.50 (m, 4 H, PhCO), 7.50–6.94 (m, 46 H, Ph), 5.93 (t, 1 H, $J_{1'',2''} = J_{2'',3''} = 9.5$ Hz, H-2''), 5.80–5.60 (m, 1 H, -C*H*=), 5.32 (dd, 1 H, $J_{3'',4''}$ 3 Hz, H-3''), and 5.30–3.30 (m, 39 H, sugar C*H* and CH_2, PhCH_2, and OCH_2CH=CH_2).

Anal. Calc. for $C_{91}H_{92}O_{18}$ (1473.72): C, 74.17; H, 6.29. Found: C, 74.13; H, 6.32.

1-Propenyl O-*(2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-α-*D*-galactopyranoside* (**15**). — A mixture of **1a** (1.35 g, 2.3 mmol), 1-propenyl 2-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-galactopyranoside[3] (**14**; 1.06 g, 2.1 mmol), and silver triflate (600 mg, 2.3 mmol) was dried using a liquid-nitrogen Dewar[4]. The vacuum was broken by admitting dry N_2, the container was quickly sealed with a septum, and then tetramethylurea (0.28 mL, 2.3 mmol), 2,6-dimethylpyridine (0.14 mL, 1.20 mmol), and dry dichloromethane (30 mL) were injected. The mixture was stirred for 2 h, when t.l.c. (19:1 toluene–acetone) showed complete conversion into product (R_F 0.48). The suspension was filtered, washed with saturated aq. NaCl and $NaHCO_3$, and dried ($MgSO_4$). Evaporation of the solvent left a syrup, which crystallized overnight. Extraction of the solid with boiling 8:1 hexane–ether afforded **15** (1.94 g, 88%), m.p. 130–131°, $[\alpha]_D$ +71° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 6.03 (dd, 1 H, $^3J_{vic}$ 6.2, $^4J_{allylic}$ 1.6 Hz, OC*H*=), 5.88 (dd, 1 H, $J_{2',3'}$ 10.5 Hz, H-2'), 5.39 (dd, 1 H, $J_{2,3}$ 10.3 Hz, H-2), 5.30 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.27 (dd, 1 H, $J_{3',4'}$ 2.4 Hz, H-3'), 5.05 (d, 1 H, $J_{1',2'}$ 7.7 Hz, H-1'), 1.54 (dd, 3 H, $^3J_{vic}$ 6.9 Hz, =CHCH_3).

In a series of preparations of **15**, the yields were in the range 60–90%. Some batches crystallized only after column chromatography (49:1 toluene–acetone).

Anal. Calc. for $C_{64}H_{62}O_{14}$ (1055.19): C, 72.85; H, 5.92. Found: C, 72.41; H, 5.89.

Conversion of **15** *into the glycosyl chloride.* — A solution of **15** (610 mg, 0.58 mmol) and iodine (~440 mg, ~1.75 mmol) in 10:1 oxolane–water[14] (6.5 mL) was kept overnight at room temperature. Dilution with dichloromethane (20 mL), extraction with aq. 5% $Na_2S_2O_3$ (2 × 30 mL), and washing gave a colorless solution which turned slightly yellow when dried with $MgSO_4$. Concentration of the solution and column chromatography (~50 g of silica gel) of the residue with chloroform (1.5 bed vol.) and then 9:1 chloroform–methanol (1.5 bed vol.) gave syrupy *O*-(2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2-*O*-benzoyl-4,6-di-*O*-

benzyl-α-D-galactopyranose (**16**; 575 mg, 98%), $[\alpha]_D$ +43° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: spectrum similar to that of **15**, but lacking signals for the propenyl group; δ 5.53 (unresolved dd, 1 H, $J_{1,2} \cong J_{1,OH} \cong 3$ Hz, H-1) and 2.92 (d, 1 H, O*H*).

To a solution of the foregoing, dry 1-hydroxy compound in dry dichloromethane (10 mL) was added dry *N,N*-dimethylformamide (0.1 mL), and the container was sealed with a septum vented with a 25-gauge needle. Oxalyl chloride (0.20 mL) was then slowly injected at 0°. On standing overnight at ~4°, the starting material was fully converted into product, R_F 0.52 (19:1 toluene–acetone). Excess reagent was destroyed with ice, the solution was washed with ice–water and cold, saturated aq. $NaHCO_3$, then dried, and concentrated. Vacuum drying of the residue gave *O*-(2,3-di-*O*-benzoyl-4,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-galactopyranosyl chloride (**17**) as an off-white foam in quantitative yield, R_F 0.77 (19:1 toluene–acetone), $[\alpha]_D$ +73° (*c* 3.5, chloroform). ^{1}H-N.m.r. data: δ 6.42 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1); the spectrum was otherwise similar to that of **16**.

Compound **17** was also prepared by the treatment[1] of **16** with tris(dimethylamino)phosphine and carbon tetrachloride. The product (93%) was purified by column chromatography.

1-Propenyl O-(2,3-di-O-benzoyl-4,6-di-O-benzyl-β-D-galactopyranosyl)-(1→3)-O-(2-O-benzoyl-4,6-di-O-benzyl-β-D-galactopyranosyl)-(1→3)-2-O-benzoyl-4,6-di-O-benzyl-α-D-galactopyranoside (**18**). — Glycosyl acceptor **14** (235 mg, 0.47 mmol) was coupled with **17** (540 mg, 0.52 mmol) in the presence of silver triflate (132 mg, 0.51 mmol), Drierite (2 g), tetramethylurea (0.06 mL, 0.51 mmol), and 2,6-dimethylpyridine (0.03 mL, 0.26 mmol). The procedure was as described for the preparation of **15**, except that a solution of dry **17** in dry dichloromethane (5 mL) was added last to the reaction mixture. The mixture was stirred for 2 h at room temperature, when t.l.c. (19:1 toluene–acetone) indicated a major product at R_F 0.49 plus traces of **14** and **16**. Work-up, with column chromatography (49:1 toluene–acetone) of the crude product, furnished **18** (440 mg, 63%), as a foam, $[\alpha]_D$ +27° (*c* 1.4, chloroform). N.m.r. data: ^{1}H at 470 MHz, δ 5.99 (dd, 1 H, $^3J_{vic}$ 6.28, $^4J_{allylic}$ 1.76 Hz, OCH=), 5.81 (dd, 1 H, $J_{2'',3''}$ 10.2 Hz, H-2″), 5.57 (dd, 1 H, $J_{2',3'}$ 10.5 Hz, H-2′), 5.23–5.27 (m, 2 H, H-1,2), 5.08 (dd, 1 H, $J_{3'',4''}$ 3 Hz, H-3″), 4.83 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1′), 4.71 (d, 1 H, $J_{1'',2''}$ 7.8 Hz, H-1″), 4.46 (dd, 1 H, =C*H*CH$_3$), 1.48 (dd, 3 H, $^3J_{vic}$ 6.78 Hz, =CHC*H*$_3$); ^{13}C at 50 MHz, δ 104.5 (O*C*H=), 102.4, 101.9 (C-1′ and C-1″), and 96.4 (C-1).

Anal. Calc. for $C_{91}H_{88}O_{20}$ (1501.69): C, 72.78; H, 5.91. Found: C, 72.72; H, 5.93.

O-β-D-Galactopyranosyl-(1→3)-O-β-D-galactopyranosyl-(1→3)-D-galactopyranose (**19**). — (*a*) *From* **18**. Compound **18** (241 mg) was treated with 0.5M sodium methoxide in 5:1 methanol–ether (5 mL) at 0°. The mixture was then allowed to attain room temperature. The reaction was complete in 2 h (t.l.c.). The solution was diluted with dichloromethane, washed with cold water, cold aq. 1% acetic acid, and cold, saturated $NaHCO_3$, then dried, and concentrated. Rapid

column chromatography (3 g of silica gel) of the residue with chloroform and then 9:1 chloroform–methanol gave the 2,2′,2″,3″-tetrol (164 mg, 94%), which had no i.r. absorption for C=O. The ^{1}H-n.m.r. spectrum was similar to that of **18**, but it lacked signals for PhCO and the signals for H-2,2′,2″,3″ were no longer at low field.

The tetrol (63 mg) in 10:1 oxolane–water (1.5 mL) was mixed with trifluoroacetic acid (1.5 mL), and the mixture was stored for 1 h at room temperature and then concentrated. Column chromatography (9:1 chloroform–methanol) of the residue gave the hydrolysis product (1,2,2′,2″,3″-pentol) in quantitative yield.

A solution of the pentol (98 mg) in 9:1 methanol–water was stirred with Pd/C (48 mg) under hydrogen (1 atm.) for 3 days to afford **19** (46 mg, 97%), m.p. 210–220° (dec.), $[\alpha]_D^{25}$ +52° (*c* 1.2, water) (lit.[15] $[\alpha]_D^{25}$ +51°, lit.[16] $[\alpha]_D$ +56°). ^{13}C-N.m.r. data (D_2O): δ 104.3 (C-1″), 104.1 (C-1′), 96.0 (C-1β), and 92.3 (C-1α).

(*b*) *From* **12** *and* **13**. The debenzoylation of **12** proceeded slowly at room temperature, but when the compound (400 mg) was heated under reflux in methanolic 0.09M sodium methoxide (11 mL), the reaction was complete in a few minutes. A portion (200 mg) of the 2′,2″,3″-triol obtained by deionization [Rexyn 101 (H^+) resin] and concentration of the solution was treated to isomerize its allyl group, as described above for the conversion of **4** into **5**. The resulting propenyl glycoside was hydrolyzed as for **15**, to give the 1,2′,2″,3″-tetrol, hydrogenolysis of which, as in (*a*), furnished **19** (70 mg, 93% from the triol). The application of the same steps to **13** also gave **19**.

Conversion of **12** *into the propyl glycoside* **20**; *periodate analysis of* **20**. — A portion (70 mg) of the 2′,2″,3″-triol obtained by the debenzoylation of **12** as described above, in aqueous 95% ethanol (25 mL), was stirred under hydrogen in the presence of Pd/C. After 40 h, the catalyst was removed and the solvent was evaporated to give syrupy propyl *O*-β-D-galactopyranosyl-(1→3)-*O*-β-D-galactopyranosyl-(1→3)-α-D-galactopyranoside. The ^{1}H-n.m.r. spectrum showed the expected signals at δ 1.8 ($CH_2CH_2CH_3$) and 1.0 (CH_2CH_3), but no signals for Ph. A portion (35 mg) of the propyl glycoside in water (2 mL) was treated with sodium metaperiodate (50 mg). The solution was kept for 8 h at room temperature, then neutralized with 0.25M barium hydroxide, and filtered. The filtrate was treated with borohydride, deionized, acidified, and left overnight. T.l.c. (2:1:1 ethyl acetate–water–ethanol) then revealed a single product, R_F identical to that of authentic **7**.

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, Diabetes, Digestive and Kidney Diseases, NIH. The 470-MHz n.m.r. spectra were recorded at the Purdue University Biochemical Magnetic Resonance Laboratory, supported by grant RR01077 from the Biotechnology Resources Program of the Division of Research Resources, NIH.

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