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Syntheses and insulin-like activity of phosphorylated galactose derivatives

Hugo-Norberto Caro, Manuel Martín-Lomas and Manuel Bernabé

Grupo de Carbohidratos, Instituto de Química Orgánica General, C.S.I.C., Juan de la Cierva 3, 28006 Madrid (Spain)

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ABSTRACT

The syntheses of the poly-phosphorylated galactosides **6**, **8**, **10**, **13**, **16**, and **20**, isolated as sodium salts, have been performed. The non-phosphorylated disaccharide **17** and trisaccharide **21** have been prepared via glycosylation of the 2-(trimethylsilyl)ethyl galactosides **3** and **2**, respectively, and subsequent complete deprotection. Preliminary insulin-like activity of the phosphorylated derivatives is reported.

INTRODUCTION

Several lines of evidence have shown that insulin stimulates the generation of low molecular weight mediators which serve as intermediates in the intracellular insulin signalling process[1–4]. Saltiel and Cuatrecasas[5,6] reported the purification and partial identification of two related substances, generated from liver plasma in response to insulin, containing carbohydrate glycosidically linked to inositol and phosphate. Mato et al.[7] reported on the chemical composition of an inositol glycan which inhibited cyclic AMP-dependent protein kinase. This inositol glycan contained *myo*-inositol, non-*N*-acetylated D-glucosamine, galactose, and phosphate. In the intact glycolipid (GPI), the inositol is linked to diacylglycerol through a phosphodiester linkage and the substance seems to contain an average of two additional phosphate groups localized at the non-reducing end of the oligosaccharide on the galactose residues[8]. The structure of the oligosaccharide and the exact location of these phosphate groups remain unknown.

As part of studies of the structure of this inositol phospho-glycan (IPG), we have carried out syntheses and preliminary studies of the insulin-like activity of the

Correspondence to: Professor M. Bernabé, Grupo de Carbohidratos, Instituto de Química Orgánica General, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain.

phosphorylated compounds **6**, **8**, **10**, **13**, **16**, and **20**, as well as syntheses of the non-phosphorylated disaccharide **17** and trisaccharide **21**.

RESULTS AND DISCUSSION

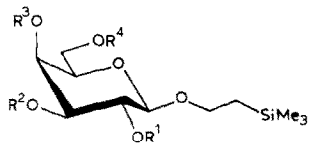
Synthesis.—The syntheses of the disaccharide glycosides **14–17** required selective protection of HO-3, HO-4, and HO-6 in the acceptor **3**. Acetonation of compound **1** (ref. 9) was achieved by treatment with 2,2-dimethoxypropane in acetone as described[10], to give mainly the 3,4-*O*-isopropylidene derivative **2** (70%). Protection of HO-6 with the *tert*-butyldiphenylsilyl group, using the procedure described by Glaudemans[11], proceeded rapidly and gave compound **3** in 96% yield. Mercuric salt-promoted glycosylation of **3** with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in benzene at 60°C gave the β-disaccharide **14** in 94% yield. Hydrolysis of the isopropylidene group of **14** with aqueous 90% trifluoroacetic acid in dichloromethane at 0°C (80%), treatment with dibenzyloxy(diisopropylamino)-phosphine[12] and 1*H*-tetrazole in acetonitrile–dichloromethane, and further oxidation with catalytic $RuCl_3$ and $NaIO_4$ in a biphase system[13,14] gave derivative **15** in 82% yield. The conversion of **15** into the 3,4-bisphosphate **16**, isolated as the sodium salt (80%), was accomplished by sequential removal of the *tert*-butyldiphenylsilyl group with tetrabutylammonium fluoride in tetrahydrofuran, deacetylation, and catalytic hydrogenolysis (10% Pd–C) in a buffered solvent mixture (methanol–acetic acid–sodium acetate, pH 5), in order to avoid hydrolysis of the disaccharide.

Disaccharide **17** was obtained from compound **14** by acid hydrolysis with aqueous 90% trifluoroacetic acid in dichloromethane, cleavage of the silyl ether group, and deacetylation as described above.

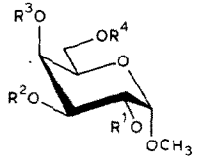
Compound **2** was also used to synthesise the trisaccharide derivatives **18–21** and the monosaccharide bisphosphate derivatives **6** and **13**. Thus, mercuric salt-promoted glycosylation of **2** with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in benzene at room temperature and treatment of the crude reaction mixture with aqueous 90% trifluoroacetic acid in CH_2Cl_2 at 0°C afforded compound **18** (48%). Treatment of **18** with dibenzyloxy(diisopropylamino)phosphine and then oxidation with $NaIO_4$–$RuCl_3$ (→ **19**, 66%), deacetylation, and catalytic hydrogenolysis, as described for **15**, gave **20** isolated as the sodium salt (93%). Deacetylation of **18** gave **21** in quantitative yield.

The conversion of **2** into the 3,4-bisphosphate derivative **6** was accomplished by benzylation (→ **4**, 82%), acid hydrolysis, treatment with the phosphitylating reagent, oxidation (→ **5**, 73%), and catalytic hydrogenolysis, as described above. These steps were also followed to obtain compound **13**, starting from methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[15], in 85% overall yield.

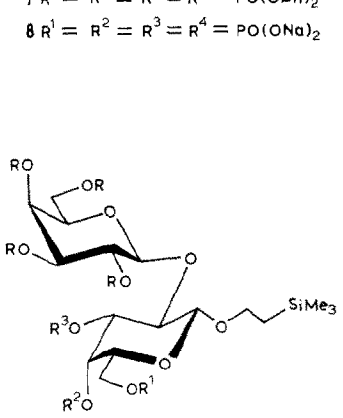
Finally, treatment of both compounds **1** and methyl α-D-galactopyranoside with the phosphitylating reagent and oxidation under the conditions described above afforded compounds **7** (61%) and **9** (82%) which, after hydrogenolysis as indicated for compound **15**, gave **8** and **10** in quantitative yield.

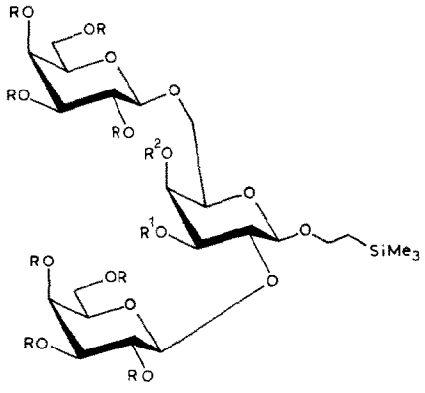


1 $R^1 = R^2 = R^3 = R^4 = H$
2 $R^1 = R^4 = H, R^2, R^3 = C(CH_3)_2$
3 $R^1 = H, R^2, R^3 = C(CH_3)_2, R^4 = TBDPS$
4 $R^1 = R^4 = Bn, R^2, R^3 = C(CH_3)_2$
5 $R^1 = R^4 = Bn, R^2 = R^3 = PO(OBn)_2$
6 $R^1 = R^4 = H, R^2 = R^3 = PO(ONa)_2$
7 $R^1 = R^2 = R^3 = R^4 = PO(OBn)_2$
8 $R^1 = R^2 = R^3 = R^4 = PO(ONa)_2$



9 $R^1 = R^2 = R^3 = R^4 = PO(OBn)_2$
10 $R^1 = R^2 = R^3 = R^4 = PO(ONa)_2$
11 $R^1 = R^4 = Bn, R^2 = R^3 = H$
12 $R^1 = R^4 = Bn, R^2 = R^3 = PO(OBn)_2$
13 $R^1 = R^4 = H, R^2 = R^3 = PO(ONa)_2$





14 R = Ac, R^1 = TBDPS, $R^2, R^3 = C(CH_3)_2$
15 R = Ac, R^1 = TBDPS, $R^2 = R^3 = PO(OBn)_2$
16 $R = R^1 = H, R^2 = R^3 = PO(ONa)_2$
17 $R = R^1 = R^2 = R^3 = H$
18 R = Ac, $R^1 = R^2 = H$
19 R = Ac, $R^1 = R^2 = PO(OBn)_2$
20 R = H, $R^1 = R^2 = PO(ONa)_2$
21 $R = R^1 = R^2 = H$

TBDPS = *tert*-butyldiphensilyl

Insulin-like activity.—Preliminary biological assays were performed with compounds **6**, **8**, **10**, **13**, **16**, and **20** by studying the effects of these phosphate derivatives on the activity of cyclic AMP-dependent protein kinase (PKA)[16], an enzyme which is regulated by insulin and IPG[6]. The results (see Table I) indicate that significant inhibition on the activity of this enzyme was produced by compounds **8** and **10**. Compound **20** was less active (only 14% inhibition) at the same concentration (100 μM), and compounds **8**, **13**, and **16** did not show any effect at all.

With the aim of determining the effects of compounds **8**, **10**, and **20** on intact cells, the incorporation of [^{3}H]thymidine in DNA of human fibroblasts (IMR 90) was carried out[17]. Compounds **8** and **10** stimulate the incorporation of [^{3}H]thymi-

TABLE I

Insulin-like activity for compound **6**, **8**, **10**, **13**, **16**, and **20**

Addition		Activity of PKA[16] (%)	Thymidine incorporation[17]
Compound	Concentration (μM)		
None		100	100
IPG	1	70 ±5	205±10
6	100	100	110±15
8	100	62 ±5.3	200±10
10	100	68.5±4.9	190± 3
13	100	100	110±10
16	100	100	95± 6
20	100	86 ±2	120± 8
Insulin	0.01	–	210±10

dine twofold at a concentration 100 μM, mimicking the effects of insulin and IPG (see Table I). The other phosphate derivatives did not produce any significant effect on this biological system.

EXPERIMENTAL

General methods.—Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. TLC was performed on Silica Gel GF_{254} (Merck) with detection by charring with H_2SO_4. Flash-column chromatography was performed on Silica Gel 60, 40–63 μm (Merck). ^{1}H NMR spectra were recorded with a Varian XL-300, ^{13}C NMR spectra with a Bruker AM-200 or Bruker AM-360, and ^{31}P NMR spectra with a Varian XL-300 or Bruker AM-360 spectrometer. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. Biological assays were performed as described elsewhere[16,17].

NMR spectroscopy.—For recording ^{1}H NMR spectra of phosphorylated compounds, samples (10–20 mg) of **6**, **8**, **10**, **13**, **16**, and **20**, previously deuterated with D_2O, were dissolved in 0.5–0.7 mL of a solution of NaOD in D_2O (pD ~ 12) and degassed in the NMR tube under Ar. All experiments were performed at 30°C. Chemical shifts are given in ppm, using dioxane as external reference. ^{31}P NMR spectra are referenced to external aq 80% H_3PO_4.

2-(Trimethylsilyl)ethyl 3,4-O-isopropylidene-β-D-galactopyranoside (**2**).—Compound **1** (ref. 9) (505 mg, 1.80 mmol) was dissolved in acetone (35 mL) and 2,2-dimethoxypropane (1 mL), *N*,*N*-dimethylformamide (1 mL), and H_2SO_4 (10 μL) were added[10]. The mixture was stirred for 24 h at room temperature after which Na_2CO_3 was added to neutralize the solution. The solvents were evaporated and the residue was column-chromatographed (1:3 acetone–hexane) to yield **2** (0.403 g, 70%); mp 93–94°C (from hexane–acetone); $[\alpha]_D$ +7.3° (*c* 1.2, $CHCl_3$). ^{1}H NMR data (300 MHz, $CDCl_3$): δ 4.18 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.15 (dd, 1 H, $J_{4,5}$ 2, $J_{3,4}$ 5.6 Hz, H-4), 4.08 (dd, 1 H, $J_{3,4}$ 5.6, $J_{2,3}$ 7.3 Hz, H-3), 4.0 (m, 2 H, C*H*HCH$_2$Si, H-5), 3.83 (m, 2 H, H-6a,6b), 3.35 (m, 2 H, CH*H*CH$_2$Si, H-2), 1.49,

1.32 (s, 6 H, 2 CH_3), 0.99 (m, 2 H, CH_2CH_2Si), and 0.14 (s, 9 H, $Si(CH_3)_3$); ^{13}C (50 MHz), δ 110.41, 101.78, 78.85, 73.94, 73.68, 73.42, 67.44, 62.46, 28.08, 26.34, 18.28, and −1.46. Anal. Calcd for $C_{14}H_{28}O_6Si$: C, 52.47; H, 8.81. Found: C, 52,71; H, 9.00.

*2-(Trimethylsilyl)ethyl 6-O-(*tert*-butyldiphenylsilyl)-3,4-O-isopropylidene-β-*D*-galactopyranoside* (**3**).—Compound **2** (1.00 g, 3.13 mmol) was dissolved in *N,N*-dimethylformamide (7 mL). *tert*-Butyldiphenyl chloride (0.9 ml, 3.45 mmol), followed by silver nitrate[11] (0.595 g, 3.53 mmol) were added and the mixture was stirred in the dark at room temperature for 2 h. The mixture was filtered (Celite), and the precipitate was washed with $CHCl_3$. The combined filtrates were concentrated, diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), and concentrated. Product **3** (1.59 g, 96%) was isolated by column chromatography (5:1 hexane–EtOAc) as a syrup; $[\alpha]_D$ −3.5° (*c* 1.5, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.70 (m, 4 H, Ph), 7.38 (m, 6 H, Ph), 4.25 (dd, 1 H, $J_{3,4}$ 5.4, $J_{4,5}$ 2.1 Hz, H-4), 4.16 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 4.07 (dd, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 5.5 Hz, H-3), 4.0 (m, 3 H, $CHHCH_2Si$, H-6a,6b), 3.86 (dt, 1 H, $J_{4,5}$ 2, $J_{5,6a,b}$ 6 Hz, H-5), 3.55 (m, 2 H, $CHHCH_2Si$, H-2), 2.49 (d, 1 H, *J* 2.2 Hz, HO-2), 1.51, 1.34 (s, 6 H, 2 CH_3), 1.06 (s, 9 H, CH_3), 1.12 (m, 2 H, OCH_2CH_2Si), and 0.13 (s, 9 H, $Si(CH_3)_3$); ^{13}C (50 MHz), δ 135.58, 133.44, 133.39, 129.67, 127.66, 127.60, 109.97, 101.78, 78.68, 73.88, 73.66, 73.24, 67.10, 62.70, 28.17, 26.72, 26.29, 19.18, 18.24, and −1.47. Anal. Calcd for $C_{30}H_{46}O_6Si_2$: C, 64.48; H, 8.30. Found: C, 64.43; H, 8.46.

*2-(Trimethylsilyl)ethyl 2,6-di-O-benzyl-3,4-O-isopropylidene-β-*D*-galactopyranoside* (**4**).—Compound **2** (126 mg, 0.4 mmol) was added to a suspension of NaH (190 mg, 0.4 mmol) in *N,N*-dimethylformamide (1 ml) at 0°C. The suspension was stirred at that temperature for 15 min and then benzyl bromide (0.2 ml, 1.7 mmol) was added. The solution was allowed to warm slowly to room temperature. After 2 h, the reaction was quenched by addition of MeOH at 0°C, diluted with CH_2Cl_2 (15 ml) and washed several times with water, dried (Na_2SO_4), and concentrated. The residue was column-chromatographed (8:1 hexane–EtOAc) to give **4** (164 mg, 82%); mp 92–93°C (from hexane–acetone); $[\alpha]_D$ +21° (*c* 1.1, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.36–7.23 (m, 10 H, Ph), 4.82 (d, 1 H, J_{gem} −11.8 Hz, PhC*H*), 4.77 (d, 1 H, J_{gem} −11.8 Hz, PhC*H*), 4.61 (d, 1 H, J_{gem} −11.8 Hz, PhC*H*), 4.53 (d, 1 H, J_{gem} −11.9 Hz, PhC*H*), 4.29 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.10 (m, 2 H, H-3,4), 4.00 (m, 1 H, *J* 7.6, *J* 9.6 Hz, $CHHCH_2Si$), 3.88 (m, 1 H, $J_{4,5}$ 1.5, $J_{5,6a}$ 5.1, $J_{5,6b}$ 6.9 Hz, H-5), 3.78 (dd, 1 H, $J_{5,6a}$ 5.1, $J_{6a,6b}$ −10.1 Hz, H-6a), 3.75 (dd, 1 H, $J_{5,6b}$ 6.9, $J_{6a,6b}$ −10.0 Hz, H-6b), 3.55 (m, 1 H, *J* 7.6, *J* 9.6 Hz, $CHHCH_2Si$),3.35 (m, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 3.2 Hz, H-2), 1.32, 1.30 (s, 6 H, 2 CH_3), 1.02 (m, 2 H, *J* 8.7 Hz, CH_2CH_2Si), and −0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C (50 MHz), δ 138.50, 138.31, 128.39, 128.17, 127.61, 127.47, 109.87, 102.47, 79.83, 79.16, 73.91, 73.61, 72.27, 69.69, 67.17, 27.79, 26.39, 18.45, 18.45, and −1.43. Anal. Calcd for $C_{28}H_{40}O_6Si$: C, 67.17; H, 8.05. Found: C, 67.18; H, 7.88.

*2-(Trimethylsilyl)ethyl 2,6-di-O-benzyl-β-*D*-galactopyranoside 3,4-bis(dibenzyl phosphate)* (**5**).—To a solution of compound **4** (130 mg, 0.26 mmol) in CH_2Cl_2 (3

mL) at 0°C was added aq 90% trifluoroacetic acid (0.3 mL). After 30 min (TLC; 6:1 hexane–EtOAc), 1:1 toluene–EtOAc (20 mL) were added and removed in vacuo at ~ 40°C. A second portion of 1:1 toluene–EtOAc (20 mL) was added and removed. The residue was dissolved in 1:1 acetonitrile–CH_2Cl_2 (4 mL), and 1*H*-tetrazole (109 mg, 1.6 mmol) and dibenzyloxy(diisopropylamino)phosphine[12] (360 mg, 1 mmol) were added at room temperature with stirring. After 1 h (TLC; 1:1 hexane–EtOAc), water (3.5 mL), $RuCl_3 \cdot 3H_2O$ (2 mg, 0.01 mmol), and $NaIO_4$ (334 mg, 1.56 mmol) were added and the mixture was vigorously stirred for 1 h. Then the mixture was diluted with CH_2Cl_2 (10 mL) and washed twice with water (10 mL). The aqueous phase was extracted twice with CH_2Cl_2 (10 mL), the organic phases were combined and dried (Na_2SO_4), and the solvent was evaporated. Column chromatography of the residue (3:1 → 2:1 hexane–EtOAc) afforded syrupy **5** (185 mg, 73%); $[\alpha]_D$ +16° (*c* 1, $CHCl_3$). NMR data (C_6D_6): ^1H (300 MHz), δ 7.54–7.08 (m, 30 H, Ph), 5.5 (dd, 1 H, $J_{3,4}$ 2.9, $J_{4,P}$ 9.6 Hz, H-4), 5.47–5.22 (m, 6 H, 3 PhCH_2), 5.1 (d, 1 H, J_{gem} −11.5 Hz, PhC*H*), 5.03 (m, 2 H, PhCH_2), 4.84 (d, 1 H, J_{gem} −11.5 Hz, PhC*H*), 4.80 (m, 1 H, $J_{3,P-4}$ 1.8, $J_{3,4}$ 3.1, $J_{3,P-3}$ 9.6 Hz, H-3), 4.47 (d, 1 H, J_{gem} −11.9 Hz, PhC*H*), 4.35 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 4.31 (d, 1 H, J_{gem} −11.9 Hz, PhC*H*), 4.11 (dt, 1 H, *J* 7.6, 9.9 Hz, C*H*HCH$_2$Si), 4.03 (dd, 1 H, $J_{1,2}$ 7.6, $J_{2,3}$ 9.9 Hz, H-2), 3.89 (dd, 1 H, $J_{5,6a}$ 6.7, $J_{6a,6b}$ −9.5 Hz, H-6a), 3.77 (dd, 1 H, $J_{5,6b}$ 6.2, $J_{6a,6b}$ −9.5 Hz, H-6b), 3.61 (dt, 1 H, *J* 6.9, 9.6 Hz, CH*H*CH$_2$Si), 1.06 (m, 2 H, CH$_2$CH_2Si), and 0.0 (s, 9 H, Si(CH$_3$)$_3$). Anal. Calcd for $C_{53}H_{62}O_{12}P_2Si$: C, 64.88; H, 6.37. Found: C, 65.10; H, 6.21.

*2-(Trimethylsilyl)ethyl β-*D*-galactopyranoside 3,4-bis(disodium phosphate)* (**6**).—Compound **5** (65 mg, 0.07 mmol) was dissolved in MeOH (1.5 mL) and buffered aq AcOH–NaOAc (1 mL, pH 5, 0.5 M), and the mixture was treated with Pd–C (10%, ~ 10 mg) and H_2 at atmospheric pressure for 2 h with stirring at room temperature. TLC (4:1 $CHCl_3$–MeOH) showed a single product at the origin. The mixture was filtered (Celite) and partially evaporated, and the solution was treated with Amberlite IR-120 (Na^+ form, water) and concentrated. The residue was passed through a column (1 × 15 cm) of Sephadex G-15 (water) and the appropriate fractions were lyophilized to obtain **6** (34 mg, 97%) as an amorphous solid; $[\alpha]_D$ −24° (*c* 0.6, M NaOH). NMR data (D_2O, pD ~ 12): ^1H (300 MHz), δ 4.45 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.44 (dd, 1 H, $J_{4,P}$ 10.4, $J_{3,4}$ 3.2 Hz, H-4), 4.09 (m, 1 H, $J_{3,P-4}$ 1.1, $J_{3,4}$ 3.4, *J* 10.7 Hz, H-3), 3.98 (m, 1 H, *J* 5.4, *J* 9.9 Hz, C*H*HCH$_2$Si), 3.77–3.65 (m, 5 H, H-2,5,6a,6b, CH*H*CH$_2$Si), 1.03 (m, 2 H, CH$_2$CH_2Si), and 0.02 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C (90 MHz), δ 103.31 (C-1), 75.71, 75.11, 71.63, 68.87, 59.86, 18.46, and −1.76; ^{31}P (145 MHz), δ 5.56 and 4.5. Anal. Calcd for $C_{11}H_{22}O_{12}P_2SiNa_4$: C, 25.01; H, 4.20. Found: C, 24.51; H, 5.20.

*2-(Trimethylsilyl)ethyl β-*D*-galactopyranoside 2,3,4,6-tetrakis(dibenzyl phosphate)* (**7**).—To a solution of compound **1** (203 mg, 0.73 mmol) in 1:1 acetonitrile–CH_2Cl_2 (10 mL) were added 1*H*-tetrazole (609 mg, 8.7 mmol) and dibenzyloxy(diisopropylamino)phosphine (2.00 g, 5.8 mmol) with stirring. After 1.5 h, water (21 mL), $RuCl_3 \cdot 3H_2O$ (2 mg, 0.01 mmol), and $NaIO_4$ (1.02 g, 4.76 mmol) were added and

the mixture was vigorously stirred for 1 h. Then the mixture was diluted with CH_2Cl_2 (15 mL) and washed twice with water (10 mL). The aqueous phase was extracted twice with CH_2Cl_2 (10 mL), the organic phases were combined and dried (Na_2SO_4), and the solvent was evaporated. Column chromatography of the residue (1:1 hexane–EtOAc) afforded syrupy **7** (580 mg, 61%), $[\alpha]_D$ +6.6° (*c* 0.9, $CHCl_3$). NMR data (C_6D_6): ^1H (300 MHz), δ 7.38–6.94 (m, 40 H, Ph), 5.4 (dd, 1 H, $J_{3,4}$ 2.7, $J_{4,P}$ 9.2 Hz, H-4), 5.37–4.94 (m, 17 H, H-2, 8 PhCH_2), 4.69 (btt, 1 H, $J_{3,P\text{-}4}$ 1.9, *J* 9.7 Hz, H-3), 4.39 (m, 2 H, H-6a,6b), 4.28 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.93 (dt, 1 H, *J* 8.9, *J* 7.7 Hz, C*H*HCH$_2$Si), 3.55 (dt, 1 H, *J* 7.5, *J* 9.7 Hz, CH*H*CH$_2$Si), 3.35 (bt, 1 H, $J_{5,6a,b}$ 6.7 Hz, H-5), 0.89 (m, 2 H, *J* 8.9 Hz, CH$_2$CH_2Si), and −0.16 (s, 9 H, Si(CH$_3$)$_3$). Anal. Calcd for $C_{67}H_{76}O_{18}P_4Si$: C, 60.90; H, 5.80. Found: C, 60.91; H, 5.79.

2-(Trimethylsilyl)ethyl β-D-galactopyranoside 2,3,4,6-tetrakis(disodium phosphate) (**8**).—Compound **7** (200 mg, 0.15 mmol) was dissolved in MeOH (3 mL) and buffered aq AcOH–NaOAc (1 mL, pH 5, 0.5 M), and the mixture was treated with Pd–C (10%, ~ 10 mg) and H_2 at atmospheric pressure for 2 h with stirring. The mixture was filtered (Celite) and partially evaporated, and the solution was treated with Amberlite IR-120 (Na^+ form) and concentrated. The residue was passed through a column (1 × 15 cm) of Sephadex G-15 (water) and the appropriate fractions were lyophilized to obtain **8** (99 mg, 85%) as an amorphous solid; $[\alpha]_D$ −1.9° (*c* 1.2, M NaOH). NMR data (D_2O, pD ~ 12): ^1H (300 MHz), δ 4.53 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1), 4.47 (m, 1 H, $J_{3,4}$ 2.6, $J_{4,P\text{-}3}$ 4.9, $J_{4,P}$ 9.7 Hz, H-4), 4.10 (ddd, 1 H, $J_{1,2}$ 5.9, *J* 8.9, *J* 9.7 Hz, H-2), 4.04–3.81 (m, 5 H, H-3,5,6a,6b, C*H*HCH$_2$Si), 3.67 (m, 1 H, *J* 4.9, *J* 5.74, *J* 8.2 Hz, CH*H*CH$_2$Si), and −0.09 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C (50 MHz), δ 102.65 (C-1), 76.35, 75.20, 73.90, 72.37, 69.27, 65.72, 18.82, and −1.09; ^{31}P (145 MHz), δ 4.74, 4.64, 4.14, and 3.96. Anal. Calcd for $C_{11}H_{20}O_{18}P_4SiNa_8$: C, 17.02; H, 2.60. Found: C, 17.01; H, 2.70.

Methyl α-D-galactopyranoside 2,3,4,6-tetrakis(dibenzyl phosphate) (**9**).—Methyl α-D-galactopyranoside (212 mg, 1.1 mmol) was dissolved in 1:1 acetonitrile–CH_2Cl_2 (10 mL) and treated with 1*H*-tetrazole (1.148 g, 16 mmol) and dibenzyloxy(diisopropylamino)phosphine (3.618 g, 10.4 mmol). After 2 h (TLC; 1:2 hexane–EtOAc), water (30 mL), $NaIO_4$ (1.536 g, 6.33 mmol), and $RuCl_3 \cdot 3H_2O$ (3 mg, 0.015 mmol) were added and vigorous stirring was continued for 2 h. Then, the mixture was extractively worked up as described for **5**. Column chromatography (2:1 hexane–EtOAc) afforded syrupy **9** (940 mg, 82%); $[\alpha]_D$ +37° (*c* 0.73, $CHCl_3$). NMR data (C_6D_6): ^1H (300 MHz), δ 7.29–7.18 (m, 40 H, Ph), 5.07–5.82 (m, 18 H, H-1,4,8 PhCH_2), 4.75 (m, 1 H, $J_{3,P\text{-}4}$ 1.3, $J_{3,P\text{-}3}$ 11.5, $J_{3,2}$ 10 Hz, H-3), 4.62 (m, 1 H, $J_{1,2}$ 3.4, *J* 10.2, *J* 6.8 Hz, H-2), 4.05 (m, 2 H, H-6a,6b), 3.79 (bdt, 1 H, $J_{4,5}$ ~ 1, $J_{5,6a,b}$ 6.5 Hz, H-5), and 3.25 (s, 3 H, OCH$_3$). Anal. Calcd for $C_{63}H_{66}O_{18}P_4$: C, 61.27; H, 5.39. Found: C, 60.99; H, 5.19.

Methyl α-D-galactopyranoside 2,3,4,6-tetrakis(disodium phosphate) (**10**).—Compound **9** (106 mg, 0.083 mmol) was dissolved in MeOH (2 mL) and buffered aq AcOH–NaOAc (1 mL, pH 5, 0.5 M), and the mixture was treated with Pd–C

(10%, ~10 mg) and H_2 at atmospheric pressure for 2 h with stirring at room temperature. Then the mixture was treated as described for **6**, to obtain **10** (54 mg, 94%) as an amorphous solid; $[\alpha]_D$ +64° (*c* 0.9, M NaoH). NMR data (D_2O, pD ~12): ^1H (300 MHz), δ 5.07 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.52 (bd, 1 H, $J_{H,P}$ 8.9, $J_{4,5}$ 0.9 Hz, H-4), 4.30 (m, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.6 Hz, H-2), 4.22 (bt, 1 H, $J_{3,P}$ 10.9 Hz, H-3), 4.16 (m, $J_{5,P}$ 4.4, $J_{5,6a}$ 7.6, $J_{5,6b}$ 7.9 Hz, H-5), 4.03 (m, 2 H, H-6a,6b), and 3.44 (s, 3 H, OCH_3); ^{13}C {^1H} (75 MHz), δ 99.9 (C-1), 75.0 (d, $J_{P,C}$ 5.8 Hz, C-4), 73.5 (m, C-3), 72.5 (t, $J_{P,C}$ 5.7 Hz, C-2), 70.9 (dd, *J* 4.0, *J* 8.2 Hz, C-5), 65.9 (d, $J_{P,C}$ 4.6 Hz, C-6), and 56.8 (OCH_3); ^{31}P (121 MHz), δ 5.18, 4.63, 4.6 and 3.47. Anal. Calcd for $C_7H_{10}O_{18}P_4Na_8$: C, 12.19; H, 1.46. Found: C, 12.85; H, 2.10.

Methyl 2,6-di-O-benzyl-α-D-galactopyranoside 3,4-bis(dibenzyl phosphate) (**12**).—Methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[15] (86 mg, 0.24 mmol) was dissolved in 1:1 acetonitrile–CH_2Cl_2 (4 mL) and treated with 1*H*-tetrazole (136 mg, 1.9 mmol) and dibenzyloxy(diisopropylamino)phosphine (368 mg, 1.01 mmol). After 1 h (TLC; 1:1 hexane–EtOAc), oxidation was carried out by adding water (3.5 mL), $RuCl_3 \cdot 3H_2O$ (2 mg, 0.01 mmol), and $NaIO_4$ (337 mg, 1.56 mmol) with vigorous stirring. After 1 h, the reaction mixture was worked up as described for **5** and the residue was column-chromatographed (3:1 hexane–EtOAc) to yield **12** (215 mg, 88%) as a syrup; $[\alpha]_D$ +33° (*c* 1, $CHCl_3$). NMR data (C_6D_6): ^1H (300 MHz), δ 7.38–7.00 (m, 30 H, Ph), 5.43 (dd, 1 H, $J_{3,4}$ 3, $J_{4,P}$ 9 Hz, H-4), 5.39–5.20 (m, 6 H, 3 PhC*H*$_2$), 5.18 (m, 1 H, $J_{3,P-4}$ 1.7, $J_{3,4}$ 3, $J_{3,P}$ 11.1 Hz, H-3), 4.98 (ddd, 2 H, J_{gem} −11.7, $J_{H,P}$ 11.6 Hz, PhC*H*$_2$), 4.67 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.48 (d, 1 H, J_{gem} −11.9 Hz, PhC*H*), 4.37 (d, 1 H, J_{gem} −11.9 Hz, PhC*H*), 4.31 (d, 1 H, J_{gem} −11.9 Hz, PhC*H*), 4.22 (d, 1 H, J_{gem} −11.9 Hz, PhC*H*), 4.02 (dd, 1 H, $J_{1,2}$ 3.4, $J_{2,3}$ 10.1 Hz, H-2), 3.86 (m, 1 H, $J_{4,5}$ 1, $J_{5,6a}$ 6.3, $J_{5,6b}$ 6.5 Hz, H-5), 3.78 (dd, 1 H, $J_{5,6a}$ 5.9, $J_{6a,6b}$ −9.4 Hz, H-6a), 3.69 (dd, 1 H, $J_{5,6b}$ 6.7, $J_{6a,6b}$ −9.4 Hz, H-6b), and 3.03 (s, 3 H, OCH_3). Anal. Calcd for $C_{49}H_{52}O_{12}P_2$: C, 65.77; H, 5.86. Found: C, 66.01; H, 6.15.

Methyl α-D-galactopyranoside 3,4-bis(disodium phosphate) (**13**).—Compound **12** (80 mg, 0.09 mmol) was dissolved in MeOH (2 mL) and buffered aq AcOH–NaOAc (0.6 mL, pH 5, 0.5 M), and the mixture was treated with Pd–C (10%, ~10 mg) and H_2 at atmospheric pressure for 2 h with stirring at room temperature. Then the mixture was treated as described for **6**, to obtain **13** (39 mg, 97%) as an amorphous solid; $[\alpha]_D$ +70° (*c* 0.6, M NaOH). NMR data (D_2O, pD ~12): ^1H (300 MHz), δ 4.81 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.48 (m, 1 H, $J_{3,4}$ 3.4, $J_{4,P}$ 10, *J* ~1 Hz, H-4), 4.25 (m, 1 H, $J_{3,4}$ 3.4, $J_{2,3}$ 10, $J_{3,P-4}$ ~0.9 Hz, H-3), 4.01 (dd, 1 H, $J_{1,2}$ 3.9, $J_{2,3}$ 10.3 Hz, H-2), 3.87 (dt, 1 H, $J_{4,5}$ ~1, $J_{5,6a}$ 6.2, $J_{5,6b}$ 6.8 Hz, H-5), 3.73 (dd, 1 H, $J_{6a,6b}$ −11.8, $J_{5,6b}$ 6.8 Hz, H-6b), 3.69 (dd, 1 H, $J_{6a,6b}$ −11.8, $J_{5,6a}$ 6.2 Hz, H-6a), and 3.39 (s, 3 H, OCH_3). ^{13}C {^1H} (75 MHz), δ 100.7 (C-1), 74.7 (C-3), 74.0 (C-4), 71.5 (C-5), 68.6 (C-2), 62.2 (C-6), and 56.7 (OCH_3); ^{31}P (121 MHz), δ 6.30 (dd, $J_{P,H-3}$ 9 Hz, P-3) and 5.09 (d, $J_{P,H-4}$ 9.9 Hz, P-4). Anal. Calcd for $C_7H_{12}O_{12}P_2Na_4$: C, 19.02; H, 2.74. Found: C, 19.15; H, 3.01.

*2-(Trimethylsilyl)ethyl 6-O-(*tert*-butyldiphenylsilyl)-3,4-O-isopropylidene-2-O-*

(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (**14**).—To a stirred mixture of **3** (0.37 g, 0.68 mmol), mercuric cyanide (0.343 g, 1.36 mmol), mercuric bromide (0.673 g, 1.87 mmol), and powdered 4A molecular sieves (1.04 g) in benzene (17 mL) was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (0.67 g, 1.7 mmol) in benzene (3.5 mL) under Ar, and the mixture was kept in the dark with stirring at 60°C. After 2 h (TLC; 1:1 hexane–EtOAc), the reaction mixture was cooled to room temperature, filtered (Celite), washed with satd aq $NaHCO_3$ (20 mL), satd aq KBr (10 mL), and water (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (3:2 hexane–EtOAc) gave syrupy **14** (0.57 g, 94%); $[\alpha]_D$ +9° (*c* 1, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.67 (m, 4 H, Ph), 7.33 (m, 6 H, Ph), 5.37 (dd, 1 H, $J_{4',5'}$ 1.1, $J_{3',4'}$ 3,4 Hz, H-4'), 5.21 (dd, 1 H, $J_{1',2'}$ 8, $J_{2',3'}$ 10.6 Hz, H-2'), 5.03 (dd, 1 H, $J_{3',4'}$ 3.4, $J_{2',3'}$ 10.5 Hz, H-3'), 4.8 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 4.25 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.19 (dd, 1 H, $J_{4,5}$ 2, $J_{3,4}$ 5.7 Hz, H-4), 4.13 (m, 2 H, C*H*HCH$_2$Si, H-5 or H-5'), 4.05 (t, 1 H, *J* ~6.3 Hz, H-3), 3.95 (m, 4 H, H-6a,6b,6'a,6'b), 3.77 (dt, 1 H, $J_{4,5}$ 2.1, $J_{5,6}$ 6.2 Hz, H-5 or H-5'), 3.58 (dd, 1 H, $J_{2,3}$ 6.6, $J_{1,2}$ 7.8 Hz, H-2), 3.54 (m, 1 H, C*H*HCH$_2$Si), 2.13, 2.07, 2.01, 1.97 (s, 12 H, 4 OAc), 1.46, 1.30 (s, 6 H, 2 CH_3), 1.04 (s, 9 H, 3 CH_3), 1.00 (m, 2 H, CH_2CH_2Si), and −0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C (50 MHz), δ 170.2, 170.17, 170.13, 169.6, 135.6, 133.4, 129.7, 127.7, 127.6, 109.8, 101.6, 101.1, 82.01, 78.8, 73.2, 73.0, 71.0, 70.6, 69.4, 67.0, 62.7, 61.0, 28.0, 26.7, 26.3, 20.9, 20.6, 19.2, 18.2, and −1.4. Anal. Calcd for $C_{44}H_{64}O_{15}Si_2$: C, 59.44; H, 7.26. Found: C, 59.18; H, 7.10.

*2-(Trimethylsilyl)ethyl 6-O-(*tert*-butyldiphenylsilyl)-2-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside 3,4-bis(dibenzyl phosphate)* (**15**).—To a solution of compound **4** (164 mg, 0.18 mmol) in CH_2Cl_2 (3.6 mL) at 0°C was added aq 90% trifluoroacetic acid (0.36 mL). After 30 min (TLC; 1:1 hexane–EtOAc), 1:1 toluene–EtOAc (15 mL) was added twice and removed in vacuo at ~40°C. The residue was column-chromatographed (1:1 hexane–EtOAc) to afford partially deprotected disaccharide (122 mg, 80%). A portion (100 mg, 0.12 mmol) was dissolved in 1:1 acetonitrile–CH_2Cl_2 (4 mL), and 1*H*-tetrazole (82 mg, 12 mmol) and dibenzyloxy(diisopropylamino)phosphine (248 mg, 7.2 mmol) were added at room temperature with stirring. After 1 h (TLC; 1:1 hexane–EtOAc), water (3.5 mL), $NaIO_4$ (152 mg, 0.71 mmol), and $RuCl_3 \cdot 3H_2O$ (2 mg, 0.01 mmol) were added and the mixture was vigorously stirred for 1 h. Then (TLC; 1:1 hexane–EtOAc) the mixture was treated as described for compound **5**. Column chromatography (2:1 hexane–acetone) afforded syrupy **15** (520 mg, 76%); $[\alpha]_D$ −1.3° (*c* 1.75, $CHCl_3$). NMR data (C_6D_6): ^1H (300 MHz), δ 7.78 (m, 3 H, Ph), 7.48 (m, 3 H, Ph), 7.1 (m, 24 H, Ph), 5.64 (dd, 1 H, $J_{1',2'}$ 8.1, $J_{2',3'}$ 10.5 Hz, H-2'), 5.5 (dd, 1 H, $J_{3',4'}$ 3.2, $J_{4',5'}$ 1 Hz, H-4'), 5.51 (dd, 1 H, $J_{P,H}$ 8.3, J_{gem} −11.6 Hz, PhC*H*), 5.39 (dd, 1 H, $J_{P,H}$ 7, J_{gem} −11.9 Hz, PhC*H*), 5.36 (m, 1 H, $J_{3,4}$ 2.7, $J_{P,H}$ 8.9, *J* ~0.5 Hz, H-4), 5.29 (ABq, 2 H, J_{gem} −12 Hz, PhCH_2), 5.15 (dd, 1 H, $J_{3',4'}$ 3.5, $J_{2',3'}$ 10.4 Hz, H-3'), 5.16 (dd, 1 H, $J_{P,H}$ 6.9, J_{gem} −12.1 Hz, PhC*H*), 5.03 (dd, 1 H, $J_{P,H}$ 8, J_{gem} −11.9 Hz, PhC*H*), 5.00 (d, 1 H, $J_{1',2'}$ 8.1 Hz, H-1), 4.87 (dd, 1 H, $J_{P,H}$ 7.3, J_{gem}

−11.9 Hz, PhC*H*), 4.78 (dd, 1 H, J_{PH} 8.3, J_{gem} −11.9 Hz, PhC*H*), 4.63 (m, 1 H, H-3), 4.15 (m, 7 H, H-1,2,6a,6b,6'a,6'b, C*H*HCH$_2$Si), 3.62 (m, 1 H, CH*H*CH$_2$Si), 3.48 (m, 1 H, H-5 or H-5'), 3.28 (m, 1 H, H-5 or H-5'), 2.13, 1.72, 1.65, 1.61 (s, 12 H, 4 OAc), 1.19 (s, 9 H, 3 CH$_3$), 1.07 (m, 2 H, OCH$_2$C*H*$_2$Si), and 0.03 (s, 9 H, Si(CH$_3$)$_3$). Anal. Calcd for $C_{69}H_{86}O_{21}P_2Si_2$: C, 60.51; H, 6.33. Found: C, 60.28; H, 6.07.

2-Trimethylsilyl)ethyl 2-O-β-D-galactopyranosyl-β-D-galactopyranoside 3,4-bis(disodium phosphate) (**16**).—Compound **15** (94 mg, 0.067 mmol) was dissolved in anhyd tetrahydrofuran (2.5 mL), and 1.1 M tetrabutylammonium fluoride in tetrahydrofuran (70 μl, 0.075 mmol) was added. After 12 h (TLC; 1:1 hexane–EtAcO) the solvent was evaporated and the residue was percolated through a short-path column of silica gel (1:1 hexane–EtOAc) to obtain the 6-*O*-deprotected disaccharide (60 mg, 80%). A portion (30 mg, 0.026 mmol) was dissolved in MeOH (1 mL), and M NaOMe (5 μl, ~5 μmol) was added. After 30 min, the mixture was neutralized with Amberlite IR-120 (H^+) and concentrated. The residue was dissolved in MeOH (2 mL) and buffered aq AcOH–NaOAc (0.2 mL, pH 5, 0.5 M), and the mixture was treated with Pd–C (10%, ~10 mg) and H_2 at atmospheric pressure for 2 h with stirring at room temperature. Then the mixture was treated as described for **6**, to obtain **16** (17 mg, 94%) as an amorphous solid; $[\alpha]_D$ −10° (*c* 0.6, M NaOH). NMR data (D_2O, pD ~12): ^{1}H (300 MHz), δ 4.64 (d, 1 H, $J_{1',2'}$ 7.4 Hz, H-1'), 4.53 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.47 (bd, 1 H, $J_{4,P}$ 6.8 Hz, H-4), 4.15 (bt, 1 H, *J* 9.8 Hz, H-3), 3.95 (m, 1 H, C*H*HCH$_2$Si), 3.91 (d, 1 H, $J_{3',4'}$ 3 Hz, H-4'), 3.88 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 9.8 Hz, H-2), 3.79 (m, 1 H, H-5), 3.76–3.68 (m, 5 H, H-6a,6b,6'a,6'b, CH*H*CH$_2$Si), 3.65 (dd, 1 H, $J_{2',3'}$ 10, $J_{3',4'}$ 3.4 Hz, H-3'), 3.66 (m, 1 H, H-5), 1.0 (m, 2 H, CH$_2$C*H*$_2$Si), and 0.01 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C (75 MHz), δ 106.9, 103.8, 81.5, 77.4, 77.1, 76.6, 75.5, 74.0, 73.9, 73.5, 71.0, 70.6, 63.1, 61.8, 20.3, and −0.5; ^{31}P (121 MHz): δ 6.3 (d, 1 P, *J* 10.8 Hz), 5.97 (d, 1 P, *J* 9.3 Hz). Anal. Calcd for $C_{17}H_{32}O_{17}P_2SiNa_4$: C, 29.57; H, 4.67. Found: C, 28.23; H, 5.82.

2-(Trimethylsilyl)ethyl 2-O-β-D-galactopyranosyl-β-D-galactopyranoside (**17**).—Compound **14** (148 mg, 0.16 mmol) was dissolved in MeOH (8 mL), and M NaOMe (0.8 mL) was added at room temperature. After 2 h, the solution was neutralized with Amberlite IR-12- (H^+), filtered, and concentrated. The residue was passed through a short-path column of silica gel (1:1 hexane–EtOAc) and the appropriate fractions were concentrated to obtain the deacetylated derivative (100 mg, 86%). The residue was dissolved in dry tetrahydrofuran (4 mL) at 0°C and treated with 1.1 M tetrabutylammonium fluoride in tetrahydrofuran (0.16 mL, 0.18 mmol). The solution was allowed to warm to room temperature; after 3 h, more tetrabutylammonium fluoride was added (160 μl, 0.18 mmol) and stirring was continued overnight at room temperature. After 20 h, deprotection was completed, the solvent was evaporated, and the residue was percolated through a short-path column of silica gel (1:2 hexane–EtOAc). Finally, a portion (63 mg, 0.13 mmol) was dissolved in MeOH (2 mL), and aq 10% acetic acid was added (10 mL). The solution was warmed at 100°C and, after 1 h (TLC; 4:1 $CHCl_3$–MeOH), the

solvents were evaporated in vacuo and the residue was column-chromatographed (3:1 $CHCl_3$–MeOH) to give **17** (50 mg, 82%) as an amorphous solid; $[\alpha]_D$ −2° (*c* 1, H_2O). NMR data (D_2O): ^1H (300 MHz): 4.75 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 4.52 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.05 (m, 1 H, C*H*HCH$_2$Si), 3.94 (t, 2 H, *J* ~2.5 Hz, H-4,4'), 3.84 (dd, 1 H, $J_{2',3'}$ 9.7, $J_{3',4'}$ 3.2 Hz, H-3'), 3.74 (dd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ ~10 Hz, H-2'), 3.75 (m, 7 H, H-5,5',6a,6b,6'a,6'b, CH*H*CH$_2$Si), 3.57 (dd, 1 H, $J_{1,2}$ 7.6 Hz, $J_{2,3}$ 9.8 Hz, H-2), 1.05 (m, 2 H, CH$_2$C*H*$_2$Si), and 0.2 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C (50 MHz), δ 104.6, 102.07, 80.04, 76.91, 76.33, 76.13, 74.59, 74.15, 73.8, 72.8, 70.58, 70.39, 69.9, 69.71, 69.49, 61.95, 19.35, 18.9, and −1.28. Anal. Calcd for $C_{17}H_{34}O_{11}Si$: C, 46.14; H, 7.74. Found: C, 46.42; H, 7.28.

*2-(Trimethylsilyl)ethyl 2,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-β-*D*-galactopyranoside* (**18**).—To a stirred mixture of compound **2** (400 mg, 1.25 mmol), mercuric cyanide (505 mg, 2 mmol), mercuric bromide (1.13 g, 3.13 mmol), and 4A molecular sieves in benzene (30 mL) was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (1.3 g, 3.13 mmol) in benzene (10 mL) at room temperature under Ar, and the reaction was stirred in the dark for 18 h (TLC; 1:1 hexane–EtOAc). Then the mixture was treated as described for compound **14**, and the residue (2.13 g) was percolated through a silica gel column (1:1 hexane–EtOAc) in order to eliminate excess galactopyranosyl bromide. The residue (700 mg) was dissolved in CH_2Cl_2 (14 mL), and aq 90% trifluoroacetic acid (1.4 mL) was added at 0°C. After 30 min, the solution was diluted with CH_2Cl_2 (15 mL) washed twice with satd aq $NaHCO_3$ (10 mL) and water (10 mL), and dried (Na_2SO_4). Column chromatography (1:1 hexane–acetone) afforded **18** as a syrup which crystallized on standing (564 mg, 48% from **2**). Compound **18** had: mp 98–99°C (from hexane–acetone); $[\alpha]_D$ −1° (*c* 1.2, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 5.35 (m, 2 H, H-4',4''), 5.16 (2 dd, 2 H, *J* 8, *J* 10 Hz, H-2',2''), 4.97 (2 dd, 2 H, *J* 3, *J* 10 Hz, H-3',3''), 4.85 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 4.54 (d, 1 H, $J_{1'',2''}$ 8 Hz, H-1''), 4.30 (d, 1 H, $J_{1,2}$ 7 Hz, H-1), 4.13–4.05 (m, 4 H), 4.00–3.80 (m, 6 H), 3.58–3.5 (m, 4 H), 2.84 (d, 1 H, *J* ~4 Hz, HO), 2.57 (d, 1 H, *J* ~3 Hz, HO), 2.11, 2.10, 2.05, 2.02, 2.01, 1.99, 1.95, 1.94 (s, 24 H, 8 OAc), 0.93 (m, 2 H, CH$_2$C*H*$_2$Si), and 0.01 (s, 9 H, Si(CH$_3$)$_3$). Anal. Calcd for $C_{39}H_{60}O_{24}Si$: C, 49.78; H, 6.43. Found: C, 50.04; H, 6.51.

*2-(Trimethylsilyl)ethyl 2,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-β-*D*-galactopyranoside 3,4-bis(dibenzyl phosphate)* (**19**).—Compound **18** (357 mg, 0.38 mmol) was dissolved in 1:1 acetonitrile–CH_2Cl_2 (6 mL), and 1*H*-tetrazole (280 mg, 4 mmol) and dibenzyloxy(diisopropylamino)phosphine (786 mg, 2.28 mmol) were added at room temperature. After 1 h (TLC; 3:2 hexane–EtOAc), water (5 mL), $NaIO_4$ (488 mg, 2.28 mmol), and $RuCl_3 \cdot 3H_2O$ (4 mg, 0.015 mmol) were added and the mixture was vigorously stirred. After 1.5 h, the mixture was treated as described for compound **5** and the residue was column-chromatographed (2:1 hexane–acetone) to give **19** (357 mg, 66%) as a syrup; $[\alpha]_D$ −1.3° (*c* 1.35, $CHCl_3$). NMR data (C_6D_6): ^1H (300 MHz), δ 7.5 (m, 2 H, Ph), 7.24–7.04 (m, 18 H, Ph), 5.68 (2 dd, 2 H, *J* 7.9, *J* 9.5 Hz, H-2',2''), 5.49 (bs, 2 H, H-4',4''), 5.44 (dd, 1 H,

$J_{P,H}$ 8.4, J_{gem} −11.9 Hz, PhC*H*), 5.34 (dd, 1 H, $J_{P,H}$ 7.2, J_{gem} −11.9 Hz, PhC*H*), 5.3–4.66 (m, 10 H, H-4,1′,3′,3″, 3 PhCH_2), 4.57 (m, 1 H, *J* 0.8, *J* 9.3, *J* 2.5 Hz, H-3), 4.35 (d, 1 H, $J_{1'',2''}$ 7.9 Hz, H-1″), 4.29 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.29–4.01 (m, 8 H, H-2,6a,6b,6′a,6′b,6″a,6″b, C*H*HCH$_2$Si), 3.67 (m, 1 H, *J* 7.7, *J* 9.3 Hz, CH*H*CH$_2$Si), 3.52 (dt, 1 H, $J_{4'',5''}$ 0.8, $J_{5'',6''a}$ 7.0, $J_{5'',6''b}$ 7.4 Hz, H-5″), 3.38 (dt, $J_{4',5'}$ 1.1, $J_{5',6'a}$ 6.7, $J_{5',6'b}$ 6.6 Hz, H-5′), 3.30 (bt, $J_{5,6a}$ 5.6, $J_{5,6b}$ 5.5 Hz, H-5), 2.08, 1.90, 1.73, 1.72, 1.71, 1.65, 1.61, 1.57 (s, 24 H, 8 OAc), 1.15 (m, 2 H, CH$_2$CH_2Si), and 0.12 (s, 9 H, Si(CH$_3$)$_3$). Anal. Calcd for $C_{67}H_{86}O_{30}P_2Si$: C, 55.06; H, 5.93. Found: C, 55.26; H, 5.90.

2-(Trimethylsilyl)ethyl 2,6-di-O-(β-D-galactopyranosyl)-β-D-galactopyranoside 3,4-bis(disodium phosphate) (**20**).—Compound **19** (180 mg, 0.12 mmol) was dissolved in MeOH (6 mL) and treated with M NaOMe (0.180 mL). After 1 h, the solution was neutralized with Amberlite IR-120 (H^+), filtered, concentrated, and column-chromatographed (4:1 $CHCl_3$–MeOH). The appropriate fractions were concentrated to yield the deacylated derivative of **19** (125 mg, 94%), which was dissolved in MeOH (5 mL) and AcOH–NaOAc buffer (0.7 mL, pH 5, 0.5 M), and the solution was treated with Pd–C (10%, ~20 mg) and H_2 at atmospheric pressure for 2 h with stirring at room temperature. The mixture was filtered (Celite) and partially evaporated, treated with Amberlite IR-120 (Na^+ form), and concentrated. The concentrate was passed through a column (1 × 15 cm) of Sephadex G-15 (water), and the appropriate fractions were lyophilized to obtain **20** (95 mg, 93%) as an amorphous solid; $[\alpha]_D$ −2.2° (*c* 0.6, M NaOH). NMR data (D_2O, pD ~12): ^1H (300 MHz), δ 4.72 (d, 1 H, $J_{1',2'}$ 8 Hz, H-1′), 4.55 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.47 (d, 1 H, $J_{1'',2''}$ 7.7 Hz, H-1″), ~4.5 (bd, 1 H, overlapping with H-1, H-4), 4.23 (bt, 1 H, *J* ~8 Hz, H-3), 4.09 (d, 1 H, $J_{6a,6b}$ −10.1 Hz, H-6a), 4.06–3.97 (m, 1 H, C*H*HCH$_2$Si), 3.93 (d, 1 H, $J_{6a,6b}$ −10.2 Hz, H-6b), 3.91 (dd, $J_{3',4'}$ 3, $J_{4',5'}$ < 0.5 Hz, H-4′), 3.88 (dd, 1 H, $J_{3'',4''}$ 3.3, $J_{4'',5''}$ < 0.5 Hz, H-4″), 3.85 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 10.2 Hz, H-2), 3.83–3.6 (m, 8 H, H-5,5′,5″,6′a,6′b,6″a,6″b, C*H*CH$_2$Si), 3.66 (dd, 1 H, $J_{2',3'}$ 10.2, $J_{3',4'}$ 3 Hz, H-3′), 3.62 (dd, 1 H, $J_{2'',3''}$ 9.7, $J_{3'',4''}$ 3.3 Hz, H-3″), 3.50 (dd, 1 H, $J_{1'',2''}$ 7.7, $J_{2'',3''}$ 9.7 Hz, H-2″), 3.46 (dd, 1 H, $J_{1',2'}$ 8, $J_{2',3'}$ 10.2 Hz, H-2′), 1.02 (m, 2 H, CH$_2$CH_2Si), 0.01 (s, 9 H, Si(CH$_3$)$_3$); ^{13}C (50 MHz), δ 105.29, 104.64, 102.46, 81.34, 76.87, 76.24, 76.14, 74.74, 74.32, 74.20, 72.47, 71.30, 71.25, 70.49, 69.92, 69.79, 62.53, 62.01, 19.29, and −0.93; ^{31}P (121 MHz), δ 5.3 (d, 1 P, *J* 10.6 Hz) and 3.71 (d, 1 P, *J* 9.1 Hz). Anal. Calcd for $C_{23}H_{42}O_{22}P_2SiNa_4 \cdot 3H_2O$: C, 30.47; H, 5.34. Found: C, 30.76; H, 6.37.

2-(Trimethylsilyl)ethyl 2,6-di-O-(β-D-galactopyranosyl)-β-D-galactopyranoside (**21**).—Compound **18** (62 mg, 0.065 mmol) was dissolved in MeOH (3 mL), and M NaOMe (0.3 mL) was added at room temperature. After 2 h, the solution was neutralized with Amberlite IR-120 (H^+), filtered, and concentrated. The residue was column-chromatographed (4:1 $CHCl_3$–MeOH) to afford amorphous **21** (38 mg, 97%); $[\alpha]_D$ −6.5° (*c* 0.6, H_2O). NMR data (D_2O): ^1H (300 MHz), δ 4.69 (d, 1 H, $J_{1',2'}$ 7.7 Hz, H-1′), 4.52 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.43 (d, 1 H, $J_{1'',2''}$ 7.7 Hz, H-1″), 4.04–3.69 (m, 1 H, C*H*HCH$_2$Si), 3.98 (dd, 1 H, $J_{3,4}$ 3.2, *J* < 0.5 Hz, H-4),

3.93 (dd, 1 H, $J_{3',4'}$ 3.2, $J_{4',5'} < 0.5$ Hz, H-4'), 3.92 (dd, 1 H, $J_{3'',4''}$ 3.4, $J_{4'',5''} < 0.5$ Hz, H-4''), 3.84 (dd, 1 H, $J_{2,3}$ 9.4, $J_{3,4}$ 3.4 Hz, H-3), ~3.8 (m, 1 H, $CHHCH_2Si$), 3.74 (m, 8 H, H-5',5'',6a,6b,6'a,6'b,6''a,6''b), 3.73 (dd, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 9.4 Hz, H-2), 3.73 (m, 1 H, H-5), 3.66 (dd, 1 H, $J_{2',3'}$ 10, $J_{3',4'}$ 3.2 Hz, H-3'), 3.63 (dd, 1 H, $J_{2'',3''}$ 9.9, $J_{3'',4''}$ 3.4 Hz, H-3''), 3.57 (dd, 1 H, $J_{1',2'}$ 7.7, $J_{2',3'}$ 10 Hz, H-2'), 3.52 (dd, 1 H, $J_{1'',2''}$ 7.7, $J_{2'',3''}$ 9.9 Hz, H-2''), 1.02 (m, 2 H, CH_2CH_2Si), 0.02 (s, 9 H, $Si(CH_3)_3$); ^{13}C (90 MHz), 104.19, 103.94, 101.63, 79.54, 75.96, 75.96, 75.93, 74.49, 73.54, 73.36, 72.38, 71.51, 69.56, 69.48, 69.38, 69.28, 61.76, 61.53, 18.52, and −1.69. Anal. Calcd for $C_{23}H_{44}O_{16}Si$: C, 45.69; H, 7.33. Found: C, 45.72; H, 7.60.

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