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SYNTHESIS OF 2,2,2-TRICHLOROETHYL 3,6-DI-*O*-BENZYL-2-DEOXY-2-PHTHALIMIDO-β-D-GLUCOPYRANOSIDE, AND ITS REACTION WITH GLYCOSYL HALIDES*

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ABSTRACT

2,2,2-Trichloroethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**9**) was synthesized in 6 steps from the readily available 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose in 25% overall yield by employing the stannyl method for the regioselective activation of hydroxyl groups. Dibenzyl ether **9** was then glycosylated with appropriate glycosyl donors to afford lactosamine and chitobiose derivatives in good yield.

INTRODUCTION

Glycan chains linked to glycoproteins at cell surfaces carry such typical, common sequences[2] as **1** and **2**. A synthetic approach towards such sequences could be executed only when an efficient method for the glycosylation of the 4-hydroxyl group of a suitably protected GlcNAc residue had become available.

In 1958, glycosylation of the 1,3,6-triacetate **3** was first conducted, although in very low yield[3]. Since then, several 3,6-di-*O*-substituted derivatives of GlcNAc, such as **4**, have been prepared as suitably glycosyl acceptors[4] for the synthesis of disaccharides. In a preceding paper[1], we described the synthesis of the 6-*O*-acyl-3-*O*-benzyl derivative **5**. We now report an efficient synthesis of the 3,6-dibenzyl ether **9** from tetraacetate[5] **6**, and also efficient glycosylation of **9** with three kinds of glycosyl halide.

RESULTS AND DISCUSSION

The intermediate **11** for synthesis of the dibenzyl ether **9** could be prepared by some modifications of the original procedure reported by Lemieux *et al.*[6]. The

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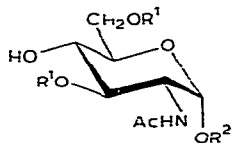
—β-Gal-(1→4)-β-GlcNAc-(1→2)-α-Man-(1→

1

—β-Man-(1→4)-β-GlcNAc-(1→4)-β-GlcNAc-(1→Asn

2

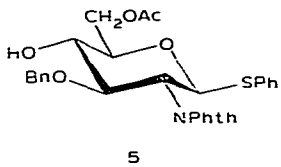


3 $R^1 = R^2 = Ac$

4 $R^1 = Bn, R^2 = All$

All = $CH_2{=}CH{-}CH_2-$

Bn = $PhCH_2$



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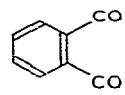
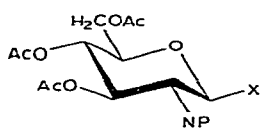
Phth =



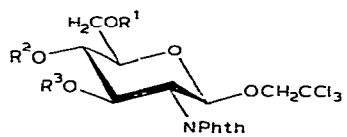
reaction of β-tetraacetate **6** with $Bu_3SnOCH_2CCl_3$ in the presence of $SnCl_4$ according to a reported procedure[7] gave a 78% yield of crystalline β-glycoside **10**. The α anomer[6] of **6**, however, gave only a poor yield of **10** under the same conditions. The reaction of β-chloride **7** with $Bu_3SnOCH_2CCl_3$ at 80° gave only glycal **21** in 12% yield, and 50% of **7** was recovered unchanged. Deacetylation of **10** to **11** was conducted both under acidic conditions according to Lemieux *et al.*[6] in 76% yield, and under basic conditions (Zemplén) in 64% yield.



6 X = OAc

7 X = Cl

8 X = Br



9 $R^1 = R^3 = Bn, R^2 = H$

10 $R^1 = R^2 = R^3 = Ac$

11 $R^1 = R^2 = R^3 = H$

12 $R^1 = R^3 = Bz\ R^2 = H$

13 $R^1 = R^2 = Bz, R^3 = H$

14 $R^1 = Bz, R^2 = R^3 = H$

15 $R^1 = Bn, R^2 = R^3 = H$

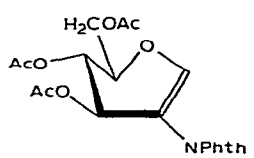
16 $R^1 = R^2 = Bn\ R^3 = H$

17 $R^1 = R^2 = R^3 = Bn$

18 $R^1 = R^2 = H, R^3 = Bn$

19 $R^1 = Ac, R^2 = H, R^3 = Bn$

20 $R^1 = R^3 = Bn, R^2 = Ac$



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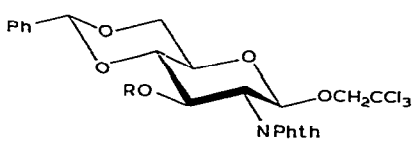
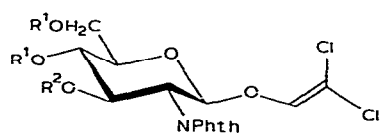
Regioselective activation of the three hydroxyl groups of **11** could be performed by the stannylation–acylation procedure[8]. Stannylation of **11** with 3 equivalents of

$(Bu_3Sn)_2O$, and subsequent treatment with 3 equivalents of benzoyl chloride for 1.5 h at 20–25°, afforded the 3,6-dibenzoate **12** and the monobenzoate **14** in 80 and 11% yield, respectively. However, stannylation of **11**, and subsequent benzoylation for 16 h at 20–25°, led to the isolation of 3,6-dibenzoate **12** and 4,6-dibenzoate **13** in 82 and 5% yield, respectively. The structure of **12** was assigned according to the ^{1}H- and ^{13}C-n.m.r. data, which showed a deshielded, double doublet at δ 6.08, with $J_{2,3}$ 10 and $J_{3,4}$ 8 Hz for H-3, and two deshielded signals for C-3 and C-6, at δ 73.3 and 63.2. Thus, it was concluded that the stannylation–acylation sequence applied to **11** gave the 3,6-dibenzoate as the major product. Examination of the stannylation–alkylation sequence[9] of **11**, however, showed poor regioselectivity. Thus, stannylation of **11** with 3 equivalents of $(Bu_3Sn)_2O$, and subsequent reaction with benzyl bromide for 4 days at 75–80°, gave the monobenzyl ether **15** in 60% yield. Further reaction with benzyl bromide, at 100–105°, led to the isolation of 3,6-dibenzyl ether **9**, 4,6-dibenzyl ether **16**, and **15**, in 9.3, 4.3, and 14.1% yield, respectively. The structure of benzyl ether **15** was determined from its ^{13}C-n.m.r data, which showed a deshielded signal for C-6 at δ 70.3. The structure of **9** was also assigned from its ^{13}C-n m r data, which showed two deshielded signals for C-3 and C-6, at δ 79 6 and 70.1, respectively, and a shielded signal for C-2 at δ 56.1, due to the β-effect. Furthermore, structure **9** was confirmed by an unambiguous synthesis described later. The structure of dibenzyl ether **16** was assigned according to its ^{13}C-n.m.r. data, which showed two deshielded signals for C-4 and C-6, at δ 79.3 and 69.7, respectively, and the signal for C-2 at δ 58.0 with no β-effect. As stannylation of **11** and subsequent benzylation gave only a poor yield of the desired benzyl ether **9**, an alternative, synthetic sequence was next studied.

Benzylidenation of **11** with benzaldehyde and $ZnCl_2$ afforded the known benzylidene derivative[6] **22** in 70% yield. Subsequent benzylation of **22** with benzyl bromide and NaH gave crystalline benzyl ether **23** and a minor product (**25**) in 81 5 and 4% yield, respectively. The structure of the minor product **25** was assigned from the presence, in its ^{1}H-n m.r. spectrum, of a singlet at δ 6.68 for a vinylic proton, and a singlet at δ 5.62 for a dialkoxy benzyl proton of a benzylidene group. Similar dehydrochlorination was observed as a side reaction in the benzylation of **11** to give **17**, and **24** was isolated in 3.2% yield. Acid solvolysis of the benzylidene group of **23** in 60% aq. AcOH gave the 3-benzyl ether **18** and its 6-acetate **19** in 81.4 and 3 5% yield. The ^{13}C-n.m.r. spectrum of **18** reasonably showed a deshielded signal for C-3 at δ 79.6 and a shielded signal for C-2 at δ 56.1. Selective benzylation of the primary

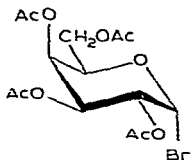


22 R = H
23 R = Bn



24 $R^1 = R^2 =$ Bn

25 $R^1, R^1 =$ >CHPh $R^2 =$ Bn



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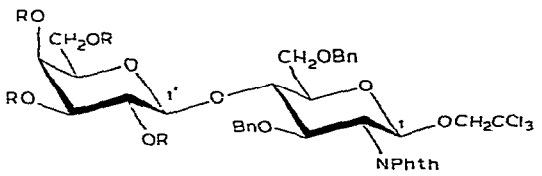
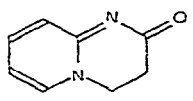


27 R = Ac
28 R = H



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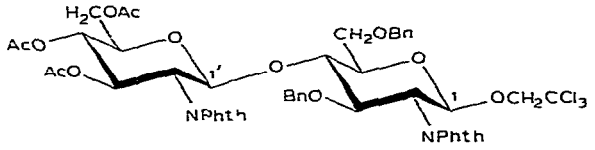


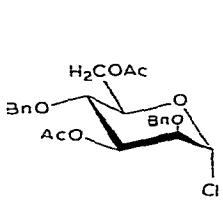
30

hydroxyl group of **18** could be effected, giving **9** in 89% yield, by the stannyl method, as for the transformation of **11** into **15**. The structure of **9** was assigned according to the synthetic sequence, and also by its transformation into acetate **20**, which showed in its ^{1}H-n.m.r. spectrum a deshielded triplet for H-4 at δ 5.14 (with $J_{3,4} = J_{4,5} =$ 9.5 Hz), thus proving selective monobenzylation at the 6-hydroxyl group in **18** Thus, the dibenzyl ether **9** was prepared in 6 steps, starting from the readily available tetra-acetate **6**, in 25% overall yield. The same dibenzyl ether **9** could also be prepared in 3 steps *via* direct benzylation of triol **11**, but in only 5% overall yield from **6**.

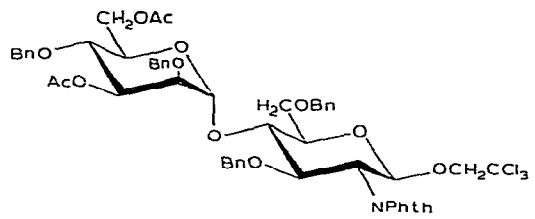
As the key glycosyl acceptor **9** was now available by virtue of an efficient procedure, the reaction of **9** with glycosyl donors was next studied. Having such glycan sequences as **1** and **2** in mind, glycosyl donors **26**, **8**, and **31** were chosen for the experiments. Treatment of **9** plus the D-galactosyl bromide **26** in the presence of silver triflate and 1,1,3,3-tetramethylurea at 20–25° according to the Hanessian–Banoub conditions[11] afforded the lactosamine derivative **27** in 73% yield. A newly formed anomeric stereochemistry in **27** and its deacetylation product **28** was assigned as β according to the ^{13}C-n.m.r. data for **27** and **28**, which showed a signal for C-1′ at δ 100.3 with $^1J_{CH}$ 164.8 Hz, and at δ 102.9 with $^1J_{CH}$ 155.9 Hz, respectively[12].

Glycosylation of **9** with β-bromide **8** in the presence of silver triflate and the proton sponge[13] **29** afforded a 61% yield of the protected chitobiose **30**. The structure of **30** was assigned from its ^{1}H- and ^{13}C-n.m.r. data. The ^{1}H-n.m.r. spectrum of **30** revealed two doublets, at δ 5.55 with J 8 Hz and δ 4.95 with J 10 Hz, for H-1 and H-1′, respectively, and the ^{13}C-n.m.r. spectrum showed two signals, for C-1 and C-1′, at δ 96.6 with $^1J_{CH}$ 166.5 Hz and δ 98.6 with $^1J_{CH}$ 160.0 Hz, respectively, in agreement with the β-D configuration of C-1′.

Finally, the reaction of **9** with the 2,4-di-*O*-benzyl-α-D-mannopyranosyl chloride **31** under the Hanessian–Banoub conditions resulted in the formation of the product of α-D-mannosylation, giving rise to **32** in 58.2% yield. The α configuration



31



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of C-1′ of **32** was assigned from the presence of a signal for C-1′ at δ 98.6, with $^1J_{CH}$ 170 6 Hz, in its ^{13}C-n.m r. spectrum.

In conclusion, an efficient route for the synthesis of the glycosyl acceptor **9** has been developed, and its reactivity towards the glycosyl donors **26**, **8**, and **31** has been proved.

EXPERIMENTAL

General. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 141 polarimeter for solutions in $CHCl_3$ at 25°, unless otherwise noted. Column chromatography was performed on columns of Silica Gel Merck (70–230 mesh; E. Merck, Darmstadt, Germany). Thin-layer chromatography was conducted on precoated plates (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany) of Silica Gel 60 F_{254}. I.r. spectra were recorded with an EPI-G2 Hitachi spectrophotometer, as KBr discs for the crystalline samples, and as neat films for the liquid samples ^{1}H-N.m.r. spectra were recorded with a Varian HA-100 n.m.r. spectrometer, using tetramethylsilane as the internal standard. ^{13}C-N.m.r. spectra were recorded with a JNM-FX 100FT n m.r. spectrometer operated at 25.05 MHz. The values of δ_C and δ_H are expressed in p.p.m. downwards from the internal standard for the solutions in $CDCl_3$, unless otherwise noted.

*2,2,2-Trichloroethyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**10**). — (*A*) To a solution of β-acetate **6** (477 mg, 1 mmol) and $Bu_3SnOCH_2CCl_3$ (450 mg, 1 mmol) in $Cl(CH_2)_2Cl$ (5 mL) was added $SnCl_4$ (0.12 mL, 1 mmol). The mixture was stirred for 15 h at 25°, and poured into ice–water (50 mL, containing 0.5 g of NaOAc) and EtOAc (50 mL). Insoluble substances were filtered off through Celite, and the aq. phase was extracted with EtOAc. The organic layers were combined, successively washed with H_2O, aq. $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated to give an oil. Trituration with ether gave crystalline **10** (440.2 mg, 77.7%), m.p. 188–189°, $[\alpha]_D$ +5.6° (*c* 0.68); R_F 0.49 in 20:1 $CHCl_3$–Me_2CO; δ_H: 5 92 (dd, $J_{2,3}$ 11, $J_{3,4}$ 10 Hz, H-3), 5.60 (d, $J_{1,2}$ 8 Hz, H-1), 5.19 (t, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), and 2.12, 2.04, and 1.88 (s, 3 OAc); δ_C: 98.8 (C-1, $^1J_{CH}$ 164 7 Hz), 54 3 (C-2), 70.1 (C-3), 68.7 (C-4), 72.0 (C-5), 61.7 (C-6), 80.6 (O-CH_2CCl_3), 95.6 (CCl_3), 20.4 (Ac), 20.6 (Ac), and 20.7 (Ac).

Anal. Calc. for $C_{22}H_{22}Cl_3NO_{10}$: C, 46.62; H, 3.91; Cl, 18.77; N, 2.47. Found: C, 46.67; H, 3.84; Cl, 18.59; N, 2.45.

(*B*) The α anomer of **6** (1 mmol) was treated as described in (*A*) for 24 h at 25°. The usual processing, and chromatography on SiO_2 (200 g) with 20:1 $CHCl_3$–Me_2CO, afforded **10** (157.2 mg, 27.7%), and the α anomer of **6** was recovered in 46.6% yield.

*3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-2-phthalimido-*D-arabino-*hex-1-enitol* (**21**). — A solution of β-chloride **7** (454 mg, 1 mmol) and $Bu_3SnOCH_2CCl_3$ (450 mg, 1 mmol) in $Cl(CH_2)_2Cl$ (5 mL) was stirred for 6 days at 75–80°. The mixture was cooled, and evaporated, and the residue was chromatographed on SiO_2 (120 g) with 15:1 $CHCl_3$–Me_2CO to give **21** as an oil (49.1 mg, 11.8%); $[\alpha]_D$ −15.0° (*c* 0.20); R_F 0.53 in 15:1 $CHCl_3$–Me_2CO; δ_H: 6.77 (s, H-1), 5.61 (d, *J* 4 Hz, H-3), and 5.32 (t, $J_{3,4} = J_{4,5} = 4$ Hz, H-4).

Anal. Calc. for $C_{20}H_{19}NO_9$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.29; H, 4.82; N, 3.34.

About 50% of chloride **7** was recovered from the less-polar fractions.

*2,2,2-Trichloroethyl 2-deoxy-2-phthalimido-β-*D-*glucopyranoside* (**11**). — (*A*) Compound **10** was treated in aq. HCl–Me_2CO according to the procedure of Lemieux *et al.*[6], to give crystalline **11** (75.6%).

(*B*) A suspension of **10** (283 mg, 0.5 mmol) in MeOH (2.5 mL)–0.1M NaOMe in MeOH (2 mL) was stirred for 23 h at 20°. Neutralization with Amberlist 15 (H^+), filtration, evaporation of the filtrate, and chromatography of the residue on SiO_2 (30 g) with 1:1 EtOAc–Et_2O, gave **11** (141 mg, 64.0%), m.p. 231–232°, $[\alpha]_D$ −36.0° (*c* 1.05, Me_2CO); R_F 0.54 in 1:1 EtOAc–Et_2O; δ_H: 5.4 (d, *J* 8 Hz, H-1), 4.33 (d, CH_2CCl_3); δ_C (CD_3COCD_3): 99.9 (C-1, $^1J_{CH}$ 169 Hz), 57.7 (C-2), 72.4 (C-3), 71.8 (C-4), 77.9 (C-5), 62.5 (C-6), 81.1 (OCH_2CCl_3), and 97.4 (CCl_3).

Anal. Calc. for $C_{16}H_{16}Cl_3NO_7$: C, 43.61; H, 3.66; Cl, 24.14; N, 3.18. Found: C, 43.71; H, 3.68; Cl, 23.58; N, 3.25.

*2,2,2-Trichloroethyl 3,6-di-O-benzoyl-2-deoxy-2-phthalimido-β-*D-*glucopyranoside* (**12**), *2,2,2-trichloroethyl 4,6-di-O-benzoyl-2-deoxy-2-phthalimido-β-*D-*glucopyranoside* (**13**), *and 2,2,2-trichloroethyl 6-O-benzoyl-2-deoxy-2-phthalimido-β-*D-*glucopyranoside* (**14**). — (*A*) A mixture of **11** (427 mg, 0.97 mmol) and $(Bu_3Sn)_2O$ (899 mg, 1.5 mmol) in benzene (50 mL) was boiled for 3 h under reflux, with continuous removal of water, cooled, concentrated to 10 mL, and treated with BzCl (422 mg, 3 mmol) for 1.5 h at 20–25°. Evaporation *in vacuo*, and chromatography of the residue on SiO_2 (200 g) with 10:1 $CHCl_3$–Me_2CO, afforded crystalline dibenzoate **12** (505 mg, 80.3%), m.p. 91–93°, $[\alpha]_D$ +43.8° (*c* 0.32); R_F 0.36 in 15:1 $CHCl_3$–Me_2CO; δ_H: 6.08 (dd, $J_{2,3}$ 10, $J_{3,4}$ 8 Hz, H-3), 5.07 (d, $J_{1,2}$ 8 Hz, H-1), 4.57 (dd, $J_{1,2}$ 8, $J_{2,3}$ 10 Hz, H-2), and 3.64 (bs, OH); δ_C (CD_3COCD_3): 98.6 (C-1, $^1J_{CH}$ 166.0 Hz), 54.2 (C-2), 73.3 (C-3), 70.0 (C-4), 74.4 (C-5), 63.2 (C-6), 80.3 (CH_2CCl_3), and 95.6 (CCl_3).

Anal Calc. for $C_{30}H_{24}Cl_3NO_9$: C, 55.53; H, 3.73; Cl, 16.39; N, 2.16. Found: C, 55.63; H, 3.81; Cl, 16.36; N, 2.08.

Further elution gave monobenzoate **14** (60.1 mg, 11.4%), m.p. 181.5–182.5°, $[\alpha]_D$ −57.5° (*c* 0.32); R_F 0.05 in 15:1 $CHCl_3$–Me_2CO; δ_H: 5.44 (d, $J_{1,2}$ 8 Hz, H-1);

δ_C (CD_3COCD_3): 99.0 (C-1, $^1J_{CH}$ 162.4 Hz), 56.0 (C-2), 71.3 (C-3), 70.6 (C-4), 74.1 (C-5), 63.5 (C-6), 80.3 (CH_2CCl_3), and 95.8 (CCl_3).

Anal. Calc. for $C_{23}H_{20}Cl_3NO_8$: C, 50.71; H, 3 70; Cl, 19.53; N, 2.57. Found: C, 51.16; H, 3.73; Cl, 19.08; N, 2.45.

(*B*) When the reaction described in (*A*) was continued for 16 h, t.l.c. showed the disappearance of monobenzoate **14** and the formation of 4,6-dibenzoate **13** as a minor product [along with the major product **12** (82%)]. 4,6-Dibenzoate **13** was isolated in 5% yield by chromatography on SiO_2 with 15:1 $CHCl_3$–Me_2CO; $[\alpha]_D$ −5.9° (*c* 0.22); R_F 0.39 in 15:1 $CHCl_3$–Me_2CO; δ_H: 5.55 (d, $J_{1,2}$ 8 Hz, H-1), 5.39 (t, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), and 3.15 (bs, OH).

Anal. Calc. for $C_{30}H_{24}Cl_3NO_9$: C, 55.53; H, 3.73; Cl, 16.39; N, 2.16. Found: C, 55.62; H, 3.89; Cl, 16.42; N, 2.13.

2,2,2-Trichloroethyl 6-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**15**). — Compound **11** (430 mg, 0.98 mmol) was stannylated with $(Bu_3Sn)_2O$ (899 mg, 1.5 mmol) in benzene (50 mL). The benzene was evaporated *in vacuo*, and the residue was dissolved in benzyl bromide (5 mL) and stirred for 4 days at 75–80° under argon. The benzyl bromide was evaporated *in vacuo*, and a solution of the residue in CH_2Cl_2 was washed with 0.2M aq. Na_2S (4 × 10 mL), dried ($MgSO_4$), and evaporated to dryness; chromatography of the residue on SiO_2 (150 g) with 5:1 CH_2Cl_2–Me_2CO afforded the monobenzyl ether **15** (310.7 mg, 59.8%), $[\alpha]_D$ −43.2° (*c* 0.41); R_F 0.35 in 5:1 CH_2Cl_2–Me_2CO; δ_H: 7.59–7.81 (m, 4 H, phthalimido), 7.30 (s, 5 H, benzyl), 5.36 (d, $J_{1,2}$ 8 Hz, H-1), 4.60 (s, CH_2Ph), 3.52 (d, *J* 1 Hz, OH), and 3.37 (d, *J* 4 Hz, OH); δ_C (CD_3COCD_3): 99.8 (C-1, $^1J_{CH}$ 166.2 Hz), 57.7 (C-2), 72.1 (C-3), 71.8 (C-4), 76.9 (C-5), 70.3 (C-6), 80 8 (CH_2CCl_3), 97.1 (CCl_3), and 73.5 (6-*O*-CH_2Ph).

Anal. Calc. for $C_{23}H_{22}Cl_3NO_7$: C, 52.04; H, 4.18; Cl, 20.04; N, 2.64. Found: C, 52.35; H, 4.27; Cl, 19.24; N, 2.64.

2,2,2-Trichloroethyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**9**) *and 2,2,2-trichloroethyl 4,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside* (**16**). — Compound **11** (880 mg, 2 mmol) was stannylated with $(Bu_3Sn)_2O$ (3 mmol) in benzene (100 mL). Evaporation of the benzene, and treatment of the residue with benzyl bromide (10 mL), with stirring, for 1 day at 75° and for 8.5 days at 100–105° under argon, followed by processing as for **15**, and chromatography on SiO_2 (300 g) with 15:1 CH_2Cl_2–Me_2CO, gave 3,6-dibenzyl ether **9** (116 mg, 9.3%), R_F 0.43 in 20:1 CH_2Cl_2–Me_2CO, which was identified with the authentic sample described later. From the less polar fraction was isolated the 4,6-dibenzyl ether **16** (53.7 mg, 4.3%), $[\alpha]_D$ −20.3° (*c* 1.435); R_F 0.48 in 20·1 CH_2Cl_2–Me_2CO; δ_H: 7.56–7.8 (m, 4 H, phthaloyl), 7.32 (s, 5 H, benzyl), 7.23 (s, 5 H, benzyl), and 5.33 (d, $J_{1,2}$ 8 Hz, H-1); δ_C (CD_3COCD_3): 99.7 (C-1, $^1J_{CH}$ 166 2 Hz), 58.0 (C-2), 72.1 (C-3), 79.3 (C-4), 75.9 (C-5), 69.7 (C-6), 80.8 (CH_2CCl_3), 97.1 (CCl_3), 75.1 (4-*O*-CH_2Ph), and 73.5 (6-*O*-CH_2Ph).

Further elution with 5:1 CH_2Cl_2–Me_2CO afforded monobenzyl ether **15** (150 mg, 14.1%).

2,2,2-Trichloroethyl 3,4,6-tri-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**17**) *and 2,2-dichlorovinyl 3,4,6-tri-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside* (**24**). — To a suspension of NaH (60%, 200 mg) in $HCONMe_2$ (5.5 mL) was added a solution of **11** (427 mg, 0.97 mmol) in $HCONMe_2$ (2 mL) and benzyl bromide (0.6 mL, 5 mmol) at −10 to 0°. After being stirred for 4.5 h at 0–10°, the mixture was processed, and the crude product was chromatographed on SiO_2 (150 g) with 20:1 toluene–EtOAc to give tribenzyl ether **17** (160.1 mg, 23.2%), m.p. 103–106°, $[\alpha]_D$ +27.2° (*c* 1.16); R_F 0.36 in 20:1 toluene–EtOAc: δ_H: 7.62 (s, 4 H, phthaloyl), 7.31 and 7.12 (s, 2 benzyl), 6.82–7.05 (m, 5 H, benzyl), and 5.33 (d, $J_{1,2}$ 8 Hz, H-1); δ_C (CD_3COCD_3): 99.7 (C-1, $^1J_{CH}$ 161.8 Hz), 56.3 (C-2), 80.1 (C-3), 79.7 (C-4), 75.8 (C-5), 69.3 (C-6), 80.7 (CH_2CCl_3), 97.0 (CCl_3), 75.2 (3-*O*-CH_2Ph and 4-*O*-CH_2Ph), and 73.6 (6-*O*-CH_2Ph).

Anal. Calc. for $C_{37}H_{34}Cl_3NO_7$: C, 63.50; H, 4.82; N, 1.97. Found: C, 63.70; H, 5.08; N, 1.88.

A minor product (**24**) was also isolated from the less polar fractions (20.8 mg, 3.2%): m.p. 99–102°, $[\alpha]_D$ +35.0°; R_F 0.41 in 20:1 toluene–EtOAc; δ_H: 7.66 (s, 4 H, phthaloyl), 7.32 and 7.23 (s, 2 benzyl), 6.82–7.05 (m, 5 H, benzyl), 6.71 (s, *H*C=CCl_3), and 5.41 (d, $J_{1,2}$ 9 Hz, H-1).

Anal. Calc. for $C_{37}H_{33}Cl_2NO_7$: C, 65.88; H, 4.93; Cl, 10.51; N, 2.08 Found: C, 65.45; H, 5.16; Cl, 9.59; N, 1.91.

2,2,2-Trichloroethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**22**). — To a suspension of **11** (5.7 g, 13 mmol) in benzaldehyde (13.8 g, 130 mmol) was added, portionwise, powdered $ZnCl_2$ (1.8 g, 13 mmol) with vigorous stirring. The mixture was stirred for 1 day at 20–25°, and was then slowly poured into a vigorously stirred bilayer of saturated $NaHCO_3$ (100 mL), *i*-Pr_2O (100 mL), and petroleum ether (200 mL). The precipitated crystals were collected, washed with water and petroleum ether, and air-dried (7.9 g). Recrystallization from *i*-PrOH (80 mL) gave **22** (4.80 g, 70.0%), m.p. 203–205°, $[\alpha]_D$ −43.1° (*c* 0.54); R_F 0.42 in 15:1 $CHCl_3$–Me_2CO; δ_H: 5.56 (s, 1 H, benzylidene) and 5.42 (d, $J_{1,2}$ 8 Hz, H-1); δ_C (CD_3COCD_3): 100.4 (C-1, $^1J_{CH}$ 165.7 Hz), 57.9 (C-2), 67.4 (C-3), 82.4 (C-4), 68.5 (C-5), 68.8 (C-6), 81.0 (CH_2CCl_3), and 97.0 (CCl_3).

Anal. Calc. for $C_{23}H_{20}Cl_3NO_7$: C, 52.24; H, 3.81; Cl, 20.11; N, 2.65. Found: C, 52.39; H, 3.89; Cl, 19.08; N, 2.58.

2,2,2-Trichloroethyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**23**) *and 2,2-dichlorovinyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside* (**25**). — To a suspension of NaH (60%; 1.76 g, 44 mmol) in 1,2-dimethoxyethane (DME, 25 mL) was added dropwise a solution of **22** (15.55 g, 29.4 mmol) in dry DME (25 mL) at −5 to 0°, and the mixture was stirred for 1 h at 20°. To this mixture was added dropwise benzyl bromide (5.2 mL, 44 mmol) at 0–5°, and the mixture was stirred for 3 h at 20–25°. The usual processing afforded an oily residue that crystallized from 1:1 hexane–petroleum ether to give **23** (14.84 g, 81.5%) which contained a trace of less polar byproduct **25**. An analytical sample of **23** was obtained by chromatography on SiO_2 with 20:1 toluene–EtOAc; m.p.

154.0–155.5°, $[\alpha]_D$ +32.6° (*c* 0.31); R_F 0.47 in 20:1 toluene–EtOAc; δ_H: 7.68 (s, 4 H, phthaloyl), 7.35–7.6 (m, 5 H, benzylidene), 6.84–7.1 (m, 5 H, benzyl), 5.63 (s, 1 H, benzylidene), and 5.44 (d, $J_{1,2}$ 8 Hz, H-1).

Anal. Calc. for $C_{30}H_{26}Cl_3NO_7$: C, 58.22; H, 4.24; N, 2.26. Found: C, 58.35; H, 4.24; N, 2.26.

A less polar byproduct (**25**) was isolated in 4% yield by chromatography on SiO_2 with 20:1 toluene–EtOAc; $[\alpha]_D$ +37.0° (*c* 0.135); R_F 0.54 in 20:1 toluene–EtOAc; δ_H: 7.70 (s, 4 H, phthaloyl), 7.3–7.6 (m, 5 H, benzylidene), 6.85–7.05 (m, 5 H, benzyl), 6.68 (s, $-HC=CCl_2$), 5.62 (s, benzylidene), and 5.47 (d, $J_{1,2}$ 8 Hz, H-1).

2,2,2-Trichloroethyl 3-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**18**) *and 2,2,2-trichloroethyl 6-O-acetyl-3-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside* (**19**). — A suspension of **23** (14.63 g, 23.6 mmol) in 3:2 AcOH–H_2O (200 mL) was stirred for 1.5 h at 95–100°. Evaporation *in vacuo*, and chromatography of the residue on SiO_2 (500 g) with 3:1 toluene–EtOAc, gave **18** (10.95 g, 87.5%); crystals (10.17 g, 81.4%) from Et_2O–petroleum ether, m.p. 85.0–86.5°, $[\alpha]_D$ +10.5° (*c* 0.965), +33.3° (*c* 0.585, acetone); R_F 0.11 in 3:1 toluene–EtOAc; δ_H (CD_3COCD_3): 7.80 (s, 4 H, phthaloyl), 6.9–7.1 (m, 5 H, benzyl), and 5.47 (d, $J_{1,2}$ 8 Hz, H-1); δ_C (CD_3COCD_3): 99.6 (C-1, $^1J_{CH}$ 163.3 Hz), 56.1 (C-2), 79.6 (C-3), 72.9 (C-4), 77.8 (C-5), 62.3 (C-6), 80.7 (CH_2CCl_3), 97.2 (CCl_3), and 74.7 (3-O-CH_2Ph)

Anal. Calc. for $C_{23}H_{22}Cl_3NO_7$: C, 52.04; H, 4.18; Cl, 20.04; N, 2.64. Found: C, 52.78; H, 4.25; Cl, 19.05; N, 2.67.

From the less polar fractions of the chromatogram, 6-acetate **19** (478.5 mg, 3.5%) was isolated; crystals from EtOAc—*i*-Pr_2O, m.p. 167.5–168.5°, $[\alpha]_D$ −7.0° (*c* 0.345); R_F 0.32 in 3:1 toluene–EtOAc; δ_H: 7.68 (s, 4 H, phthaloyl), 6.9–7.1 (m, 5 H, benzyl), 5.37 (d, $J_{1,2}$ 8 Hz, H-1), and 2.14 (s, OAc); δ_C (CD_3COCD_3): 101.2 (C-1, $^1J_{CH}$ 164.7 Hz), 57.4 (C-2), 80.8 (C-3), 73.9 (C-4), 76.4 (C-5), 64.9 (C-6), 82.3 (CH_2CCl_3), 96.4 (CCl_3), 76.3 (3-O-CH_2Ph), and 22.0 (OAc).

Anal. Calc. for $C_{25}H_{24}Cl_3NO_8$: C, 52.42; H, 4.22; Cl, 18.57; N, 2.45. Found: C, 52.43; H, 4.26; Cl, 17.44; N, 2.45.

2,2,2-Trichloroethyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**9**). — A suspension of **18** (9.82 g, 18.5 mmol) and $(Bu_3Sn)_2O$ (11.1 g, 18.6 mmol) in toluene (500 mL) was boiled under reflux, with continuous removal of water, for 4.5 h, cooled, and evaporated *in vacuo*. A solution of the residue in benzyl bromide (95 mL) was stirred for 6 days at 80–85° under argon, cooled, and evaporated *in vacuo*. A solution of the residue in CH_2Cl_2 was successively washed with 0.2M aqueous Na_2S (95 mL) and H_2O, dried ($MgSO_4$), and concentrated. Chromatography of the concentrate on SiO_2 (1 kg) with $CHCl_3$–Me_2CO (30:1–10:1) gave dibenzyl ether **9** (10.27 g, 89.4%), $[\alpha]_D$ +10.1° (*c* 0.685), R_F 0.24 in 30:1 $CHCl_3$–Me_2CO; δ_H: 7.68 (bs, 4 H, phthaloyl), 7.32 (s, 5 H, benzyl), 6.9–7.15 (m, 5 H, benzyl), 5.38 (d, $J_{1,2}$ 8 Hz, H-1), and 2.93 (bs, OH); δ_C (CD_3COCD_3): 99.7 (C-1, $^1J_{CH}$ 166.2 Hz), 56.1 (C-2), 79.6 (C-3), 72.9 (C-4), 76.7 (C-5), 70.1 (C-6), 80.8 (CH_2CCl_3), 96.9 (CCl_3), 74.8 (3-O-CH_2Ph), and 73.6 (6-O-CH_2Ph).

Anal. Calc. for $C_{30}H_{28}Cl_3NO_7$: C, 58.03; H, 4.55; Cl, 17.13; N, 2.26. Found: C, 58.04; H, 4.49; Cl, 16.63; N, 2.25.

2,2,2-Trichloroethyl 4-O-acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**20**). — Compound **9** (280 mg, 0.45 mmol) was treated with Ac_2O (1.5 mL) and pyridine (1.5 mL) for 16 h at 20°. The usual processing, and chromatography on SiO_2 (20 g) with 10:1 toluene–EtOAc, gave crystalline **20** (296 mg, 99.3%), m.p. 115–117°, $[\alpha]_D$ +38.4° (*c* 0.55); R_F 0.76 in 15:1 CH_2Cl_2–Me_2CO; δ_H: 7.95 (bs, 4 H, phthaloyl), 7.28 (s, 5 H, benzyl), 6.84–7.08 (m, 5 H, benzyl), 5.36 (d, $J_{1,2}$ 8 Hz, H-1), and 5.14 (t, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4).

Anal. Calc. for $C_{32}H_{30}Cl_3NO_8$: C, 57.97; H, 4.56; Cl, 16.05; N, 2.11. Found: C, 57.82; H, 4.46; Cl, 15.22; N, 2.06.

2,2,2-Trichloroethyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**27**). — To a mixture of **7** (124 mg, 0.2 mmol), $AgOSO_2CF_3$ (141 mg, 0.55 mmol), and 1,1,3,3-tetramethylurea (0.1 mL) was added a solution of **26** (164 mg, 0.4 mmol) in $Cl(CH_2)Cl$ (1.5 mL) at 20°, and the mixture was stirred under argon for 21 h at 20–25°. The usual processing, and chromatography on SiO_2 (20 g) with 3:1 toluene–EtOAc, afforded **27** (138 mg, 72.6%), $[\alpha]_D$ −12.4° (*c* 1.05); R_F 0.37 in 3:1 toluene–EtOAc; δ_H: 7.7–7.55 (4 H, phthaloyl), 7.35 (s, 5 H, benzyl), 7.15–6.8 (m, 5 H, benzyl), 2.03 (OAc), 2.00 (2 OAc), and 1.95 (OAc): δ_C: 100.3 (C-1', $^1J_{CH}$ 164.8 Hz), 99.1 (C-1, $^1J_{CH}$ 165.0 Hz).

Anal. Calc. for $C_{38}H_{46}Cl_3NO_{16}$: C, 55.56; H, 4.87; N, 1.47. Found: C, 55.37; H, 4.75; N, 1.24.

2,2,2-Trichloroethyl 3,6-di-O-benzyl-2-deoxy-4-O-β-D-galactopyranosyl-2-phthalimido-β-D-glucopyranoside (**28**). — A solution of **27** (69 mg, 0.07 mmol) in MeOH (10 mL)–Et_3N (0.5 mL) was stirred for 15 h at 60°, cooled, and evaporated. Chromatography of the residue on SiO_2 (7 g) with 10:1 $CHCl_3$–MeOH gave **28** (32 mg, 58.2%); R_F 0.32 in 10:1 $CHCl_3$–MeOH; δ_C: 99.0 (C-1, $^1J_{CH}$ 164.7 Hz), 55.5 (C-2), 77.8 (C-3), 77.3 (C-4), 74.5 (C-5), 69.3 (C-6), 102.9 (C-1', $^1J_{CH}$ 155.9 Hz), 72.2 (C-2'), 73.7 (C-3'), 67.9 (C-4'), 74.9 (C-5'), 62.4 (C-6'), 80.3 (CH_2CCl_3), 96.0 (CCl_3), 74.9 (3-*O*-CH_2Ph), and 73.4 (6-*O*-CH_2Ph).

2,2,2-Trichloroethyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-4-O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-glucopyranoside (**30**). — To a mixture of **9** (186 mg, 0.3 mmol), $AgOSO_2CF_3$ (240 mg), and 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyridin-2-one (**29**; 132 mg) was added a solution of **8** (299 mg, 0.6 mmol) in $Cl(CH_2)Cl$ (4 mL) under argon. The mixture was stirred for 16 h at 20–25°, and filtered through Celite. The filtrate was successively washed with dilute HCl, H_2O, aqueous $NaHCO_3$, and aqueous NaCl, dried ($MgSO_4$), and evaporated. Chromatography of the residue on SiO_2 (20 g) with 3:1 toluene–EtOAc afforded **30** (189 mg, 60.7%), $[\alpha]_D$ −17.0° (*c* 0.5); R_F 0.63 in 2:1 toluene–EtOAc; δ_H 8.0–7.6 (m, 4 H, phthaloyl), 7.6 (bs, phthaloyl), 7.32 (s, 5 H, benzyl), 7.2–6.8 (m, 5 H, benzyl), 5.79 (dd, *J* 8, 9 Hz, H-3'), 5.55 (d, $J_{1,2}$ 8 Hz, H-1), 4.95 (d, $J_{1',2'}$ 10 Hz, H-1'), and 1.99, 1.96, and 1.84 (3 Ac); δ_C: 98.6 (C-1, $^1J_{CH}$ 160 Hz) and 96.6 (C-1', $^1J_{CH}$ 166.5 Hz).

Anal Calc. for $C_{44}H_{47}Cl_3N_2O_{16}$: C, 57.84; H, 4.56; N, 2 70 Found: C, 57 55; H, 4.48; N, 2.45.

2,2,2-Trichloroethyl 3,6-di-O-benzyl-2-deoxy-4-O-(3,6-di-O-acetyl-2,4-di-O-benzyl-α-D-mannopyranosyl)-2-phthalimido-β-D-glucopyranoside (**32**). — To a solution of 3,6-dibenzyl ether **9** (125 mg, 0.20 mmol), $AgOSO_2CF_3$ (160 mg, 0.62 mmol), and 1.1.3.3-tetramethylurea (0.2 mL) in CH_2Cl_2 (0.25 mL) was added a solution of D-mannopyranosyl chloride **31** (180 mg, 0.39 mmol) in CH_2Cl_2 (0.25 mL) at −10°, and the mixture was stirred for 1.5 days at 20–25°. The mixture was diluted with CH_2Cl_2, and filtered through Celite, and the filtrate was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Chromatography of the residue on SiO_2 (100 g) with 6:1 toluene–EtOAc afforded **32** as a colorless glass (122 mg, 58.2%); $[\alpha]_D$ +32.1° (*c* 0.265); R_F 0.66 in 3:1 toluene–EtOAc: δ_H 7.62 (s, 4 H, phthaloyl), 7.25 (s, 5 H, benzyl), 6.8–7.0 (m, 5 H, benzyl), 5.31 (d, $J_{1,2}$ 8 Hz, H-1), and 1.93 and 1.99 (s, 2 OAc): δ_C: 99.7 (C-1, $^1J_{CH}$ 166 Hz), 55.3 (C-2), 79.3 (C-3), 78.7 (C-4), 74.6 (C-5), 68 7 (C-6), 80.1 (CH_2CCl_3), 95.7 (CCl_3), 98.6 (C-1′, $^1J_{CH}$ 170.6 Hz), 76.1 (C-2′), 73.1 (C-3′,4′), 70.6 (C-5′), 63.2 (C-6′), 72.3, 73.1, and 74 4 (4 CH_2Ph, in the ratio of 1:1:2), and 20.7 and 20.9 (2 Ac).

Anal. Calc. for $C_{54}H_{54}Cl_3NO_{14}$: C, 61 92; H, 5 20; Cl, 10 16; N, 1 34 Found: C, 62.09; H, 5.20; Cl, 9.63; N, 1.27.

Further elution afforded recovered **9** (45.3 mg, 36%).

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