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Preparation of disaccharides having a β-D-mannopyranosyl group from *N*-phthaloyllactosamine derivatives by double or triple S_N2 substitution

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ABSTRACT

Condensation of 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose with methyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside, followed by alkaline methanolysis, gave a derivative of lactosamine that has an unsubstituted β-D-galactopyranosyl group. Tributyltin oxide-mediated allylation gave a good yield of the 3′-*O*-allyl (**9**) and a poor yield of the 3′,6′-di-*O*-allyl ether (**8**). Protection of **9** at O-6′ was achieved by reductive opening of the 4′,6′-*O*-anisylidene derivative, to give the 6′-*O*-(4-methoxybenzyl) ether **15**. Conversion of **8** and **15** to their 2′,4′-bis(trifluoromethanesulfonates), followed by S_N2 reaction with benzoate, gave the corresponding β-D-mannopyranosyl disaccharides. However, the model methyl 3-*O*-allyl-β-D-galactopyranoside and **9** were converted into β-D-mannopyranosyl derivatives in better yield (52–55%) by a one-pot, triple S_N2 substitution of the tris(trifluoromethanesulfonates).

INTRODUCTION

The difficulties of 1,2-*cis* coupling in oligosaccharide synthesis are well-known. We have recently reported a mode of building the very important β-D-mannopyranosyl residue in oligosaccharides which bypass this difficult step. Condensation with participation of a specifically tailored D-glucopyranosyl derivative gave a β-D-glucopyranoside, which was transformed in excellent yield[1] into a β-D-mannoside by inversion at C-2. However, conversion of a β-D-galactopyranoside into a β-D-mannopyranoside also deserves attention. One of us has reported, in a preliminary paper, the transformation of methyl β-D-galactopyranoside into methyl β-D-mannopyranoside by double inversion at C-4 and C-2, after protection of other positions[2]. β-D-Galactopyranosyl groups are very easily introduced by either chemical or immobilized-enzyme[3] procedures. We are aware that the extension of this approach to free oligosaccharides is fraught with problems, such as the differentiation of the terminal, nonreducing β-D-galactopyranosyl group from other sugar residues, and the preparation of trifluoromethanesulfonates (triflates) in the presence of amido groups. As a contribution to the inversion reaction proper, we describe herein, in the same vessel, the syntheses of protected β-D-(1→4)-linked 2-deoxy-2-phthalimido-β-D-glucopyranosides from *N*-phthaloyllactosamine involving double and triple nucleophilic substitution.

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RESULTS AND DISCUSSION

The starting material, methyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-β-D-galactopyranosyl-2-phthalimido-β-D-glucopyranoside (**7**) was prepared in the following way. A Koenigs–Knorr-type coupling of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride[4] with methanol gave the peracetylated methyl β-D-glycoside **1** which was *O*-deacetylated by alkaline methanolysis, and converted into the benzylidene acetal **2**. Benzylation of OH-3, followed by reductive opening of the benzylidene acetal group according to Garegg *et al.*[5] gave, in 70% yield, the amorphous dibenzyl ether **4**, characterized as its crystalline 3-acetate **5**. Coupling of **4** with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose, in the presence of trimethylsilyl triflate as promoter[6], gave the protected lactosamine derivative **6** in 72% yield. This was *O*-deacetylated by alkaline methanolysis to give disaccharide **7**, which has an unsubstituted β-D-galactopyranosyl group.

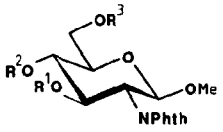
Our first intention was to prepare the 3',6'-di-allyl ether **8** under the conditions described for the preparation of methyl 3,6-di-*O*-allyl-β-D-galactopyranoside, which was obtained in 61% yield from the tributyltin derivative by refluxing for 48 h in acetonitrile solution with allyl bromide, in the presence of *N*-methylimidazole[2]. Unexpectedly, the primary alcoholic function in **7** proved to be very poorly reactive. Refluxing for 95 h gave mainly the 3'-allyl ether **9** in 64% yield with only 16% of the expected 3',6'-allyl ether **8**, both characterized as the benzoates **10** and **11** respectively. This decreased nucleophilicity could be pre-existent in disaccharide **7**, or peculiar to the organotin reaction.

Double inversion of **8** proceeded as with the model β-D-galactopyranoside[2]. The bis(triflate) **12** was obtained in near quantitative yield within 6 h at 0°. It is well-known that nucleophilic substitution in a pyranoside is much more difficult at C-2 than at any other position. No reaction at all is observed with the classical leaving groups. Thus, we expected that the reaction of **12** would occur in two discrete steps. Indeed, t.l.c. examination (2:1 hexane–ethyl acetate) indicated that the treatment of the bis(triflate) **12** with excess tetrabutylammonium benzoate in toluene solution converted it, within 45 min at room temperature, into a less polar product, most probably the D-*gluco* monobenzoate, and then heating for 1 h at 100° gave the D-*manno* benzoate **18** in 47% yield. This difference of reactivity was the key to the success of the double inversion, as we had observed that nucleophilic substitution at C-2 was normal for glucopyranoside[1], but led to ring contraction of galactopyranosides[7]. Thus, it was essential that the D-*galacto* derivative be completely transformed into the intermediate D-*gluco* benzoate, before the onset of the more difficult C-2 substitution, which begins appreciably only at 100°.

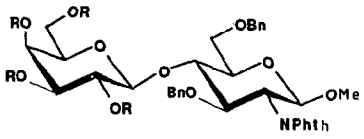
The very low yield of diallyl ether made this route unsatisfactory. As the organotin procedure gave selectively the 3'-allyl ether in high yield, at first we sought to protect the primary hydroxyl group in another way. Acetal exchange from 4-methoxybenzaldehyde dimethyl acetal in the presence of 4-toluenesulfonic acid gave the crystalline 4-methoxybenzylidene acetal **14** in 83% yield. Reductive opening of this acetal in oxolane solution with excess sodium cyanoborohydride and trifluoroacetic acid[8] gave

the 4-methoxybenzyl ether **15** in 86% yield, characterized as the benzoate **16**. Again, diol **15** was converted into the bis(triflate) **17** in near quantitative yield, and double inversion with benzoate gave the D-*manno* derivative **20** in 40% yield.

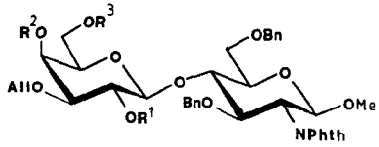
To avoid protecting the primary alcohol group, the amorphous 3-allyl ether **21** of methyl β-D-galactopyranoside was prepared, as model compound in 61% yield and characterized as the tribenzoate **22**. The tris(triflate) **23** was obtained in 90% yield



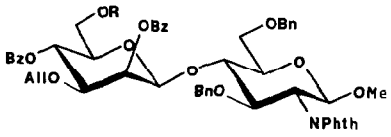
1 $R^1=R^2=R^3=Ac$
2 $R^1=H;R^2,R^3=PhCH$
3 $R^1=Bn;R^2,R^3=PhCH$
4 $R^1=R^3=Bn;R^2=H$
5 $R^1=R^3=Bn;R^2=Ac$



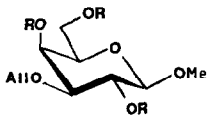
6 R = Ac
7 R = H



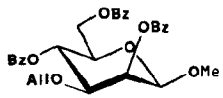
8 $R^1=R^2=H,R^3=All$
9 $R^1=R^2=R^3=H$
10 $R^1=R^2=Bz,R^3=All$
11 $R^1=R^2=R^3=Bz$
12 $R^1=R^2=SO_2CF_3,R^3=All$
13 $R^1=R^2=R^3=SO_2CF_3$
14 $R^1=H;R^2,R^3=CHC_6H_4OMe(4)$
15 $R^1=R^2=H;R^3=CH_2C_6H_4OMe(4)$
16 $R^1=R^2=Bz;R^3=CH_2C_6H_4OMe(4)$
17 $R^1=R^2=SO_2CF_3;R^3=CH_2C_6H_4OMe(4)$



18 R=All
19 R=Bz
20 $R=CH_2C_6H_4OMe(4)$



21 R = H
22 R = Bz
23 $R=SO_2CF_3$



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within 5 h at 0°. It reacted quantitatively with excess benzoate in toluene solution at room temperature in 45 min to give a single product on t.l.c. examination, most probably the D-*gluco* derivative arising from substitution at C-4 and C-6. Heating for 1 h at 100° gave the tribenzoate **24** in 55% yield. In the same way, tris(trifluoromethanesulfonylation) of the 3'-*O*-allyl ether **9**, followed by displacement with benzoate, gave the tribenzoate **19**, a derivative of β-D-Man-(1→4)-β-D-GlcNAc in 52% yield.

The proof for the β-D-*manno* configuration of **18**, **19**, and **24** rests on the determination of the coupling constants for H-1'–4' of the nonreducing group. The data indicated an axial–equatorial–axial–axial orientation, possible only with β-D-*manno* hexapyranoses, since practically all hexopyranoses adopt the $^1C_4$(D) conformation.

EXPERIMENTAL

General methods. — Optical rotations were measured for solutions in trichloromethane. ^{1}H-N.m.r. spectra were recorded at 250 MHz for solutions in (^{2}H)chloroform with Me_4Si as reference; the assignations of coupling constants given in Table I are not duplicated in the text. Silica gel chromatographic columns and t.l.c. plates were used for purification and monitoring.

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**1**). — A mixture of HgO (580 mg, 2.68 mmol), $HgCl_2$ (30 mg, 0.12 mmol), powdered Drierite (2 g), and methanol (3 mL) in dichloromethane (30 mL) was stirred for 1 h at room temperature. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (**4** 1.2 g, 2.65 mmol) was then added, and the stirring continued for 48 h. The usual treatment gave **1** (1.02 g, 86%), m.p. 158–159° (from ethanol), $[\alpha]_D^{20}$ +42° (*c* 1.1); lit.[9], m.p. 160°, $[\alpha]_D^{20}$ +44° (*c* 1).

TABLE I

^{1}H–^{1}H Coupling constants (Hz) for D-*galacto* and D-*manno* derivatives

Protons	D-galacto *compounds*								
	6	**8**	**9**	**10**	**11**	**14**	**15**	**16**	**22**
1',2'	8	8	8	8	8	8	8	8	8
2',3'	10	10	10	10	10	10	10	10	9.5
3',4'	3.5	3.5	3.5	3.5	3	3.5	3.5	3.5	3.5
4',5'	0	[a]	[a]	0	0	[a]	0	0	0

Protons	D-manno *compounds*			
	18	**19**	**20**	**24**
1',2'	0	0	0	0
2',3'	3.5	3	3	3.5
3',4'	9.5	9.5	9.5	9.5
4',5'	9.5	9.5	9.5	9.5

[a] Not determined.

Methyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**2**). — A solution of **1** (6.5 g, 12.5 mmol) and sodium methoxide (0.22 g) in 1:1 methanol–1,4-dioxane (200 mL) was kept for 1 h at room temperature. The base was neutralized with Dowex 50 (H^+) cation-exchange resin, the suspension filtered, and the solution concentrated to dryness. The residue was dissolved in acetonitrile (80 mL). After the addition of α,α-dimethoxytoluene (11 mL, 72.5 mmol) and 4-toluensulfonic acid (50 mg), the solution was stirred for 12 h at room temperature, the acid neutralized with a few drops of triethylamine, and the solution concentrated to dryness. Chromatography 4:1, toluene–ethyl acetate), separated **2** (4.77 g, 80%), m.p. 192–193°(from ethyl acetate–hexane), $[\alpha]_D^{20}$ −33° (*c* 2); ^{1}H-N.m.r.: δ 2.60 (d, 1 H, *J* 2 Hz, OH), 3.42 (s, 3 H, OMe), 3.64 (m, 2 H, H-3,5), 3.84 (dd, 1 H, H-6a), 4.23 (dd, 1 H, *J* 8 and 10.5 Hz, H-2), 4.41 (dd, 1 H, H-6b), 4.63 (m, 1 H, H-4), 5.20 (d, 1 H, *J* 8 Hz, H-1), 5.58 (s, 1 H, C*H*Ph), and 7.3–7.9 (m, 9 H, arom.).

Anal. Calc. for $C_{22}H_{21}NO_7$: C, 64.22; H, 5.15; N, 3.40; O, 27.22. Found: C, 64.46; H, 5.15; N, 3.37; O, 27.43.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**3**). — A solution of **2** (4.43 g, 10.8 mmol) in *N,N*-dimethylformamide (30 mL) was cooled to 0°. Sodium hydride (603 mg, 15.1 mmol) was first added, and then, after 15 min, benzyl bromide (1.6 mL, 13 mmol). The mixture was kept for 1 h at 0° and then for 3 h at room temperature. After the usual treatment (ether extraction), the crude product was purified by chromatography (2:1 hexane–ethyl acetate) to give amorphous **3** (4.32 g, 80%), $[\alpha]_D^{20}$ +54° (*c* 1.8); ^{1}H-n.m.r.: δ 3.40 (s, 3 H, Me), 3.65 (m, H-5), 3.78–3.91 (m, 2 H, H-3,6a), 4.20 (dd, 1 H, *J* 8 and 10 Hz, H-2), 4.38–4.47 (m, 2 H, H-4,6b), 4.49, 4.80 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 5.13 (d, 1 H, *J* 8Hz, H-1), 5.62 (s, 1 H, C*H*Ph), and 6.8–7.7 (m, 14 H, arom.).

Anal. Calc. for $C_{29}H_{27}NO_7$: C, 69.45; H, 5.43; N, 2.79; O, 22.33. Found: C, 69.84; H, 5.24; N, 2.63; O, 22.23.

Methyl 4-O-acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**5**). — Powdered molecular sieves 3Å (9.2 g) and $NaBH_3CN$ (2.48 g) were added to a solution of **3** (2 g, 4 mmol) in anhydrous oxolane (60 mL), which was cooled to −5°. After dropwise addition of a saturated solution of HCl in ether (30 mL), the mixture was kept for 5 h at room temperature, and then filtered, washed with $NaHCO_3$, and concentrated to dryness. Chromatography of the residue gave amorphous **4** (1.4 g, 70%); ^{1}H-N.m.r.: δ 2.95 (d, 1 H, *J* 2 Hz, OH), 3.37 (s, 3 H, OMe), 3.65 (m, 1 H, H-5), 3.78–3.89 (m, 3 H, H-3,4,6a), 4.18–4.27 (m, 2 H, H-2,6b), 4.59, 4.65 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.50, 4.76 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 5.06 (d, 1 H, *J* 8 Hz, H-1), and 6.9–7.7 (m, 14 H, arom.).

Acetylation with acetic anhydride–pyridine of **4** gave crystalline **5**, m.p. 94–95° (from ethanol–water), $[\alpha]_D^{20}$ +79° (*c* 0.55); ^{1}H-N.m.r.: δ 1.95 (s, 3 H, Ac), 3.4 (s, 3 H, OMe), 3.62 (d, 2 H, *J* 5 Hz, H-6a,6b), 3.75 (m, 1 H, H-5), 4.23 (dd, 1 H, *J* 8 and 10.5 Hz, H-2), 4.43 (dd, 1 H, *J* 9 and 10.5 Hz, H-3), 5.07 (d, 1 H, *J* 8 Hz, H-1), 5.13 (dd, 1 H, *J* 9 and 10.5 Hz, H-4), and 6.9–7.7 (m, 14 H, arom.).

Anal. Calc. for $C_{31}H_{31}NO_8$: C, 68.24; H, 5.73; N, 2.57; O, 23.46. Found: C, 68.09;

H, 5.99; N, 2.54; O, 23.66.

*Methyl-3,6-di-*O*-benzyl 4-*O*-2-deoxy-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-2-phthalimido-β-*D*-glucopyranoside* (**6**). — A solution of 4 (1.423 g, 2.83 mmol) and 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (1.176 g, 3.12 mmol) in dichloromethane (50 mL) was stirred under N_2 in the presence of powdered 4 Å molecular sieves for 30 min at −20°. Then trimethylsilyl triflate (1.2 mL, 6.24 mmol) was added slowly, and the mixture was kept for 1 h at −20° and 3 h at room temperature. After neutralization with triethylamine, and a two-phase treatment, chromatography of the extract (3:2, hexane–ethyl acetate) gave **6** (1.67 g, 72%) as an amorphous product, $[\alpha]_D^{20}$ +23° (*c* 1); ^{1}H-N.m.r.: δ 1.96–2.10 (4 s, 4 × 3 H, 4 Ac), 3.37 (s, 3 H, OMe), 3.8 (d, 1 H, *J* 3 Hz, H-4), 4.25 (dd, 1 H, *J* 8 and 10.5 Hz, H-2), 4.57, 4.76 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.42, 4.85 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.57 (d, 1 H, *J* 8 Hz, H-1'), 4.84 (dd, 1 H, *J* 3.5 and 10 Hz, H-3'), 5.01 (d, 1 H, *J* 8 Hz, H-1), 5.14 (dd, 1 H, *J* 8 and 10.5 Hz, H-2'), 5.26 (d, 1 H, *J* 3.5 Hz, H-4'), and 6.85–7.70 (m, 14 H, arom.).

Anal. Calc. for $C_{43}H_{47}NO_{16}$: C, 61.94; H, 5.68; N, 1.68; O, 30.70. Found: C, 61.78; H, 5.85; N, 1.60; O, 30.71.

*Methyl 4-*O*-(3-*O*-allyl-2,4,6-tri-*O*-benzoyl-β-*D*-galactopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**11**) *and methyl 3,6-di-*O*-benzyl-2-deoxy-(4-*O*-(3,6-di-*O*-allyl-2,4-di-*O*-benzoyl-β-*D*-galactopyranosyl)-2-phthalimido-β-*D*-glucopyranoside* (**10**). — A solution of **6** (930 mg, 1.13 mmol) and sodium methoxide (80 mg) in methanol (50 mL) was kept for 2 h at room temperature. After neutralization with Dowex 50 (H^+), cation-exchange resin, filtration and evaporation gave **7** which was used in the next step without purification. To a solution of crude **7** (721 mg, 1.1 mmol) and tributyltin oxide (988 mg, 1.65 mmol) in acetonitrile (40 mL) was added powdered 4Å molecular sieves (3 g), and the suspension refluxed for 20 h. Then allyl bromide (4 mL) and *N*-methylimidazole (0.1 mL, 1.1 mmol) were added, and the mixture was again refluxed for 96 h. The suspension was filtered and the filtrate concentrated to dryness. Chromatography (17:3 dichloromethane–acetone) first gave the 3,6-diallyl ether **8**, amorphous (120 mg, 16%); ^{1}H-n.m.r.: δ 2.5 (s, 1 H, OH), 3.23 (s, 1 H, OH), 3.25 (dd, 1 H, *J* 3.5 and 10 Hz, H-3'), 3.38 (s, 3 H, OMe), 4.37 (dd, 1 H, *J* 8 and 10 Hz, H-2), 4.56 (d, 1 H, *J* 8 Hz, H'-1), 4.61, 4.77 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.43, 4.86 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 5.00 (d, 1 H, *J* 8 Hz, H-1), 5.09–5.37 (m, 4 H, CH–CH_2), 5.72–6.03 (m, 2 H, 2 C*H*–CH$_2$), and 6.8–7.7 (m, 14 H, arom.).

The 3-allyl ether **9** was eluted next, amorphous (510 mg, 64%); ^{1}H-n.m.r.: δ 3.21 (dd, 1 H, *J* 3.5 and 10 Hz, H-3'), 3.30 (t, 1 H, OH), 3.39 (s, 3 H, OMe), 4.36 (dd, 1 H, *J* 8 and 10 Hz, H-2), 4.51 (d, 1 H, *J* 8 Hz, H-1'), 4.66, 4.76 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.43, 4.86 (2 d, 2 H, *J* 12 Hz, CH$_2$Ph), 5.04 (d, 1 H, *J* 8 Hz, H-1), 5.21–5.37 (m, 2 H, CH–CH_2), 6.03–5.88 (m, 1 H, C*H*–CH$_2$), and 6.8–7.7 (m, 14 H, arom.).

Compound **8** was converted into **10**, $[\alpha]_D^{20}$ +75° (*c* 0.5); ^{1}H-n.m.r.: δ 3.34 (s, 3 H, OMe, 4.30 (dd, 1 H, *J* 8 and 10 Hz, H-2), 4.60, 4.76 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.46, 4.96 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.81 (d, 1 H, *J* 8 Hz, H-1'), 4.95 (d, 1 H, *J* 8 Hz, H-1), 5.03–5.22 (m, 4 H, 2 CH–CH_2), 5.52 (dd, 1 H, *J* 8 and 10 Hz, H-2'), 5.74 (d, 1 H, *J* 3.5 Hz, H-4'), 5.57–5.83 (m, 2 H, 2 C*H*–CH$_2$), and 6.80–8.20 (m, 24 H, arom.).

Anal. Calc. for $C_{55}H_{55}NO_{14}$: C, 69.24; H, 5.81; N, 1.47; O, 23.48. Found: C, 68.96; H, 5.81; N, 1.32; O, 23.28.

Compound **9** was converted into **11**, m.p. 85–87° from (ethanol–water), $[\alpha]_D^{20}$ +81° (*c* 0.4); ^{1}H-n.m.r.: δ 3.32 (s, 3 H, OMe), 4.32 (dd, 1 H, *J* 8 and 10 Hz, H-2), 4.63, 4.75 (2 d, 2 H, *J* 12 Hz, C*H*$_2$Ph), 4.45, 5.00 (2 d, 2 H, *J* 12 Hz, C*H*$_2$Ph), 4.80 (d, 1 H, *J* 8 Hz, H-1′), 4.94 (d, 1 H, *J* 8 Hz, H-1), 5.02–5.20 (m, 2 H, CH–C*H*$_2$), 5.52 (dd, 1 H, 8 and 10 Hz, H-2′), 5.58–5.70 (m, 1 H, C*H*–CH$_2$), 5.72 (d, 1 H, *J* Hz, H-4′), and 6.7–8.2 (m, 29 H, arom.).

Anal. Calc. for $C_{59}H_{55}NO_{15}$: C, 69.61; H, 5.44; N, 1.38; O, 23.57. Found: C, 69.59; H, 5.41; N, 1.33; O, 23.56.

*Methyl 3,6-di-*O*-benzoyl-2-deoxy-4-*O*-(3,6-di-*O*-allyl-2,4-di-*O*-benzoyl-β-*D*-mannopyranosyl)-2-phthalimido-β-*D*-glucopyranoside* (**18**). — Trifluoromethanesulfonic anhydride (1.98 mmol) was slowly added to a solution of **8** (240 mg, 0.33 mmol) and pyridine (3.96 mmol) in dichloromethane (5 mL) cooled to −20°. After 6 h at 0°, t.l.c. (2:1, hexane–ethyl acetate) indicated that the reaction was practically complete. The solution was poured into ice–$NaHCO_3$, and the bis(triflate) **12** was extracted in the usual way (300 mg, 94%). A solution of **12** and tetrabutylammonium benzoate (934 mg, 8 eq.) in toluene (5 mL) was kept for 45 min at room temperature, and then heated at 100° for 1 h. Evaporation followed by chromatography of the residue (19:1 toluene–acetone) gave **18**, amorphous (140 mg, 47%), $[\alpha]_D^{20}$ +24° (*c* 0.2); ^{1}H-n.m.r.: δ 3.36 (s, 3 H, OMe), 3.52 (dd, 1 H, *J* 3.5 and 9.5, H-3′), 4.29–4.84 (2 d, 2 H, *J* 13 Hz, PhC*H*$_2$), 4.56–4.86 (2 d, 2 H, *J* 12 Hz, PhC*H*$_2$), 4.84 (s, 1 H, H-1′), 4.95 (d, 1 H, *J* 8 Hz, H-1), 4.93–5.21 (m, 4 H, 2 CH–C*H*$_2$), 5.45 (dd, 1 H, *J* 9.5 and 9.5 Hz, H-4′), 5.64 (d, 1 H, *J* 3.5 Hz, H-2′), 5.58–5.81 (m, 2 H, 2 C*H*–CH$_2$), and 6.7–8.2 (m, 24 H, arom.).

Anal. Calc. for $C_{55}H_{55}NO_{14}$: C, 69.24; H, 5.81; N, 1.47; O, 23.41. Found: C, 69.47; H, 6.02; N, 1.49; O, 23.51.

*Methyl 4-*O*-[3-*O*-allyl-4,6-*O*-(4-methoxybenzylidene)-β-*D*-galactopyranosyl]-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**14**). — A mixture of **9** (270 mg, 0.39 mmol), 4-methoxybenzaldehyde dimethylacetal (1.2 mL, 1.17 mmol), and 4-toluenesulfonic acid (20 mg) in acetonitrile (10 mL) was stirred for 5 min at room temperature. The acid was neutralized with triethylamine (a few drops) and the mixture concentrated to dryness. Chromatography of the residue (19:1 dichloromethane–acetone) gave crystalline **14** (267 mg, 83%), m.p. 102–103° (from ether–hexane), $[\alpha]_D^{20}$ +55° (*c* 0.5); ^{1}H-n.m.r.: δ 3.07 (s, 1 H, OH), 3.27 (dd, 1 H, *J* 3.5 and 10 Hz, H-3′), 3.38 (s, 3 H, OMe), 3.73 (s, 3 H, ArOCH_3), 4.4 (dd, 1 H, *J* 8 and 10 Hz, H-2), 4.59 (d, 1 H, *J* 8 Hz, H-1′), 4.57, 4.60, 4.76, 4.97 (4 d, 4 H, *J* 12 Hz, 2 C*H*$_2$Ph), 5.03 (d, 1 H, *J* 8 Hz, H-1), 5.17–5.36 (m, 2 H, CH–C*H*$_2$), 5.40 (s, 1 H, PhC*H*), 5.85–6.05 (m, 1 H, C*H*–CH$_2$), and 6.7–7.7 (m, 18 H, arom.).

Anal. Calc. for $C_{45}H_{49}NO_{13}$: C, 67.06; H, 5.99; N, 1.70; O, 25.25. Found: C, 67.08; H, 6.03; N, 1.71; O, 25.09.

*Methyl 4-*O*-[3-*O*-allyl-2,4-di-*O*-benzoyl-6-*O*-(4-methoxybenzyl)-β-*D*-galactopyranosyl]-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**16**). — A mixture of **14** (209 mg, 0.26 mmol), $NaBH_3CN$ (164 mg, 2.6 mmol), and powdered 3Å

molecular sieves in anhydrous oxolane (10 mL) was stirred for 30 min at room temperature. Trifluoroacetic acid was added (0.8 mL), the mixture was stirred for 48 h at room temperature, and then the acid was neutralized with triethylamine (a few drops). Filtration and evaporation of the filtrate gave a residue from which **15** was separated by column chromatography as an amorphous compound (180 mg, 86%).

Compound **15** was converted into **16**, m.p. 84–86° (from ethanol–water), $[\alpha]_D^{20}$ +47° (*c* 0.4); ^{1}H-n.m.r.: δ 3.34 (s, 3 H, OMe), 3.74 (s, 3 H, ArOCH_3), 4.80 (d, 1 H, *J* 8 Hz, H-1'), 4.95 (d, 1 H, *J* 9 Hz, H-1), 5.00–5.21 (m, 2 H, CH–CH_2), 5.45 (d, 1 H, *J* 8 and 10 Hz, H-2'), 5.51 5.71 (m, 1 H, C*H*–CH$_2$), 5.73 (d, 1 H, *J* 3.5 Hz, H-4'), and 6.6–8.2 (m, 28 H, arom.).

Anal. Calc. for $C_{60}H_{59}NO_{15}\cdot H_2O$: C, 68.49; H, 5.84; N, 1.33; O, 24.34. Found: C, 68.40; H, 5.76; N, 1.30; O, 24.52.

Methyl 4-O-[3-O-allyl-2,4-di-O-benzoyl-6-O-(4-methoxybenzyl)-β-D-mannopyranosyl]-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**20**). — Trifluoromethanesulfonic anhydride (1.02 mmol) was slowly added to a solution, cooled to −20°, of **15** (140 mg, 0.17 mmol) and pyridine (2.04 mL) in dichloromethane (5 mL). After 18 h at 0°, the solution was poured onto ice–$NaHCO_3$. Extraction gave the bis(triflate) **19** which was dissolved in toluene (5 mL). Tetrabutylammonium benzoate (493 mg, 8 equiv.) was added, and the solution was kept for 1 h at room temperature, and the for 1 h at 100°. Chromatography (2:1 hexane–ethyl acetate) gave **20** (70 mg, 40%), m.p. 74–76°, (from ethanol–water), $[\alpha]_D^{20}$ 25° (*c* 0.2); ^{1}H-n.m.r.: δ 3.37 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.75 (s, 3 H, ArOCH_3), 4.84 (s, 1 H, H-1'), 4.95 (d, 1 H, *J* 8 Hz, H-1), 4.97–5.17 (m, 2 H, CH–CH_2), 5.50 (dd, 1 H, *J* 9.5 and 9.5 Hz, H-4'), 5.55–5.76 (m, 1 H, C*H*–CH$_2$), 5.66 (d, 1 H, *J* 3.5 Hz, H-2'), and 6.6–8.2 (m, 28 H, arom.).

Anal. Calc. for $C_{60}H_{59}NO_{15}\cdot H_2O$: C, 68.49; H, 5.84; N, 1.33; O, 24.34. Found: C, 68.50; H, 5.70; N, 1.26; O, 24.35.

Methyl 4-O-[3-O-allyl-2,4,6-tri-O-benzoyl-β-D-mannopyranosyl]-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**19**). — Trifluoromethanesulfonic anhydride (2.7 mmol) was slowly added to a solution, cooled to −20°, of **9** (208 mg, 0.3 mmol) and pyridine (5.4 mmol) in dichloromethane (5 mL). After 18 h at 0°, the solution was poured onto ice–$NaHCO_3$, and triflate **13** was extracted in the usual way. A solution of **13** and tetrabutylammonium benzoate (1.3 g, 12 equiv.) in toluene (5 mL) was kept for 3 h at room temperature, and at 100° for 1 h to give **19** which was separated by chromatography (2:1 hexane–ethyl acetate) (155 mg, 52%), m.p. 84–86° (from ethanol–water), $[\alpha]_D^{20}$ +30° (*c* 0.5); ^{1}H-n.m.r.: δ 83.33 (s, 3 H, OMe), 3.54 (dd, 1 H, *J* 3.5 and 9 Hz, H-3'), 4.30 (dd, 1 H, *J* 5 Hz and 12 Hz, H-6'a), 4.66 (dd, 1 H, *J* 3.5 and 12 Hz, H-6'b), 4.34, 4.79 (2 d, 2 H, *J* 13 Hz, CH_2Ph), 4.54, 487 (2 d, 2 H, *J* 12 Hz, CH_2Ph), 4.89 (s, 1 H, H-1'), 4.96 (d, 1 H, *J* 8 Hz, H-1), 4.93–5.18 (m, 2 H, CH–CH_2), 5.64 (dd, 1 H, *J* 9,5 and 9.5 Hz, H-4'), 5.69 (d, 1 H, *J* 3 Hz, H-2'), 5.58–5.77 (m, 1 H, C*H*–CH$_2$), and 6.50–8.20 (m, 29 H, arom.).

Anal. Calc. for $C_{59}H_{55}NO_{15}$: C, 69.61; H, 5.44; N, 1.38; O, 23.57. Found: C, 69.39; H, 5.57; N, 1.38; O, 23.31.

Methyl 3-O-allyl-2,4,6-tri-O-benzoyl-β-D-galactopyranoside (**22**). — A mixture of

methyl β-D-galactopyranoside (970 mg, 5 mmol), tributyltin oxyde (7.5 mmol), and powdered 4A molecular sieves in acetonitrile (40 mL) was refluxed for 20 h. Allyl bromide (4 mL) and tetrabutylammonium bromide (2.5 mmol) were added, and the mixture was refluxed again for 24 h. The suspension was filtered and the filtrate concentrated to dryness. Chromatography (2:1 hexane–ethyl acetate) gave the 3-allyl ether **21** (705 mg, 61%), which was characterized by its 2,4,6-tribenzoate **22**, m.p. 136–138° (from ethanol–water), $[\alpha]_D^{20}$ +61° (*c* 0.6); ^{1}H-n.m.r.: δ 3.54 (s, 3 H, OMe), 3.83 (dd, 1 H, *J* 3.5 and 9.5 Hz, H-3), 4.60 (d, 1 H, *J* 8 Hz, H-1), 5.01–5.21 (m, 2 H, CH–CH_2), 5.51 (dd, 1 H, *J* 8 and 9.5 Hz, H-2), 5.56–5.77 (m, 1 H, C*H*–CH_2), 5.86 (d, 1 H, *J* 3.5, H-4), and 7.3–8.2 (m, 15 H, arom.).

Anal. Calc. for $C_{31}H_{30}O_9$: C, 68.12; H, 5.63; O, 26.35. Found: C, 68.00; H, 5.54; O, 26.63.

*Methyl 3-*O*-allyl-2,4,6-tri-*O*-benzoyl-β-*D*-mannopyranoside* (**24**). — Trifluoromethanesulfonic anhydride (4.5 mmol) was slowly added to a solution of **21** (234 mg, 1 mmol) and pyridine (12 mmol) in dichloromethane (5 mL), cooled to −20°. The solution was kept for 5 h at 0° and then poured onto ice–$NaHCO_3$, and the tris(triflate) **23** was extracted in the usual manner (570 mg, 90%). A solution of **23** and tetrabutylammonium benzoate (3.92 g, 10.8 mmol) in toluene (5 mL) was kept for 45 min at room temperature, and then for 1 h at 100°. Extraction in the usual way, followed by chromatography (2:1, hexane–ethyl acetate) gave **24** (300 mg, 55%), amorphous, $[\alpha]_D^{20}$ −98° (*c* 0.5); ^{1}H-n.m.r. data: δ 3.51 (s, 3 H, OMe), 3.90 (dd, 1 H, *J* 3.5 and 9.5 Hz, H-3), 4.69 (s, 1 H, H-1), 5.77 (dd, 1 H, *J* 9.5 and 9.5 Hz, H-4), 5.38 (d, 1 H, *J* 3.5 Hz, H-2), and 7.10–8.20 (m, 15 H, arom.).

Anal. Calc. for $C_{31}H_{30}O_9$: C, 68.12; H, 5.63; O, 26.35. Found: C, 68.08; H, 5.77; O, 26.53.

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