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SYNTHESIS OF THE TRISACCHARIDE MOIETY OF GANGLIOTRIOSYL CERAMIDE (ASIALO GM_2)*

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ABSTRACT

The synthesis of the trisaccharide methyl glycoside β-D-GalNAc-(1→4)-β-D-Gal-(1→4)-β-D-Glc-OMe, which corresponds to the carbohydrate portion of gangliotriosylceramide (asialo GM_2), was accomplished by the reaction of 4-*O*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-D-galactopyranosyl bromide (**18**) with a benzylated derivative of methyl 4-*O*-β-D-galactopyranosyl-β-D-glucopyranoside. Comparative studies with a 6′-benzyl ether and a 6′-benzoate revealed that the substituent at O-6′ is crucial to the outcome of glycosylations at O-4′, the ether derivative being much the more reactive. *tert*-Butyl 4-*O*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-D-galactopyranoside, which was readily converted into the corresponding bromide **18**, was obtained from the *gluco* derivative *via* a single-step, crown ether-assisted epimerization.

INTRODUCTION

Several biologically important oligosaccharides, including the Streptococcal group C antigen[1], the Forssman glycosphingolipid[2,3], and certain internal sequences of gangliosides[4] contain 2-acetamido-2-deoxy-β-D-galactopyranosyl units. Both the carbohydrate moiety of asialo GM_2, also referred to as gangliotriosylceramide, and the internal sequence of GM_1 contain this 2-acetamido-2-deoxy-D-galactopyranosyl residue β-linked to O-4′ of lactose[4].

Gangliotriosylceramide has been established as a tumor-specific, cell-surface marker for mouse sarcoma[5], and its presence in several cell-lines is correlated with malignancy[6–10]. A monoclonal antibody with specificity for the carbohydrate determinant of asialo GM_2 was recently reported, and was shown to suppress lymphoma growth[4]. The synthesis of this biologically important trisaccharide in the form of its methyl glycoside, for use as an inhibitor, was therefore of interest.

Two difficulties militate against the efficient synthesis of such structures as

*Dedicated to Professor Raymond U. Lemieux.
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asialo GM_2: the OH-4′ group of lactose is weakly reactive, and use of the phthalimido coupling-process at this center has yet to be reported (*c.f.*, ref. 11). Secondly, suitable reactive derivatives of 2-amino-2-deoxy-D-galactose are usually difficult to obtain and expensive. We report here a new method for the synthesis of a suitably benzylated derivative of lactose, and an efficient synthesis of a derivative of 2-deoxy-2-phthalimido-D-galactopyranosyl bromide, which, together, provide an effective solution to this problem.

RESULTS AND DISCUSSION

Shapiro and his co-workers synthesized asialo GM_2 by sequential, chain-extension reactions commencing at the nonreducing terminus[12]. Glycosylations of the relatively unreactive 4-hydroxyl groups of D-galactose and D-glucose were accomplished with the corresponding, partially acetylated 1,6-anhydrohexose derivatives[13,14]. Yields of ~25% (ref. 13) and ~50% (ref. 14) were recorded for each of the successive Koenigs–Knorr reactions. If suitable protecting groups are employed in order to provide an OH-4′ derivative of lactose that is sufficiently reactive to be glycosylated by a 2-deoxy-2-phthalimido-D-galactopyranosyl halide, the synthesis of asialo GM_2 may be envisaged as a one-step, glycoside synthesis. Coupling at O-4′ of lactose *via* the phthalimido process was cited in a recent review as one of the unsolved problems in the synthesis of biologically important glycosides[11].

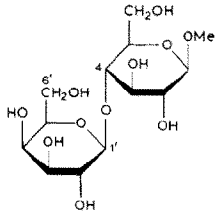
In recent studies on the synthesis of the Forssman pentasaccharide[15] and the P-antigen-globoside[16], it was again found that the OH-4′group of lactose possesses very low reactivity. Consequently, benzyl ethers, which enhance the reactivity of neighboring hydroxyl groups in glycosylation reactions, were our preferred protecting groups for lactose, rather than esters[17].

The most accessible routes to selectively blocked derivatives of lactose having an unsubstituted OH-4′ group are *via* the 4′,6′- or 3′,4′-acetal derivatives. Benzyl 4-*O*-β-D-galactopyranosyl-β-D-glucopyranoside gives the 3′,4′-isopropylidene acetal in good yield[18], and the 4′,6′-benzylidene acetal in moderate yield[19]. Lactose gives the 4′,6′-isopropylidene acetal in 76% yield by use of 2,2-dimethoxypropane in *N*,*N*-dimethylformamide (DMF) at room temperature[20], whereas higher temperatures lead to a mixture of the 3′,4′- and 4′,6′-acetals[21].

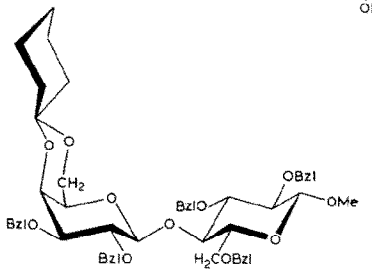
Because acetalation under kinetic control was more likely to favor formation of the 4′,6′- over the 3′,4′-acetal of lactose, we chose to use 1-ethoxycyclohexene[22] in order to prepare methyl 4-*O*-(4,6-*O*-cyclohexylidene-β-D-galactopyranosyl)-β-D-glucopyranoside from methyl 4-*O*-β-D-galactopyranosyl-β-D-glucopyranoside (**1**). At 20° in DMF solution, this reaction gave a 5:4 mixture of the 4′,6′- and 3′,4′-acetals, whereas, at 0° and 60°, the ratios were 6:1 and 1:9, respectively. A minor by-product was also formed at 60°. The highest overall yield of acetals was obtained at 20°, and therefore this temperature was used for large-scale synthesis of the 3′,4′- and 4′,6′-cyclohexylidene acetals. These noncrystalline compounds were not isolated, but were benzylated under standard conditions, to yield the isomeric,

penta-*O*-benzyl 4′,6′- and 3′,4′-cyclohexylidene derivatives **2** and **3**. Hydrolysis of these acetals with aqueous acetic acid gave two crystalline compounds, methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**4**) and the isomeric 2,3,6,2′,6′-penta-*O*-benzyl derivative **9**. Interestingly, the concentration of a solution of **4** in aqueous acetic acid gave the 6′-acetate **5** in virtually quantitative yield.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**6**) could be readily prepared from the two isomeric diols **4** and **9**, or from a crude mixture of the two. Stannylation of either **4** or **9** with bis(tributyltin) oxide[23], followed by reaction with benzyl bromide in the presence of tetrabutylammonium bromide[24], gave **6** in 95 and 87% yield, respectively. As the anticipated activation[23] of the OH-6′ and OH-3′ groups in the respective diols **4** and **9** was observed, the reaction was conducted with a crude mixture of **4** and **9**. Based upon **1**, the yield of **6** in a four-step reaction, without isolation of intermediates, was 55% after column chromatography. The 6′-benzoate **7** was prepared from **4** by selective benzoylation at 4°. Acetylation of the isomeric diols **4** and **9** re-

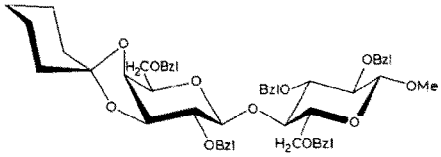


1



2

Bzl = $PhCH_2$



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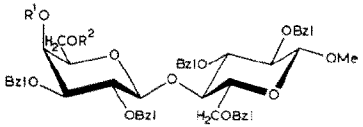
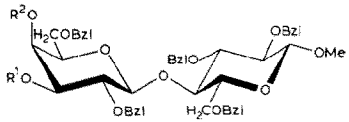


4 $R^1 = R^2 = H$
5 $R^1 = H, R^2 = Ac$
6 $R^1 = H, R^2 = Bzl$
7 $R^1 = H, R^2 = Bz$
8 $R^1 = R^2 = Ac$



9 $R^1 = R^2 = H$
10 $R^1 = R^2 = Ac$

TABLE I

^{13}C-CHEMICAL SHIFTS[a] OF PARTIALLY BENZYLATED D-GLUCO- AND D-GALACTO-PYRANOSIDES

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	OCH_3	*Benzylic* CH_2[b]
[c]	105.0	82.0	84.0	70.4	75.1	62.5	—	—	—	—	—	—	57.4	74.8, 75.3
[d]	104.9	81.9	84.1	71.6	74.3	70.3	—	—	—	—	—	—	57.2	74.8, 75.4, 73.8
[e]	105.0	82.6	85.0	78.2	75.2	69.2	—	—	—	—	—	—	57.2	74.9, 75.8, 75.2, 73.7
2	104.7	81.9	83.2	77.3	75.2	68.5	102.6	78.9	79.8	66.9	65.1	61.9	57.0	74.9, 75.2, 73.0, 75.8, 71.4
3	104.8	82.0	83.0	76.4	75.2	68.4	101.9	81.2	79.1	73.5	72.2	69.1	57.0	75.0, 75.6, 73.3, 73.3, 72.2
4	104.8	81.2	82.8	76.9	75.2	68.3	102.7	79.4	81.1	67.3	74.1	62.4	57.1	74.9, 75.6, 73.3, 75.4, 72.3
9	104.8	81.9	82.8	76.6	75.2	68.4	102.6	80.1	73.0	68.8	73.6	68.8	57.1	75.0, 75.2, 73.3, 75.0, 73.6
5	104.8	81.8	82.7	76.4	75.2	68.2	102.3	79.2	80.8	66.2	72.3	62.4	57.0	74.8, 75.2, 73.2, 75.2, 71.7
6	104.8	81.9	82.9	76.6	75.3	68.4	102.6	79.5	81.3	66.3	72.9	68.6	57.0	74.9, 75.3, 73.3, 75.3, 72.1, 73.6
7	104.8	81.9	82.6	76.7	75.3	68.3	102.5	79.4	81.0	66.5	72.5	63.1	57.1	74.9, 75.3, 73.3, 75.3, 72.1
8	104.9	81.9	82.7	76.6	75.7	68.3	102.4	79.4	79.6	66.3	70.6	61.6	57.1	75.0, 75.4, 73.3, 75.2, 72.2
10	104.8	81.9	82.8	76.5	75.0	68.1	102.4	77.6	71.6	68.0	73.0	66.9	57.1	75.0, 75.3, 73.4, 75.0, 73.4

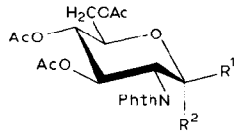
[a]Determined for solutions in $CDCl_3$. [b]In ascending order, $C_6H_5CH_2$ at 2, 3, 6, 2',...6'. [c]Methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside. [d]Methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside. [e]Methyl tetra-*O*-benzyl-β-D-glucopyranoside.

spectively gave the 4′,6′-diacetate **8**, and the 3′,4′-diacetate **10**, which were used for structural confirmation by n.m.r. spectroscopy.

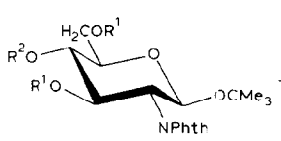
The structures assigned compounds **2–10** were confirmed by their ^{13}C-n.m.r. spectra, and, in some instances, were supported by their ^{1}H-n.m.r. spectra. At 80 MHz, insufficient dispersion of crucial, proton resonances was observed, and, therefore, use was made of ^{13}C data recorded at 20 MHz (see Table I). Accordingly, the assignments of three benzylated methyl β-D-glucopyranosides are reported, in order to facilitate comparison with assignments made for the benzylated lactose derivatives **2–10**. ^{13}C-N.m.r. data for acetals **2** and **3** showed quaternary, acetal carbon atoms at δ 98.8 and 110.4 in deuteriochloroform, and the typical shift-difference characteristic of the acetal carbon atoms of dioxane and dioxolane ring-systems[25].

The structures of the benzylated diols **4** and **9** were assigned by ^{1}H-n.m.r. spectroscopy of their respective diacetates, **8** and **10**. Thus, **10** gave two-proton multiplets, at δ 5.70 and 5.23, with coupling constants characteristic of those expected for H-4′ and H-3′, respectively. By comparison, **8** showed only one, readily identifiable, downfield-shifted proton, namely, H-4′ at δ 5.50. The ^{13}C-n.m.r. data for compounds **4** and **9** were consistent with the assigned structure. Thus, **4** showed C-6′ and C-4′ at δ 62.4 and 67.3, shifts characteristic of unsubstituted centers, and C-3′ at δ 81.1 indicated an etherified carbon atom. In comparison, **9** showed C-3′ at δ 73.0, and C-4′ at δ 68.8, whereas C-6′, with a chemical shift of δ 68.8 (see Table I), was clearly etherified. The carbon atoms of the β-D-glucopyranose moiety were assigned by comparison with model compounds, the 2,3-di-*O*-benzyl- (ref. 26), 2,3,6-tri-*O*-benzyl-, and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides[27] (see Table I). The data of Ogawa and co-workers[28] were used in order to assign the resonances of the β-D-galactopyranosyl group. To facilitate assignments, especially of methylene carbon atoms of benzyl ether substituents, spectra were recorded with, and without, proton decoupling.

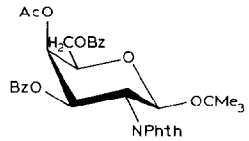
A 2-deoxy-2-phthalimido-D-galactopyranosyl halide was considered to constitute the most effective derivative for the introduction of a β-linked, 2-amino-2-deoxy-galactopyranosyl group at O-4′ of lactose. Tri-*O*-acetyl-2-deoxy-2-phthalimido-D-galactopyranosyl halides may be readily prepared from the corresponding 2-amino-2-deoxy-D-galactose hydrochloride in analogous fashion to the *gluco* isomer, albeit in lower overall yield[29]. For this reason, and the ~200-fold higher cost of 2-amino-2-deoxy-D-galactose hydrochloride than of the *gluco* compound, an alternative route to the D-galactosyl halides was investigated. Horner *et al.*[30] reported a convenient synthesis of 2-amino-2-deoxy-D-galactose by inversion at C-4 of the *gluco* isomer, and we adapted this procedure, starting with a *tert*-butyl glycoside. *tert*-Butyl alcohol reacted with **11** in the presence of silver salicylate[31] to give crystalline glycoside **13** in 72% yield. Transesterification to **14**, followed by selective benzoylation of **14**, gave the 3,6-dibenzoate **15** in 65% yield. The crystalline methanesulfonate **16** was readily prepared from **15**, and acetate displacement in the presence of crown ether proceeded satisfactorily at 130°, to give the galac-



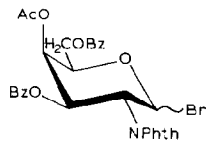
11 R^1 = Br, R^2 = H
12 R^1 = H, R^2 = Cl



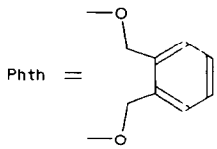
13 R^1 = R^2 = Ac
14 R^1 = R^2 = H
15 R^1 = Bz, R^2 = H
16 R^1 = Bz, R^2 = $MeSO_2$



17



18



topyranoside **17** in 70% yield. Recently, an analogous 4-*O*-(*p*-bromophenylsulfonyl) compound was subjected to displacement by benzoate, but in hexamethylphosphoric triamide as the solvent, and higher temperatures were required[32]. Use of the crown ether reported here permitted the displacement of the methylsulfonyloxy group in a solution in DMF. *tert*-Butyl 4-*O*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-galactopyranoside (**17**) was converted into the glycosyl bromide **18** by either of two procedures: (*a*) hydrogen bromide in acetic acid containing acetic anhydride converted **17** into **18** after 30 min at room temperature, or (*b*) a cleaner reaction was achieved by treatment of **17** with dibromomethyl methyl ether, and this was considered the method of choice for the preparation of **18**. This galactosyl bromide was finally caused to react with the selectively blocked, lactose derivative **6**.

Glycosylations at O-4′ of lactose are well known for their difficulty[11]. The reactivity of OH-4′ is sufficiently low that it does not react at all if the OH-3′ group is also exposed to glycosylation[18,33]. Glycosylation at O-4′ has been achieved by three groups, and, in all cases, an α-D-galactopyranosidic linkage was established[15,16,34,35]. The most precise and exhaustive of these studies, by Paulsen and Bünsch[15], initially employed a hexa-*O*-acetyl-6′-*O*-benzoyllactose derivative having a free OH-4′ group. Systematic variation of the glycosyl halide showed that less-reactive halides bearing ester instead of ether groups at O-3 and O-4 gave un-

satisfactory yields of trisaccharides. When the alcohol component was changed to a penta-*O*-benzyllactose derivative having a 6′-*O*-benzoyl group, better yields of a trisaccharide containing the 4′-linked α-D-galactopyranosyl group resulted, but only with reactive glycosyl halides. Also critical in this work was the catalyst, a mixture of silver carbonate and silver perchlorate, the ratio of which needed to be carefully optimized. In light of these findings, we chose first to optimize the reaction of **6** and **7** with the cheaper, and more accessible, bromide **11**. This followed our observation that reaction of bromide **18** with **6** failed to yield the desired trisaccharide under the standard, phthalimido coupling-conditions using silver triflate–collidine[36]. Because the reactivity of the glycosyl halides could not be readily improved, we tried to optimize the reactivities of the catalyst and the hydroxyl component.

The yields of trisaccharides **19–21** under a variety of reaction conditions are recorded in Table II. The most important and immediate observation was that the lactose compound **6**, possessing a 6′-*O*-benzyl group, gave a 54% yield of trisaccharide **20**, whereas the analogous 6′-benzoate **7** gave only 8% of trisaccharide **19**. This result is in marked contrast to the work of Sinäy[17], who studied the reactivity of O-4 of 2-acetamido-2-deoxy-D-glucopyranosides; his findings indicated that the O-6 substituent could be either an ester or an ether without affecting glycosylation at O-4. Here, it is shown that these results cannot be generalized.

Glycosylation of the preferred hydroxyl compound **6** by **18** was then optimized and, as with the work of Paulsen and Bünsch[15], the ratio of the catalysts, silver perchlorate and silver carbonate, proved critical. With these salts in the ratio of 1:20, the optimized yield of **21** was 48.5%, while maintaining the excess of the valuable halide as low as possible (see Table II). With a single exception[37], the phthalimido coupling-procedure employs the promoter–base combination of silver triflate–collidine[36]. However, it is shown here that, under the special circumstances

TABLE II

YIELDS OF KOENIGS–KNORR REACTIONS WITH VARIATION OF GLYCOSYL BROMIDE, AGLYCON SUBSTITUTION PATTERN, AND PROMOTER/ACID ACCEPTOR

Lactose derivative	*Glycosyl halide*	*Molar ratio of glycosyl halide: aglycon*	*Promoter/acid acceptor (wt/wt ratio)*	*Trisaccharide product*	*Isolated yield[a] (%)*
7	**11**	2.0	$AgClO_4/Ag_2CO_3$, 1:11	**19**	8
6	**11**	2.0	$AgClO_4/Ag_2CO_3$, 1:11	**20**	54
6	**18**	1.7	$AgClO_4/Ag_2CO_3$, 1:11	**21**	38
6	**18**	1.5	$AgClO_4/Ag_2CO_3$, 1:20	**21**	48.5
6	**18**	3.0	AgTrfl/collidine, 1:1	**21**	0
6	**18**	3.0	$AgTrfl/Ag_2CO_3$, 1:7.5	**21**	0
6	**12**	2.0	$AgTrfl/UMe_4$[b]	**20**	8
6	**12**	1.0	$AgTrfl/Ag_2CO_3$, 1:10	**21**	13

[a]Yields are calculated on the basis of aglycon employed (not on the basis of aglycon reacted less aglycon recovered). [b]1,1,3,3-Tetramethylurea.

of an unreactive aglycon and a moderately reactive glycosyl halide[38], these conditions have to be modified. Thus, when the less-reactive chloride **12** reacts with **6** in the presence of the very strong catalyst silver triflate, the trisaccharide **21** is obtained, albeit in low yield, but, the same reaction with bromide **11** gave no trisaccharide product, indicating that the catalyst was too strong for this more-reactive glycosyl halide. In this context, it may also be noted that silver triflate and silver perchlorate exhibit significantly different catalytic properties when used in conjunction with silver carbonate (see Table II), and it would seem dubious in general to equate the two.

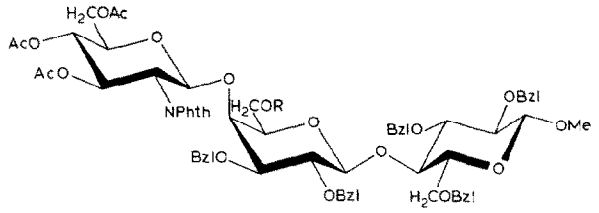
The fully protected trisaccharide **21** was deblocked in three steps. First, acyl groups were transesterified, to give the intermediate **22**. This benzylated, phthalimido compound was converted into the acetamido derivative **23** by treatment with hydrazine hydrate under standard conditions[35], followed by *N*-acetylation. Finally, hydrogenolysis of **23** in the presence of palladium-on-charcoal in ethanol gave the deblocked trisaccharide **24**. The final product (**24**) and inter-

TABLE III

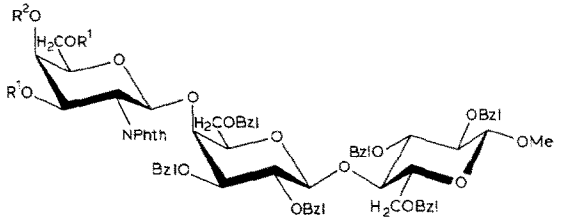
^{13}C CHEMICAL SHIFTS OF TRISACCHARIDES SYNTHESIZED

Atom	**19** *($CDCl_3$)*	**20** *($CDCl_3$)*	**21** *($CDCl_3$)*	**22** *($CDCl_3$)*	**23** *($CDCl_3$)*	**24** *(CD_3OD)*	**24** *(D_2O)*
C-1	104.7	104.7	104.7	104.7	104.8	104.4	103.9
C-2	81.7	81.7	81.8	81.6	82.1	74.7	74.0
C-3	82.5	82.8	82.8	82.8	82.5	76.0	75.9
C-4	76.3	76.2	76.5	76.5	76.4	80.9	79.9
C-5	75.5	75.2	75.3	75.0	75.5	76.2	75.9
C-6	68.2	68.2	68.2	68.0	68.1	61.7	61.3
C-1′	101.7	101.9	102.1	102.0	102.4	105.1	104.3
C-2′	80.1	80.3	80.3	80.1	80.7	74.3	72.3
C-3′	80.1	80.6	80.6	80.4	81.9	74.7	73.7
C-4′	75.0	75.9	75.6	74.9	75.2	78.3	77.4
C-5′	71.2	72.8	73.2	74.3	74.9	76.7	76.0
C-6′	63.0	69.0	69.0	68.0	67.5	61.8	61.9
C-1″	99.1	99.3	99.8	99.9	103.0	105.1	104.3
C-2″	54.7	54.9	51.8	54.7	56.5	55.2	53.9
C-3″	70.1	70.2	68.2	72.3	74.9	72.6	72.3
C-4″	69.0	68.5	67.0	69.3	67.8	69.5	69.1
C-5″	71.2	71.4	70.7	74.9	76.7	76.3	76.0
C-6″	61.7	61.8	61.9	62.6	62.5	62.6	62.0
OCH_3	57.0	57.0	57.0	57.0	57.0	57.4	58.4
	75.0	74.9	74.9	74.9	75.1		
benzylic	75.1	75.2	75.1	75.0	75.5		
CH_2[a]	73.1	73.1	73.2	73.1	73.3		
	75.5	75.9	76.2	75.7	75.7		
	73.1	72.8	72.8	71.3	71.3		
		73.1	73.3	73.2	73.3		
acetyl	20.6	20.7	20.8		22.1	23.2	23.6
		20.6					

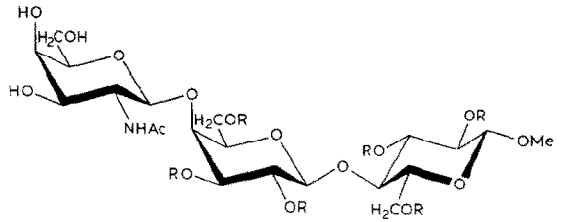
[a]In the order of $C_6H_5CH_2$ on O-2, 3, 6, 2′,...6′.



7 + 11 ⟶ **19** R = Bz
6 + 11 ⟶ **20** R = Bzl



6 + 18 ⟶ **21** R^1 = Bz, R^2 = Ac
22 R^1 = R^2 = H



23 R = Bzl
24 R = H

mediates **22** and **23** were prepared to analytical purity, and the overall, isolated yield of **24** from **21** was 68%. Trisaccharides **19–21** and **22–24** were characterized by ^{13}C-n.m.r. data (see Table III), which are consistent with the structures assigned. The presence of β linkages was confirmed by carbon–proton coupling-constants, and by the ^{1}H-n.m.r. spectrum of **24**.

This synthesis of the trisaccharide component of asialo GM_2 demonstrates a practical method for preparation of 2-deoxy-2-phthalimido-D-galactopyranosyl bromide **18** from 2-amino-2-deoxy-D-glucose hydrochloride, and the successful glycosylation by **18** of the relatively unreactive OH-4′ group of lactose. Halide **18** is thus an effective intermediate for the synthesis of 2-amino-2-deoxy-β-D-galactopyranosides. Benzyl ethers as protecting groups conveniently maximized the

reactivity of O-4′ of lactose when silver perchlorate and silver carbonate were used as the promoter and the acid acceptor in precise ratios. Reactions conducted under a variety of conditions confirmed the observation[31] that an unreactive hydroxyl group of the reaction partner requires relatively reactive halides and catalysts, but also revealed that the nature of the neighboring protecting-groups influences the reactivity of the hydroxylic component, demonstrating the critical balance of the three factors essential for efficient Koenigs–Knorr reactions.

EXPERIMENTAL

General. — The general methods and materials employed in this work were similar to those described in a recent publication from this laboratory[39]. N.m.r. spectra (^{13}C and ^{1}H) were recorded at 20 and 79.9 MHz, respectively. Proton chemical-shifts are expressed relative to internal, 1% tetramethylsilane (Me_4Si) for chloroform-*d* and benzene-d_6 solutions, and relative to sodium 2,2,3,3-tetradeuterio-4,4-dimethyl-4-silapentanoate for deuterium oxide solutions. Carbon-13 shifts are expressed relative to internal and external Me_4Si, for solutions in chloroform-*d* and deuterium oxide, respectively.

Methyl 4-O-β-D-galactopyranosyl-β-D-glucopyranoside (**1**). — Hepta-*O*-acetyllactosyl bromide[40] (23.0 g, 32.7 mmol) was dissolved in dry methanol (200 mL), and the solution was stirred with silver salicylate[41] (9.0 g, 36.7 mmol) for 18 h. The mixture was then filtered, the filtrate evaporated, the residue dissolved in ethyl acetate (200 mL), and the solution washed with potassium hydrogencarbonate solution. Although t.l.c. with 2:1 ethyl acetate–Skellysolve B showed mainly one product, crystallization was difficult, and the crude product was transesterified with sodium (0.2 g) in methanol (200 mL). Compound **1** (8.0 g) crystallized, and, following de-ionization of the mother liquors with Rexyn-101 (H^+) resin, and concentration to 50 mL, a further 1.5 g of **1** (total yield, 82%) was obtained. The crystalline product had m.p. 207–209° and $[\alpha]_D$ +9.7° (*c* 1.75, water) [lit.[41] m.p. 206°, $[\alpha]_D$ +5.6° (*c* 3, water)].

Methyl 2,3,6-tri-O-benzyl-4-O-(2,3-di-O-benzyl-4,6-O-cyclohexylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (**2**) *and methyl 2,3,6-tri-O-benzyl-4-O-(2,6-di-O-benzyl-3,4-O-cylohexylidene-β-D-galactopyranosyl)-β-D-glucopyranoside* (**3**). — To a solution of **1** (8 g, 22 mmol) in dry DMF (50 mL) were added 1-ethoxycyclohexene[43] and *p*-toluenesulfonic acid (0.3 g), and the mixture was kept overnight at 20°; t.l.c. in 17:2:1 ethyl acetate–methanol–water then showed two major components. Triethylamine (5 mL) was added, and the solution was evaporated to a syrup. The resulting mixture of 3,4- and 4,6-cyclohexylidene acetals was dissolved in DMF (200 mL), and this solution was added to sodium hydride (19 g, 395 mmol). The suspension was stirred for 10 min, cooled to 4°, and benzyl bromide (25 mL, 204 mmol) was added dropwise. After 18 h, methanol (50 mL) was added, and after 2 h, the base was neutralized with hydrochloric acid. The mixture was poured into water (1 L), the crude products were extracted with ethyl acetate (3 ×

200 mL), the extracts combined, and evaporated, and the benzylated acetals (**2** and **3**) separated by preparative, 4-MPa l.c. with 3:1 Skellysolve B–ethyl acetate. The faster-moving component was **3** (10.0 g, 51%), recovered as a homogeneous syrup, $[\alpha]_D$ +15.1° (*c* 3, dichloromethane). The slower-moving product **2** (8.3 g, 43%) also resisted crystallization; $[\alpha]_D$ +22.2° (*c* 1.5, dichloromethane).

Anal. Calc. for $C_{54}H_{62}O_{11}$: C, 73.15; H, 7.05. Found for **2**: C, 73.26; H, 7.16. Found for **3**: C, 73.30; H, 7.11.

*Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**4**). — A solution of acetal **2** (8.3 g) in 80% aqueous acetic acid (100 mL) was heated for 60 min at 70°, cooled, evaporated, and the residual acetic acid co-distilled with toluene, to give, in virtually quantitative yield, a product that corresponded to the 6′-acetate. This compound was *O*-deacetylated in methanol (100 mL) containing a catalytic amount of sodium methoxide. Following de-ionization, and evaporation, the title compound crystallized. Recrystallization from ethyl acetate–Skellysolve B gave **2** (7.0 g, 92%); m.p. 124.5–127.0°, $[\alpha]_D$ +30.2° (*c* 0.9, chloroform).

Anal. Calc. for $C_{48}H_{54}O_{11}$: C, 71.44; H, 6.75. Found: C, 71.35; H, 6.83.

*Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**9**). — The acetal **3** (10.0 g, 11.3 mmol) was treated as described for **2**, with the exception of the *O*-deacetylation step, which was omitted. The syrupy diol **9** crystallized on standing, and was recrystallized from ethyl acetate–Skellysolve B, to give 6.1 g (67%) of **9**; m.p. 100–102°, $[\alpha]_D$ +23.9° (*c* 0.9, chloroform).

Anal. Calc. for $C_{48}H_{54}O_{11}$: C, 71.44; H, 6.75. Found: C, 71.62; H, 6.86.

*Methyl 4-*O*-(6-*O*-acetyl-2,3-di-*O*-benzyl-β-*D*-galactopyranosyl)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**5**). — The acetal **2** was hydrolyzed, and the solution evaporated, as described for the preparation of **4**. The acetate **5** was purified by chromatography, to yield a homogeneous syrup; $[\alpha]_D$ +24.0° (*c* 0.6 dichloromethane).

Anal. Calc. for $C_{50}H_{56}O_{12}$: C, 70.74; H, 6.65. Found: C, 70.94; H, 6.75.

*Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**6**). — *(A) From the diol* **9**. A solution of **9** (1.41 g, 1.75 mmol) and bis(tributyltin) oxide (667 μL, 1.31 mmol) in toluene (150 mL) was boiled overnight under reflux, with continuous removal of water. After addition of tetrabutylammonium bromide (282 mg, 0.87 mmol) and benzyl bromide (627 μL, 5.2 mmol), the solution was kept for 10 h at 80°. Chromatographic purification on silica gel with 3:1 Skellysolve B–ethyl acetate as the eluant gave 1.49 g (95%) of **6**.

(B) From the diol **4**. Treatment of **4** (204 mg, 0.25 mmol) with bis(tributyltin) oxide (97 μL, 0.19 mmol), tetrabutylammonium bromide (41 mg, 0.13 mmol), and benzyl bromide (0.76 mmol), as described under A, gave, after chromatography, 198 mg (87%) of pure, syrupy **6**.

(C) From a crude mixture of **4** *and* **9**. A mixture containing compounds **2** and **3** (2.26 g) was hydrolyzed as described for the synthesis of **4**. After being dried over

phosphorus pentaoxide, the crude mixture of diols **4** and **9** (2.02 g, 2.5 mmol) was dissolved in toluene (150 mL) containing bis(tributyltin) oxide (0.98 mL, 1.92 mmol), and the solution was boiled overnight under reflux, with continuous removal of water. Benzyl bromide (0.9 mL, 7.46 mmol) and tetrabutylammonium bromide (0.4 g, 1.23 mmol) were added to the cooled mixture, which was then heated for 18 h at 80°. Purification as described under A gave **6** as a homogeneous syrup; yield (1.09 g) (based upon the mixture of **2** and **3**, 48%); $[\alpha]_D$ +22.2° (*c* 5.7, dichloromethane).

Anal. Calc. for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.86; H, 6.86.

*Methyl 4-O-(6-O-benzoyl-2,3-di-O-benzyl-β-*D*-galactopyranosyl)-2,3,6-tri-O-benzyl-β-*D*-glucopyranoside* (**7**). — A solution of diol **4** (500 mg, 0.62 mmol) in pyridine (10 mL) was treated with benzoyl chloride (140 μL, 1.2 mmol) at 4°. After 24 h, more benzoyl chloride (100 μL, 0.86 mmol) was added. The mixture was kept for a further 6 h, diluted with dichloromethane (100 mL), washed successively with cold, aqueous HCl solution (1%) and water, and evaporated. Column chromatography with 2:1 Skellysolve B–ethyl acetate as the eluant gave 354 mg (63%) of syrupy compound **7**; $[\alpha]_D^{24}$ +19.2° (*c* 3.0, dichloromethane).

Anal. Calc. for $C_{55}H_{58}O_{12}$: C, 72.51; H, 6.42. Found: C, 72.29; H, 6.39.

*Methyl 2,3,6-tri-O-benzyl-4-O-(4,6-di-O-acetyl-2,3-di-O-benzyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**8**). — A solution of **4** (320 mg, 0.40 mmol) in absolute pyridine (10 mL) and acetic anhydride (5 mL) was kept overnight at 5°, evaporated, traces of solvents co-distilled with toluene, and the residue passed through a small column of silica gel, to give pure diacetate **8** as a syrup (339 mg, 96%); $[\alpha]_D^{24}$ +27.3° (*c* 1.1, dichloromethane); ^{1}H-n.m.r. (C_6D_6): δ 1.76 (s, 3 H, OAc), 1.79 (s, 3 H, OAc), and 5.50 (dd, ~t, 1 H, $J_{3',4'}$ 3.4, $J_{4',5'}$ ~1.0 Hz, H-4').

Anal. Calc. for $C_{52}H_{58}O_{13}$: C, 70.10; H, 6.56. Found: C, 69.67; H, 6.73.

*Methyl 2,3,6-tri-O-benzyl-4-O-(3,4-di-O-acetyl-2,6-di-O-benzyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**10**). — A solution of **9** (220 mg, 273 μmol) in absolute pyridine (10 mL) and acetic anhydride (5 mL) was kept overnight at 5°, evaporated, traces of solvents co-distilled with toluene, and the residue passed through a micro-column of silica gel, to give pure, syrupy compound **10** (228 mg, 94%); $[\alpha]_D^{24}$ +2.0° (*c* 2.4, dichloromethane); ^{1}H-n.m.r. (C_6D_6): δ 1.71 (s, 3 H, OAc), 1.81 (s, 3 H, OAc), 5.23 (dd, 1 H, $J_{3',4'}$ 3.4, $J_{2',3'}$ 10.0 Hz, H-3'), 5.70 (dd, 1 H, $J_{3',4'}$ 3.4, $J_{4',5'}$ ~1.0 Hz, H-4').

Anal. Calc. for $C_{52}H_{58}O_{13}$: C, 70.10; H, 6.56. Found: C, 69.49; H, 6.75.

tert-*Butyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**13**). — To a solution of *tert*-butyl alcohol (60 mL, 636 mmol) in absolute dichloromethane (70 mL) were added silver salicylate[41] (24.5 g, 100 mmol) and silver triflate (2.39 g, 9 mmol), and the suspension was stirred while a solution of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide[36] (**11**; 46.3 g, 95.6 mmol) in dichloromethane (70 mL) was added dropwise. Stirring was continued for 90 min in the dark, the mixture was filtered through a pad of Celite, the filtrate diluted with dichloromethane (500 mL), successively washed with potassium hydro-

gencarbonate solution, sodium thiosulfate solution, and water, dried (anhydrous sodium sulfate), and evaporated to a syrup which crystallized from ethyl acetate–Skellysolve B. Two crops of crystals of **13** (27.2 g) were collected, and, after preparative, 4-MPa l.c., the mother liquors yielded a further 7.2 g of **13** (total yield 34.4 g, 72%); m.p. 138–139°, $[\alpha]_D^{23}$ +19.0° (*c* 1.1, chloroform); ^{1}H-n.m.r. (CD_3Cl_3): δ 1.10 (s, 9 H, CMe_3), 1.76 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 5.10 (d,d, 1 H, $J_{3,4} \approx J_{4,5} \approx 10$ Hz, H-4), 5.46 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 5.88 (d,d, 1 H, $J_{2,3}$ 10.8, $J_{3,4}$ 9.1 Hz, H-3), 7.60–7.95 (m, 4 H, ArH), and 3.70–4.50 (m, 4 H, other ring protons).

Anal. Calc. for $C_{24}H_{29}NO_{10}$: C, 58.65; H, 5.95; N, 2.85. Found: C, 58.75; H, 5.88; N, 2.67.

tert-*Butyl 2-deoxy-2-phthalimido-β*-D-*glucopyranoside* (**14**). — To a solution of compound **13** (25.0 g) in methanol was added a catalytic amount of sodium methoxide solution, and the pH was maintained above 7 by addition of sodium methoxide as required. After 20 min, the solution was treated with Rexyn 101 (H^+) ion-exchange resin, and evaporated, to yield a foam (17.3 g) which was homogeneous by t.l.c. in 17:2:1 ethyl acetate–methanol–water and gave the correct elemental analysis, but was not readily crystallized. Crystals of **14** were obtained from ethanol–Skellysolve B; m.p. 197–198°, $[\alpha]_D^{23}$ −40.7° (*c* 1.0, water); ^{1}H-n.m.r. ($CDCl_3$): δ 1.03 (s, 9 H, CMe_3), 5.31 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), and 7.86 (s, 4 H, ArH).

Anal. Calc. for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.35; N, 3.83. Found: C, 59.33; H, 6.49; N, 3.74.

tert-*Butyl 3,6-di*-O-*benzoyl-2-deoxy-2-phthalimido-β*-D-*glucopyranoside* (**15**). — Syrupy **14** (16.2 g, 44 mmol) was dried over phosphorus pentaoxide, and then dissolved in dry pyridine (40 mL) diluted with absolute dichloromethane (100 mL). The solution was stirred, and cooled to −10°, and benzoyl chloride (10.5 mL, 90 mmol) was added dropwise. The mixture was allowed to warm, and kept overnight at room temperature. The solution was then poured into 10% hydrochloric acid (400 mL), the mixture extracted three times with dichloromethane (250 mL), and the extracts were combined, successively washed with potassium hydrogencarbonate solution and water, dried, and evaporated, to give a syrup (38 g) which was purified by 4-MPa l.c. using 2:1 Skellysolve B–ethyl acetate as the solvent. This yielded 16.7 g (65%) of compound **15**; m.p. 129–130.5°, $[\alpha]_D^{23}$ +68.9° (*c* 1.2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.14 (s, 9 H, CMe_3), 3.50–4.75 (m, 5 H, H-2,4,5,6,6′), 5.61 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 6.03 (d,d, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 8.5 Hz, H-3), and 7.20–8.20 (m, 14 H, ArH); addition of trichloroacetyl isocyanate gave ^{1}H-n.m.r. ($CDCl_3$): δ 5.31 (d,d, 1 H, $J_{3,4} \approx J_{4,5} = 9.5$ Hz, H-4), 5.54 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 6.16 (d,d, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 9.5 Hz, H-3), and 8.38 (s, 1 H, $CCl_3CONHCO$-).

Anal. Calc. for $C_{32}H_{31}NO_9$: C, 66.64; H, 5.42; N, 2.43. Found: C, 66.81; H, 5.43; N, 2.54.

tert-*Butyl 3,6-di*-O-*benzoyl-2-deoxy-4*-O-*(methylsulfonyl)-2-phthalimido-β*-D-*glucopyranoside* (**16**). — A solution of dibenzoate **15** (16.7 g, 29 mmol) in dry

pyridine (140 mL) was cooled to 0°, methanesulfonyl chloride (3.4 mL, 43 mmol) was added dropwise with stirring, and the reaction was allowed to warm overnight to room temperature. The mixture was poured into ice-cold, 10% hydrochloric acid (500 mL), and the mixture was extracted with ethyl acetate (3 × 400 mL). The extracts were combined, successively washed repeatedly with 5% hydrochloric acid (500 mL), potassium hydrogencarbonate, and water, dried, and evaporated, to give a syrup (19.5 g) which crystallized in two successive crops of **16** (17.0 g, 90%); m.p. 188.5–189.5°, $[\alpha]_D^{23}$ +71.1° (*c* 1.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.09 (s, 9 H, CMe_3), 2.86 (s, 3 H, $-SO_2CH_3$), 3.90–4.90 (m, 4 H, H-2,5,6), 5.05 (dd, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 9.9 Hz, H-4), 5.60 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 6.27 (dd, 1 H, $J_{2,3}$ 10.7, $J_{3,4}$ 8.9 Hz, H-3), and 7.15–8.10 (m, 14 H, ArH).

tert-*Butyl 4-*O*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-β-*D*-galacto-pyranoside* (**17**). — To a solution of the methanesulfonate **16** (11.4 g, 17.5 mmol) in dry *N,N*-dimethylformamide (120 mL) were added dicyclohexano-18-crown-6 (1.0 g, 2.6 mmol) together with dry potassium acetate (6.0 g, 61 mmol). The suspension was stirred, kept for 14 h at 130°, cooled, poured into ice–water (1 L), and the mixture extracted with ethyl acetate (3 × 300 mL); the extracts were combined, washed with water, dried, and evaporated, to give crude product (12.0 g) which, on preparative, 4-MPa l.c., gave pure D-galactopyranoside **17** (7.6 g, 70%); $[\alpha]_D$ +21.9° (*c* 0.6, dichloromethane); ^{1}H-n.m.r. ($CDCl_3$): δ 1.12 (s, 9 H, CMe_3), 2.17 (s, 3 H, $COCH_3$), 4.16–4.62 (m, 3 H, H-5,6), 4.76 (dd, 1 H, $J_{2,3}$ 11.3 Hz, H-2), 5.58 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 5.76 (bd, 1 H, $J_{4,5}$ ~1 Hz, H-4), 6.13 (dd, 1 H, $J_{3,4}$ 3.6 Hz, H-3), and 7.10–8.10 (m, 14 H, ArH).

*4-*O*-Acetyl-3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-*D*-galactopyranosyl bromide* (**18**). — (*A*) The *tert*-butyl galactopyranoside **17** (4.0 g, 6.5 mmol) was dissolved in a mixture of acetic anhydride (2 mL) and 30% hydrogen bromide in acetic acid (12 mL). After 30 min at room temperature, t.l.c. in 4:1 toluene–ethyl acetate showed that all of the starting material (R_F 0.40) had been converted into compound **18** (R_F 0.47). The solution was diluted with chloroform (100 mL), the acid removed by washing with 10% potassium hydrogencarbonate solution, and the organic layer evaporated to give compound **18** as a syrup (3.5 g, 88%) that was found by ^{1}H-n.m.r. spectroscopy to be an 8:3 mixture of the β and α anomers.

(*B*) A solution of **17** (941 mg, 1.68 mmol) in dry dichloromethane (5 mL) was stirred in the presence of dibromethyl methyl ether[44] (315 μL, 3.36 mmol) and a catalytic amount of dry zinc bromide under an atmosphere of dry nitrogen. After 2 h, the suspension was rapidly filtered through cotton wool, and the filtrate freeze-dried for 5 h, yielding 1.022 g (100%) of syrupy bromide **18**; ^{1}H-n.m.r. ($CDCl_3$): δ 2.13 [s, OAc (α anomer)], 2.22 [s, OAc (β anomer)], 6.58 (d, 0.73 H, $J_{1,2}$ 9.5 Hz, H-1β), and 6.79 (d, 0.27 H, $J_{1,2}$ 3.4 Hz, H-1α).

*Methyl O-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl)-(1→4)-*O*-(6-*O*-benzoyl-2,3-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside)* (**19**). — A mixture of thoroughly dried 6′-benzoate **7** (483 mg, 0.53 mmol), silver carbonate (550 mg), and silver perchlorate (50

mg) was suspended in absolute dichloromethane (15 mL), and stirred with 4A molecular sieve (2 g) and Drierite (1 g) for 2 h under nitrogen. A solution of **11** (556 mg, 1.1 mmol) in absolute dichloromethane was then added during several hours. After being stirred for 18 h, the mixture was filtered, the filtrate evaporated, and the residue immediately chromatographed on silica gel with 2:1 (v/v) Skellysolve B–ethyl acetate as the eluant, yielding 55 mg (8%) of pure, syrupy **19**; $[\alpha]_D^{24}$ +28.2° (*c* 0.7, dichloromethane).

Anal. Calc. for $C_{75}H_{77}NO_{21}$: C, 67.81; H, 5.84; N, 1.05. Found: C, 67.96; H, 5.98; N, 1.11.

Methyl O-*(3,4,6-tri*-O-*acetyl-2-deoxy-2-phthalimido-β*-D-*glucopyranosyl)-(1→4)*-O-*(2,3,6-tri*-O-*benzyl-β*-D-*galactopyranosyl)-(1→4)-(2,3,6-tri*-O-*benzyl-β*-D-*glucopyranoside)* (**20**). — A mixture of thoroughly dried **6** (500 mg, 0.56 mmol), silver carbonate (550 mg), and silver perchlorate (50 mg) was suspended in absolute dichloromethane (15 mL), and stirred with 4A molecular sieve (2 g) and Drierite (1 g) for 2 h under nitrogen; then a solution of bromide **11** (555 mg, 1.1 mmol) in absolute dichloromethane (35 mL) was added during several hours. After being stirred overnight, the mixture was filtered, the filtrate evaporated, and the residue immediately chromatographed on silica gel with 3:1 (v/v) Skellysolve B–ethyl acetate as the eluant, yielding unreacted starting-material **6** (134 mg, 27%) and **20** (396 mg, 54%); $[\alpha]_D^{24}$ +25.0° (*c* 1.3, dichloromethane); ^{13}C-n.m.r. ($CDCl_3$): δ 104.7 ($J_{C\text{-}1,H\text{-}1}$ 159 Hz, C-1), 101.9 ($J_{C\text{-}1',H\text{-}1'}$ 159 Hz, C-1′), and 99.3 ($J_{C\text{-}1'',H\text{-}1''}$ 162 Hz, C-1″).

Anal. Calc. for $C_{75}H_{79}NO_{20}$: C, 68.53; H, 6.06; N, 1.07. Found: C, 68.31; H, 5.98; N, 1.02.

Methyl O-*(4*-O-*acetyl-3,6-di*-O-*benzoyl-2-deoxy-2-phthalimido-β*-D-*galactopyranosyl)-(1→4)*-O-*(2,3,6-tri*-O-*benzyl-β*-D-*galactopyranosyl)-(1→4)-(2,3,6-tri*-O-*benzyl-β*-D-*glucopyranoside)* (**21**). — A mixture of thoroughly dried **6** (1.0 g, 1.1 mmol), silver carbonate (1.0 g), and silver perchlorate (50 mg) was suspended in absolute dichloromethane (20 mL), and stirred with 4A molecular sieve (3 g) and Drierite (1 g) for 2 h under nitrogen. A solution of bromide **18** (1.02 g, 1.68 mmol) in absolute dichloromethane (40 mL) was added during several hours. After being stirred overnight, the mixture was processed as described for compound **20**. The yield of recovered, unreacted lactoside **6** was 225 mg (22.5%), and of chromatographically pure **21** was 777 mg (48.5%); $[\alpha]_D^{24}$ +31.5° (*c* 0.7, dichloromethane); ^{13}C-n.m.r. ($CDCl_3$): δ 104.7 ($J_{C\text{-}1,H\text{-}1}$ 157 Hz, C-1), 102.1 ($J_{C\text{-}1',H\text{-}1'}$ 159 Hz, C-1′), and 99.8 ($J_{C\text{-}1'',H\text{-}1''}$ 167 Hz, C-1″).

Anal. Calc. for $C_{85}H_{83}NO_{20}$: C, 70.97; H, 5.82; N, 0.97. Found: C, 70.74; H, 5.77; N, 1.01.

Methyl O-*(2-deoxy-2-phthalimido-β*-D-*galactopyranosyl)-(1→4)*-O-*(2,3,6-tri*-O-*benzyl-β*-D-*galactopyranosyl)-(1→4)-(2,3,6-tri*-O-*benzyl-β*-D-*glucopyranoside)* (**22**). — A solution of the fully protected trisaccharide **21** (1.2 g, 834 μmol) in absolute methanol (50 mL) and absolute cyclohexane (15 mL) was treated with sodium methoxide (1 mL of a 2%, w/v, solution of sodium in methanol). After ~2 h, the

solution was de-ionized with Rexyn 101 (H^+) ion-exchange resin, filtered, the filtrate evaporated, and the residue chromatographed on silica gel with 3:1 (v/v) Skellysolve B–ethyl acetate as the eluant. Pure **22** (735 mg, 75%) was obtained as a syrup; $[\alpha]_D^{24}$ −12.2° (*c* 2.0, dichloromethane); ^{13}C-n.m.r. ($CDCl_3$): δ 104.7 ($J_{C\text{-}1,H\text{-}1}$ 160 Hz, C-1), 102.0 ($J_{C\text{-}1',H\text{-}1'}$ 159 Hz, C-1′), and 99.9 ($J_{C\text{-}1'',H\text{-}1''}$ 164 Hz, C-1″).

Anal. Calc. for $C_{69}H_{73}NO_{18}$: C, 68.81; H, 6.11; N, 1.16. Found: C, 69.01; H, 6.28; N, 1.08.

Methyl O-*(2-acetamido-2-deoxy-β-*D-*galactopyranosyl)-(1→4)-*O-*(2,3,6-tri-*O-*benzyl-β-*D-*galactopyranosyl)-(1→4)-(2,3,6-tri-*O-*benzyl-β-*D-*glucopyranoside)* (**23**). — A solution of the *O*-deacylated trisaccharide **22** (753 mg, 625 μmol) in ethanol (50 mL) and 85% hydrazine hydrate (1.5 mL) was boiled under reflux for 4 h, and then evaporated under diminished pressure. The resulting syrup was thoroughly dried, dissolved in methanol (100 mL), treated with acetic anhydride (10 mL), and the mixture kept for 18 h at 20°. Evaporation of traces of solvent, and co-distillation with toluene, left a solid from which non-carbohydrate material was removed by crystallization from ethyl acetate. The combined mother liquors were applied to a column of silica gel which was eluted with ethyl acetate, to yield 675 mg (96%) of **23**; $[\alpha]_D^{24}$ +5.4° (*c* 0.9, dichloromethane).

Anal. Calc. for $C_{63}H_{73}NO_{17}$: C, 67.79; H, 6.59; N, 1.25. Found: C, 67.96; H, 6.77; N, 1.21.

Methyl O-*2-acetamido-2-deoxy-β-*D-*galactopyranosyl-(1→4)-*O-*β-*D-*galacto-pyranosyl-(1→4)-β-*D-*glucopyranoside* (**24**). — A solution of **23** (526 mg, 0.47 mmol) in ethanol (50 mL) was hydrogenolyzed at 505 kPa in the presence of 10% palladium-on-carbon (100 mg). After 60 h, the suspension was filtered, and the filtrate was evaporated, yielding 258 mg (95%) of pure trisaccharide **24**; $[\alpha]_D^{24}$ −10.1° (*c* 0.8, methanol); ^{13}C-n.m.r. (CD_3OD): δ 105.1 ($J_{C\text{-}1',H\text{-}1'}$ 159 Hz, C-1′,1″) and 104.4 ($J_{C\text{-}1,H\text{-}}$ 158 Hz, C-1); ^{1}H-n.m.r. (D_2O): δ 4.43 (d, *J* 8.0 Hz), 4.46 (d, *J* 7.9 Hz), and 4.68 (d, 1 H, *J* 8.2 Hz, H-1″).

Anal. Calc. for $C_{21}H_{36}NO_{16}$: C, 45.16; H, 6.49; N, 2.51. Found: C, 45.33; H, 6.60; N, 2.64.

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NOTE ADDED IN PROOF

After submission of this paper, we became aware of related work by S. Sabesan and R. U. Lemieux (*Can. J. Chem.*, in press). These authors, by using nitromethane as solvent, experienced no difficulty in glycosylating the O-4′ position of lactose.

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