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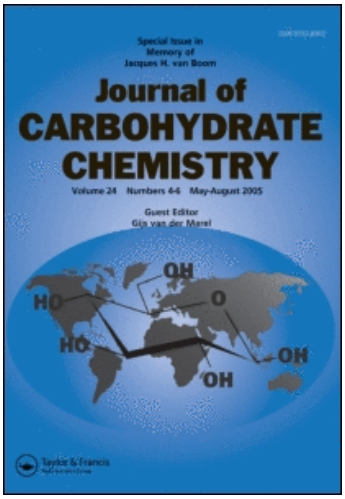

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J. CARBOHYDRATE CHEMISTRY, 9(2&3), 135-158 (1990)

ALTERNATIVE SYNTHESES OF (1→3)-β-D-GALACTO-OLIGOSACCHARIDES

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Dedicated to Professor Franz Effenberger on the occasion of his 60th birthday

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ABSTRACT

Galactosyl halides bearing different substituents at *O*-3 [*i.e.* acetyl (**15**), benzoyl (**14**), benzyl (**3**), bromoacetyl (**12**), and the 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl group (**17**)] have been prepared, and used to study the stereoselectivity of the coupling reaction to position *O*-3 of different galactose derivatives [*i.e.* methyl 2,4,6-tri-*O*-acetyl- (**9**) and 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (**7**), 1,2,4,6-tetra-*O*-benzoyl-β-D-galactose (**6**) and *O*-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-β-D-galactose (**33**)], as well as to benzoic acid. In more polar solvents, using silver trifluoromethanesulfonate as the promoter, a higher proportion of β-linked products was formed, whereas with silver perchlorate as the promoter the α-linked product predominated. Under basic conditions, applied to prevent anomerisation of 1-*O*-benzoylated nucleophiles **6** and **33**, no orthoesters were found as end products. Under those conditions, a better overall yield of the β-(1→3)-linked galactotriose **31** was obtained by condensation of the disaccharide glycosyl donor **17** and the monosaccharide glycosyl acceptor **6** than by condensation of **14** and **33**. The disaccharide glycosyl chloride **17** was obtained in 75% yield by the cleavage of the corresponding methyl glycoside with dichloromethyl methyl ether.

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INTRODUCTION

We recently described a general synthesis for the preparation of methyl β-glycosides of (1→3)-β-D-galacto oligosaccharides.[2] Starting from a single, readily available precursor, namely methyl 3-*O*-benzyl-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (2), we prepared oligosaccharides up to and including the heptaoside, by both stepwise and blockwise syntheses. However, occasionally the yields of the desired β-linked products were low, due to the lack of stereoselectivity and undesired side-reactions. Here we report attempts to improve the yields of β-(1→3)-couplings in the D-galactose series, and the exploration of some of the factors which might have an influence on the stereoselectivity in this type of glycosylation. Anderson and coworkers[3,4] observed that the substituent at *O*-4 in the D-galactosyl donors can noticeably influence the stereoselective outcome of the glycosylation reaction. It has also been noted[5] that yields over 90% of the desired (1→3)-β-linked products were obtained from the reaction of allyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside with 2-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-galactopyranosyl chloride, variously substituted at *O*-3. That finding suggests that benzyl ether groups in the nucleophile at the positions adjacent to the one to be glycosylated favorably influence the formation of the 1,2-*trans* linkage. However, the preparation of the benzylated synthons[6] from allyl α-D-galactopyranoside (not commercialy available) requires 6 and 9 steps, respectively. The starting materials used in our original approach[2] for the synthesis of (1→3)-β-linked galacto-oligosaccharides (compounds **3** and **7**) can be prepared each in 3 steps from (commercially available) methyl β-D-galactopyranoside. To preserve this advantage we decided to evaluate the influence of the substituent at *O*-3, in otherwise fully acylated α-D-galactopyranosyl halides, on the stereoselectivity of the condensation with acylated glycosyl acceptors.

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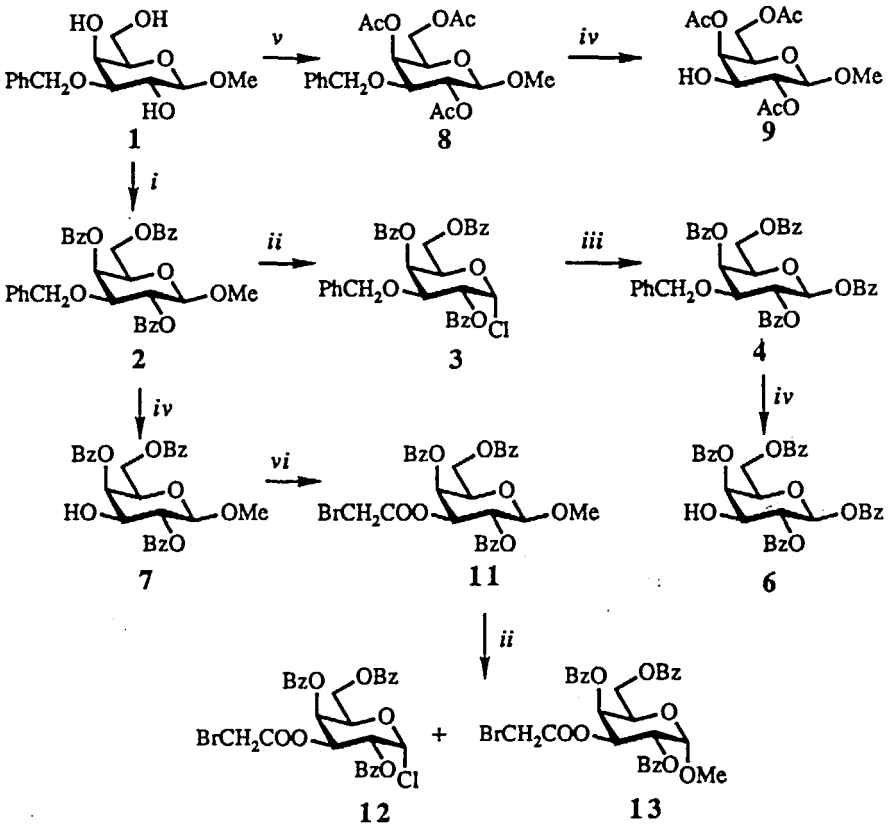
RESULTS

Most galactosyl donors and acceptors (Scheme I) used in this study were prepared from a single precursor, methyl 3-*O*-benzyl-β-D-galactopyranoside (**1**), readily available from methyl β-D-galactopyranoside.[7] Benzoylation of **1** gave methyl 3-*O*-benzyl-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (**2**),[7] which was converted to 3-*O*-benzyl-2,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl chloride (**3**) by treatment with dichloromethyl methyl ether (DCMME).[8] Reaction of **3** with silver benzoate in acetonitrile yielded 3-*O*-benzyl-1,2,4,6-tetra-*O*-benzoyl-β-D-galactopyranose (**4**) in 89% yield. Hydrogenolysis of **2** and **4** gave nucleophiles **7** (ref. 7) and **6** (91%), respectively. The galactosyl-acceptor methyl 2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (**9**) was prepared in a similar manner, by acetylation of

Scheme I



i : BzCl, pyridine, ref. 7; *ii* : Cl_2CHOMe, $ZnCl_2$, ref.8; *iii* : AgOBz;
iv : Pd/C, H_2; *v* : Ac_2O, pyridine; *vi* : $BrCH_2COBr$, collidine.

1, to give methyl 3-*O*-benzyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (**8**, 91%), and subsequent hydrogenolysis of **8**, to give **9** in a virtually theoretical yield. Bromoacetylation of **7** followed by treatment of the formed **11** with DCMME yielded crystalline chloride **12** (81%). As found[8-10] in other conversions of methyl β-D-glycosides to glycosyl chlorides by DCMME,[11] the cleavage of **11**→**12** was accompanied by anomerisation of the glycoside. Thus methyl 3-*O*-bromoacetyl-2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (**13**) was isolated from this reaction (3%). In the preparation of galactosyl chlorides, it was observed[10] that a bromoacetyl group (at position *O*-6) in methyl β-D-galactopyranosides

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Table I N.m.r. spectra of **6**, **10**, **11** and **12**

atom/ coupling-constant	chemical shift (δ)			
	6	**10**	**11**	**12**
H-1	6.19 d	4.74 d	4.66 d	6.60 d
H-2	5.72 dd	5.84 dd	5.65 dd	5.70 dd
H-3	4.32 dd	5.61 dd	5.41 dd	5.83 dd
H-4	5.86 bd	5.83 bd	5.85 bd	5.98 bd
H-5	4.39 bd	4.04 bt	4.26 bt	4.87 t
H-6a	4.58 dd	3.85 dd	4.67 dd	4.60 dd
H-6b	4.45 dd	3.67 dd	4.40 dd	4.42 dd
OCH_3		3.58 s	3.60 s	
$BrCH_2a$			3.68 d	3.72 d
$BrCH_2b$			3.63 d	3.66 d
$J_{1,2}$	8.3	7.9	7.8	4.1
$J_{2,3}$	10.0	10.4	10.5	11.5
$J_{3,4}$	3.4	3.4	3.4	3.2
$J_{4,5}$	<1.0	<1.0	<1.0	<1.0
$J_{5,6a}$	6.1	6.6	5.4	6.6
$J_{5,6b}$	6.1	7.0	6.8	6.1
$J_{6a,6b}$	11.0	11.9	11.2	11.5
J_{CH_2}			12.7	12.6
C-1	92.7	102.5	102.3	91.3
C-2	72.3	69.9	69.3	68.4
C-3	71.7	71.8	72.9	69.2
C-4	70.3	69.0	67.7	67.9
C-5	72.5	74.0	71.1	69.9
C-6	62.2	60.6	61.8	61.7
OCH_3		57.2	57.1	
$BrCH_2$			25.0	24.9

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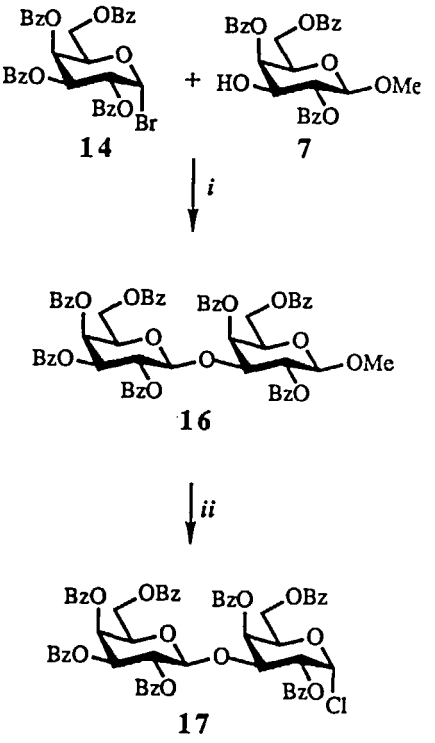
decreased their reactivity with DCMME when compared to a benzoyl group at that position. Analogously, under similar conditions, the conversion **11**→**12** was considerably slower than that[8] of the methyl β-D-galactopyranoside **2** to **3** (3h for **11**→**12** *vs.* 1h for **2**→**3**).

The key compound in our previous blockwise synthesis of higher β-(1→3)-linked galactooligosaccharides was *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactosyl chloride (**17**). It was prepared[2] from the corresponding 1-*O*-acetyl-β-D-galactobiose, and it allowed the synthesis of larger building blocks in this series. Similarly to other conversions of acetylated[11] and benzoylated[12] methyl glycosides of disaccharides to glycosyl chlorides, we have now greatly simplified the preparation of **17** by direct treatment of **16** with DCMME (Scheme II).

Scheme II



i : AgOTf, ref. 7;
ii : Cl_2CHOMe, $ZnCl_2$

Coupling reactions are presented in Tables II and III. Nucleophile **33** (entry 17, table III) was prepared in theoretical yield (see Experimental) from β-**27** (entry 14, Table III) by treatement with thiourea. 2,4,6-Trimethylpyridine was used as a base in this debromoacetylation reaction, to prevent anomerisation of **33**. It was previously found, that the pseudohydantoin hydrobromide, formed during debromoacetylation,[13,14] is sufficiently acidic to cause acetyl group migration.[15]

DISCUSSION

In their study of the factors which influence the stereoselectivity of the silver trifluoromethanesulfonate (silver triflate)-promoted Koenigs-Knorr reaction, Garegg and

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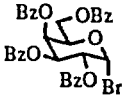
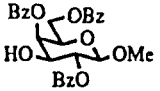
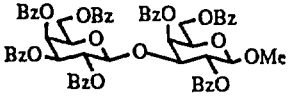
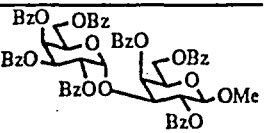
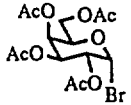
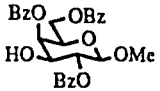
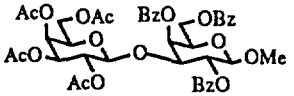
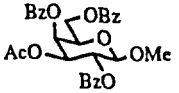
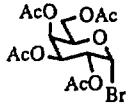
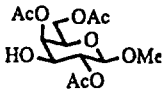
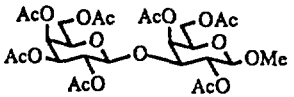
Table II Condensation of glycosyl halides **3**, **14** and **15** with acceptors **7**, **9**, **10**, and benzoic acid under various conditions.

Entry	Donor	Acceptor	Conditions[a]/ Solvent	Products	
					
	14	**7**		**16**	**18**
1			A CH_2Cl_2	68%	27%
2			A toluene	58%	32%
3[b]			A toluene/CH_3NO_2	85%	not determined
					
	15	**7**		**19**	**20**
4			A CH_2Cl_2	59%	13%
					
	15	**9**		**21**	
5			A CH_2Cl_2	50%	several byproducts

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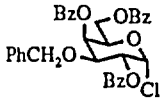
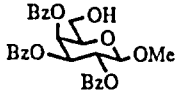
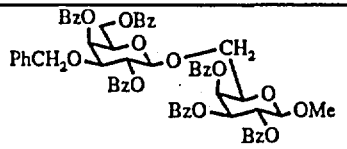
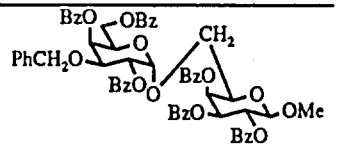
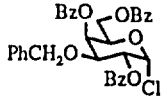
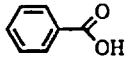
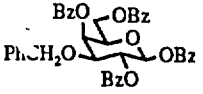
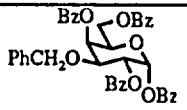
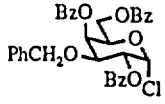
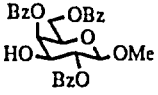
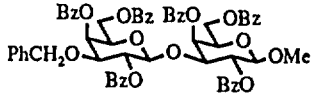
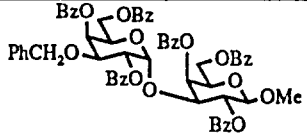
					
	3	**10**		**22**	**23**
6			A CH_2Cl_2	85%	<8.5%[c]
					
	3			**4**	**24**
7			A CH_2Cl_2	32%	41%
8			A CH_3CN[d]	37%	traces
9			A toluene/CH_3NO_2	41%	17.5%
					
	3	**7**		**25**	**26**
10			A CH_2Cl_2	37%	not determined[e]
11			B CH_2Cl_2	decomposition	
12			C toluene	12%	50%[c]

[a] A: AgOTf, acidic conditions; B: $AgClO_4$, acidic conditions; C: $AgClO_4$, basic conditions. [b] data from ref.7 [c] contains one unidentified byproduct [d] incomplete reaction after 15 h at room temp. [e] several byproducts were formed.

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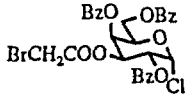
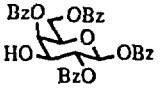
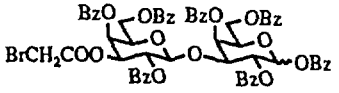
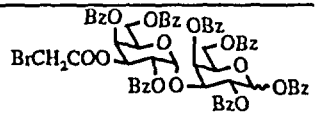
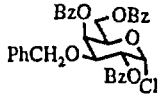
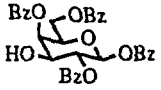
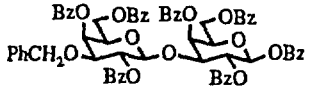
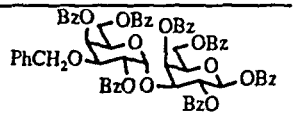
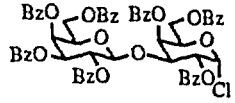
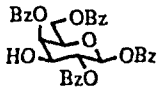
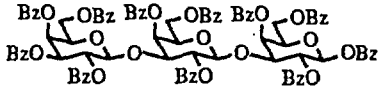
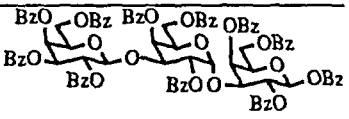
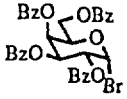
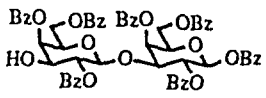
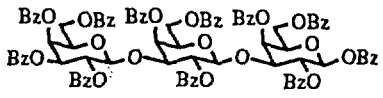
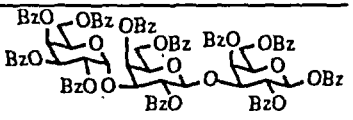
Table III Condensation of glycosylhalides **3**, **12**, **14** and **17** with acceptors **6** and **33** under various conditions.

Entry	Donor	Acceptor	Conditions[a]/ Solvent	Products	
					
	12	**6**		α,β-**27**	α,β-**28**
13			A CH_2Cl_2	62% (α:β = 2:1)	not determined[b]
14			B CH_2Cl_2	58% (pure β)	35% (α:β = 1:2)[b,c]
					
	3	**6**		**29**	**30**
15			B CH_2Cl_2	40%	49%
					
	17	**6**		**31**	**32**
16			B CH_2Cl_2	63%	24%[b]
					
	14	**33**		**31**	**34**
17			B CH_2Cl_2	36%	43%

[a] A: AgOTf, acidic conditions; B: AgOTf, basic conditions [b] several by products formed [c] isomerisation during chromatography

coworkers[16] noted a significant solvent dependence: in less polar solvents a larger amount of *simple* β-D-glucosides was formed. In this work, that trend[16] could not be fully confirmed and, in some cases, with the decreased polarity of the solvent used (entry 1-3 and 7-9, also see below), the α/β-ratio of the formed (1→3)-linked glycosylation products actually increased. Care must be taken, however, since the condensation of **7** and **14** in dichloromethane (α:β=1:2.5, entry 1), and that performed in toluene (α:β=1:1.8, entry 2) are not quite comparable. This, because a silver triflate-promoted Koenigs-Knorr reaction performed in dichloromethane is largely a heterogenous reaction, and may follow a different mechanism[17] than the one operative under homogenous conditions, such as in the reaction conducted in toluene. In the glycosylation of benzoic acid with chloride **3** (entry 7-9), the solvent dependence is even more dramatic. Anomerization under acidic conditions of the initially formed β-1-*O*-benzoyl derivatives cannot be excluded, but it is unlikely to account for the considerable amount of the α-benzoate found among the final products of the reactions carried out in dichloromethane or in a toluene/nitromethane mixture (entries 7, 9). This, because β → α anomerization would be expected to take place more readily in a polar solvent such as acetonitrile than in dichloromethane. When the reaction was carried out in acetonitrile (entry 8), the total yield of the desired product was unimpressive, but only a trace of the α-product **24** was formed (TLC). The significant decrease in the reactivity of **3** in acetonitrile, compared with dichloromethane, is due to an intermediate adduct of the solvent and the formed oxonium ion.[18] It was noted previously that in silver carbonate-promoted glycosylations no reaction took place when acetonitrile was used as the solvent.[17] From the outcome of the reaction of silver benzoate with **3**, which led exclusively to the β-1-*O*-benzoylated derivative **4**, it is clear that a different mechanism must be involved in this case. The highly stereoselective formation of β-1-*O*-acyl derivatives in the reaction of **3** with silver acetate in acetonitrile[8] and of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with silver propionate[17] was also observed. Paulsen[19] in fact found that the regioselectivity in the glycosylations of lactose derivatives, having 3^2- and 4^2-*O* free, depended strongly on whether a homogenous or a heterogenous catalyst was used. Interestingly, the observed solvent-dependence of the stereoselectivity of β-(1→3) couplings in the galactose series was reversed when silver perchlorate was used as the promotor (entries 11-12). Here, the α-linked disaccharide **26** became the major product when toluene was used as the solvent and when the reaction was conducted under basic conditions. The latter conditions were applied, since under acidic conditions, in dichloromethane as the solvent (entry 11), the reaction components decomposed (TLC). We do not have an explanation for the failure of the latter condensation of **3** and **7** (for successful condensations under similar conditions see ref. 20, 21), but the results clearly demonstrate the importance of the promotor and the acid formed from it (triflic acid *vs.* perchloric acid) upon the overall outcome of the glycosylation reaction.

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Replacement of the benzoyl protecting groups in the glycosyl donor (entry 4), or in both the donor and the acceptor, with acetyl groups (entry 5) did not affect the stereoselectivity. However, several by-products were formed during the coupling of 2,3,4,6-tetra-O-benzoyl-α-D-galactopyranosyl bromide (**15**) to **7** and **9** which complicated the isolation, and lowered the yields, of products **19** and **21**. In the case of donor **15** and nucleophile **7**, an intermolecular transesterification took place during the condensation, and the acetylated methyl galactoside **20** was isolated in 13% yield. This side-reaction can be anticipated as a complication[16] in silver triflate-promoted Koenigs-Knorr reactions using acetylated glycosyl halides, and was previously observed in β-(1→6)-couplings.[22,23] On the other hand, a noteworthy advantage of the use of fully acetylated donor **15** and acceptor **9** (entry 4) is that crystalline **21** is obtained and, thus, the final purification of **21** is facilitated. Compound **21** was previously obtained as an intermediate in an oligosaccharide synthesis, but was not fully characterized.[24] The fully benzoylated disaccharide **16** was obtained in 84% overall yield by deacetylation of **21** and subsequent benzoylation, without isolation of the intermediate, unprotected disaccharide.

A comparison of the condensation of 2,4,6-tri-*O*-benzoyl-3-*O*-benzyl-α-D-galactopyranosyl chloride (**3**) with **10** (entry 6) and **7** (entry 10), respectively, clearly shows how the targeted position influences the glycosylation. According to the mechanism proposed by Garegg,[16] rearrangement of an intermediate orthoester (**A**), through an ion-pair (**B** and **C**), is the rate-determing step in the Koenigs-Knorr reaction (Scheme III, path **a**). Thus, the condensation of the nucleophile **7**, derived from a secondary alcohol, requires the more reactive intermediate **C** and, therefore, **7** reacts with lack of stereoselectivity. The more reactive alcohol **10** proceeds *via* **B** and thus gives mainly the β-product **22**. The observed solvent-dependence of the stereoselectivity of the coupling reactions investigated cannot be explained by this model because in a more polar solvent the reaction *via* intermediate **C** should be favored and, consequently, lead to a α/β-ratio close to 1. As mentioned above, especially in a heterogenous system (such as silver triflate/dichloromethane or silver benzoate/acetonitrile) another mechanism may be involved in the Koenigs-Knorr reaction, *e.g.* one which does not proceed *via* an orthoester intermediate (Scheme III, path **b**).[17] In the case of silver benzoate the reaction can proceed *via* **F**, to give the β-product. In a reaction carried out under heterogenous catalysis and in a less polar solvent path **b** could dominate, and this would lead to the formation of α- and β-product *via* **D** and **E**. Intermediate **E** can also react *via* **B**, to give the β-product. This pathway should be favored in more polar solvents where the reaction takes place under homogenous conditions. On the other hand, the pathway *via* **E** and **B** should also result in orthoester formation when basic conditions are applied. In path **b**, however, no orthoester formation is involved, and the α/β-ratio is determined by such factors as the bulkiness of

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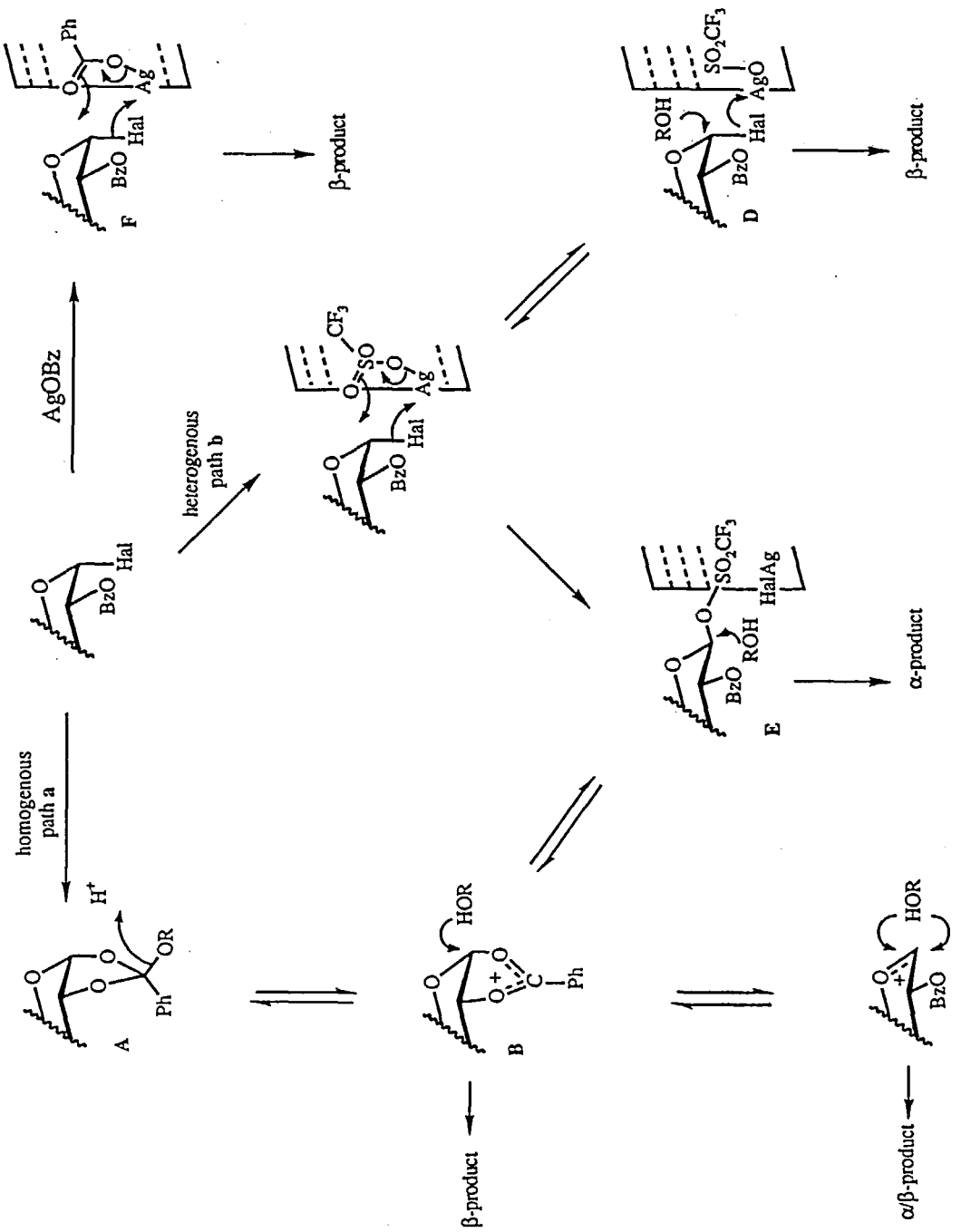
Scheme III



the alcohol, the nature of the solvent (which may participate in the transition state), or the specific silver salt used as the promotor. That this is so is suggested by the outcome of those reactions which were performed in the presence of an excess of 2,4,6-trimethylpyridine (entry 14-17). These basic conditions were required to prevent anomerisation[25] of the 1-*O*-acylated nucleophiles **6** and **33** (entry 13). Under those conditions the formation of a significant amount of orthoester could never be detected, even though the use of an excess of base in Koenigs-Knorr reactions is the classical condition for orthoester preparation.[26] Only in the condensation of the bromoacetylated glycosyl chloride **12** (entry 14) and of the disaccharide chloride **17** (entry 16) with the nucleophile **6**, was one of the by-products presumed to be an orthoester. In the carbon NMR spectra of these compounds, a peak at 121.1 and 121.2 ppm, respectively, could be assigned to the quartenary carbon atom of an orthoester[25] (details not given in the Experimental).

Replacement of the benzyl protecting group in donor **3** by a bromoacetyl group, retaining the option to further extend the chain, resulted in a more stereoselective formation of the desired β-product (entry 14 and 15). This, however, was not an overall improvement, because pure bromoacetylated disaccharide **β-27** was difficult to isolate.

Entries 16 and 17 demonstrate the advantage of a blockwise synthesis of higher β-D-(1→3)-linked galactooligosaccharides over a stepwise approch. Condensation of the disaccharide chloride **17** and of the monosaccharide **6** gave a higher yield of the β-product than the coupling of **14** to the disaccharide-nucleophile **33**.

In summary, the formation of β-D-galactopyranosyl linkage strongly depends on the nature of the nucleophile and, when the glycosyl acceptor is a carbohydrate derivative, on the glycosylated position. Also, our results indicate that the formation of β-(1→3)-linkage does not fully follow the generally accepted orthoester-mechanism.[16,19] Especially in the reactions carried out under heterogenous conditions, an alternative pathway has to be considered. We have found that substituents at position *O*-3 in the glycosyl donor affect the outcome of the glycosylation reaction. This finding suggests a more complex mechanism than that involving a simple orthoester intermediate, the formation of which should be affected only by the nature of the substituent at *C*-2.

EXPERIMENTAL

General Methods. Optical rotations were measured at 25° with a Perkin-Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (TLC) on precoated

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slides of Silica Gel G F254 (Analtech) was performed with solvent mixtures of appropriately adjusted polarity consisting of *A*, carbon tetrachloride-acetone; *B*, toluene-acetone; *C*, ethyl acetate-petroleum ether; *D*, toluene-tetrahydrofuran; *E*, carbon tetrachloride-ethyl acetate; *F*, toluene-ethyl acetate. Detection was effected by charring with 5% sulfuric acid in ethanol and, when applicable, with UV light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, No. 9385, or No. 15111). To chromatograph glycosyl chlorides, the silica gel was dried at 160 °C for 16 h. NMR data in Table I were extracted from spectra taken for solutions in $CDCl_3$, using a Bruker AM 500 spectrometer and standard software supplied by the manufacturer. The assignments reported therein were made by homonuclear *and* heteronuclear 2-dimensional NMR correlation spectroscopy. NMR data presented in Experimental were extracted from spectra measured at 25 °C with a Varian XL 300 spectrometer. In these cases, proton-signal assignments were made by first-order analysis of the spectra, and were supported by homonuclear decoupling experiments. Of the two magnetically non-equivalent geminal protons, the one resonating at a lower field is denoted Ha and the one resonating at a higher field is denoted Hb. Carbon-signal assignments found therein were made by mutual comparison of the spectra, and by comparison with spectra of related substances.[2] The superscripts used in reporting the NMR data for oligosaccharides denote the sugar residues or groups containing the designated proton or carbon atom. These are serially numbered, beginning with the reducing residue. For example, $H\text{-}1^2$ refers to H-1 of the second sugar residue. All chemical shifts are reported relative to TMS. Reactions requiring anhydrous conditions were performed under argon using common laboratory glassware, and reagents and solvents were handled with Hamilton, Series 1000 gas-tight syringes. Unless stated otherwise, solutions in organic solvents were dried with anhydrous magnesium sulfate, and concentrated at 2 kPa/40 °C. The preparation of methyl 2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (**10**), which was used as a glycosyl acceptor for comparative purposes, is described elsewhere.[11]

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1,2,4,6-Tetra-*O*-benzoyl-3-*O*-benzyl-β-D-galactopyranose (**4**). - To a solution of **3** (2.01 g, 3.35 mmol) in acetonitrile (10 mL) was added silver benzoate (1.14 g, 5.00 mmol), and the suspension was stirred in the dark at 50 °C for 24 h. After filtration and washing of the solids with dichloromethane, the combined filtrates were washed with aqueous thiosulfate solution and the organic layer was dried and concentrated. Chromatography (solvent *E*, 15:1) of the residue, gave **4** (2.05 g, 89%), as a white foam, $[\alpha]_D$ +66.8° (*c* 1.1, chloroform), ^1H NMR ($CDCl_3$): δ 6.07 (d, 1H, H-1, $J_{1,2}$ 8.4), 6.02 (bd, 1H, H-4, $J_{3,4}$ 3.4, $J_{4,5} < 1$), 5.88 (bt, 1H, H-2, $J_{2,3}$ 9.8), 4.76 (d, 1H, CH_2a, *J* 12.9), 4.57 (d, 1H, CH_2b), 4.62 (dd, 1H, H-6a, $J_{6a,6b}$ 11.5), 4.47 (dd, 1H, H-6b), 4.35 (t, 1H, H-5, $J_{5,6}$ 6.4) and 3.97 (dd, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ 93.06 (C-1), 76.25 (C-3), 72.57 (C-5), 71.34 (CH_2), 70.01 (C-2), 66.61 (C-4) and 62.40 (C-6).

Anal. Calcd for $C_{41}H_{34}O_{10}$: C, 71.71; H, 4.99. Found: C, 71.60; H, 5.00.

1,2,4,6-Tetra-*O*-benzoyl-β-D-galactopyranose (6). - A solution of **4** (535 mg, 0.78 mmol) in 2-methoxyethanol (25 mL) was hydrogenolyzed in the presence of palladium on charcoal (5%, ~300 mg), until TLC (solvent *A*, 10:1) showed complete conversion of **4**. After filtration through Celite, the filtrate was concentrated, and the residue was crystallized from ethanol-carbon tetrachloride, to give **6** (422 mg, 91%), mp 222 °C, $[\alpha]_D$ +12.9° (*c* 0.8, chloroform).

Anal. Calcd for $C_{34}H_{28}C_{10}$: C, 68.45; H, 4.73. Found: C, 68.19; H, 4.78.

Methyl 2,4,6-Tri-*O*-acetyl-3-*O*-benzyl-β-D-galactopyranoside (8). - Methyl 3-*O*-benzyl-β-D-galactopyranoside[7] (**1**), (2.84 g, 10.0 mmol) was acetylated with acetanhydride/pyridine (1:2, 30 mL) and a catalytic amount of N,N-dimethylaminopyridine, to give **8** (3.74 g, 91%), mp (from ethanol, twice) 123 °C, $[\alpha]_D$ +51.4° (*c* 1.9, chloroform), ref. 27: mp 121-123 °C, $[\alpha]_D$ +48° (chloroform); ^{1}H NMR ($CDCl_3$) δ: 5.57 (bd, 1H, H-4, $J_{3,4}$ 3.4, $J_{4,5}$ <1), 5.12 (dd, 1H, H-2, $J_{1,2}$ 8.1, $J_{2,3}$ 10), 4.70 (d, 1H, CH_2a, *J* 12.2), 4.40 (d, 1H, CH_2b), 4.30 (d, 1H, H-1), 4.18 (d, 2H, H-6a,6b, $J_{5,6}$ 6.6), 3.54 (dd, 1H, H-3), 3.48 (s, 3H, OCH_3), 2.16, 2.08 and 2.04 (3 x s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 102.11 (C-1), 76.82 (C-3), 70.97, 70.46 (C-2,5), 65.99 (C-4), 61.99 (C-6), 56.65 (OCH_3), 20.92, 20.81 and 20.73 (3 x CH_3).

Methyl 2,4,6-Tri-*O*-acetyl-β-D-galactopyranoside (9). - Compound **8** (2.05 g, 5.0 mmol) was hydrogenolyzed as described for the preparation of **6**, to give, after recrystallisation from acetone/petroleum ether, **9** (1.58 g, 99%), mp 110-111 °C, $[\alpha]_D$ -22.3° (*c* 1.1, chloroform), ref. 28: mp 110 °C; ^{1}H NMR ($CDCl_3$) δ: 5.34 (bd, 1H, H-4, $J_{3,4}$ 2.8, $J_{4,5}$ <1), 4.98 (dd, 1H, H-2, $J_{1,2}$ 7.9, $J_{2,3}$ 10), 4.36 (d, 1H, H-1), 4.17 (bd, 2H, H-6a,6b), 3.87-3.80 (m, 2H, H-3,5), 3.52 (s, 3H, OCH_3), 2.77 (d, 1H, OH, $J_{3,OH}$ 6.6), 2.18, 2.13 and 2.07 (3 x s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 101.94 (C-1), 72.77 (C-2), 71.71 (C-3), 71.13 (C-5), 69.93 (C-4), 56.98 (OCH_3), 21.10, 20.88 and 20.81 (3 x CH_3).

Methyl 2,4,6-Tri-*O*-benzoyl-3-*O*-bromoacetyl-β-D-galactopyranoside (11). - Bromoacetyl bromide (2.02 g, 10.0 mmol) in dichloromethane (10 mL) was added dropwise at 0 °C to a solution of methyl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside[7] (**7**), (4.05 g, 8.0 mmol) and 2,4,6-trimethylpyridine (1.21 g, 10.0 mmol) in dichloromethane (50 mL. After stirring for 15 min at room temperature, the mixture was filtered and the filtrate was washed successively with dilute, aqueous HCl and sodium hydrogen carbonate solution. After concentration of the organic layer, the residue was chromatographed (solvent *A*, 10:1), to give **11** (5.00 g, 99.6 %), as a white foam, $[\alpha]_D$ +43.9° (*c* 1.6, chloroform).

Anal. Calcd for $C_{30}H_{27}BrO_{10}$: C, 57.43; H, 4.34; Br, 12.74. Found: C, 57.38; H, 4.34; Br, 12.65.

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2,4,6-Tri-*O*-benzoyl-3-*O*-bromoacetyl-α-D-galactopyranosyl Chloride (12). - To a solution of **11** (4.71 g, 7.5 mmol) in chloroform (10 mL) was added dichloromethyl methyl ether (7.0 mL) and zinc chloride (~20 mg), and the mixture was stirred at 60 °C for 3 h, when TLC (solvent *A*, 10:1) showed conversion of **11** into a major and a minor, faster moving product. After concentration of the mixture, and coevaporation with toluene, the residue was chromatographed (gradient, toluene to solvent *F*, 15:1), to give first **12** (3.83 g, 81%), mp 132 °C (from diethyl ether/petroleum ether 1:1), $[\alpha]_D$ +143.7° (*c* 1.0, chloroform).

Anal. Calcd for $C_{29}H_{24}BrClO_9$: C, 55.13; H, 3.83; Br, 12.65; Cl, 5.61. Found: C, 55.22; H, 3.88; Br, 12.70; Cl, 5.64.

Eluted next was **13** (0.16 g, 3%, as a white foam), $[\alpha]_D$ +109.6° (*c* 0.4, chloroform); ^{1}H NMR ($CDCl_3$) δ: 5.90 (bd, 1H, H-4, $J_{3,4}$ 3.4, $J_{4,5}$ <1), 5.78 (dd, 1H, H-3, $J_{2,3}$ 10.7), 5.52 (dd, 1H, H-2, $J_{1,2}$ 3.5), 5.30 (d, 1H, H-1), 4.59 (dd, 1H, H-6a, $J_{6a,6b}$ 10.3), 4.53 (t, 1H, H-5, $J_{5,6a}$ 6.9, $J_{5,6b}$ 5.0), 4.37 (dd, 1H, H-6b), 3.71 (d, 1H, $BrCH_2$a, *J* 12.5), 3.64 (d, 1H, $BrCH_2$b) and 3.46 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 97.49 (C-1), 69.69 (C-3), 69.03, 68.87 (C-2,4), 66.67 (C-5), 62.48 (C-6), 55.74 (OCH_3) and 25.07 ($BrCH_2$). MS (ci, NH_3), m/e: 644, 646 (~1:1), $(MH+NH_3)^+$; 595, 597 (~1:1), $(MH-MeOH)^+$.

***O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl chloride (17).** - To a solution of methyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside[7] (**16**, 1.675 g, 1.54 mmol) and dichloromethyl methyl ether (7.0 mL) in chloroform (15 mL) was added $ZnCl_2$ (~30 mg) and the mixture was stirred at 60 °C for 2 h, when TLC (solvent *A*, 5:1) showed the formation of a single faster moving product. Work up, as described for the preparation of **12**, gave, after chromatography (gradient, solvent *A*, 20:1 to 15:1), **17** (1.26 g, 75%, white foam), $[\alpha]_D$ +144° (*c* 1.1, chloroform), ref. 2: +145° (*c* 0.9, chloroform); NMR spectra were identical with those reported.[2]

***O*-(2,4,6-Tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-*O*-benzoyl-β-D-galactopyranose (33).** - To a solution of β-**27** (357.6 mg, 0.3 mmol) in methanol/dichloromethane 1:1 (20 mL) was added thiourea (91.3 mg, 1.4 mmol) and 2,4,6-trimethylpyridine (36.5 mg, 0.3 mmol), and the mixture was stirred at room temperature until TLC (solvent *A*, 5:1) showed that the reaction was complete (~2h). After evaporation of the solvent, chromatography (solvent *A*, 5:1) gave **33** (325 mg, theoret. yield), $[\alpha]_D$ +25.6° (*c* 0.7, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.08 (bd, 1H, H-4^1, $J_{31,41}$ 3.2, $J_{41,51}$ <1), 6.03 (d, 1H, H-1^1, $J_{11,21}$ 8.3), 5.93 (bb, 1H, H-2^1, $J_{21,31}$ 9.7), 5.67 (bd, 1H, H-4^2, $J_{32,42}$ 3.4, $J_{42,52}$ <1), 5.17 (dd, 1H, H-2^2, $J_{12,22}$ 7.7, $J_{22,32}$ 10.0), 4.95 (d, 1H, H-1^2), 4.64 (dd, 1H, H-6a^2, $J_{52,6a2}$ 6.9, $J_{6a2,6b2}$ 11.4), 4.50 (dd, 1H, H-6a^1,

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$J_{5^1,6a^1}$ 6.9, $J_{6a^1,6b^1}$ 11.6), 4.45 (dd, 1H, H-6b^1, $J_{5^1,6b^1}$ 5.5), 4.39 (dd, 1H, H-3^1), 4.37 (dd, 1H, H-6b^2, $J_{5^2,6b^2}$ 6.4), 4.25 (bt, 1H, H-5^1), 4.13 (bt, 1H, H-5^2) and 3.95 (dd, 1H, H-3^2); ^{13}C NMR ($CDCl_3$): δ 101.2 (C-1^2), 93.1 (C-1^1), 76.7 (C-3^1), 73.7 (C-2^2), 73.0 (C-5^1), 71.7 (2C, C-3^2,5^2), 70.4, 70.2 (2C, 1C, C-4^1,4^2,2^1), 62.7 (C-6^1) and 62.3 (C-6^2).

General Procedure for the Coupling Reactions (Table II, III). - A solution of glycosyl acceptor, glycosyl halide and 2,4,6-trimethylpyridine in the appropriate solvent was added to a mixture of silver triflate in the same solvent, at -20°→0 °C for glycosyl bromides **14** and **15**, and at room temperature for glycosyl chlorides **3**, **12** and **17**. The mixture was stirred until the reaction was complete, neutralized to litmus (if neccessary) by addition of 2,4,6-trimethylpyridine, and filtered. The filtrate was diluted with dichloromethane and washed with dilute, aqueous thiosulfate solution and water. The residue obtained after concentration was chromatographed.

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Methyl *O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-galacto-pyranoside (16) and Methyl *O*-(2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (18). - A) *Entry 1*: from **7** (101.3 mg, 0.2 mmol), **14** (197.8 mg, 0.3 mmol) and 2,4,6-trimethylpyridine (30.3 mg, 0.25 mmol) in dichloromethane (2 mL), and silver triflate (102.8 mg, 0.4 mmol) in dichloromethane (1 mL), after 15 min at 0 °C, as described in the general procedure. Chromatography (gradient, solvent *B*, 30:1 to 15:1) gave first **18** (59 mg, 27%, white foam), $[\alpha]_D$ +131.9° (*c* 0.9, chloroform), ^{1}H NMR ($CDCl_3$): δ 5.83 (bd, 1H, H-4^1, $J_{3^1,4^1}$ 3.9, $J_{4^1,5^1} < 1$), 5.82 (d, 1H, H-1^2, $J_{1^2,2^2}$ 4.1), 5.76 (dd, 1H, H-2^1, $J_{1^1,2^1}$ 7.7, $J_{2^1,3^1}$ 10), 5.75 (dd, 1H, H-2^2, $J_{2^2,3^2}$ 10.5), 5.52 (dd, 1H, H-3^2, $J_{3^2,4^2}$ 3.4), 5.36 (bd, 1H, H-4^2), 4.57 (dd, 1H, H-6a^2, $J_{5^2,6a^2}$ 6.8, $J_{6a^2,6b^2}$ 11.3), 4.46 (d, 1H, H-1^1), 4.50-4.40 (m, 2H, H-5^2,6b^1), 4.32 (dd, 1H, H-3^1), 4.25 (dd, 1H, H-6b^2, $J_{5^2,6b^2}$ 4.3), 4.23 (dd, 1H, H-6a^1, $J_{5^1,6a^1}$ 4, $J_{6a^1,6b^1}$ 10), 3.95 (bt, 1H, H-5^1) and 3.55 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 102.5 (C-1^1), 92.8 (C-1^2), 72.8 (C-3^1), 71.4 (C-5^1), 70.2 (C-4^2), 68.9 (C-3^2), 67.9 (C-5^2), 67.7 (C-4^1), 67.4 (C-2^2), 65.2 (C-2^1), 62.5 (C-6^2), 62.1 (C-6^1) and 57.0 (OCH_3).

Anal. Calcd for $C_{62}H_{52}O_{18}$: C, 68.63; H, 4.83. Found: C, 68.53; H, 4.86.

Eluted next was **16** (148 mg, 68%), $[\alpha]_D$ +91.0° (*c* 1.5, chloroform), ref. 7: +91.0° (*c* 1.26, chloroform), ^{1}H and ^{13}C NMR ($CDCl_3$) spectra were consistent with those reported.[7]

B) *Entry 2*: from **7** (506.5 mg, 1.0 mmol), **14** (991.1 mg, 1.35 mmol) and 2,4,6-trimethylpyridine (145.3 mg, 1.3 mmol) in toluene (5 mL), and silver triflate (513.9 mg, 2.0 mmol) in toluene (6 mL), after 30 min at -20 °C, as described in the general procedure. Chromatography gave first **18** (344.3 mg, 32%).

Eluted next was **16** (630.4 mg, 58 mg).

C) from **21**: compound **21** (1.30 g, 2.0 mmol) was dissolved in methanol (200 mL), a catalytic amount of sodium methanolate in methanol was added, and the solution was stirred at 40 °C for 3h. After neutralisation with Dowex 50 (H^+) and concentration, the solution of the residue in pyridine (50 ml) was treated at room temperature with benzoylchloride (2.80 g, 20 mmol). Work-up in the usual way gave **16** (1.82 g, 84%).

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (19) and Methyl 3-*O*-Acetyl-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (20). - *Entry 4*: from **7** (2.03 g, 4.0 mmol), **15** (2.06 g, 5.0 mmol) and 2,4,6-trimethylpyridine (545 mg, 4.5 mmol) in dichloromethane (10 mL), and silver triflate (1.54 g, 6.0 mmol) in dichloromethane (10 mL), after 20 min at -20 °C, as described in the general procedure. Chromatography (gradient solvent *C*, 4:1 to 3:2) gave first **20** (295 mg, 13%, white foam), $[\alpha]_D$ +40.0° (*c* 0.6, chloroform); ^{1}H NMR ($CDCl_3$): δ 5.85 (bd, 1H, H-4, $J_{3,4}$ 3.4, $J_{4,5}$ <1), 5.61 (dd, 1H, H-2, $J_{1,2}$ 7.9, $J_{2,3}$ 10.5), 5.39 (dd, 1H, H-3), 4.67 (dd, 1H, H-6a, $J_{5,6a}$ 6.4, $J_{6a,6b}$ 11.2), 4.66 (d, 1H, H-1), 4.39 (dd, 1H, H-6b, $J_{5,6b}$ 6.7), 4.25 (bt, 1H, H-5), 3.57 (s, 3H, OCH_3) and 1.88 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 102.5 (C-1), 71.3, 71.1 (C-3,5), 69.7 (C-4), 68.0 (C-2), 62.0 (C-6), 57.1 (OCH_3) and 20.5 (CH_3).

Anal. Calcd for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.15. Found: C, 65.59; H, 5.19.

Eluted next was **19** (1.97 g, 59%), $[\alpha]_D$ +26.2° (*c* 1.4, chloroform); ^{1}H NMR ($CDCl_3$): δ 5.80 (bd, 1H, H-4^1, $J_{3^1,4^1}$ 3.3, $J_{4^1,5^1}$ <1), 5.63 (dd, 1H, H-2^1, $J_{1^1,2^1}$ 7.9, $J_{2^1,3^1}$ 9.8), 5.23 (bd, 1H, H-4^2, $J_{3^2,4^2}$ 3.3, $J_{4^2,5^2}$ <1), 4.98 (dd, 1H, H-2^2, $J_{1^2,2^2}$ 7.8, $J_{2^2,3^2}$ 10.4), 4.73 (dd, 1H, H-3^2), 4.63 (d, 1H, H-1^2), 4.58 (d, 1H, H-1^1), 4.57 (dd, 1H, H-6a^1, $J_{5^1,6a^1}$ 6.0, $J_{6a^1,6b^1}$ 11.8), 4.49 (dd, 1H, H-6b^1, $J_{5^1,6b^1}$ 7.1), 4.19 (dd, 1H, H-3^1), 4.16 (bt, 1H, H-5^1), 4.13 (dd, 1H, H-6a^2, $J_{5^2,6a^2}$ 6.0, $J_{6a^2,6b^2}$ 11.2), 3.98 (dd, 1H, H-6b^2, $J_{5^2,6b^2}$ 7.3), 3.80 (bt, 1H, H-5^2), 3.51 (s, 3H, OCH_3), 2.03, 1.98, 1.84 and 1.49 (4 x s, 12H, 4 x CH_3); ^{13}C NMR ($CDCl_3$): δ 102.1 (C-1^1), 101.4 (C-1^2), 77.1 (C-3^1), 72.0 (C-5^1), 71.5 (C-2^1), 70.8, 70.7 (C-4^1,5^2), 70.2 (C-3^2), 68.5 (C-2^2), 66.7 (C-4^2), 63.1 (C-6^1), 61.1 (C-6^2), 56.7 (OCH_3), 20.7, 20.5, 20.4 and 19.8 (4 x CH_3).

Anal. Calcd for $C_{42}H_{44}O_{18}$: C, 60.28; H, 5.30. Found: C, 60.11; H, 5.36.

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (21). - *Entry 5*: from **9** (1.44 g, 4.5 mmol), **15** (2.26 g, 5.5 mmol) and 2,4,6-trimethylpyridine (0.61 g, 5.0 mmol) in dichloromethane (12 mL), and silver triflate (1.67 g, 6.5 mmol) in dichloromethane (12 mL), after 20 min at -20 °C, as described in the general procedure. TLC (solvent *D*, 3:1) showed one major product, together with several slower and faster moving by-products. Chromatography (gradient solvent *A*, 5:1 to 3:2) gave **21**(1.46 g, 50%), mp 189.5-190 °C (CH_2Cl_2/n-hexane, twice), $[\alpha]_D$ -7.7° (*c* 0.8, chloroform); ^{1}H NMR ($CDCl_3$): δ 5.39 (bd,

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1H, H-4^2, $J_{32,42}$ 3.4, $J_{42,52}$ <1), 5.35 (bd, 1H, H-4^1, $J_{31,41}$ 3.3, $J_{41,51}$ <1), 5.19 (dd, 1H, H-2^1, $J_{11,21}$ 8.1, $J_{21,21}$ 10), 5.09 (dd, 1H, H-2^2, $J_{12,22}$ 7.9, $J_{22,32}$ 10.5), 4.94 (dd, 1H, H-3^2), 4.57 (d, 1H, H-1^2), 4.30 (d, 1H, H-1^1), 4.16-4.07 (m, 4H, H-6a^1,6b^1,6a^2,6b^2), 3.86, 3.83 (2 x bt, 2 x 1H, H-5^1,5^2), 3.85 (dd, 1H, H-3^1), 3.49 (s, 3H, OCH_3), 2.17, 2.13, 2.11, 2.08, 2.06, 2.03 and 1.97 (7 x s, 21H, 7 x CH_3); ^{13}C NMR ($CDCl_3$): δ 101.8 (C-1^1), 101.1 (C-1^2), 75.9 (C-3^1), 71.4, 70.9, 70.7 (1C, 2C, 1C, C-3^2,4^1,5^1,5^2), 69.0, 68.7 (C-2^1,2^2), 66.8 (C-4^2), 62.2 (C-6^1), 61.0 (C-6^2) and 56.6 (OCH_3).

Anal. Calcd for $C_{27}H_{38}O_{18}$: C, 49.85; H, 5.89. Found: C, 49.88; H, 5.92.

Methyl *O*-(3-*O*-Benzyl-2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (22) and *O*-(3-*O*-Benzyl-2,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside (23). - *Entry 6*: from **10** (101.3 mg, 0.2 mmol), **3** (180.3 mg, 0.3 mmol) and 2,4,6-trimethylpyridine (30.3 mg, 0.25 mmol) in dichloromethane (2 mL), and silver triflate (102.8 mg, 0.4 mmol) in dichloromethane (1 mL), after 15 min at room temperature, as described in the general procedure. Chromatography (solvent *A*, 20:1) gave first **23** (18.0 mg, ~8.5%), contaminated with an unidentified by-product.

Eluted next was **22** (182.7 mg, 85%, white foam), $[\alpha]_D$ +114.5° (*c* 0.7, chloroform); ^{1}H NMR ($CDCl_3$): δ 5.89 (bd, 1H, H-4^2, $J_{32,42}$ 2.9, $J_{42,52}$ <1), 5.84 (bd, 1H, H-4^1, $J_{31,41}$ 3.4, $J_{41,51}$ <1), 5.66 (dd, 1H, H-2^1, $J_{11,21}$ 7.8, $J_{21,31}$ 10.4), 5.52 (dd, 1H, H-2^2, $J_{12,22}$ 8.0, $J_{22,32}$ 9.9), 5.49 (dd, 1H, H-3^1), 4.70 (d, 1H, $PhCH_2$a, J_{CH_2} 12.7), 4.68 (d, 1H, H-1^2), 4.53 (d, 1H, H-1^1), 4.50 (d, 1H, $PhCH_2$b), 4.44 (dd, 1H, H-6a^2, $J_{52,6a2}$ 6.8, $J_{6a2,6b2}$ 11.5), 4.33 (dd, 1H, H-6b^2, $J_{52,6b2}$ 6.1), 4.15 (m, 2H, H-6a^1,6b^1), 4.03 (bt, 1H, H-5^2), 3.78 (dd, 1H, H-3^2), 3.76 (m, 1H, H-5^1) and 3.16 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 102.1 (C-1^1), 101.3 (C-1^2), 76.0 (C-3^2), 73.1 (C-5^1), 71.7 (C-3^1), 71.4 (C-5^2), 71.0 (C-2^2), 70.9 ($PhCH_2$), 69.8 (C-2^1), 68.8 (C-4^1), 68.2 (C-6^1), 66.4 (C-4^2), 62.3 (C-6^2) and 56.7 (OCH_3).

Anal. Calcd for $C_{62}H_{54}O_{17}$: C, 69.53; H, 5.08. Found: C,69.44; H, 5.13.

1,2,4,6-Tetra-*O*-benzoyl-3-*O*-benzyl-β-D-galactopyranose (4) and 1,2,4,6-Tetra-*O*-benzoyl-3-*O*-benzyl-α-D-galactopyranose (24). - *Entry 7*: from benzoic acid (146.5 mg, 1.2 mmol), **3** (601.1 mg, 1.0 mmol) and 2,4,6-trimethylpyridine (109.1 mg, 0.9 mmol) in dichloromethane (5 mL), and silver triflate (359.7 mg, 1.4 mmol) in dichloromethane (5 mL), after 15 min at room temperature as described in the general procedure. Chromatography (solvent *E*, 15:1) gave first **24** (281 mg, 41%, white foam), $[\alpha]_D$ +170.2° (*c* 0.8, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.82 (d, 1H, H-1, $J_{1,2}$ 3.6), 6.12 (bd, 1H, H-4, $J_{3,4}$ 3.0, $J_{4,5}$< 1), 5.81 (dd, 1H, H-2, $J_{2,3}$ 10.4),

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4.83 (d, 1H, CH_2a, J 12.5), 4.64 (d, 1H, CH_2b), 4.61-4.55 (m, 2H, H-5,6a, $J_{5,6}$ 4.6, $J_{6a,6b}$ 9.6), 4.43 (dd, 1H, H-6b) and 4.36 (dd, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ 90.99 (C-1), 72.72 (C-3), 71.32 (CH_2Ph), 69.79 (C-5), 69.00 (C-2), 67.30 (C-4) and 62.47 (C-6).

Anal. Calcd for $C_{41}H_{34}O_{10}$: C, 71.71; H, 4.99. Found: C, 71.86; H, 5.04.

Eluted next was **4** (218 mg, 32%).

Entry 8: same as in entry 7, but in acetonitrile, after 15 min at room temperature, as described in the general procedure, TLC (solvent *E*, 10:1) showed no reaction; after 15 h at room temperature, chromatography gave **4** (252.7 mg, 37%).

Entry 9: same as in entry 7, but in toluene/nitromethane 1:1, after 15 min at room temperature, as described in the general procedure. Chromatography gave first **24** (120.5 mg, 17.5%).

Eluted next was **4** (282.9 mg, 41%).

Methyl *O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (25) and Methyl *O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (26). - *Entry 10*: from **7** (101.3 mg, 0.2 mmol), **3** (180.3 mg, 0.3 mmol) and 2,4,6-trimethylpyridine (30.3 mg, 0.25 mmol) in dichloromethane (2 mL), and silver triflate (102.8 mg, 0.4 mmol) in dichloromethane (1 mL), after 15 min at room temperature, as described in the general procedure. Chromatography (solvent *A*, 20:1) gave first 74.7 mg of a mixture of several unidentified products (^{1}H NMR).

Eluted next was **25** (79.8 mg, 37%), $[\alpha]_D$ +71° (*c* 1.0, chloroform), ref. 2: +72° (*c* 0.8, chloroform).

Entry 11: same as in entry 10, but now with silver perchlorate (83.0 mg, 0.4 mmol) in dichloromethane (1 mL). TLC (solvent *A*, 5:1), after 15 min at room temperature, showed the presence of several products resulting from decomposition of the starting materials.

Entry 12: same as in entry 11, but now with 2,4,6-trimethylpyridine (83.0 mg, 0.4 mmol) and toluene as solvent. After 30 min at 0 °C, as described in the general procedure; chromatography (gradient, toluene to solvent *B*: 25:1) gave first **26** (106.5 mg, ~50%), slightly contaminated with an unidentified by-product; ^{1}H NMR ($CDCl_3$), definite signals: δ 5.80 (bd, 1H, H-4^1, $J_{3^1,4^1}$ 3.0, $J_{4^1,5^1}$ <1), 5.74 (d, 1H, H-1^2, $J_{1^2,2^2}$ 3.5), 5.67 (dd, 1H, H-2^1, $J_{1^1,2^1}$ 8.0, $J_{2^1,3^1}$ 10.3), 5.49 (dd, 1H, H-2^2, $J_{2^2,3^2}$ 10.5), 5.26 (bd, 1H, H-4^2, $J_{3^2,4^2}$ 2.8, $J_{4^2,5^2}$ <1), 4.94-4.62 (m, 2H, H-6a^1,6a^2), 4.33 (d, 1H, PhCH_2a, J_{CH_2} 11.8), 4.29 (d, 1H, H-1^1), 4.19 (dd, 1H, H-3^1), 4.11 (d, 1H, PhCH_2b), 4.09 (dd, 1H, H-6b^2, $J_{5^2,6b^2}$ 6.5, $J_{6a^2,6b^2}$ 11.3), 3.85 (bt, 1H, H-5^1), 3.74 (dd, 1H, H-3^2) and 3.49 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 102.3 (C-1^1), 92.5 (C-1^2), 77.2 (C-3^2), 73.4 (C-3^1),

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71.7, 70.2 (C-5^1,5^2), 71.4 ($PhCH_2$), 69.2, 68.0, 67.8 (C-2^1,2^2,4^1), 65.2 (C-4^2), 63.0 (C-6^1), 62.1 (C-6^2) and 56.9 (OCH_3).

· *O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-bromoacetyl-β-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-*O*-benzoyl-β-D- (β-27) and α-D-galactopyranose (α–27) and *O*-(2,4,6-Tri-*O*-benzoyl-3-*O*-bromoacetyl-α-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-*O*-benzoyl-β-D-galactopyranose (28). - *Entry 13*: from **12** (631.9 mg, 1.0 mmol) and 2,4,6-trimethylpyridine (87.0 mg, 0.8 mmol) in dichloromethane (5 mL) and **6** (374.7 mg, 0.63 mmol), and silver triflate (308.3 mg, 1.2 mmol) in dichloromethane (6 mL), after 30 min at room temperature, as described in the general procedure. Chromatography (gradient, solvent *A*, 15:1 to 10:1) gave first 140 mg of a mixture of several by-products (^{1}H NMR).

Eluted next was α,β-**27** (α:β ~2:1, 468.0 mg, 62%); ^{1}H NMR ($CDCl_3$) showed definite signals of α-**27**: δ 6.78 (d, 1H, H-1^1, $J_{11,21}$ 3.8), 6.20 (bd, 1H, H-4^1, $J_{31,41}$ 3.1, $J_{41,51}$ <1), 5.80 (dd, 1H, H-2^1, $J_{21,31}$ 10.5), 5.77 (bd, 1H, H-4^2, $J_{32,42}$ 3.4, $J_{42,52}$ <1), 5.44 (dd, H-2^2, together with H-2^2 of β-**27**), 5.25 (dd, 1H, H-3^2, $J_{22,32}$ 10.4), 5.08 (d, 1H, H-1^2, $J_{12,22}$ 7.6), 4.76 (dd, 1H, H-$6a^2$, $J_{52,6a2}$ 5.6, $J_{6a2,6b2}$ 10.4), 4.59 (m, 1H, H-$6a^1$), 3.59 (d, 1H, $BrCH_2a$, J_{CH2} 12.8) and 3.50 (d, 1H, $BrCH_2b$); ^{13}C NMR ($CDCl_3$) of α-**27**: δ 101.7 (C-1^2), 90.8 (C-1^1), 77.4 (C-3^1), 74.2 (C-5^1), 72.6 (C-3^2), 71.1 (C-5^2), 70.8 (C-2^1), 70.0 (C-4^1), 69.4 (C-2^2), 67.3 (C-4^2), 62.8 (C-6^1), 61.7 (C-6^2) and 24.9 ($BrCH_2$).

Entry 14: from **6** (0.60 g, 1.0 mmol), **12** (0.95 g, 1.50 mmol) and 2,4,6-trimethylpyridine (0.24 g, 2.0 mmol) in dichloromethane (30 mL), and silver triflate (0.51 g, 2.0 mmol) in dichloromethane (5 mL), after 30 min at room temperature, as described in the general procedure. Chromatography (gradient, solvent *A*, 15:1 to10:1) gave first a mixture of α,β-**28** (α:β ~1:2, 0.41 g, 35%); ^{1}H NMR ($CDCl_3$) definite signals: δ 6.94 (d, 1H, H-1^1, α-**28**, $J_{11,21}$ 3.9) and 6.04 (d, 1H, H-1^1, β-**28**, $J_{11,21}$ 8.0); ^{13}C NMR ($CDCl_3$), definite signals: δ 98.3 (C-1^2, α,β-**28**), 93.0 (C-1^1, β-**28**) and 91.8 (C-1^1, α-**28**).

Eluted next was β-**27** (0.69 g, 58%), $[\alpha]_D$ +39.4° (*c* 0.3, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.09 (bd, 1H, H-4^1, $J_{41,51}$ <1), 6.04 (d, 1H, H-1^1, $J_{11,21}$ 8.3), 5.91 (dd, 1H, H-2^1, $J_{21,31}$ 9.8), 5.74 (bd, 1H, H-4^2, $J_{32,42}$ 3.3, $J_{42,52}$ <1), 5.44 (dd, 1H, H-2^2, $J_{12,22}$ 7.7, $J_{22,32}$ 10.4), 5.21 (dd, 1H, H-3^2), 4.97 (d, 1H, H-1^2), 4.70 (dd, 1H, H-$6a^2$, $J_{52,6a2}$ 6.9, $J_{6a2,6b2}$ 11.1), 4.49 (m, 2H, H-$6a^1$,$6b^1$), 4.38-4.30 (m, 2H, H-3^1,$6b^2$), 4.28, 4.23 (2 x bt, 2 x 1H, H-5^1,5^2), 3.56 (d, 1H, $BrCH_2a$, J_{CH2} 12.7) and 3.48 (d, 1H, $BrCH_2b$); ^{13}C NMR ($CDCl_3$): δ 101.6 (C-1^2), 93.0 (C-1^1), 76.7 (C-3^1), 73.0 (C-5^1), 72.6 (C-3^2), 71.3 (C-5^2), 70.3, 70.1 (C-2^1,4^1), 69.3 (C-2^2), 67.4 (C-4^2), 62.7 (C-6^1), 61.8 (C-6^2) and 24.8 ($BrCH_2$).

Anal. Calcd for $C_{63}H_{51}BrO_{10}$: C. 63.48: H. 4.31. Found: C. 63.20: H. 4.59.

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O-(2,4,6-Tri-O-benzoyl-3-O-benzyl-β-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-O-benzoyl-β-D-galactopyranose (29) and O-(2,4,6-Tri-O-benzoyl-3-O-benzyl-α-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-O-benzoyl-β-D-galactopyranose (30). - *Entry 15*: from **6** (119.3 mg, 0.2 mmol), **3** (180.3 mg, 0.3 mmol) and 2,4,6-trimethylpyridine (60.6 mg, 0.5 mmol) in dichloromethane (2 mL), and silver triflate (102.8 mg, 0.4 mmol) in dichloromethane (1 mL), after 30 min at room temperature, as described in the general procedure. Chromatography (solvent *A*, 15:1) gave first **30** (114.5 mg, 49%), $[\alpha]_D$ +117.3° (*c* 0.5, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.01 (d, 1H, H-1^1, $J_{1^1,2^1}$ 8.1), 5.87 (dd, 1H, H-2^1, $J_{2^1,3^1}$ 10.0), 5.85 (bd, 1H, H-4^1, $J_{3^1,4^1}$ 3.4, $J_{4^1,5^1}$ <1), 5.77 (d, 1H, H-1^2, $J_{1^2,2^2}$ 3.7), 5.54 (dd, 1H, H-2^2, $J_{2^2,3^2}$ 10.4), 5.23 (bd, 1H, H-4^2, $J_{3^2,4^2}$ 3.3, $J_{4^2,5^2}$ <1), 4.74-4.43, 4.40-4.18 (2 x m, 5H, H-3^1,6a^1,6b^1,6a^2,6b^2), 4.57 (d, 1H, CH_2a, J_{CH_2} 12.3), 4.38 (d, 1H, CH_2b), 4.12 (bt, 1H, H-5^1), 3.97 (bt, 1H, H-5^2) and 3.75 (dd, 1H, H-3^2); ^{13}C NMR ($CDCl_3$): δ 92.9, 92.6 (C-1^1,1^2), 77.4 (C-3^2), 73.1 (C-3^1), 72.2, 71.4 (C-5^1,5^2), 69.5, 69.1 (C-2^1,2^2), 67.8 (C-4^1), 65.1 (C-4^2), 63.2 (C-6^2) and 61.7 (C-6^1).

Anal. Calcd for $C_{68}H_{56}O_{18}$: C, 70.34; H, 4.86. Found: C, 69.84; H, 4.97.

Eluted next was **29** (91.8 mg, 40%), $[\alpha]_D$ +59.1° (*c* 0.8, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.08 (bd, 1H, H-4^1, $J_{3^1,4^1}$ 3.6, $J_{4^1,5^1}$ <1), 6.02 (d, 1H, H-1^1, $J_{1^1,2^1}$ 8.3), 5.90 (dd, 1H, H-2^1, $J_{2^1,3^1}$ 9.6), 5.81 (bd, 1H, H-4^2, $J_{3^2,4^2}$ 3.3, $J_{4^2,5^2}$ <1), 5.33 (dd, 1H, H-2^2, $J_{1^2,2^2}$ 7.9, $J_{2^2,3^2}$ 10.0), 4.86 (d, 1H, H-1^2), 4.64 (dd, 1H, H-6a^2, $J_{5^2,6a^2}$ 6.4, $J_{6a^2,6b^2}$ 11.3), 4.58 (d, 1H, PhCH_2a, J_{CH_2} 12) 4.48 (m, 2H, H-6a^1,6b^2), 4.37 (m, 2H, H-6b^2,PhCH_2b), 4.28 (dd, 1H, H-3^1), 4.26 (bt, 1H, H-5^1), 4.07 (bt, 1H, H-5^2) and 3.66 (dd, 1H, H-3^2); ^{13}C NMR ($CDCl_3$): δ 101.8 (C-1^2), 93.1 (C-1^1), 77.4 (C-3^1), 76.0 (C-3^2), 73.0 (C-5^1), 71.5 (C-5^2), 71.3 (C-2^2), 70.9 (PhCH_2), 70.8 (C-4^1), 70.4 (C-2^1), 66.3 (C-4^2), 62.8 (C-6^1) and 62.5 (C-6^2).

Anal. Calcd for $C_{68}H_{56}O_{18}$: C,70.34; H, 4.86. Found: C, 69.87; H, 4.92.

O-(2,3,4,6-Tetra-O-benzoyl-β-D-galactopyranosyl)-(1→3)-(2,4,6-tri-O-benzoyl-β-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-O-benzoyl-β-D-galactopyranose (31) and O-(2,3,4,6-Tetra-O-benzoyl-β-D-galactopyranosyl)-(1→3)-(2,4,6-tri-O-benzoyl-α-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-O-benzoyl-β-D-galactopyranose (32). - *Entry 16*: from **6** (178.9 mg, 0.3 mmol), **17** (435.8 mg, 0.4 mmol) and 2,4,6-trimethylpyridine (60.6 mg, 0.5 mmol) in dichloromethane (6 mL), and silver triflate (154.2 mg, 0.6 mmol) in dichloromethane (2 mL), after 30 min at room temperature, as described in the general procedure. Chromatography (gradient, solvent *A*, 15:1 to 5:1) gave first **32** (121.6 mg, 24%), $[\alpha]_D$ +87.3° (*c* 0.6, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.02 (d, 1H, H-1^1, $J_{1^1,2^1}$ 7.6), 6.01 (bd, 1H, H-4^1, $J_{3^1,4^1}$ 3.0, $J_{4^1,5^1}$ <1), 5.84 (bd, 1H, H-4^3, $J_{3^3,4^3}$ 3.3, $J_{4^3,5^3}$

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<1), 5.76 (bd, 1H, H-4^2, $J_{32,42}$ 2.7, $J_{42,52}$ <1), 5.71 (d, 1H, H-1^2, $J_{12,22}$ 3.6), 5.60 (dd, 1H, H-2^2, $J_{22,32}$ 10.3), 5.40 (dd, 1H, H-2^3, $J_{13,23}$ 7.8, $J_{23,33}$ 10.3), 5.37 (dd, 1H, H-2^1, $J_{21,31}$ 10.9), 5.27 (dd, 1H, H-3^3), 4.63 (d, 1H, H-1^3), 4.50-4.40 (m, 4H, H-$6a^1$,$6b^1$,$6a^2$,$6a^3$), 4.38-4.30 (m, 2H, H-3^1,3^2), 4.21-4.10 (m, 2H, H-5^1,5^2), 4.06-4.00 (m, 2H, H-$6b^2$,$6b^3$) and 3.78 (bt, 1H, H-5^3); ^{13}C NMR ($CDCl_3$): δ 101.4 (C-1^3), 93.0 (C-1^1), 92.6 (C-1^2), 73.4 (C-3^2), 72.5, 72.4 (C-3^1,5^1), 71.6 (C-5^2), 70.7 (2C, C-3^3,5^3), 69.5 (2C, C-2^2,2^3), 69.1 (C-4^2), 68.1 (C-4^1), 67.4 (C-4^3), 65.3 (C-2^1), 63.4 (C-6^2), 61.8 (C-6^3) and 60.8 (C-6^1).

Anal. Calcd for $C_{95}H_{76}O_{27}$: C, 69.17; H, 4.64. Found: C, 68.94; H, 4.70.

Eluted next was **31** (312.8 mg, 63%), $[\alpha]_D$ +68.8° (*c* 0.5, chloroform); ^{1}H NMR ($CDCl_3$): δ 6.00 (bd, 1H, H-4^1, $J_{31,41}$ 3.3, $J_{41,51}$ <1), 5.95 (bd, 1H, H-4^3, $J_{33,43}$ 3.2, $J_{43,53}$ <1), 5.93 (d, 1H, H-1^1, $J_{11,21}$ 8.3), 5.82 (dd, 1H, H-2^1, $J_{21,31}$ 9.7), 5.80 (bd, 1H, H-4^2, $J_{32,42}$ 3.5, $J_{42,52}$ <1), 5.42 (dd, 1H, H-2^2, $J_{12,22}$ 7.8, $J_{22,32}$ 10.4), 5.38 (dd, 1H, H-2^3, $J_{13,23}$ 7.7, $J_{23,33}$ 9.5), 5.24 (dd, 1H, H-3^3), 4.87 (d, 1H H-1^2), 4.82 (d, 1H, H-1^3), 4.64, 4.56, 4.43 (3 x dd, 3 x 1H, H-$6a^1$,$6a^2$,$6a^3$, $J_{5,6}$ 6.2, 7.3, 5.5, $J_{6,6}$ 11.2, 11.5, 11.5), 4.40 (m, 2H, H-5^3,$6b^3$), 4.37-4.24 (m, 2H, H-3^1,3^2) and 4.16-4.07 (m, 4H, H-5^1,5^2,$6b^1$,$6b^2$); ^{13}C NMR ($CDCl_3$): δ 101.7 (C-1^2), 101.3 (C-1^3), 93.1 (C-1^1), 76.8, 76.7 (C-3^1,3^2), 73.0 (C-5^1), 72.0 (C-2^2), 71.5, 71.4, 71.2 (C-2^1,5^2,5^3), 70.3 (2C, C-3^2,4^2), 70.0 (C-4^1), 69.5 (C-2^3), 67.6 (C-4^3), 62.7 (2C, C-6^1,6^2) and 61.7 (C-6^3).

Anal. Calcd for $C_{95}H_{76}O_{27}$: C, 69.17; H, 4.64. Found: C, 69.30; H, 4.70.

***O*-(2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl)-(1→3)-(2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl)-(1→3)-1,2,4,6-tetra-*O*-benzoyl-β-D-galactopyranose (34).** - *Entry 17*: from **33** (267.7 mg, 0.25 mmol), **14** (230.8 mg, 0.35 mmol) and 2,4,6-trimethylpyridine (60.6 mg, 0.5 mmol) in dichloromethane (1 mL), and silver triflate (128.5 mg, 0.5 mmol) in dichloromethane (1 mL), after 15 min at 0 °C to room temperature, as described in the general procedure. Chromatography (gradient, solvent *A*, 15:1 to 5:1) gave first **34** (176.3 mg, 43%), $[\alpha]_D$ +87.3° (*c* 0.6, chloroform); ^{1}H NMR ($CDCl_3$), definite signals: δ 6.02 (bd, 1H, H-4^1, $J_{31,41}$~3, $J_{41,51}$ <1), 5.96 (d, 1H, H-1^1, $J_{11,21}$ 8.3), 5.83 (dd, 1H, H-2^1, $J_{21,31}$ 9.7), 5.73 (d, 1H, H-1^3, $J_{13,23}$ 3.2), 5.54 (dd, 1H, H-3^3, $J_{23,33}$ 11.6, $J_{33,43}$ 3.1), 5.53 (bd, 1H, H-4^3, $J_{43,53}$ <1), 5.51 (bd, 1H, H-4^2, $J_{32,42}$~3, $J_{42,52}$ <1), 5.33-5.29 (m, 2H, H-2^2,2^3) and 4.85 (d, 1H, H-1^2, $J_{12,22}$ 7.7); ^{13}C NMR ($CDCl_3$): δ 101.5 (C-1^2), 98.2 (C-1^3), 93.0 (C-1^1), 76.8 (C-3^1), 73.6 (C-3^2), 72.9 (C-5^1), 71.8, 71.5 (C-2^1,2^2), 70.3, 70.2, 70.1 (C-2^3,5^2,5^3), 69.5, 68.7, 68.6 (C-3^3,4^1,4^2), 66.1 (C-4^3), 62.7 (C-6^1), 62.3 and 62.2 (C-6^2,6^3).

Anal. Calcd for $C_{95}H_{76}O_{27}$: C, 69.17; H, 4.64. Found: C, 68.93; H, 4.71.

Eluted next was **31** (146.5 mg, 36%).

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