



Conformationally restricted 3,5-*O*-(di-*tert*-butylsilylene)- β -D-galactofuranosyl thioglycoside donor for 1,2-*cis* α -D-galactofuranosylation

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ABSTRACT

A conformationally restricted 2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilylene)- β -D-thiogalactofuranoside donor was prepared from benzyl α -D-galactofuranoside and its donor capability was studied for stereoselective 1,2-*cis* α -D-galactofuranosylation. An unusual chemical behavior in benzylation and hydrogenolysis reactions was observed after the introduction of the 3,5-*O*-(di-*tert*-butylsilylene) protecting group into the galactofuranosyl moiety. The influence of the solvent, temperature, and activating system was evaluated. The NIS/AgOTf system, widely used in 1,2-*cis* β -arabinofuranosylation, was not satisfactory enough for 1,2-*cis* galactofuranosylation. However, moderate to high α -selectivity was obtained with all the acceptors employed when using *p*-NO₂PhSCl/AgOTf as a promoting system, in CH₂Cl₂ at –78 °C. The order of the addition of the reactants (premixing or preactivation) did not affect substantially the stereochemical course of the glycosylation reaction. The α -D-Galf-(1→6)-D-Man linkage was achieved with complete diastereoselectivity by preactivation of the conformationally constrained thioglycoside donor.

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1. Introduction

Galactofuranose-containing oligosaccharides have attracted much attention because Galf is not found in mammals whereas it is a common constituent in pathogenic microorganisms such as *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, and *Klebsiella pneumoniae*.^{1–3} Interestingly, Galf is found in β -configuration in all cases. For that reason, Galf metabolism has been proposed as a potential target for chemotherapy,⁴ and in this context, studies on its biosynthesis are currently being performed.^{2,5,6} Although not so widely distributed, α -D-Galf in 1,2-*cis* configuration has also been found in several pathogenic bacteria such as *Escherichia coli* O167⁷ and O85,⁸ *Salmonella enterica* O53⁹ and O17,⁸ *Pragia fontium*,¹⁰ *Streptococcus pneumoniae* 22F,¹¹ and pathogenic fungi such as *Paracoccidioides brasiliensis*,¹² and others.^{1,13} The biosynthetic pathway of this unit as well as its metabolism is still unknown. Stereoselective methods for the synthesis of α -D-Galf-containing oligosaccharides are of great interest bearing in mind that the availability of these derivatives will allow to perform further biological assays.

The glycosylation reaction involves too many factors and, at the present time, is an intense and relevant area of research.^{14–18} In

fact, studies on stereoselective furanosylation are more limited compared to pyranosides,^{16,19} in which the 1,2-*cis* β -manno type glycosidic linkage and α -2-deoxypyranoside linkage are the most difficult to achieve stereoselectively.¹⁶ The complexity for constructing 1,2-*cis* α -D-Galf linkages could be compared to stereochemically related 1,2-*cis* β -arabinofuranosyl linkage which has been extensively studied^{20–23} probably due to its presence in the *M. tuberculosis* arabinogalactan and lipoarabinomannan.²⁴ No general method for α -D-galactofuranosylation as a single diastereomer has been accomplished yet.^{1,2} A strong influence of the acceptor has been usually observed by the use of tetrabenzylated galactofuranosyl donors such as trichloroacetimidates^{25–28} or thioglycosides.²⁹ Recently, the preparation of a α -D-Galf glycolipid analog was described by the Lemieux-type halide ion-catalyzed glycosylation with a high α/β diastereomeric ratio and a moderate yield.³⁰ A complete stereoselective α -D-galactofuranosylation was first described employing a tetrabenzylated carboxybenzyl galactofuranoside in the synthesis of agelagalastatin.³¹ Presumably, a S_N2-type displacement of a α -triflate intermediate is involved. It is worthy to point out that a tetrabenzylated substitution on the donor was a requirement for a complete control of the stereochemistry in the construction of the terminal α -D-Galf-(1→2)-D-Man linkage.³² The 2,3-anhydrosugar methodology was also used in α -D-galactofuranosylation. In this indirect method, a complete diastereoselection was achieved in the glycosylation reaction but not

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in the subsequent epoxide ring opening.^{33,34} The intramolecular aglycon delivery strategy is an interesting example that was successfully employed in the synthesis of a 1,2-*cis* α -D-fucofuranoside, a 6-deoxy analogue of α -D-galactofuranose.³⁵ More recently, a complete stereoselective formation of the α -D-Galf(1 \rightarrow 2)Rha linkage in the synthesis of a trisaccharide constituent of *Streptococcus pneumoniae* 22F was carried out by the trichloroacetimidate method, after tuning the reactivity of the galactofuranosyl donor and the rhamnoside acceptor.³⁶

The less pronounced anomeric effect and the flexible ring of furanose increase the difficulty to obtain 1,2-*cis* linkages stereoselectively. Inspired by studies on C-glycosylation of five-membered ring oxacarbenium ions performed by Woerpel et al.,³⁷ 3,5-O-di-*tert*-butylsilylene^{21,22} and 3,5-O-tetra-isopropylidisiloxanylidene²³ conformationally locked arabinofuranoside donors were developed to avoid the eclipsing interaction between the incoming nucleophile acceptor and H-2 of the oxacarbenium ion in the presumably E₃ conformation,²¹ leading to 1,2-*cis* glycosides with high diastereoselectivity. The development of these donors^{21–23,38–40} (Fig. 1) allowed the synthesis of relevant β -arabinofuranoside-containing oligosaccharides found in nature.^{21,23,39–43} The conformationally restricted 2,3-O-xylylene-protected Araf thioglycoside donor was also developed allowing the synthesis of an oligosaccharide fragment of mannose-capped mycobacterial lipoarabinomannan.⁴⁴

Focusing on 3,5-O-di-*tert*-butyl-silylene protection in β -arabinofuranosylation, several methods of glycosylation proved to be highly β -selective among several acceptors, which includes the extensively studied thioglycoside,^{21,22,38–41} sulfoxide,²² and trichloroacetimidate^{38,39} method (Fig. 1). A complete β -diastereoselectivity was observed using the conformationally constrained trichloroacetimidate donor **1-5** in the synthesis of a hexasaccharide and related fragments of plant cell wall-constituent rhamnogalacturonan II, whereas a slightly reduced anomeric selectivity was obtained employing the 1-thioarabinofuranoside analog **1-2**.³⁹

In view of these results, conformationally restricted 3,5-O-(di-*tert*-butylsilylene)-D-galactofuranosyl trichloroacetimidate donors **9** and **10**⁴⁵ (Fig. 2) have been evaluated for 1,2-*cis* α -galactofuranosylation aimed at favoring the entrance of the nucleophile acceptor from the inside α -face in the presumed E₃ oxacarbenium intermediate (Fig. 2) avoiding the eclipsing interaction with H-2 in the β -face trajectory. Unexpectedly, and contrary to it was depicted the case of the arabinofuranosyl counterpart, almost no 1,2-*cis* α -selectivity was observed when employing the non-participating solvent CH₂Cl₂.⁴⁵ On the other hand, modest to high selectivity was observed using diethylether as solvent at –78 °C, suggesting a participating effect on the intermediate.⁴⁵ Interestingly, the opposite situation had been observed with the flexible analogous, trichloroacetimidate 2,3,5,6-tetra-O-benzyl- β -D-galactofuranoside (**11**, Fig. 2) in which ethereal solvents gave no selectivity or slightly favored the β product, whereas CH₂Cl₂ favored the 1,2-*cis* α -product.²⁸

Moreover, higher α -selectivity was obtained with 6-O-acetyl substituted constrained trichloroacetimidate donor **9** rather than 6-O-benzyl analogue **10** which excludes a remote participation

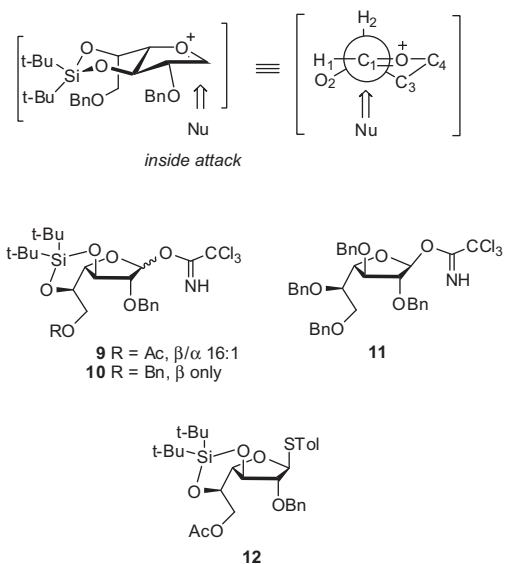


Figure 2.

effect and it suggests its involvement in a stereoelectronic effect due to the presence of an electron withdrawing group.⁴⁵

Taking into consideration the fact that selectivity is affected by the glycosylation method as well as the promoter used, as it was demonstrated in the thioarabinofuranosyl counterpart by Crich et al.,²² we decided to investigate the conformationally restricted thioglycoside **12**, which is the analogue of trichloroacetimidate **9** (Fig. 2).

In this article, we describe the synthesis of *p*-tolyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilyl)-1-thio- β -D-galactofuranoside (**12**) and we discuss its ability as a donor in the glycosylation reaction, its scope, and its limitation.

2. Results and discussion

The synthesis of galactofuranosyl derivatives involves the selection of the corresponding galactofuranosyl precursor. In this case, at first sight, the employment of a thiogalactofuranoside as starting material was evident. At the beginning, we selected *p*-tolyl 1-thio- β -D-galactofuranoside (**13**) aimed at following a similar reaction sequence performed by us in the synthesis of conformationally locked imidate **9**.⁴⁵ This sequence would involve regioselective 2,6-di-O-benzoylation of **13** and further 3,5-O-di-*tert*-butylsilylene incorporation. For that purpose, selective 2,6-di-O-benzoylation was first attempted by treatment of **13** with 2.2 equiv of benzoyl chloride at –15 °C. However, a complex mixture of products was obtained which included 6-O-, 5,6-di-O-, 2,6-di-O-, and 3,6-di-O-benzoyl thiotolylgalactofuranosyl derivatives. Selective pivaloylation of **13** at –15 °C was also attempted but a complex mixture was obtained once again despite the bulky protecting group. These results were in agreement with those previously described that showed the selective benzoylation of *p*-tolyl 5,6-O-isopropylidene-1-thio- β -D-galactofuranoside by treatment with benzoyl chloride (1 equiv) to lead to 2-O and 3-O derivatives in 45% and 26% yield, respectively.⁴⁷ Moreover, protection with the bulky silylating agent *tert*-butyldimethylsilyl chloride gave the 2-O-silyl derivative in 60% yield together with 3-O-derivative in 12% yield.⁴⁸ Clearly, thiogalactofuranoside **13** was not a convenient starting material since the difficulty exhibited to protect selectively the 2-OH position by direct acylation. For that reason, it was decided to incorporate the thiocresyl moiety in a later stage, that is, once the 3,5-O-DTBS has been introduced (Fig. 3).

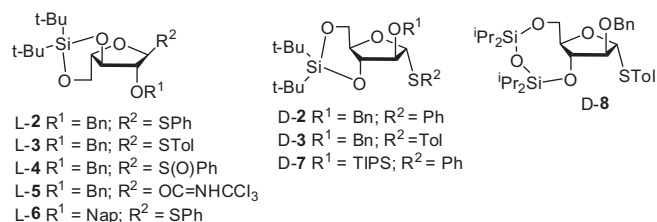


Figure 1. Examples of conformationally constrained donors used for 1,2-*cis* β -Araf linkage construction.

2.1. Synthesis of conformationally constrained D-galactofuranosyl thioglycoside donor 12

Retrosynthetic analysis of **12** indicated that the thiocresyl moiety could be incorporated β -diastereoselectively from trichloroacetimidate donor **14** containing the 3,5-O-DTBS protecting group and the 2-OBz participating group (Fig. 3). In this context, benzyl α -D-galactofuranoside (**15**) emerged as a convenient precursor because it could be 2,6-di-O-benzoylated selectively, with the anomeric benzyl group orthogonal to the benzoyl and 3,5-O-DTBS moieties. In addition, **15** was recently employed for the first time in the synthesis of a hexasaccharide constituent of *Trypanosoma cruzi* as a new precursor of the internal Galf moiety.⁴⁹ This compound was straightforwardly prepared by anomeric O-alkylation from galactose in one step.⁴⁹ Selective benzoylation of **15** by treatment with 2.2 equiv of benzoyl chloride in pyridine at -15°C afforded **16** in 63% yield (Scheme 1). The 2,6-di-O-substitution was unambiguously established by analysis of the ^1H NMR spectra. The signals corresponding to H-2 and H-6a,b of **16** downshifted compared to the same signals of **15**. The ^1H NMR spectrum of **16** showed the presence of the free hydroxyl groups OH-3 and OH-5 at 3.42 and 2.89 ppm, respectively, which was confirmed via the corresponding COSY spectrum.

Treatment of **16** with $t\text{-Bu}_2\text{Si}(\text{OTf})_2$ at 0°C in pyridine afforded the 3,5-O-DTBS derivative **17** in 83% yield. In the ^1H NMR spectrum of **17**, no significant changes in the chemical shifts of the H-2 and H-6 signals were observed indicating that no migration of the benzoyl groups took place despite the long reaction time. Analysis of the coupling constants indicated a change in the conformation of the furanose ring. Whereas the $J_{1,2}$ appeared almost unaltered ($J_{1,2} = 5.2$ Hz) compared to the flexible precursor **16**, the corresponding coupling constants of the spin system 2,3 and 3,4 have increased substantially ($J_{2,3} = 9.2$ and $J_{3,4} = 9.8$ Hz, respectively). These values are in agreement to an almost *trans*-diaxial relationship between H-3 and H-4, as it was observed for the allyl analogue recently described.⁴⁵ The ^{13}C NMR spectrum showed the protection of the C-4 below 75 ppm, which also pointed out the conformation change.⁴⁵ In order to incorporate the thiocresyl moiety, removal of the anomeric benzyl group was attempted by heterogeneous catalytic transfer hydrogenolysis. However, on reaction of **17** with ammonium formate in the presence of 10% of palladium on charcoal in refluxing methanol,⁵⁰ the starting material was recovered unaltered. Standard catalytic hydrogenation with 10% of palladium on charcoal in ethyl acetate at 3 atm was also attempted considering the good results previously obtained over a structurally related flexible benzyl α -D-galactofuranosyl derivative.⁴⁹ After 3 h, the starting material **17** had not been fully consumed, but TLC analysis showed two new more polar compounds. After 24 h, disappearance of **17** was complete, but desired **18** was obtained in only 15% yield (Scheme 2). The ^1H NMR spectrum of **18** indicated a mixture of α/β anomers together with an unusual high amount of the open form in 1:2.5:1 ratio, respectively, as shown by the integration of the anomeric signals H-1 α (δ 5.65), H-1 β (δ 5.35),

and H-2 of the open form (δ 5.58). These signals correlated (HSQC-DEPT) with the signals at δ 94.3 (C-1 α), δ 101.2 (C-1 β), and δ 79.2 (C-2 open form), respectively. The aldehydic hydrogen atom of the open form of **18** appeared as a deshielded singlet (δ = 9.79 ppm) that correlated (HSQC-DEPT) with a signal at δ 197.8 in the ^{13}C NMR spectrum, which was consistent with a carbonyl of the open form.⁵¹ This high proportion of the open form has been recently described in DTBS furanose derivatives, but this behavior was not studied either in 3,5-O-DTBS-arabinofuranose or 3,5-O-DTBS-galactofuranose derivatives.⁵¹ This finding suggests that the 3,5-O-DTBS protecting group introduces enough strain to consider the energy of the open form near the energy of the furanose forms. Surprisingly, a more polar compound was obtained as the main reaction product (66%) identified as the corresponding alditol, 2,6-di-O-benzoyl-3,5-O-(di-*tert*-butylsilanediyl)-D-galactitol (**19**, Scheme 2). Its structure was in agreement with the presence of the signals assigned to C-6 and C-1, which appeared at δ 65.3 and 62.9 ppm, respectively, in the HSQC spectrum. The structure of **19** was confirmed by oxidation in neutral conditions with oxalyl chloride in DMSO at -78°C followed by treatment with triethylamine to form **18** (57%) matching the spectroscopic data (Scheme 2). The over reduction by-product **19** could also be expected as a further reduction of the aldehyde open form of **18**. It is worth mentioning that standard catalytic hydrogenolysis of a flexible α -benzyl galactofuranoside derivative was previously accomplished straightforwardly.⁴⁹

In an attempt to avoid the formation of **19**, the hydrogen pressure was reduced to 1 atm in EtOAc unsuccessfully. However, when using methanol as a solvent at a hydrogen pressure of 3 atm, and after 48 h of reaction, the unusual by-product alditol **19** was suppressed, and desired **18** was obtained in 79% yield (Scheme 1). We hypothesized that methanol could stabilize the furanose form by hydrogen bonding with the anomeric hydroxyl or it could temporally protect the reactive aldehyde of the open form by formation of a methylacetal.

The next step was the activation of the anomeric center of **18** as trichloroacetimidate. In order to avoid transposition by-product, temperatures as low as -78°C had to be employed. Activation of **18** with trichloroacetonitrile and DBU at -78°C gave trichloroacetimidate **14** as an α/β mixture in 1:2 ratio. The introduction of the thiocresyl moiety was performed by reaction of **14** with TMSOTf as catalyst in CH_2Cl_2 at -78°C to room temperature to give **20** in 70% yield. The corresponding ^1H NMR spectrum showed that H-1 appeared as a doublet with a $J_{1,2}$ 4.7 Hz. This value indicated a 1,2-*trans* configuration of the anomeric center in agreement with the values observed for constrained 1,2-*trans* α -thioarabinofuranosides **1-2**,²¹ **D-2**,³⁸ **D-3**²² and the 2-O-acetyl analogue of **D-3**²² (Fig. 1). The shielded C-1 signal (δ 89.7) was also in agreement with the presence of 1,2-*trans* β -thiogalactofuranosides⁵² as well as conformationally constrained 1,2-*trans* α -thioarabinofuranosides.^{21,22,38} In order to introduce a non participating group at O-2, debenzoylation of **20** was carried out by treatment with sodium methoxide in methanol to give **21** (88%). On reaction with

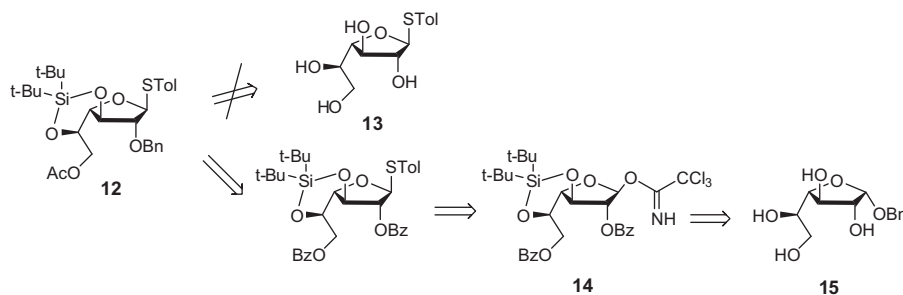
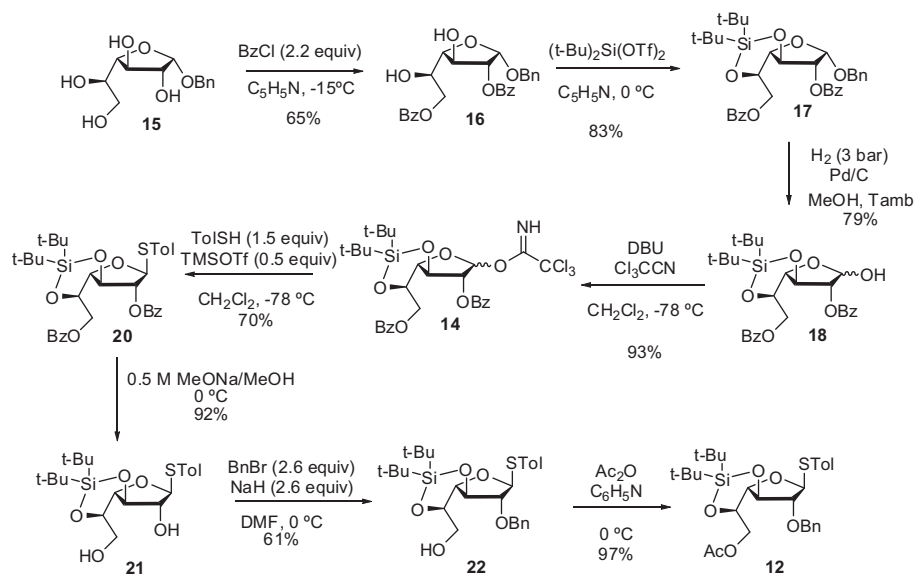
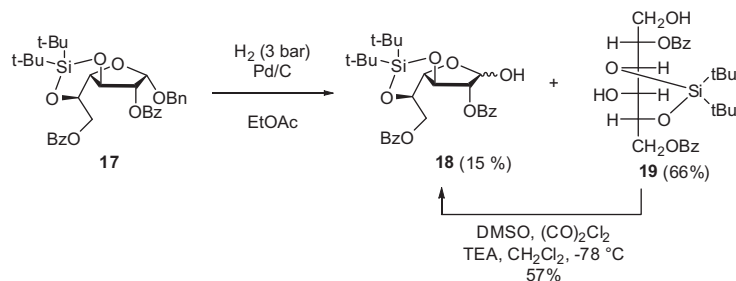


Figure 3. Retrosynthetic analysis of donor **12**.

Scheme 1. Synthesis of conformationally constrained thiogalactofuranoside **12**.Scheme 2. Hydrogenolysis of **17** using EtOAc as solvent.

benzyl bromide (2.6 equiv) and sodium hydride (2.6 equiv) in DMF at 0 °C, **21** was transformed into the 2-*O*-benzylated isomer **22** as a single stereoisomer. This compound was monitored by TLC, but decomposition took place rapidly. A similar behavior had been previously observed on the conformationally constrained analogue of **21**: allyl 3,5-*O*-DTBS- α -D-galactofuranoside.⁴⁵ For the above reasons, the reaction was repeated but rapidly quenched (18 min) to give 2-*O*-benzyl derivative **22** in 61% yield after purification. Correlations between H-6 a/b and OH-6 signals were observed in the COSY spectrum indicating the 2-*O*-benzyl substitution as expected. Moreover, C-2 signal (δ 86.7 ppm) shifted 6 ppm downfield compared to the same signal of **21** (δ 80.7 ppm). Further acetylation gave **12** in 97% yield, confirming the regiochemistry of the previous benzylation step as indicated by H-6a/b signals, which shifted downfield (0.4 ppm) compared to the same signals in its precursor **22**. X-ray of D-**3** (Fig. 1), the arabinofuranosyl analogous to **12**, showed a nearly perfect E₄ envelope conformation of the furanose ring.⁵³ Similar conformation was described for constrained 3,5-*O*-benzylidene analogous of D-**3**.²²

2.2. Glycosylation reactions

2.2.1. Choice of system promoter by glycosylation of **12** with cyclohexanol

With the conformationally locked thioglycoside donor **12** at hand, glycosylation reaction conditions had to be chosen by selection of a promoter system, solvent, and reaction temperature. As stated in the introduction, glycosylation with constrained galactofuranosyl trichloroacetimidate **9** (Fig. 2) gave higher 1,2-*cis*

selectivities by the use of diethylether as solvent at low temperatures as –78 °C compared to CH₂Cl₂ at the same reaction conditions.⁴⁵ On the other hand, the promoter system NIS/AgOTf proved to be the best one among others in 1,2-*cis* glycosylation with conformationally constrained β -thioarabinofuranosides as donors in CH₂Cl₂.^{21,22} For that reason, our first attempt was the use of this promoter in ethyl ether as solvent at –78 °C using cyclohexanol as acceptor. Unfortunately, treatment with NIS (1.5 equiv)/AgOTf (0.25 equiv) in ethyl ether and cyclohexanol at –78 °C kept the thiogalactofuranoside donor **12** (1 equiv, 0.04 M) unreacted as observed by TLC even after 20 h (Method A, entry 1). However, after raising the temperature to 25 °C and quenching by addition of TEA, the desired cyclohexyl glycoside **23**⁴⁵ was obtained as a mixture of α/β anomers in 1:1 ratio as observed by the ¹H NMR spectrum of the crude. Bearing in mind that no reaction occurred in the range –40 °C to –20 °C in ethyl ether, it was decided to study the influence of the temperature in CH₂Cl₂ as solvent. No reaction was observed again at –78 °C (entry 2) even after 24 h, but at 0 °C, the reaction was complete and after 1 h (quenched with TEA), the cyclohexyl glycoside **23** was obtained in 1.6:1 α/β ratio (entry 3) as indicated by the integration of H-2 α signal and, superimposed H-1 α and H-1 β signals. The α/β ratio was maintained by the use of ethyl ether as a solvent (0 °C) but it required 20 h for the reaction to be complete (entry 4). In contrast to the reactivity observed with conformationally constrained thioarabinofuranosyl donors,^{22,23} the NIS/AgOTf system was not reactive enough on the thiogalactofuranosyl donor **12** at low temperature to provide good 1,2-*cis* selectivities.

Crich et al. had observed that the activation method in 1,2-*cis* arabinofuranosylation had a great impact on α/β selectivities

attributed to the generation of a triflate intermediate.²² The NIS/AgOTf-mediated glycosylation allowed the formation of the triflate rapidly, whereas on the BSP/Tf₂O method the conversion of the triflate at low temperature was still incomplete. In our case, we presumed that the NIS/AgOTf activation method was not good enough because of the high temperature required for the reaction to proceed. Therefore, we looked for a promoting system capable to work at temperatures as low as -78°C . We decided to use the *p*-NO₂PhSCI/AgOTf activation system developed by Crich,⁵⁴ in order to generate the sulfonyltriflate in situ. This promoting system had been successfully applied for high yield and selective β -mannosylation in oligosaccharide synthesis,⁵⁵ for glycosylation with galacturonic acid-derived thioglycoside donors⁵⁶ and a thiogalactopyranoside donor.⁵⁷ Thus, to a mixture of donor **12**, cyclohexanol, AgOTf, and 4 Å molecular sieves in CH₂Cl₂ at -78°C was added *p*-NO₂PhSCI (entry 5, Method E). After 45 min, TLC analysis showed that thioglycoside **12** was consumed, TEA was added and cyclohexyl glycoside **23** was obtained as a 4:1 α/β anomeric mixture in 87% yield. This nice result prompted us to carry out the reaction in diethylether as solvent (entry 6) instead of CH₂Cl₂, in view of the stereoselectivity observed with the conformationally constrained trichloroacetimidate **9**. The reaction at -78°C for 20 h was not complete, whereas at -30°C (entry 7), only 1.5 h were required but with a poor stereoselectivity (2:1 α/β) compared to that performed in CH₂Cl₂. In contrast to the trichloroacetimidate donor **9**, these results indicated that the best selectivity was obtained by using a non participating solvent (CH₂Cl₂) rather than the participating solvent (ethyl ether), regardless of the reaction temperature. In addition, when toluene was used as an alternate solvent, the substrates were consumed in 40 min at -78°C (entry 8) affording exclusively the 1,2-*trans* β -glycoside **23 β** .

In summary, the selectivity strongly depends on the nature of the promoter as well as the solvent system employed. In ethyl ether, the fact that the reaction was not complete at -78°C could be attributed to a stabilizing effect of the oxonium ion. In conclusion, the best selectivity favoring the α -anomer was found when *p*-NO₂PhSCI/AgOTf was employed as the activating system, in CH₂Cl₂ as solvent at a reaction temperature of -78°C .

2.2.2. Glycosylation reactions of **12** with acceptors **24**, **26**, **28**, **30**, and **32** by *p*-NO₂PhSCI/AgOTf activation system

We next evaluated the *p*-NO₂PhSCI/AgOTf system with acceptors already tested previously on conformationally constrained galactofuranosyl trichloroacetimidate donor **9**. On reaction of **12** with 2,3,5-tri-*O*-benzoyl- β -D-galactono-1,4-lactone (**24**) by method E (Table 2), and after quenching the reaction after 30 min with TEA, the crude mixture was analyzed by ¹H NMR spectroscopy by comparison with the known disaccharides **25 α** and **25 β** previously described.⁴⁵ Integration of the anomeric hydrogens indicated a α/β mixture in 4:1 ratio. Purification of the crude gave **25** in 65% yield. In view of these results, the procedure of donor preactivation⁵⁴ was attempted in order to generate a triflate intermediate, which could be displaced by the nucleophile acceptor. Then, to a mixture of donor **12**, AgOTf and molecular sieves at -78°C treated with the *p*-NO₂PhSCI, was added acceptor **24** (Method I). In this case, the α/β ratio was the same to the one obtained with the direct procedure premixing donor and acceptor (Method E) in a slightly impaired yield (51%). The order of addition of 4-nitrobenzenesulfonyl chloride did not affect the stereochemical course of the reaction. Interestingly, the use of conformationally constrained trichloroacetimidate **9** in CH₂Cl₂ at -78°C gave much lower selectivity (1.3:1 α/β). However, in ethyl ether the α/β ratio (4.5:1 α/β) was similar to that obtained by thioglycoside **12** in CH₂Cl₂.

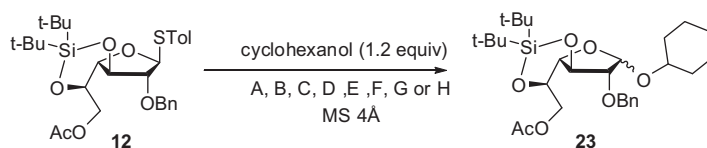
Then, it was decided to evaluate methyl 2,3,4-tri-*O*-benzoyl- α -D-mannopyranoside (**26**) as an acceptor. On reaction with thioglycoside **12** (method E), **26** was transformed into the already

depicted **27⁴⁵** as an α/β mixture in 20:1 ratio as indicated by the integration of the H-1' of each anomer in the ¹H NMR spectrum of the crude. Interestingly, on preactivation of the donor (method I), only the α -diastereomer **27 α** was detected in the ¹H NMR spectrum of the crude mixture and it was obtained in 81% yield. In this case, the order of addition of the reactant did not change substantially the reaction yield but it allowed to access **27 α** with complete diastereoselectivity. It is worth pointing out that this is the first report of a complete diastereoselective synthesis of an α -D-Galf-(1 \rightarrow 6)-D-Man linkage. Moreover, this result overcame the α/β ratio obtained with the conformationally constrained trichloroacetimidate **9** in ethyl ether (7.7:1 α/β), and with the flexible trichloroacetimidate 2,3,5,6-tetra-*O*-benzyl- β -D-galactofuranoside **11** in CH₂Cl₂ (12.6:1 α/β), both reactions were carried out at -78°C . This disaccharide unit was also obtained with complete diastereoselection after isolation by the carbobenzoxy method of glycosylation without any spectroscopic data.³² The α -D-Galf-(1 \rightarrow 6)-D-Man motif is present in the cell wall polysaccharide of the fungus *Paracoccidioides brasiliensis*, the ethiological agent of paracoccidioidomycosis, which is the most common mycosis in Latin America.¹² In order to evaluate the influence of the protecting groups in the mannosyl acceptor, the benzyl analogue methyl 2,3,4-tri-*O*-benzyl- α -D-mannopyranoside (**28**) was also assayed. Compound **28** could be considered a better nucleophile than **26** bearing in mind that it contains benzoyl electron withdrawing groups. On reaction with **28** (method E), **8** was converted into two new compounds according to TLC analysis. However, purification by column chromatography allowed the obtainment of a single stereoisomer, the α -disaccharide 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilyl)- α -D-galactofuranosyl-(1 \rightarrow 6)-2,3,4-tri-*O*-benzyl- α -D-mannopyranoside (**29 α**) in 80% yield. This compound was fully characterized spectroscopically. In the ¹H NMR spectrum, the H-1' appeared at δ 5.21 with a coupling constant ($J_{1,2}$ 5.0 Hz) characteristic of 1,2-*cis* α -galactofuranosyl linkage, which correlated with the C-1' signal at δ 99.8 in the HSQC-DEPT spectrum. However, NMR analysis of the crude product showed the signals of **29 α** together with a minor component which was assigned as the β -product as indicated by the typical signal at δ 5.03 with a coupling constant ($J_{1,2}$ 1.3 Hz) that matched this stereochemistry. Integration of the anomeric signals showed an α/β mixture of 6.3:1 ratio. The less nucleophilicity of 6-OH of the benzoylated analogue **26** compared to 6-OH of benzylated analogue **28** could be rationalized due to a better selection to discriminate the α -face toward the oxacarbenium ion.

Our study continued with rhamnosyl acceptor **30**. Very recently, we demonstrated that complete stereoselective 1,2-*cis* linkage construction of α -D-Galf(1 \rightarrow 2)Rha could be performed on glycosylation of **30** with flexible 3-*O*-benzoyl-2,5,6-tri-*O*-benzyl- β -D-galactofuranosyl trichloroacetimidate.³⁶ On the other side, conformationally constrained trichloroacetimidate **9** gave disaccharide **31** with almost no selectivity in ethyl ether (1.1:1 α/β) whereas, surprisingly, only the β diastereomer was obtained in CH₂Cl₂.⁴⁵ However, on reaction with conformationally constrained thioglycoside **12** (method E), **30** was transformed into **31** in 4:1 α/β ratio as indicated by integration of H-1 of α -anomer (δ 4.69) and H-1 of anomer β (δ 4.71) in the ¹H NMR spectrum of the crude. Purification of the residue gave **31** in 67% yield but if **12** was preactivated (method I), reaction yield diminished (52%) while keeping the α/β ratio. Interestingly, when comparing the conformationally constrained 3,5-*O*-DTBS-galactofuranosyl donors **9** and **12**, the thioglycoside method in CH₂Cl₂ gave higher α/β ratio (4:1) than the imidate method in which only the β isomer was obtained.

Finally, the mannosyl acceptor **32** was evaluated as a disaccharide precursor present in *Talaromyces flavus*. Reaction of thioglycoside **12** with **32** (method E) gave after purification **30 α** (40%) and **30 β** (13%), which were fully characterized spectroscopically. The

Table 1
Glycosylation of **12** with cyclohexanol



Entry	Method	Promoter	Solvent	Temp. (°C)	Reaction time	α:β ^a (yield) ^b
1	A	NIS (1.5 equiv), AgOTf (0.25 equiv)	Et ₂ O	−78 °C	20 h	No reaction
2	B	NIS (1.5 equiv), AgOTf (0.25 equiv)	CH ₂ Cl ₂	−78 °C	20 h	No reaction
3	C	NIS (1.5 equiv), AgOTf (0.25 equiv)	CH ₂ Cl ₂	0 °C	1 h	1.6:1
4	D	NIS (1.5 equiv), AgOTf (0.25 equiv)	Et ₂ O	0 °C	20 h	1.6:1
5	E	<i>p</i> -NO ₂ PhSCI (1.2 equiv), AgOTf (2.5 equiv)	CH ₂ Cl ₂	−78 °C	45 min	4:1 (87%) ^b
6	F	<i>p</i> -NO ₂ PhSCI (1.2 equiv), AgOTf (2.5 equiv)	Et ₂ O	−78 °C	24 h	1.5:1 ^c
7	G	<i>p</i> -NO ₂ PhSCI (1.2 equiv), AgOTf (2.5 equiv)	Et ₂ O	−30 °C	1.5 h	2:1
8	H	<i>p</i> -NO ₂ PhSCI (1.2 equiv), AgOTf (2.5 equiv)	Toluene	−78 °C	1 h	Only β

^a α/β ratio established from ¹H NMR (500 MHz or 200 MHz) spectrum of the crude.

^b Isolated yield.

^c Reaction not complete, and interrupted after 24 h.

¹H NMR spectrum of **30α** showed the signal for H-1' (δ 5.08) as a doublet (*J* = 5.3 Hz) characteristic of a 1,2-*cis* glycoside. In the HSQC-DEPT, the correlation of this signal with C-1' at δ 101.5 confirmed the α-configuration of the newly formed anomeric bond. On the other hand, the H-1' signal of **30β** appeared at δ 4.92 with a smaller coupling constant (*J* = 3.2 Hz), which correlated with C-1' at 106.2 ppm, indicating a 1,2-*trans* β-configuration of the glycosidic linkage. Analysis of the ¹H NMR spectrum of the crude mixture indicated also a α/β anomeric mixture in 3:1 ratio as it was shown by the integration of H-1'α and H-1'β. Similar α/β ratio was obtained (3.6:1) in higher yield (76%) when **12** was preactivated (method I). The synthesis of the α-D-Galf-(1→2)-Man linkage with complete control of the stereochemistry after isolation had been previously reported by the carbobenzoxy method of glycosylation without spectroscopic data.³²

3. Conclusion

Protecting groups play an important role in the glycosylation reaction.^{14–17,58} In the search of stereoselective methods of glycosylation, an interesting approach has been the use of conformationally restricted donors.^{59–62} In this sense, DTBS protecting group has been employed in pyranosylation.⁶³ Bearing in mind the high 1,2-*cis* selectivity obtained with 3,5-O-DTBS-thioarabinofuranosyl donors,^{21,22} and considering the stereochemical relationship between arabinose and galactose, a glycosylation study with a 3,5-O-DTBS-thiogalactofuranosyl analogue was performed. The synthesis of the conformationally constrained thioglycoside donor **12** was achieved from D-galactose in 8 synthetic steps from benzyl α-D-galactofuranoside (**15**) in 15% overall yield. *p*-Tolyl 1-thio-β-D-galactofuranoside could not be used as a precursor due to the difficulty to discriminate secondary hydroxyl groups by selective benzoylation in contrast to what was observed on **15**. Some unusual chemical behavior was observed by the introduction of the 3,5-O-di-*tert*-butylsilylene protecting group into the galactofuranosyl moiety to fix conformation. For instance, selective benzylation at the secondary OH-2 position over the primary 6-OH was observed in conformationally constrained thioglycoside **21** as was previously observed in the corresponding benzyl α-D-galactofuranoside analogue.⁴⁵ Standard hydrogenolysis of the conformationally constrained anomeric benzyl derivative **17** in EtOAc afforded the over-reduction product alditol **15** mainly, whereas the desired anomeric free **18** was obtained when the reaction was carried out in methanol as solvent. Moreover, preparation of imidate **14** as well

as thioglycoside **20** had to be performed at −78 °C in order to avoid undesired transposition by-products, usually related to highly reactive armed donors.⁶⁴ These unusual behaviors could be attributed to a high electron density found in the anomeric center supplied by the rich electron donor silylene group together with a favorable fixed conformation of the galactofuranosyl moiety. The stereoelectronic effects on these reactions are still unknown and deserve further studies. Recently, tuning effect on arabinofuranosyl phenyl thioglycoside donors has been presented, however the incorporation of 3,5-O-DTBS group reduced the reactivity.⁶⁵

Focusing on glycosylation reactions with thioglycoside donor **12**, in contrast to constrained trichloroacetimidate analogue **9**,⁴⁵ stereoselectivity favored the α-anomer in all the acceptors used when *p*-NO₂PhSCI/AgOTf⁵⁴ was employed as the activating system, in CH₂Cl₂ as solvent at a reaction temperature of −78 °C. On the other hand, in contrast to the 4,6-di-O-benzylidene-mannopyranosyl case,^{15,16} donor preactivation did not affect the stereochemical course of the glycosylation. Only slight differences in glycosylation selectivities were observed on preactivation of donor **12**. In fact, α-D-Galf-(1→6)-D-Man linkage was achieved with complete diastereoselectivity.

Finally, even though the nature of the acceptor strongly affected the α/β ratio in the glycosylation reaction, it is worth mentioning that, in all cases, the 1,2-*cis* α-anomer was the major component of the mixture. These results not only could bring better understanding to the furanose glycosylation field but they also provide a useful alternative method for constructing 1,2-*cis* α-galactofuranosyl linkages.

4. Experimental

4.1. General methods

TLC was performed on 0.2 mm silica gel 60 F254 aluminum-supported plates. When TEA was added to the solvent system, TLC plate required pretreatment with the elution solvent to reduce its acidity. Detection was effected by exposure to UV light or by spraying with 5% (v/v) sulfuric acid in EtOH and charring. Column chromatography was performed on silica gel 60 (230–400 mesh). Melting points are uncorrected. Optical rotations were measured at 25 °C. NMR spectra were recorded at 500 MHz (¹H) and 125.8 MHz (¹³C) or, at 200 MHz (¹H) and 50.3 MHz (¹³C). ¹H and ¹³C NMR spectra assignments were supported by homonuclear COSY and HSQC-DEPT experiments. High resolution mass spectra

Table 2Glycosylation reactions with constrained donor **12** and **24**, **26**, **28**, **30**, and **32** as acceptors

Entry	Acceptor	Product	Method	$\alpha:\beta^a$ (yield) ^b
1			E I	4:1 (65%) 4:1 (51%)
2			E I	20:1 (78%) Only α (81%)
3			E	6.3:1 (80%)
4			E I	4:1 (67%) 4:1 (52%)
5			E I	3:1 (53%) 3.6:1 (76%)

(E) CH₂Cl₂, –78 °C, *p*-NO₂PhSCl (1.2 equiv), AgOTf (2.5 equiv); (I) (1) CH₂Cl₂, –78 °C, *p*-NO₂PhSCl (1.2 equiv), AgOTf (2.5 equiv); (2) ROH.^a α/β ratio established from ¹H NMR (500 MHz) spectrum of the crude.^b Isolated yield.

(HRMS) were recorded on a BRUKER microTOF-Q II electrospray ionization mass spectrometer. Optical rotations were measured with a path length of 1 dm at 25 °C.

4.2. Benzyl 2,6-di-O-benzoyl- α -D-galactofuranoside (**16**)

To a stirred solution of benzyl α -D-galactofuranoside⁴⁹ (**15**, 2.44 g, 9.03 mmol) in dry pyridine (35 mL), cooled at –15 °C, benzoyl chloride (2.3 mL, 19.9 mmol) was slowly added during 5 h. The reaction was allowed to reach room temperature and left overnight. Ice (100 g) was added and the stirring continued for 1 h. The resulting mixture was diluted with water (100 mL) and then extracted with CH₂Cl₂ (3 × 120 mL). The organic layer was sequentially washed with 2.5 M HCl (100 mL), saturated aq NaHCO₃ (100 mL), water (3 × 100 mL), dried (Na₂SO₄), filtered, and concentrated. Column chromatography of the mixture (5:1 toluene–EtOAc) gave syrupy **16** (2.80 g, 65%); *R*_f = 0.66 (25:1 CH₂Cl₂–MeOH), [α]_D +40.1 (*c* 1, CHCl₃); ¹H NMR (CDCl₃,

500 MHz) δ 8.09–7.21 (m, 15H, aromatic), 5.42 (d, 1H, *J* = 4.8 Hz, H-1), 5.11 (dd, 1H, *J* = 7.4, 4.8 Hz, H-2), 4.81 (ddd, 1H, *J* = 7.4, 6.3, 3.6 Hz, H-3), 4.79, 4.62 (2d, 2H, *J* = 12.1 Hz, OBn); 4.44 (dd, 1H, *J* = 11.4, 6.3 Hz, H-6a), 4.37 (dd, 1H, *J* = 11.4, 5.7 Hz, H-6b), 4.20 (dd, 1H, *J* = 6.3, 3.6 Hz, H-4), 4.08 (dddd, 1H, *J* = 8.2, 6.3, 5.7, 3.6 Hz, H-5), 3.42 (d, 1H, *J* = 3.6 Hz, OH-3), 2.89 (d, 1H, *J* = 8.2 Hz, OH-5); ¹³C NMR (CDCl₃, 125.8 MHz) δ 167.0, 166.6 (COPh), 136.6, 133.6, 133.1, 129.9, 129.8, 129.7, 129.0, 128.5, 128.5, 128.4, 128.1, 127.9 (aromatic), 100.3 (C-1), 82.7 (C-4), 80.7 (C-2), 73.4 (C-3), 71.2 (CH₂Ph), 69.3 (C-5), 65.3 (C-6). HRMS (ESI) *m/z* calcd for C₂₇H₂₆NaO₈ [M+Na]⁺ 501.1525, found 501.1525.

4.3. Benzyl 2,6-di-O-benzoyl-3,5-O-(di-*tert*-butylsilanediyl)- α -D-galactofuranoside (**17**)

To a stirred solution of **16** (3.72 g, 7.8 mmol) and DMAP (108 mg, 0.88 mmol) in dry pyridine (25 mL), cooled to 0 °C, (tBu)₂Si(OTf)₂ (2.7 mL, 8.3 mmol) was added during 30 min. The mixture

was allowed to reach room temperature and after 16 h, the reaction was quenched by the addition of MeOH (2 mL). The resulting solution was coevaporated with toluene to dryness. Column chromatography (6:1 toluene–hexane) of the residue gave **17** (4.00 g, 83%) as a syrup. R_f = 0.67 (toluene–EtOAc 10:1); $[\alpha]_D^{+100.8}$ (c 1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ = 8.12–6.96 (m, 13H, aromatic), 5.46 (d, 1H, J = 5.2 Hz, H-1), 5.11 (dd, 1H, J = 9.1, 5.1 Hz, H-2), 4.94 (t, 1H, J = 9.5 Hz, H-3), 4.82 (td, 1H, J = 6.5, 3.8 Hz, H-5), 4.73 (dt, 1H, J = 7.5, 3.8 Hz, H-6a), 4.63, 4.42 (2d, 2H, J = 11.9 Hz, OBN); 4.52 (dt, 1H, J = 11.8, 5.9 Hz, H-6b), 4.23 (dd, 1H, J = 9.8, 6.7 Hz, H-4), 1.04, 1.06 (2s, 18H, 2 (CH₃)₃C). ¹³C NMR (CDCl₃, 125.8 MHz) δ = 166.5, 166.3 (COPh), 136.8, 133.3, 132.8, 130.2, 129.9, 129.7, 129.6, 128.4, 128.2, 128.0, 127.7, 127.5 (aromatic), 99.0 (C-1), 77.3 (C-2), 74.8 (C-4), 72.1 (C-3), 72.0 (C-5), 70.7 (CH₂Ph), 64.6 (C-6); 27.2, 27.1 ((CH₃)₃C); 21.7, 20.8 ((CH₃)₃C); HRMS (ESI) m/z calcd for C₃₅H₄₂NaO₈Si [M+Na]⁺ 641.2547, found 641.2557.

4.4. 2,6-Di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)-*D*-galactofuranose (**18**)

Method A: A mixture of **17** (79 mg, 0.13 mmol) dissolved in EtOAc (2 mL) and 10% Pd(C) Degussa type (20 mg) was hydrogenated at 3 atm for 24 h at rt. The catalyst was filtered over a Celite bed and the filtrate was concentrated under vacuum. Purification by column chromatography (15:1 toluene–EtOAc) gave a first fraction of **18** (10 mg, 15%) as a white foamy solid. Spectroscopic analysis showed a mixture of the open form/ α anomer/ β anomer in 1:1:2.5 ratio. R_f = 0.32 (toluene–EtOAc 6:1); $[\alpha]_D^{+42.0}$ (c 0.8, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ all signals are listed, diagnostic signals are assigned δ 9.19 (s, 1H, C-1 open), 8.18–8.01 (m, 22H, arom.), 7.67–7.53 (m, 11H, arom.), 7.52–7.40 (m, 22H, arom.), 7.28–7.24 (m, 3H, arom.), 5.65 (dd, 1H, J = 6.9, 5.3 Hz, H-1 α), 5.58 (d, 1H, J = 1.8 Hz, H-2 open), 5.35 (t, 2.5H, J = 2.7 Hz, H-1 β), 5.19 (dd, 2.5H, J = 6.7, 2.5 Hz, H-2 β), 5.10 (dd, 1H, J = 8.8, 5.3 Hz, H-2 α), 4.86 (m, 8H), 4.75 (dd, 1H, J = 11.5, 4.3 Hz), 4.67 (m, 7H), 4.54 (m, 8H), 4.14 (dd, 1H, J = 9.8, 6.5 Hz), 3.41 (d, 2.5H, J = 2.7 Hz, OH-1 β), 3.38 (d, 1H, J = 5.6 Hz, OH-4 open), 3.14 (d, 1H, J = 6.9 Hz, OH-1 α), 1.10–0.98 (m, 99H, (CH₃)₃C); ¹³C NMR (CDCl₃, 128.5 MHz) δ all signals are listed, diagnostic signals are assigned 197.8 (C-1 open), 167.1, 166.9, 166.8, 166.7, 166.6, 166.2 (COPh); 134.1, 133.6, 133.4, 133.3, 133.1, 133.06, 132.96, 130.1, 129.88, 129.86, 129.75, 129.72, 129.68, 129.66, 129.1, 128.7, 128.5, 128.44, 128.37, 128.36, 128.34; 101.2 (C-1 β), 94.3 (C-1 α), 85.4 (C-2 β), 79.2 (C-2 open), 77.7 (C-2 α), 75.4, 75.1, 74.5, 74.2, 72.3, 72.1, 71.6, 71.1, 67.4, 65.3, 64.7, 64.4, 27.2, 27.14, 27.11, 27.08, 27.06, 27.02, 26.94, 26.91, 21.68, 21.5, 21.1, 20.79, 20.75. HRMS (ESI) m/z calcd for C₂₈H₃₆NaO₈Si [M+Na]⁺ 551.2077, found 551.2050.

Next fraction from the column gave 2,6-di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)-*D*-galactitol (**19**, 45 mg, 66%) as a colorless syrup. R_f 0.41 (5:1 toluene–EtOAc); $[\alpha]_D^{+24.1}$ (c 1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 8.11–8.07 (m, 2H, arom.), 8.04–8.01 (m, 2H, arom.), 7.60 (m, 1H, arom.), 7.54 (m, 1H, arom.), 7.39–7.48 (m, 4H, arom.), 5.40 (ddd, 1H, J = 5.9, 4.7, 1.5 Hz, H-2), 4.72 (dd, 1H, J = 11.5, 3.8 Hz, H-6a), 4.63 (ddd, 1H, J = 7.5, 5.8, 3.8 Hz, H-5), 4.51 (dd, 1H, J = 11.5, 7.5 Hz, H-6b), 4.43 (dd, 1H, J = 8.7, 1.5 Hz, H-3), 4.15 (dd, 1H, J = 11.8, 5.9 Hz, H-1a), 4.04 (dd, 1H, J = 11.8, 4.7 Hz, H-1b), 3.95 (dt, 1H, J = 8.7, 5.5 Hz, H-4), 3.88 (d, 1H, J = 5.5 Hz, OH-4), 2.53 (s, 1H, OH-1), 1.03, 0.99 (2s, 18H, 2 (CH₃)₃C); ¹³C NMR (CDCl₃, 125.8 MHz) δ 168.0, 166.7 (COPh); 133.7, 132.9, 130.1, 130.0, 129.6, 129.0, 128.5, 128.3 (arom.); 74.5 (C-3), 74.3 (C-2), 72.3 (C-5), 67.4 (C-4), 65.3 (C-6), 62.9 (C-1); 27.13, 27.07 ((CH₃)₃C); 21.4, 20.9 ((CH₃)₃C). HRMS (ESI) m/z calcd for C₂₈H₃₈NaO₈Si [M+Na]⁺ 553.2228, found 553.2232.

Method B: A solution of **17** (4.61 g, 7.45 mmol) in MeOH (42 mL) was equally distributed in 12 test tubes. Pd/C Degussa type (80 mg) was added to each one. The tubes were placed in Parr apparatus and hydrogenation was performed at the same time at 3 atm for 48 h. The catalyst was filtered over a Celite bed and the filtrate was concentrated under vacuum. Purification by column chromatography (15:1 toluene–EtOAc) gave **18** (3.12 g, 79%).

4.5. *O*-(2,6-Di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)- α,β -*D*-galactofuranosyl)trichloroacetimidate (**14**)

To a stirred solution of **18** (1.10 g, 2.08 mmol) in dry CH₂Cl₂ (30 mL), trichloroacetonitrile (0.96 mL, 9.6 mmol) was added. The solution was cooled to –78 °C and then DBU (152 μ L, 1.02 mmol) was slowly added. After 3 h of stirring, the solution was carefully concentrated under reduced pressure at rt, and the dark brown residue was purified by column chromatography (100:1 toluene–TEA) to give foamy **14** (1.29 g, 93%) as a 0.6:1 α/β mixture. R_f 0.54 and 0.46 (4:1:0.05 hexane–EtOAc–TEA); ¹H NMR (CDCl₃, 200 MHz) δ 8.63 (s, 2H, NH β), 8.45 (s, 1H, NH α), 8.15–7.99 (m, 8H, arom.), 7.70–7.33 (m, 12H, arom.), 7.32–7.12 (m, 4H, arom.), 6.69 (d, 1H, J = 4.9 Hz, H-1 α), 6.33 (d, 2H, J = 2.0 Hz, H-1 β), 5.61 (dd, 2H, J = 6.3, 2.0 Hz, H-2 β), 5.35 (dd, 1H, J = 9.4, 4.9 Hz, H-2 α), 5.05–4.48 (m, 12H), 4.35 (dd, 1H, J = 9.9, 6.6 Hz, H-4 α), 1.19–0.86 (m, 74H, (CH₃)₃C); ¹³C NMR (CDCl₃, 50 MHz) signals for the β anomer δ 166.5, 165.6 (COPh); 160.7 (C=NH); 133.5, 132.9, 129.9, 129.7, 128.5, 128.3, 125.2; 103.4 (C-1); 82.4, 77.6, 77.0, 76.4, 76.1, 70.8, 64.6; 27.1, 26.9 ((CH₃)₃C); 21.6, 20.8 ((CH₃)₃C).

4.6. *p*-Tolyl 2,6-di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)-1-thio- β -*D*-galactofuranoside (**20**)

A suspension of **14** (1.29 g, 1.92 mmol), *p*-thiocresol (0.36 g, 2.88 mmol), and 4 Å molecular sieves in anhyd CH₂Cl₂ (38 mL) was vigorously stirred at room temperature for 5 min under argon. The mixture was cooled to –78 °C and TMSOTf (34 μ L, 0.19 mmol) was slowly added. After 0.5 h of stirring, the mixture was allowed to reach room temperature slowly, and the stirring continued for 12 h. The reaction was quenched by the addition of TEA (27 μ L, 0.19 mmol), and concentrated under vacuum. Column chromatography (3:1 toluene–hexane) of the residue gave **20** (0.85 g, 70%) as a colorless syrup which crystallized from hexane: mp 107–108 °C (hexane); R_f 0.56 (4:1 hexane–EtOAc); $[\alpha]_D^{+58.2}$ (c 1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 8.13–8.02 (m, 4H, arom.), 7.68–7.34 (m, 8H, arom.), 7.05 (d, 2H, J = 7.9 Hz, arom.), 5.52 (dd, 1H, J = 6.4, 4.7 Hz, H-2), 5.40 (d, 1H, J = 4.7 Hz, H-1), 4.85 (td, 1H, J = 6.6, 4.2 Hz, H-5), 4.71 (dd, 1H, J = 11.7, 4.2 Hz, H-6a), 4.62 (dd, 1H, J = 10.3, 6.4 Hz, H-3), 4.53 (dd, 1H, J = 11.7, 6.8 Hz, H-6b), 4.45 (dd, 1H, J = 10.3, 6.6 Hz, H-4), 2.31 (s, 3H, CH₃Ph), 1.03, 1.02 (2s, 18H, 2 (CH₃)₃C); ¹³C NMR (CDCl₃, 50 MHz) δ 166.5, 166.5 (COPh); 137.8, 133.4, 132.9, 132.2, 129.9, 129.7, 129.3, 128.5, 128.4 (aromatic), 89.7 (C-1), 81.5 (C-2), 75.3 (C-3), 74.8 (C-4), 70.9 (C-5), 64.5 (C-6); 27.1, 26.9 ((CH₃)₃C); 21.6, 20.8 ((CH₃)₃C); 21.1 (CH₃Ph); HRMS (ESI) m/z calcd for C₃₅H₄₃O₇SSi [M+H]⁺ 635.2499, found 635.2493.

4.7. *p*-Tolyl 3,5-*O*-(di-*tert*-butylsilanediyl)-1-thio- β -*D*-galactofuranoside (**21**)

To an externally cooled (0 °C) flask containing **20** (0.178 g, 0.28 mmol), was added cooled 0.2 M NaOMe in MeOH (10 mL) with stirring. The solution was stirred for 6 h at 0 °C, and then left overnight at –20 °C. The reaction was diluted with CH₂Cl₂ (40 mL) and washed with water until neutrality. The organic layer was dried (Na₂SO₄), filtered, and concentrated. Methyl benzoate was eliminated by co-evaporation with water and the residue

was purified by column chromatography (9:1 toluene–EtOAc) to afford **21** (0.11 g, 92%) as a colorless syrup which crystallized from hexane as needles: mp 118–119 °C; R_f = 0.30 (4:1 hexane–EtOAc); $[\alpha]_D -130.8$ (c 1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.39 (d, 2H, J = 8.0 Hz, arom.), 7.12 (d, 2H, J = 8.0 Hz, arom.), 5.21 (d, 1H, J = 5.7 Hz, H-1), 4.49 (q, 1H, J = 6.5 Hz, H-5), 4.19 (dd, 1H, J = 10.0, 6.4 Hz, H-4), 4.16 – 4.19 (m, 2H, H-2, H-3), 3.85 (dt, 1H, J = 11.6, 6.4 Hz, H-6a), 3.71 (dt, 1H, J = 11.5, 6.8 Hz, H-6b), 3.09 (br s, 1H, OH-2), 2.33 (s, 3H, CH₃Ph), 2.24 (t, 1H, J = 6.1 Hz, OH-6), 1.03, 1.00 (2s, 18H, 2 (CH₃)₃C); ¹³C NMR (CDCl₃, 128.5 MHz) δ 138.3, 132.7, 129.8, 129.7 (aromatic), 91.5 (C-1), 80.7 (C-2), 75.9 (C-3), 75.6 (C-4), 72.6 (C-5), 62.6 (C-6), 27.1, 27.1 ((CH₃)₃C); 21.5, 20.7 (2 (CH₃)₃C); 21.1 (CH₃Ph); HRMS (ESI) m/z calcd for C₂₁H₃₄NaO₅SSi [M+Na]⁺ 449.1794, found 449.1798.

4.8. *p*-Tolyl 2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-1-thio- β -D-galactofuranoside (**22**)

To a solution of **21** (0.63 g, 1.47 mmol) in dry DMF (15 mL) cooled to 0 °C was added NaH (dispersion in oil 60%, 150 mg, 3.75 mmol) immediately followed by BnBr (0.46 mL, 3.87 mmol) with stirring. After 18 min of stirring, ice (5 g) was added. The reaction mixture was rapidly diluted with CH₂Cl₂ (150 mL), washed with water (2 \times 100 mL), dried (Na₂SO₄), filtered, and concentrated. Column chromatography (toluene) of the residue afforded **22** (0.46 g, 61%) as a colorless syrup: R_f 0.44 (4:1 hexane–EtOAc); $[\alpha]_D -117.7$ (c 0.8, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.41–7.29 (m, 7H, arom.), 7.09 (d, 2H, J = 8.5 Hz, arom.), 5.30 (d, 1H, J = 5.3 Hz, H-1), 4.81, 4.72 (2d, 2H, J = 11.9 Hz, CH₂Ph); 4.48 (q, 1H, J = 6.5 Hz, H-5), 4.27 (dd, 1H, J = 10.2, 6.5 Hz, H-3), 4.20 (dd, 1H, J = 10.1, 6.5 Hz, H-3), 3.95 (dd, 1H, J = 6.5, 5.3 Hz, H-2), 3.84 (dd, 1H, J = 11.5, 6.4 Hz, H-6a), 3.70 (dd, 1H, J = 11.5, 6.6 Hz, H-6b), 2.32 (s, 3H, CH₃Ph), 2.16 (br s, 1H, OH-6), 1.04, 0.98 (2s, 18H, 2 (CH₃)₃C); ¹³C NMR (CDCl₃, 128.5 MHz) δ 138.1, 137.4, 132.6, 129.9, 129.7, 128.4, 128.0, 127.9 (aromatic); 90.3 (C-1), 86.7 (C-2), 76.0 (C-3), 75.6 (C-4), 72.6 (C-5), 72.3 (CH₂Ph), 62.6 (C-6), 27.1 (2 (CH₃)₃C), 21.5, 20.7 (2 (CH₃)₃C), 21.1 (CH₃Ph); HRMS (ESI) m/z calcd for C₂₈H₄₀NaO₅SSi [M+Na]⁺ 539.2263, found 539.2269.

4.9. *p*-Tolyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-1-thio- β -D-galactofuranoside (**12**)

To a solution of **22** (0.41 g, 0.79 mmol) in dry pyridine cooled at 0 °C was added dropwise acetic anhydride (5 mL) with stirring. After 2.5 h, the reaction was quenched with MeOH and concentrated in vacuum. Purification of the residue by column chromatography (25:1 hexane–EtOAc) afforded **12** (0.43 g, 97%) as a colorless syrup: R_f 0.58 (20:1 toluene–EtOAc); $[\alpha]_D -101.0$ (c 0.8, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.41–7.27 (m, 7H, arom.), 7.09 (d, 2H, J = 8.5 Hz, arom.), 5.31 (d, 1H, J = 5.4 Hz, H-1), 4.80, 4.72 (2d, 2H, J = 12.0 Hz, CH₂Ph); 4.61 (td, 1H, J = 7.1, 3.6 Hz, H-5), 4.33 (dd, 1H, J = 11.8, 3.6 Hz, H-6a), 4.30 (dd, 1H, J = 10.2, 6.6 Hz, H-3), 4.27 (dd, 1H, J = 11.8, 7.4 Hz, H-6b), 4.16 (dd, 1H, J = 10.2, 6.8 Hz, H-4), 3.93 (dd, 1H, J = 6.6, 5.4 Hz, H-2), 2.31 (s, 3H, CH₃CO), 2.07 (s, 3H, CH₃Ph), 1.04, 0.99 (2s, 18H, (CH₃)₃C); ¹³C NMR (CDCl₃, 128.5 MHz) δ 170.9 (CH₃CO), 137.6, 137.5, 131.9, 130.4, 129.6, 128.4, 128.0, 127.8 (aromatic); 90.0 (C-1), 86.8 (C-2), 76.6 (C-3), 74.7 (C-4), 72.2 (CH₂Ph), 70.9 (C-5), 64.2 (C-6), 27.1, 27.0 ((CH₃)₃C); 21.6, 20.7 ((CH₃)₃C), 21.1 (CH₃Ph), 20.9 (CH₃CO); HRMS (ESI) m/z calcd for C₃₀H₄₂NaO₆SSi [M+Na]⁺ 581.2369, found 581.2358.

4.10. General procedures for glycosylation reactions

4.10.1. Method A

To a solution of thioglycoside **12** (1 equiv), acceptor (1.2 equiv) dissolved in anhyd ethyl ether (3 mL/0.04 M of donor) were added

powdered 4 Å molecular sieves, and the mixture was vigorously stirred for 5 min under argon. After cooling the suspension to –78 °C, *N*-iodosuccinimide (1.5 equiv) and silver triflate (0.25 equiv) were added. The reaction was monitored by TLC, and after total disappearance of the donor (when possible), it was quenched by the addition of triethylamine (1.2 equiv). The mixture was diluted with CH₂Cl₂ (5 mL), filtered through Celite, and concentrated under vacuum.

α/β ratio was established from ¹H NMR spectrum of the crude reaction (Table 1).

4.10.2. Method B

Same procedure described for method A was followed, using anhyd CH₂Cl₂ as solvent.

4.10.3. Method C

Same procedure described for method A was followed, using anhyd CH₂Cl₂ as solvent at 0 °C.

4.10.4. Method D

Same procedure described for method A was followed at 0 °C.

4.10.5. Method E

A suspension of donor **12** (1 equiv), acceptor (1.2 equiv), AgOTf (2.5 equiv), and powdered 4 Å molecular sieves (150 mg) in anhyd CH₂Cl₂ (3.0 mL, 0.04 M of donor) was vigorously stirred at room temperature under argon. After 5 min, the mixture was cooled to –78 °C and a solution of 4-nitrobenzenesulfonyl chloride (1.2 equiv) in anhyd CH₂Cl₂ (0.3 mL) was added. The reaction was monitored by TLC, and quenched by the addition of triethylamine (1.2 equiv) after total disappearance of the donor. The mixture was diluted with CH₂Cl₂ (5 mL) and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography, as indicated in each case.

α/β ratio was established from ¹H NMR spectrum of the crude reaction (Tables 1 and 2).

4.10.6. Method F

Same procedure described for method E was followed, using anhyd ethyl ether as solvent.

4.10.7. Method G

Same procedure described for method E was followed, at –30 °C.

4.10.8. Method H

Same procedure described for method E was followed, using anhyd toluene as solvent.

4.10.9. Method I (preactivation of **12**)

A suspension of donor **12** (1 equiv), AgOTf (2.5 equiv) and powdered 4 Å molecular sieves in anhyd CH₂Cl₂ (3 mL/0.04 M of donor) was vigorously stirred at room temperature under argon. After 5 min, the mixture was cooled to –78 °C and a solution of 4-nitrobenzenesulfonyl chloride (1.2 equiv) in anhyd CH₂Cl₂ (0.3 mL) was slowly added. After 5 min of stirring, a solution of acceptor (1.2 equiv) in anhyd CH₂Cl₂ (0.3 mL) was added. The reaction was monitored by TLC, and quenched by the addition of triethylamine (1.2 equiv) after total disappearance of the donor. The mixture was diluted with CH₂Cl₂ (5 mL) and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography, as indicated in each case.

α/β ratio was established from the ¹H NMR spectrum of the crude reaction.

4.10.10. Preparation of cyclohexyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- α -D-galactofuranoside (**23 α**) and cyclohexyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- β -D-galactofuranoside (**23 β**)

Method E: Reaction of compound **12** (18 mg, 0.038 mmol) and cyclohexanol (4 μ L, 0.054 mmol) gave a crude mixture with **23 α** and **23 β** in 4:1 ratio as indicated by the ^1H NMR spectrum (δ 5.03–5.07 for superimposed H-1 **23 β** and H-1 **23 α** , 1H [(5.06 d, J = 3.2 Hz, H-1 **23 β**) and (5.05 d, 1H, J = 5.2 Hz, H-1 **23 α**); 3.85 (dd, 0.8H, J = 5.3, 9.0 Hz, H-2 **23 α**). Purification of the crude (25:1 toluene–EtOAc) gave 15 mg of **23 α** and **23 β** as a mixture (87%). All spectral data matched those of compounds **23 α** and **23 β** .⁴⁷

4.10.11. Preparation of 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- α -D-galactofuranosyl-2,3,5-tri-O-benzoyl-D-galactono-1,4-lactone (**25 α**), and 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- β -D-galactofuranosyl-2,3,5-tri-O-benzoyl-D-galactono-1,4-lactone (**25 β**)

Method E: Reaction of compound **12** (22 mg, 0.039 mmol) and 2,3,5-tri-O-benzoyl-D-galactono-1,4-lactone⁶⁶ (**24**, 23 mg, 0.047 mmol) gave a crude mixture with **25 α** and **25 β** in 4:1 ratio as indicated by the ^1H NMR spectrum (δ 5.06 (d, 1H, J = 5.1 Hz, H-1' **25 α**), 5.01 (dd, 1H, J = 2.0, 6.1 Hz, H-4 **25 α**); 4.98 (dd, 0.25H, J = 2.6, 5.2 Hz, H-4 **25 β**), 4.96 (d, 0.25H, J = 2.9 Hz, H-1' **25 β**). Purification of the crude (25:1 toluene–EtOAc) gave 24 mg of **25 α** and **25 β** as a mixture (65%). All spectral data matched those of compounds **25 α** and **25 β** .⁴⁷

Method I: Compound **12** (39 mg, 0.070 mmol) and **24** (42 mg, 0.086 mmol) gave a crude mixture with **25 α** and **25 β** in 4:1 ratio as indicated by the ^1H NMR spectrum. Purification of the crude gave 33 mg of **25 α** and **25 β** (51%).

4.10.12. Preparation of methyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- α -D-galactofuranosyl-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl- α -D-mannopyranoside (**27 α**) and methyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- β -D-galactofuranosyl-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl- α -D-mannopyranoside (**27 β**)

Method E: Compound **12** (43 mg, 0.077 mmol) and methyl 2,3,4-tri-O-benzoyl- α -D-mannopyranoside⁶⁷ (**26**, 47 mg, 0.093 mmol) gave a crude with **27 α** and **27 β** in 20:1 ratio as indicated by the ^1H NMR spectrum (δ 4.96 (d, 0.05H, J = 1.6 Hz, H-1 **27 β**), 4.87 (d, 1H, J = 4.9 Hz, H-1' **27 α**). Purification by column chromatography (20:1 toluene–EtOAc) gave 57 mg of **27 α** and **27 β** as a mixture (78%). All spectral data matched those of compounds **27 α** and **27 β** .⁴⁷

Method I: Compound **12** (31 mg, 0.056 mmol) and **26** (34 mg, 0.067 mmol) gave 42 mg of **27 α** (81%).

4.10.13. Methyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- α -D-galactofuranosyl-(1 \rightarrow 6)-2,3,4-tri-O-benzoyl- α -D-mannopyranoside (**29 α**)

Method E: Reaction of **12** (37 mg, 0.066 mmol) and methyl 2,3,4-tri-O-benzoyl- α -D-mannopyranoside⁶⁸ (**28**, 37 mg, 0.080 mmol) gave a crude with **29 α** and **29 β** as a mixture of anomers in 6.3:1 α : β ratio as indicated by the integration of H-1' α (δ 5.21, $J_{1',2'} = 5.0$ Hz) and H-1' β (δ 5.03, $J_{1',2'} = 3.2$ Hz). The crude was purified by column chromatography (20:1 toluene–EtOAc) to give syrupy **29 α** (48 mg, 80%); R_f 0.36 (10:1 toluene–EtOAc); $[\alpha]_D +59.5$ (c 1, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 7.38–7.18 (m, 20H, arom.), 5.21 (d, 1H, J = 5.0 Hz, H-1'); 4.80, 4.57 (2d, 2H, J = 11.1 Hz, PhCH_2), 4.76 (d, 1H, J = 1.7 Hz, H-1); 4.61, 4.67 (2d, 2H, J = 12.2 Hz, PhCH_2), 4.67 (s, 2H, PhCH_2), 4.59 (s, 2H, PhCH_2), 4.59 (t, 1H, J = 9.7 Hz, H-3'), 4.56 (m, 1H, H-5'), 4.44 (dd, 1H, J = 11.9, 7.1 Hz, H-6a'), 4.25 (dd, 1H, J = 11.9, 3.7, H-6b'), 3.99 (dd, 1H, J = 9.7, 6.6 Hz, H-4'), 3.90 (t, 1H, J = 9.3 Hz, H-4), 3.86 (dd, 1H, J = 3.0, 8.9 Hz, H-3), 3.84–3.80 (m, 3H, H-3, H-6a, H-6b), 3.81 (dd, 1H, J = 9.0, 5.1 Hz, H-2'), 3.77

(dd, 1H, J = 2.1, 2.0 Hz, H-2'), 3.71 (m, 1H, H-5), 3.29 (s, 3H, CH_3O), 2.03 (s, 3H, CH_3CO); 1.04, 1.00 (2s, 18H, $(\text{CH}_3)_3\text{C}$); ^{13}C NMR (CDCl_3 , 128.5 MHz) δ 170.8 (CH_3CO); 138.7, 138.6, 138.4, 138.2, 128.3, 128.2, 128.1, 127.82, 127.78, 127.76, 127.6, 127.5, 127.44, 127.40, 127.38 (aromatic), 99.8 (C-1'), 98.6 (C-1), 80.9 (C-2'), 80.2 (C-3), 75.4 (C-4'), 74.9 (PhCH_2), 74.9 (C-4), 74.8 (C-2), 73.6 (C-3), 72.6 (PhCH_2), 72.1 (C-5'), 72.0 (PhCH_2), 71.9 (C-5), 71.5 (PhCH_2), 66.3 (C-6), 64.4 (C-6'), 54.6 (CH_3O); 27.3, 27.1 ($(\text{CH}_3)_3\text{C}$); 21.7, 20.7 ($(\text{CH}_3)_3\text{C}$); 20.9 (CH_3CO). HRMS (ESI) Calcd for $\text{C}_{51}\text{H}_{66}\text{NaO}_{12}\text{Si}$ $[\text{M}+\text{Na}]^+$ 921.4216. Found: $[\text{M}+\text{Na}]^+$ 921.4248.

4.10.14. Preparation of allyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- α -D-galactofuranosyl-(1 \rightarrow 2)-3,4-di-O-benzyl- α -L-rhamnopyranoside (**31 α**) and allyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- β -D-galactofuranosyl-(1 \rightarrow 2)-3,4-di-O-benzyl- α -L-rhamnopyranoside (**31 β**)

Method E: Reaction of compound **12** (21 mg, 0.038 mmol) and allyl 3,4-di-O-benzyl- α -L-rhamnopyranoside⁶⁹ (**30**, 17 mg, 0.044 mmol) gave a crude mixture with **31 α** and **31 β** in 4:1 ratio as indicated by the ^1H NMR spectrum (δ 4.98 (d, 1H, J = 10.7 Hz, PhCH_2H , **31 α**), 4.71 (d, 0.25H, J = 1.6 Hz, H-1 **31 β**), 4.69 (d, 1H, J = 1.9 Hz, H-1 **31 α**). Purification by column chromatography (50:1 toluene–EtOAc) gave 21 mg of **31 α** and **31 β** as a mixture (67%). All spectral data matched those of compounds **31 α** and **31 β** .⁴⁷

Method I: Reaction of compound **12** (29 mg, 0.052 mmol) and **30** (22 mg, 0.057 mmol) a crude mixture with **31 α** and **31 β** in 4:1 ratio as indicated by the ^1H NMR spectrum. Purification of the crude gave 23 mg of **31 α** and **31 β** (52%).

4.10.15. Methyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- α -D-galactofuranosyl-(1 \rightarrow 2)-3-O-benzoyl-4,6-O-benzylidene- α -D-mannopyranoside (**33 α**) and methyl 6-O-acetyl-2-O-benzyl-3,5-O-(di-*tert*-butylsilanediyl)- β -D-galactofuranosyl-(1 \rightarrow 2)-3-O-benzoyl-4,6-O-benzylidene- α -D-mannopyranoside (**33 β**)

Method E: Reaction of compound **12** (51 mg, 0.091 mmol) and methyl 3-O-benzoyl-4,6-O-benzylidene- α -D-mannopyranoside⁷⁰ (**32**, 42 mg, 0.108 mmol) gave a crude mixture with **33 α** and **33 β** in 3:1 ratio as indicated by the ^1H NMR spectrum (δ 5.08 (d, 0.75H, J = 5.3 Hz, H-1' **33 α**); 4.92 (d, 0.25H, J = 3.2 Hz, H-1' **33 β**). The crude was purified by column chromatography (25:1 toluene–EtOAc) to give a first fraction of **33 α** (30 mg, 40%) as a colorless syrup: R_f = 0.36 (10:1 toluene–EtOAc); $[\alpha]_D$ 8.0 (c 1, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 8.06 (d, 2H, J = 8.4 Hz, arom.), 7.54 (t, 1H, J = 7.2 Hz, arom.), 7.44–7.12 (m, 15H, arom.), 5.52 (dd, 1H, J = 10.4, 3.2 Hz, H-3), 5.34 (s, 1H, PhCH), 5.08 (d, 1H, J = 5.3 Hz, H-1'), 4.83, 4.69 (2d, 2H, J = 12.2 Hz, PhCH_2), 4.79 (d, 1H, J = 1.6 Hz, H-1), 4.61 (t, 1H, J = 9.3 Hz, H-3'), 4.55 (dt, J = 6.5, 5.2 Hz, H-5'), 4.28 (d, 2H, J = 5.2 Hz, H-6a', H-6b'), 4.28–4.21 (m, 3H, H-2, H-4, H-6a), 3.94–3.91 (m, 2H, H-4', H-5), 3.87 (dd, 1H, J = 8.9, 5.3 Hz, H-2'), 3.82 (t, 1H, J = 10.2 Hz, H-6b), 3.41 (s, 3H, CH_3O), 2.12 (s, 3H, CH_3CO); 1.07, 0.99 (2s, 18H, 2 $(\text{CH}_3)_3\text{C}$); ^{13}C NMR (CDCl_3 , 128.5 MHz) δ 171.0 (CH_3CO), 165.8 (PhCO); 138.2, 137.4, 133.1, 129.9, 129.8, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1, 127.5, 127.2, 126.1 (arom.); 101.6 (PhCH), 101.5 (C-1'), 101.0 (C-1), 80.8 (C-2'), 76.1 (C-2), 76.0 (C-4), 75.0 (C-4'), 73.6 (C-3'), 71.6 (C-5'), 71.3 (C-3), 71.0 (PhCH_2), 68.8 (C-6), 64.4 (C-6'), 64.0 (C-5), 55.0 (CH_3O); 27.24, 27.15 ($(\text{CH}_3)_3\text{C}$); 21.6, 20.7 ($(\text{CH}_3)_3\text{C}$), 21.0 (CH_3CO). HRMS (ESI) Calcd for $\text{C}_{44}\text{H}_{56}\text{NaO}_{13}\text{Si}$ $[\text{M}+\text{Na}]^+$ 843.3382. Found: $[\text{M}+\text{Na}]^+$ 843.3416.

Next fraction from the column gave syrupy **33 β** (10 mg, 13%); R_f = 0.45 (15:1 toluene–EtOAc); $[\alpha]_D$ –37.2 (c 1, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 8.07 (d, 2H, J = 8.3, 1.3 Hz, arom.), 7.59 (t, 1H, J = 7.3 Hz, arom.), 7.51 (dd, 2H, J = 7.3, 2.0 Hz, arom.), 7.45–7.31 (m, 10H, arom.), 5.72 (s, 1H, PhCH), 5.36 (dd, 1H, J = 10.5, 3.7 Hz, H-3), 4.92 (d, 1H, J = 3.2 Hz, H-1'); 4.79, 4.69 (2d, 2H, J = 12.1 Hz,

PhCH₂), 4.69 (d, 1H, *J* = 1.6 Hz, H-1), 4.39–4.33 (m, 2H, H-2 + H-6a), 4.29 (dd, 1H, *J* = 10.5, 9.0 Hz, H-4), 4.18 (dd, 1H, *J* = 10.2, 7.2 Hz, H-3'), 4.02–3.95 (m, 4H, H-6b, H-5, H-2', H-6a'), 3.93 (dd, 1H, *J* = 11.7, 6.3 Hz, H-6b'), 3.88 (dd, 1H, 10.2, 6.9 Hz, H-4'), 3.44 (s, 3H, CH₃O), 3.15 (dt, 1H, *J* = 6.5, 4.3 Hz, H-5'), 2.07 (s, 3H, CH₃CO); 0.99, 0.95 (2s, 18H, 2 (CH₃)₃C); ¹³C NMR (CDCl₃, 128.5 MHz) δ 170.7 (CH₃CO), 165.3 (PhCO); 137.8, 137.3, 133.0, 130.2, 129.5, 129.0, 128.5, 128.4, 128.2, 127.73, 127.68, 126.2 (arom.); 106.2 (C-1'), 101.7 (PhCH), 99.9 (C-1), 87.2 (C-2'), 76.5 (C-3'), 75.9 (C-4), 75.0 (C-4'), 74.6 (C-2), 71.9 (PhCH₂), 70.3 (C-3), 70.2 (C-5'), 68.9 (C-6), 63.8 (C-5), 63.6 (C-6'), 55.0 (CH₃O); 27.2, 26.9 ((CH₃)₃C); 21.5, 20.6 ((CH₃)₃C), 20.9 (CH₃CO); HRMS (ESI) Calcd for C₄₄H₅₆NaO₁₃Si [M+Na]⁺ 843.3382. Found: [M+Na]⁺ 843.3356.

Method I: Reaction of compound **12** (47 mg, 0.084 mmol) and **32** (41 mg, 0.101 mmol) gave a crude mixture with **33α** and **33β** in 3.6:1 ratio according to ¹H NMR spectrum. Purification of the crude gave 53 mg of **33α** and **33β** (76%).

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Supplementary data

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