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Regioselective 5-*O*-Opening of Conformationally Locked 3,5-*O*-Di-*tert*-butylsilylene-D-galactofuranosides. Synthesis of (1→5)-*β*-D-Galactofuranosyl Derivatives

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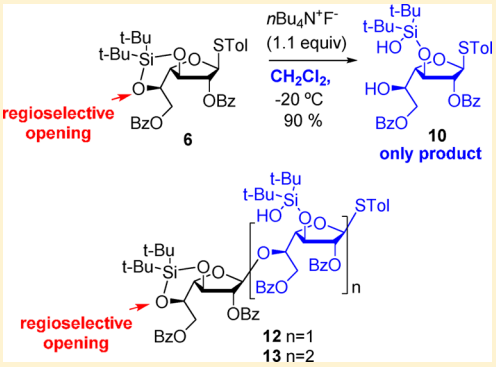
Supporting Information

ABSTRACT: The use of thiogalactofuranoside as donors for the construction of internal Gal*f* containing oligosaccharide is limited, probably due to the difficulty to functionalize thiogalactofuranoside derivatives showing O-2, O-3, and O-5 with similar reactivity. An efficient method for complete regioselective 5-*O*-opening of conformationally restricted 3,5-*O*-di-*tert*-butylsilylene-D-galactofuranoside derivatives was developed. The use of a solution nBu$_4$NF (1.1 equiv) in CH_2Cl_2 on **6** gave the 5-OH free derivative **10** as the only product (90%). 3-*O*-Di-*tert*-butylhydroxysilyl derivative **10** was stable upon purification and glycosylation reaction. Preactivation of conformationally restricted thioglycoside **6** employing *p*-NO_2-benzensulfenyl chloride/AgOTf followed by condensation over the 5-OH thioglycoside acceptor **10** gave the corresponding disaccharide **12** without autocondensation byproduct. Regioselective 5-*O*-deprotection was also successfully performed over the (1→5)-*β*-D-galactofuranosyl di- and trisaccharide derivatives **12** and **13**. This methodology allowed the differentiation between the secondary hydroxyl groups OH-3 and OH-5 of 1,2-*cis* or 1,2-*trans* D-galactofuranoside derivatives, and it still constitutes an innovative approach to access oligosaccharides of pharmacological importance.



INTRODUCTION

Glycans play an essential role in biology,[1] and the knowledge of the biological processes has driven chemical glycobiology in such a perspective[2,3] that glycotherapy has reemerge in medicine.[4] For these reasons, synthetic oligosaccharides constitute powerful tools for this purpose.[2,5] For instance, galactose in the furanose form is present in several pathogenic microorganisms, whereas it is not biosynthesized in mammals.[6−8] For that reason, Gal*f* metabolism is a promising target for chemotherapy.[9,10] In this context, the synthesis of Gal*f*-containing oligosaccharides has gained much attention as components of tools for studying their functions[11] or the biosynthetic steps[12,13] or for the development of specific antigens.[14] The synthesis of oligosaccharides containing internal Gal*f* requires a first choice of the galactofuranosyl template, which has to be functionalized or protected,[8,15] and this selection is deeply related to the method of glycosylation used. Several glycosylation methods have been essayed for this purpose;[7,8] the trichloroacetimidate method is the most widely employed according to the literature.[16−20] In contrast to pyranoses, the thioglycoside method has not been widely exploited as well[7,8] in spite of the success in oligosaccharide synthesis provided by the stability of the thio function toward a wide range of reaction conditions, which allows the manipulation of the protecting group prior to activation. The introduction of terminal Gal*f* has been described by this method,[7,8,12,21,22] however, examples of the synthesis of internal Gal*f*-oligosaccharides are more limited. Interesting examples are the synthesis of mycolyl-arabinogalactan oligosaccharide fragments,[12] a tetragalactofuranoside for the detection of *Aspergillus fumigatus*[14] and tetra and hexasaccharide fragments of the LPS of *Klebsiella pneumoniae*.[23] More recently, some thiogalactofuranosides were used for the development of regioselective furanosylation methodology.[24] The influence of the protection pattern was evaluated on several phenyl thioglycosides for reactivity tuning.[25] Very recently, thiogalactofuranosides precursors were employed for the challenging synthesis of natural products containing 1,2-*cis* Gal*f*.[26,27] The limited number of examples on the use of thiogalactofuranosyl donors could be partially attributed to the difficulty of selectively protecting the 1-thio galactofuranosyl glycoside that is usually required as the starting material. In fact, benzoylation of tolyl 1-thio-galactofuranoside with 2.2 equiv of benzoyl chloride at −15 °C gave a complex mixture of products which included 6-*O*-, 5,6-di-*O*-, 2,6-di-*O*- and 3,6-di-O-benzoyl rather than the expected 2,6-di-*O*-benzoyl derivative as the main product.[28] Moreover, selective benzoylation of *p*-tolyl 5,6-*O*-isopropylidene-1-thio-*β*-D-galactofuranoside by treatment with benzoyl chloride (1 equiv) gave the 2-*O* and 3-*O* derivatives in 45% and 26% yield, respectively.[24] Even protection with the bulky silylating agent *tert*-butyldimethylsilyl chloride gave the 2-*O*-

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silyl derivative in 60% yield together with 3-*O*-derivative in 12% yield.[23] In summary, protection of the primary OH-6 can be easily achieved, however, OH-2, OH-3, and OH-5 have similar reactivities toward acylation reactions. Particularly, access to exocyclic 5-OH thiogalactofuranosyl derivatives requires several reaction steps involving major manipulation of protecting groups.[12,14,25−27] Therefore, new strategies are needed for the development of acceptors that react regioselectively. In our recent studies on stereoselective 1,2-*cis* galactofuranosylation[28,29] following a similar approach applied for 1,2-*cis* β-arabinofuranosylation,[30−35] we have employed the 3,5-*O*-di-*tert*-butylsilyl group to impart rigidity to the galactofuranose ring in order to guide the incoming nucleophile acceptor into the inside face of the oxacarbenium ion. This protecting group has not been extensively studied in galactofuranosyl derivatives. In fact, some unusual chemical behaviors were observed after the introduction of the 3,5-*O*-di-*tert*-butylsilylene (3,5-*O*-DTBS) protecting group into the galactofuranosyl moiety. For example, almost complete selective benzylation at the secondary OH-2 position over the primary OH-6 was observed on conformationally constrained benzyl α-D-galactofuranoside derivative **1**[29] and β-thiogalactofuranoside derivative **2**[28] (Figure 1). An

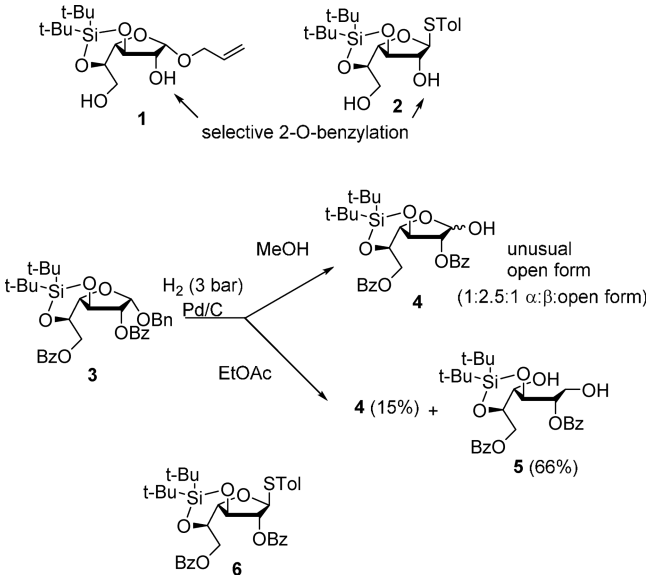

Figure 1. Conformationally locked galactofuranoside derivatives and their unusual chemical behavior.

unusual over reduction alditol byproduct **5** was observed on hydrogenolysis of **3** in ethyl acetate, whereas the anomeric free derivative **4** was obtained in methanol (Figure 1).[28] Moreover, anomeric free derivative **4** presents an important amount of the aldehyde open form (Figure 1).[28] We envisioned conformationally constrained thioglycoside **6**[28] as an interesting precursor for internal galactofuranoside-containing oligosaccharide synthesis. Very recently, the thiophenyl analogue of **6**, synthesized through a secondary product from phenyl 1-thio-β-D-galactofuranoside, was employed for reactivity tuning studies as a precursor of terminal Gal*f*.[25]

With the aim at differentiating the secondary positions OH-3 and OH-5 of the galactofuranosyl moiety, and taking into account that the use of this protecting group has not been fully exploited in galactofuranose derivatives, our attention was driven to investigate the selective opening of the silylene group present in compound **6**. The DTBS group was formerly introduced as a 1,3-diols protecting group,[36] but nowadays its use has been extended for directing the stereochemistry of glycosylation reactions. In addition to the 1,2-*cis* β-arabinofuranosylation and 1,2-*cis* α-galactofuranosylation,[28,29] this protecting group was successfully employed in pyranosylation. For example, 4,6-*O*-DTBS derivatives of galactopyranose and *N*-acetyl galactosamine donors gave 1,2-*cis* glycosidic linkage despite the presence of a participating group in O-2. Very recently, the conformationally restricted donor phenyl 2,3-di-*O*-benzyl-4,6-*O*-(di-*tert*-butylsilylene)-1-thio-α-D-mannopyranoside proved to be β-selective with a variety of activation conditions.[37] Also, phenyl 2-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilylene)-α-D-arabinofuranoside showed to be a superdisarmed donor in competitive arabinofuranosylation studies.[38]

Selective deprotection of silyl groups of the same nature could be performed taking into account steric factors; the less crowded primary position is deprotected first.[39] This fact was pivotal for the development of the new methodology regioselective silyl exchange technology (ReSET) recently described as an important tool for carbohydrate modification.[40] Some examples of removal of DTBS ethers in the presence of several silyl groups have been described,[39,41] but only few of them are effective on selective opening of DTBS.[39] For instance, a one-pot protocol for the introduction of DTBS on 1,2-diol followed by treatment of alkyl lithium was applied for selective deprotection of a primary position.[42] Treatment of $BF_3.S(CH_3)_2$ as Lewis acid was also applied to selective opening of the primary position by a fluoride ion transfer from the borane to the silicon atom. This methodology did not work for the differentiation of two secondary positions.[43] A formation of 3,5-*O*-DTBS on 2′-deoxinucleoside and further selective removal of the silyl of the primary position was also informed under basic treatment.[44] More recently, selective monodeprotection of 1,3-*O*-DTBS of primary position of some carbohydrate derivatives was described by the use of NH_4F in methanol.[45] Very recently, in the course of our investigations, a regioselective ring opening of a related silylene group, a diisopropylsilylene derived 1,3-diol, by treatment with alkyl lithium reagents was developed.[46]

Considering the modest information about this protecting group and in order to get new insight into the galactofuranose field, we report here the regioselective opening of the 3,5-*O*-DTBS group in thiogalactofuranosyl glycoside **6**, by discrimination between the secondary OH-3 and OH-5 (Figure 1). The resulting product was used as an acceptor in the glycosylation reaction (thioglycoside method) in the synthesis of a β(1−5)galactofuranosyl derivative. We have further explored the selective opening of other 3,5-*O*-DTBS-D-galactofuranosyl units present in di- and trisaccharides. Selective deprotection of any of these secondary positions would be a valuable tool for the development of galactofuranosyl acceptors or donors.

RESULTS AND DISCUSSION

The synthesis of thioglycoside **6** (Figure 1) involves five reaction steps[28] (28%) from benzyl α-D-galactofuranoside, which is obtained in one step from galactose by anomeric alkylation (64%).[16,47] For the first experiments, the 3,5-*O*-DTBS containing α-benzyl glycoside analog **3** (Figure 1),[28] precursor of the synthesis of **6**, was used as a simple model. We have first evaluated the resistance of the silylene group to a Lewis acid. Compound **3**, after 8 h of treatment with TMSOTf (1 equiv) in CH_2Cl_2 at room temperature, was recovered

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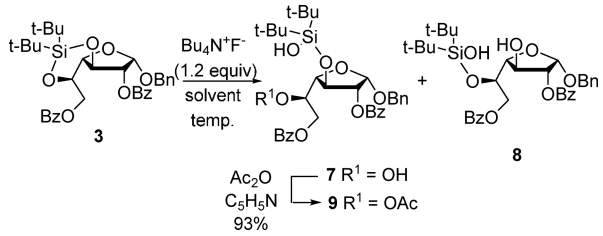
Table 1. Opening of 3,5-*O*-DTBS-D-Gal*f* Derivative 3 with *n*Bu$_4$NF



entry	reactant	solvent	temp. (°C)	reaction time (h)	**7**/**8**[a] (yield)[b]
1	TMSOTf (1 equiv)	CH_2Cl_2	0	16	no reaction
2	Bu_4NF (1.2 equiv)	THF	0	1.5	5:1 (79%)[b]
3	Bu_4NF (1.2 equiv)	THF	−78	20	no reaction
4	Bu_4NF (1.2 equiv)	CH_2Cl_2	−78	20	no reaction
5	Bu_4NF (1.2 equiv)	CH_2Cl_2	−20	18	only **7** (84%)[b]

[a]**7**/**8** ratio established from ^{1}H NMR (500 MHz) spectrum. [b]Isolated yield.

unaltered (Table 1, entry 1). Then, a selective opening was essayed using the standard conditions to remove silyl ethers but using stoichiometric amounts of fluoride ion. Thus, **3** was treated with 1.2 equiv of *n*Bu$_4$NF in THF at 0 °C, and after 1.5 h, a TLC indicated no starting material left and the formation of a more polar single spot. The mixture was extracted with water and purified by column chromatography. However, a mixture of products was obtained as indicated by the ^{1}H NMR spectrum showing two anomeric protons in 1,2-*cis* disposition at δ 5.47 (J = 4.4 Hz) and δ 5.42 (J = 4.6 Hz) in 5:1 ratio, suggesting the presence of a mixture of 5-OH and 3-OH derivatives (entry 2, see SI for the ^{1}H NMR spectrum of the mixture). In an attempt to rationalize the regiochemistry of the fluoride deprotection, acylation of this mixture with acetic anhydride and pyridine was carried out. In this case, the ^{1}H NMR spectrum showed two signals that appeared at downfield: a triplet centered at δ 6.00 and a multiplet at δ 5.67 in 1:5 ratio, respectively, suggesting that acetylation occurred at OH-3 of the minor isomer and at OH-5 of the major isomer. This preliminary result indicated that the fluoride deprotection was regioselective on the secondary OH-5. Motivated to get a complete regioselectivity, the reaction was conducted at lower temperatures; however, at −78 °C the starting material **3** remained unaltered (entry 3). Then it was decided to change the solvent system commonly used in desilylation reactions tetrahydrofuran to CH_2Cl_2. If the reaction was carried out at −78 °C, no reaction was observed (entry 4). When the temperature was raised to −20 °C and the reaction was left overnight, complete disappearance of starting material was noticed. Interestingly, after reaction workup and chromatographic purification, benzyl 2,6-di-*O*-benzoyl-3-*O*-di-*tert*-butylhydroxysilyl-α-D-galactofuranoside (**7**) was obtained as the only regioisomer in 84% yield (entry 5). The ^{1}H NMR spectrum showed the presence of the corresponding, the di-*tert*-butylsilyl group, which appeared as a singlet at δ 0.99 ppm. The anomeric signal appeared as a doublet centered at δ 5.47 (J = 4.4 Hz), which was coincident with the signal observed for the major product obtained by deprotection using THF as a solvent. The coupling constant value was in agreement with a flexible 1,2-*cis* α-galactofuranosyl derivative.[16,19,48,49] No significant changes in the chemical shifts of H-2 and H-6a,b were observed, indicating that no migration of the benzoyl groups took place, which was possible because of the basicity of the reagent. The furanose ring had lost the conformational restriction as indicated by $J_{2,3}$ and $J_{3,4}$ with lower values compared to those in the precursor **3** ($J_{2,3}$ and $J_{3,4}$ ~ 9.5 Hz). Moreover, in the ^{13}C NMR spectrum, the C-4 signal appeared at 82.7 ppm, typical of a flexible Gal*f* ring, whereas in the conformationally constrained derivative **3** (or related 3,5-*O*-DTBS-galactofuranosyl derivatives), the C-4 signal was observed upfield at 75 ppm.[28,29] The H-5 signal, which appeared superimposed to H-4 (δ 4.22−4.20), correlated (COSY) with the OH-5 at 2.93 ppm. The broad singlet at 2.76 ppm was assigned to the OH linked to the silane atom of the di-*tert*-butylhydroxylsilyl group at 3-*O*-position. HMRS data confirmed the proposed structure. It is worth pointing out that some divergences around the silicon atom in fluorine deprotections are described in the literature. Previous work in selective deprotection of DTBS group with $BF_3{\cdot}SMe_3$ included the transfer of the fluorine atom to the silicon atom from the less crowded face of the molecule, while the fluorine atom remained bonded to the silicon atom.[43] More recently, on deprotection by treatment with NH_4F, the fluorine atom also remained bonded to the silane.[45] However, a short communication on deprotection of a 3,5-*O*-DTBS derivative of ribose with *n*Bu$_4$NF informed the loss of the fluorine atom.[50] Our results are in agreement with the proposed structure. We assume that the fluorine atom attacks the silicon atom of the 3,5-*O*-di-*tert*-butylsilylene group from the less hindered face in a S_N2 manner. The resulting 3-*O*-di-*tert*-butylsilylfluoride moiety is hydrolyzed into a 3-*O*-di-*tert*-butylhydroxylsilyl group within the reaction mixture as a consequence of the presence of small amount of water in the reagent or in the water extraction. The R_f of **7** after purification was coincident while monitoring the reaction.

In order to confirm the regiochemistry of the silane opening reaction, compound **7** was acetylated under standard conditions (acetic anhydride in pyridine) to afford **9** in 93% yield. In the ^{1}H NMR spectrum of **9**, the H-5 (δ 5.67) appeared shifted downfield (1.5 ppm) compared to the same signal in its precursor, confirming the regiochemistry of the deprotection on the exocyclic 5-*O* of the silylene group. Integration of singlet at δ 1.91 indicated that only one acetyl group was introduced into the molecule. Moreover, the hydrogen atom of the silanol protecting group (SiO*H*) at O-3 appeared at δ 3.80 ppm as a broad singlet. Full assignment of the signals of ^{1}H and ^{13}C NMR spectra was performed on the basis of the HSQC and COSY spectra. The HRMS confirmed the proposed structure for **9**.

Having at hand a method for a complete regioselective opening of the 3,5-*O*-DTBS group in the simple model **3**, we

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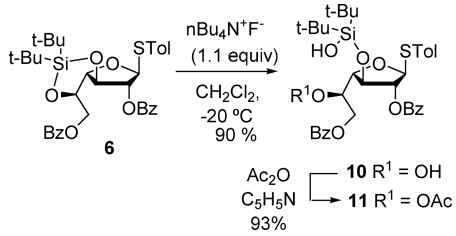
evaluated the scope of this reaction on the conformationally locked thioglycoside **6**. On reaction of **6** in CH_2Cl_2 with 1.2 equiv of nBu_4NF dissolved in CH_2Cl_2 and after 40 h at −20 °C, followed by extraction with water and column chromatography, **10** with OH-5 was obtained in 90% yield as a single regioisomer (Scheme 1). In the ^{1}H NMR spectrum of **10**, the hydrogen

Scheme 1

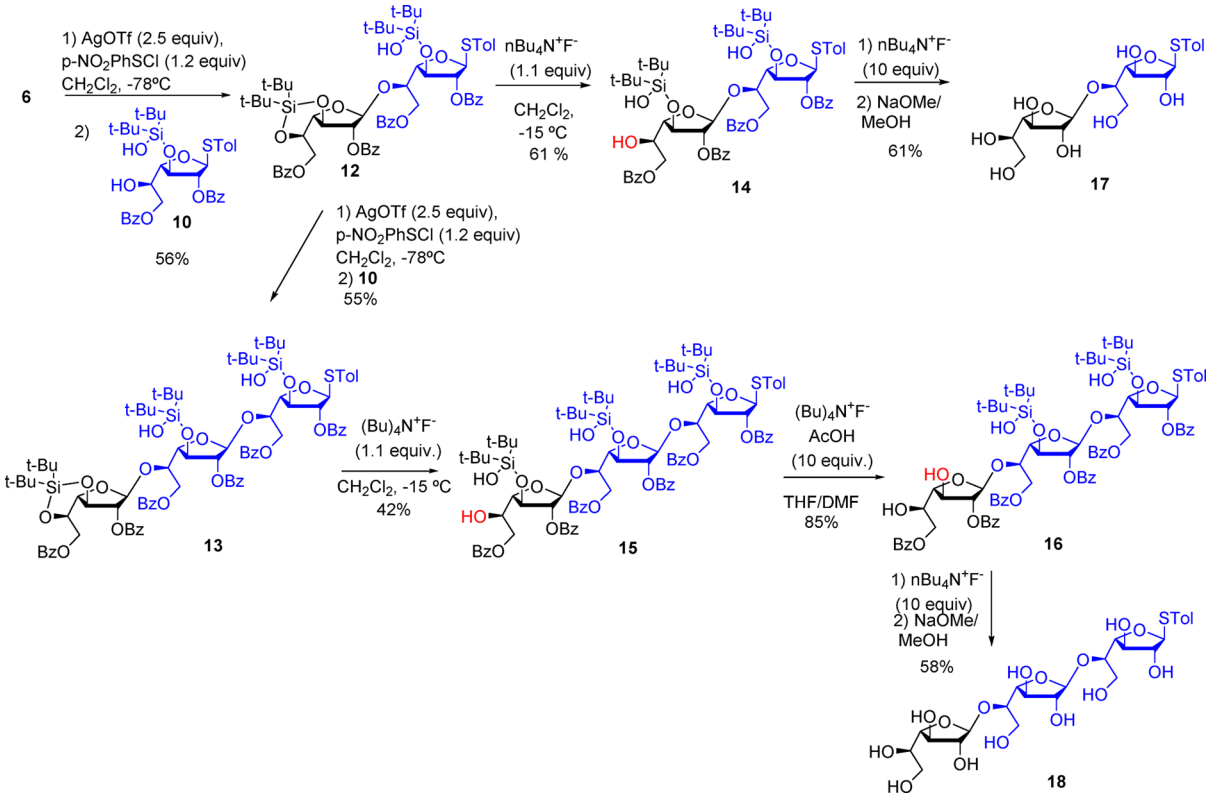


atoms of the *t*-butyl groups appeared as two singlets at 1.08 and 1.04 ppm. Whereas the H-1 in the precursor **6** appeared as a doublet (J = 4.7 Hz) because the conformational restriction, the H-1 in **10** appeared as a broad singlet (δ 5.65 ppm) typical of a flexible 1,2-*trans* β-thiogalactofuranoside,[51] showing the lost of the conformational restriction. Moreover, H-2 appeared as a triplet with a small coupling constant (J = 1.4 Hz) in comparison to the corresponding signal in the precursor **6** ($J_{2,3}$ = 6.4 Hz), showing the conformational change due to the opening of the silylene group. In the ^{13}C NMR spectrum, the deshielded resonance of C-4 (δ 84.9) also confirmed the presence of a flexible β-thiogalactofuranoside. The signal of H-5 appeared as a multiplet centered at δ 4.30, which correlated (COSY) with the OH-5 at δ 2.54, confirming the regioselective opening. Once again, a broad singlet at δ 3.66 was assigned to OH linked to the silicon atom at O-3, and it was in agreement with the HRMS data.

Acetylation by standard conditions of **10** gave **11** in 93% yield. The ^{1}H NMR spectrum of **11** did not show any substantial change in proton displacement with the exception of the signal corresponding to H-5, which appeared as the most deprotected signal of the sugar backbone at 5.70 ppm, confirming the acetylation of this position, and, consequently, the regioselective opening of the silylene favoring the 5-OH isomer. Compound **11** contained only one acetyl group as indicated by the integration of the signal at δ 1.95 ppm. The broad singlet at 3.7 ppm was assigned as the hydrogen atom of the silanol. All the signals were assigned on the basis of the COSY and HSQC-DEPT spectra. The proposed structure for **11** was confirmed by high-resolution mass spectrum data. In summary, constrained 1,2-*cis* benzyl glycoside **3** and 1,2-*trans* thioglycosides **6** reacted in the same way when treated with 1 equiv of fluoride, to give the corresponding 5-OH derivative **7** and **10**, respectively.

Use of the Thioglycoside 10 as an Acceptor. Synthesis of Galactofuran Derivatives. Thioglycoside **10** was an interesting substrate to be tested as an acceptor considering that it contains a silanol group, which was not able to undergo the acetylation reaction, together with OH-5 group in its molecule. On the other hand, after constructing the glycosidic linkage in an iterative manner, the thioglycoside function could be further activated. In order to evaluate **10** as an acceptor, the synthesis of a galactofuran oligosaccharide from *Aspergillus fumigatus* containing repeating units of β-D-Gal*f*(1→5) was envisioned. Fragments of this antigen have been synthesized previously by the use of an anomeric chloride galactofuranosyl donor and mercuric salts as a promoter.[52−54] More recently, a

Scheme 2



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biotinylated tetramer was synthesized by the thioglycoside method.[14] A trisaccharide derivative was recently synthesized as methyl glycoside as a part of methodology studies on the influence of protecting groups in galactofuranosyl donors.[25] Very recently, β(1−5)galactofuran tetrasaccharide-containing galactomannan was synthesized using selectively protected galactofuranosyl precursors, which were obtained by the newly developed pyranoside-into-furanoside (PIF) rearrangement.[18] We also decided to use conformationally constrained thiogalactofuranoside **6** as a donor because it would be plausible to further evaluate the regioselective opening of the 3,5-*O*-DTBS once the β-D-Gal*f*(1→5)-D-Gal*f* linkage had been constructed.

In order to generate the sulfenyltriflate *in situ*, the *p*-NO_2PhSCl/AgOTf activation system developed by Crich[55] was chosen as a promoter, which was successfully applied by us in 1,2-*cis* α-galactofuranosylation.[28] This promoting system had been also successfully applied with a wide range of thioglycopyranoside donors, such as 2-deoxy-2-nitro-1-thioglycosides,[56] and thioglucosamine derivatives donors,[57] for β-mannopyranosylation in oligosaccharide synthesis,[58] for glycosylation with galacturonic acid-derived thioglycoside donors[59] and with a thiogalactopyranoside donor.[60]

The glycosylation procedure with preactivation of the donor was employed.[55] Thus, to a mixture of thiogalactofuranosyl donor **6**, AgOTf, and 4 Å molecular sieves in CH_2Cl_2 at −78 °C was added *p*-NO_2PhSCl (1.1 equiv) in CH_2Cl_2. The mixture was stirred for 5 min in order to allow activation by formation of the corresponding triflate to occur. Then, a solution of thioglycoside acceptor **10** (1.1 equiv) in CH_2Cl_2 was added. The reaction was monitored by TLC, and when the starting material was consumed, the reaction was quenched by pouring into $NaHCO_3$. Purification by column chromatography gave the corresponding disaccharide **12** in 56% yield, which was fully characterized spectroscopically (Scheme 2). For example, the anomeric region of the ^{13}C NMR spectrum showed a signal at δ 105.5 corresponding to the C-1′ indicating the formation of the new β-galactofuranosyl linkage. This signal correlated (HSQC) with H-1′ with $J_{1,2}$ 2.7 Hz in agreement with conformationally constrained β-galactofuranoside derivatives.[28] Interestingly, the ^1H NMR and ^{13}C NMR spectra showed clearly the differences between the conformationally restricted galactofuranosyl residue from the nonreducing end (C-1δ > 105; protection of C-4; an increasing values of $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$, respectively) and the thiogalactofuranosyl residue of the reducing end of the new disaccharide (C-1 around 90 ppm and lower values of $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$). Thus, full assignment of the signals was straightforwardly performed. On the other hand, C-5 (δ 73.0) appeared shifted downfield in comparison to the same signal in **10** (δ 68.8) due to glycosylation. A singlet at δ 3.95 ppm was assigned to the hydroxyl group linked to the silicon atom. The proposed structure was confirmed with the aid of high-resolution mass spectrometry.

Once disaccharide **12** was obtained, it was decided to employ this compound as a donor in a new glycosylation step in order to incorporate one galactofuranosyl unit on the reducing end direction employing, once again, acceptor **10**. In this case, the disaccharide donor **12** was not conformationally constrained. To a mixture of **12**, AgOTf, and powdered 4 Å molecular sieves in CH_2Cl_2 at −78 °C and preactivated by *p*-NO_2PhSCl for 20 min was added acceptor **10**. After 1.5 h, TLC indicated the formation of a new product of higher polarity than **10**, but the starting material **12** was not completely consumed. The reaction was continued for additional 16 h at that temperature, and then, it was interrupted with sat sol $NaHCO_3$. Purification of the residue gave trisaccharide **13** in 55% yield (86% yield considering unreacted disaccharide **12**). Trisaccharide **13** has three Gal*f* units, which are quite different in terms of ^1H NMR and ^{13}C NMR signal displacements due to the conformationally locked Gal*f* of the nonreducing end, the flexible internal galactofuranoside, and the thiogalactofuranoside of the reducing end. The anomeric region of the corresponding ^{13}C NMR spectrum showed three anomeric carbons at 106.1, 105.7, and 90.5 ppm assigned to C-1′, C-1″, and C-1 based on HSQC correlations. On the other hand, C-4′ and C-4 of the flexible Gal*f* units appeared deshielded at 84.9 and 84.0 ppm, respectively, whereas the C-4″ of the constrained Gal*f* unit appeared shielded at 75.4 ppm. In the corresponding ^1H NMR spectrum, the H-1″ appeared as a doublet (δ 5.52, $J_{1,2}$ = 2.7 Hz). In spite of the superposition of the H-1′, H-1, and H-2 signals, the β 1,2-*trans* disposition of the new galactofuranosyl linkage was also confirmed by the H-2′ signal (δ 5.47) with a characteristic small $J_{1,2}$ (1.2 Hz). The two broad singlets at δ 4.15 and 4.02 were assigned to the OH from the *tert*-butylhydroxysilyl group at O-3 of internal Gal*f* and at O-3 of the reducing end Gal*f*. These assignments were in agreement with the proposed structures.

Selective 3,5-O-DTBS Opening of Disaccharide 12 and Trisaccharide 13. We next evaluated the regioselective opening of 3,5-*O*-DTBS group on constrained terminal Gal*f* in disaccharide **12** and trisaccharide **13** aimed at transforming them into acceptors at the nonreducing end. In this case, both compounds have two different kinds of silyl protecting group. Disaccharide **12** treated with 1 equiv of nBu$_4$NF in CH_2Cl_2 at −15 °C and stirred at −20 °C for 20 h produced a major compound (TLC showed no presence of substrate), which was purified by column chromatography to yield *p*-tolyl 2,6-di-*O*-benzoyl-3-*O*-di-*tert*-butylhydroxysilyl-β-D-galactofuranosyl-(1→5)-2,6-di-*O*-benzoyl-3-*O*-di-*tert*-butylhydroxysilyl-1-thio-β-D-galactofuranoside (**14**) in 61% yield. The ^1H NMR spectrum showed four singlets at high field corresponding to both *tert*-butylsilyl groups, thus a selective opening occurred, rather than a silyl removal. The ^{13}C NMR spectrum of **14** was quite diagnostic showing four signals around 80 ppm attributed to the presence of two flexible Gal*f* units in β-configuration and assigned to each C-2 and C-4. The full assignment of the signals of the NMR spectra was performed based on COSY and HSQC-DEPT spectrum. The H-1′ (δ 5.57) now appeared as a broad singlet characteristic of a flexible β-D-galactofuranoside. The H-5′ appeared as a multiplet at δ 4.17 and correlated to OH-5 at δ 2.72 which appeared as a broad doublet, confirming the selective opening of the 3,5-*O*-DTBS group at the position 5. The two broad singlets at 4.11 and 3.67 ppm were assigned as the OH of the di-*tert*-butylhydroxysilyl groups at *O*-3 of each Gal*f* unit. Mass spectrometry confirmed the obtainment of this product.

After succeeding in the regioselective opening of disaccharide **12**, selective deprotection of trisaccharide **13** was performed, and trisaccharide **15** was obtained as a single regioisomer in 41% yield. Analysis of the corresponding ^1H NMR spectrum showed six protected singlets (around 1 ppm) corresponding to the three *tert*-butyl of the silyl groups. The H-1″ signal now appeared as singlet due to the new flexible ring at the nonreducing end of the oligosaccharide. The H-5″ signal (m, δ 4.39 ppm) correlated (COSY) to the OH-5 at δ 2.82 indicating that the selective opening occurred at the O-5 position. The

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three OH from the *tert*-butylhydroxylsilylgroup bonded to O-3 of each Gal*f* units appeared at 4.25, 4.20, and 3.80 ppm. The structure was in agreement with the mass spectrometry data.

Complete silyl removal on trisaccharide **15** was attempted by reaction with an excess of nBu$_4$NF in THF, but TLC monitoring showed a complex mixture of more polar compounds probably due to partial deacylation under basic reaction condition. Alternatively, when milder conditions were used by treatment of **15** with an excess of nBu$_4$NF buffered with AcOH in anhydrous THF-DMF,[17,61] selective removal of the SitBu$_2$OH of the 3-O-position of the nonreducing end Gal*f* was obtained yielding **16** as a single product (85%) in spite of the excess of the reagent. In the ^{1}H NMR spectrum, the *tert*-butylbutylsilyl groups appeared as four singlets (∼1 ppm) with integration of 36H. Full spectroscopic assignment was performed based on bidimensional NMR spectra. The terminal nonglycosylated C-5″ appeared at 70.9 ppm. The H-3″ in **16** shifted upfield (∼0.4 ppm) in comparison with the same signal in **15** and correlated (COSY) with OH-3″ at 4.09 ppm. The proposed structure was in agreement with mass spectrometry data.

Complete removal of the protecting groups was first attempted on disaccharide **14**, by treatment with an excess of nBu$_4$NF in THF followed by debenzoylation with NaOMe in MeOH. In this case, disaccharide **17** (Scheme 2) was obtained in 61%. The ^{13}C NMR showed diagnostic signals at C-1′ and C-1 at 109.4 and 93.2 ppm, respectively. Interestingly, in the ^{1}H NMR spectrum, the H-1′ (δ 5.14) appeared as a singlet as expected for a β-Gal*f* O-glycoside, whereas the H-1 (δ 5.13) appeared as a doublet with J = 5.3 Hz. The increment of J values on β-Gal*f* thioglycosides upon deprotection has been reported previously.[51] Trisaccharide **16** was fully deprotected employing the same procedure to yield compound **18** (58% for the two reaction steps). In the corresponding ^{13}C NMR spectrum, the C-1 appeared at 93.0 ppm and correlated (HSQC) with the H-1 (δ 5.13) having a J = 5.3 Hz as expected. The C-1′and C-1″ appeared superimposed at 109.0 ppm which correlated (HSQC) with H-1′ and H-1″ at δ 5.13 and 5.11 (could be interchanged) with small J values.

CONCLUSION

A useful method for regioselective opening of 3,5-*O*-di-*tert*-butylsilylene-D-galactofuranoside derivatives has been developed by the use of nBu$_4$NF (1.1 equiv) in CH_2Cl_2. This method was applied to 1,2-*cis* α-benzyl glycoside **3** and the 1,2-*trans* thiotolyl derivative **6**. The 3-*O*-di-*tert*-butylsilylhydroxyl group was stable to carry out a further glycosylation reaction using the Crich promoting system. The 5-*O*-regioselective silylene opening was also extended to the di- and trisaccharide products of glycosylation, showing the strength of this method. This work provides a solid and reliable new approach for synthesizing galactofuranosyl-containing oligosaccharides. Certainly, these studies present a broad scope to access an orthogonal protected galactofuranosyl precursor of synthetic relevance. Further studies on the strength of the present protocol are currently being pursued in our laboratory.

EXPERIMENTAL SECTION

General Methods. TLC was performed on 0.2 mm silica gel 60 F254 aluminum-supported plates. 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. NMR spectra were recorded at 500 MHz (^{1}H) and 125.8 MHz (^{13}C) or at 200 MHz (^{1}H) and 50.3 MHz (^{13}C). ^{1}H and ^{13}C NMR spectra assignments were supported by homonuclear COSY and HSQC-DEPT experiments. High-resolution mass spectra (HRMS) were recorded on a TOF-Q electrospray ionization mass spectrometer. Optical rotations were measured with a path length of 1 dm at 25 °C. COSY and HSQC-DEPT spectra were employed to confirm the ^{1}H and ^{13}C NMR peak assignments.

Benzyl 2,6-Di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-α-D-galactofuranoside (7). Procedure A (THF as Solvent). To stirred solution of benzyl 2,6-di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside[28] (**3**, 187 mg, 0.30 mmol) in THF (2.5 mL) cooled to 0 °C, a solution of nBu$_4$NF (94 mg, 0.36 mmol, 1.2 equiv) in THF (520 uL) was added. After 1 h of stirring, TLC analysis showed complete conversion of the starting material. The reaction was diluted with CH_2Cl_2 (4 mL), and it was washed with water (3 × 3 mL), dried (Na_2SO_4), and concentrated at low pressure. Purification by column chromatography of the residue (8:1 hexane-EtAcO) afforded a mixture (152 mg; 79%, R_f 0.38 3:1 hexane-EtOAc) of **7** (see Procedure B) and a minor compound suggested benzyl 2,6-di-*O*-benzoyl-5-*O*-di-*tert*-butylhydroxysilyl-α-D-galactofuranoside (**8**) as a colorless syrup, in 5:1 ratio as determined by ^{1}H NMR of the product (see SI). ^{1}H NMR ($CDCl_3$, 500 MHz) δ for the anomeric signals of the mixture 5.47 (d, 1H, J = 4.4 Hz, H-1 of **7**), 5.42 (d, 0.2 H, J = 4.6 Hz H-1 of **8**). ^{13}C NMR (126 MHz, $CDCl_3$) δ for all signals of the mixture 166.5, 166.2, 136.5, 133.4, 133.1, 130.0, 129.8, 129.7, 129.2, 128.5, 128.4, 128.34, 128.28, 128.1, 128.0, 127.6, 99.9, 83.0, 82.7, 80.1, 79.7, 73.8, 73.3, 73.1, 71.6, 70.9, 67.8, 65.6, 65.5, 27.5, 27.32, 27.28, 27.25, 20.4, 20.0.

Procedure B (in CH_2Cl_2 as Solvent). A solution of benzyl 2,6-di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside[28] (**3**, 178 mg, 0.29 mmol) in CH_2Cl_2 (2.5 mL) was cooled to −78 °C, and a solution of nBu$_4$NF (90 mg, 0.35 mmol) in CH_2Cl_2 (500 μL) was added with stirring. After 1 h, the reaction was allowed to reach −20 °C and left overnight. After 18 h of stirring, TLC analysis showed complete conversion of the starting material. The mixture was diluted with CH_2Cl_2 (3 mL), and it was washed with water (3 × 3 mL), dried (Na_2SO_4), and concentrated at low pressure. Purification by column chromatography of the residue (8:1 hexane-EtAcO) afforded **7** (155 mg; 84%) as a colorless syrup. R_f 0.38 (3:1 hexane-EtOAc); $[\alpha]_D$ +82.2 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (m, 4H, arom.), 7.59 (m, 2H, arom.), 7.45 (m, 4H, arom.), 7.18 (m, 5H, arom.), 5.47 (d, 1H, J = 4.4 Hz, H-1), 5.17 (dd, 1H, J = 4.4, 7.3 Hz, H-2), 5.14 (dd, 1H, J = 5.7, 7.3 Hz, H-3), 4.74, 4.55 (2d, 2H, J = 11.5 Hz, CH_2Ph), 4.44 (dd, 1H, J = 11.1, 6.4 Hz, H-6a), 4.33 (dd, 1H, J = 11.1, 6.4 Hz, H-6b), 4.22 (m, 2H, H-5, H-4), 2.93 (d, 1H, J = 7.8 Hz, OH-5), 2.76 (br s, 1H, SiO*H*), 0.99 (s, 18H, (CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 166.5, 166.2 (COPh), 136.5, 133.4, 133.1, 129.9, 129.8, 129.7, 129.2, 128.5, 128.4, 128.3, 128.1, 127.9 (arom.), 99.9 (C-1), 82.7 (C-4), 80.1 (C-2), 73.3 (C-3), 71.60 (CH_2Ph), 67.8 (C-5), 65.5 (C-6), 27.29, 27.25 ((CH$_3$)$_3$C), 20.4, 20.0 ((CH$_3$)$_3$C). HRMS (ESI) m/z calcd for $C_{35}H_{44}NaO_9Si$ [M + Na]$^+$ 659.2647, found 659.2655.

Benzyl 5-O-Acetyl-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-α-D-galactofuranoside (9). To a solution of **7** (20 mg, 0.031 mmol) in dry pyridine (0.50 mL) cooled to 0 °C was added acetic anhydride (0.50 mL) with stirring. After 3 h at room temperature, the reaction was quenched with MeOH (0.25 mL) and concentrated in vacuum. The residue was co-evaporated with toluene (3 × 1 mL) to give **9** (20 mg, 93%) as a colorless syrup. R_f 0.65 (3:1 hexane-EtOAc); $[\alpha]_D$ +110.0 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.09 (dd, 2H, J = 8.4, 1.3 Hz, Ar), 8.02 (dd, 2H, J = 8.4, 1.3 Hz, Ar), 7.59 (m, 2H, Ar), 7.46 (m, 4H, Ar), 7.17 (m, 5H, Ar), 5.67 (td, 1H, J = 6.3, 1.8 Hz, H-5), 5.40 (d, 1H, J = 4.4 Hz, H-1), 5.19 (dd, 1H, J = 7.9, 4.4 Hz, H-2), 4.85 (dd, 1H, J = 7.9, 7.0 Hz, H-3), 4.80 (d, 1H, J = 12.2 Hz, CH_2Ph), 4.58 (dd, 1H, J = 7.0, 11.4 Hz, H-6a), 4.55 (dd, 1H, J = 6.0, 11.4 Hz, H-6b), 4.49 (d, 1H, J = 12.2 Hz, CH_2Ph), 4.19 (dd, 1H, J = 7.0, 1.8 Hz, H-4), 3.80 (bs, 1H, SiO*H*), 1.91 (s, 3H, CH_3CO), 1.01, 1.00 (2s, 18H, 2(CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 172.1 (CH$_3$CO), 166.2, 166.0, 137.5, 133.3, 133.2, 129.9, 129.7, 129.6, 129.3, 128.4, 128.4, 128.2, 127.5, 127.2 (Ar.), 98.6 (C-1), 80.6 (C-4), 79.4 (C-2), 73.2 (C-3), 69.6 (C-5), 69.3 (CH$_2$Ph), 63.5 (C-6), 27.3, 27.3

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((CH_3)$_3$C), 20.8, 20.8 ((CH_3)$_3$C), 19.8 (CH_3CO); HRMS (ESI) m/z calcd for $C_{37}H_{46}NaO_{10}Si$ $[M + Na]^+$ 701.2753, found 701.2759.

*p-Tolyl 2,6-Di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-1-thio-β-D-galactofuranoside (**10**).* To a solution of *p*-tolyl 2,6-di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)-1-thio-β-D-galactofuranoside[28] (**6**, 693 mg, 1.09 mmol) in CH_2Cl_2 (8.7 mL) at 0 °C, a solution of nBu$_4$NF (313 mg, 1.2 mmol) in CH_2Cl_2 (1.7 mL) was added in portions of 50 μL every 5 min with stirring. After the addition was finished, the mixture was cooled to −20 °C, and the stirring continued for 40 h when a TLC showed no starting material left. The mixture was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography (6:1 hexane-EtOAc) of the residue gave **10** (640 mg, 90%) as a colorless syrup. R_f 0.40 (10:1 toluene-EtOAc); $[\alpha]_D$ −111.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 8.01 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.61−7.54 (m, 2H, arom.), 7.46−7.39 (m, 6H, arom.), 7.09 (d, 2H, *J* = 7.9 Hz, arom.), 5.65 (s, 1H, H-1), 5.45 (t, 1H, *J* = 1.4 Hz, H-2), 4.77 (ddd, 1H, *J* = 1.0, 1.5, 4.9 Hz, H-3), 4.54 (ddd, 1H, *J* = 0.6, 2.3, 4.9 Hz, H-4), 4.53 (dd, 1H, *J* = 6.9, 11.5 Hz, H-6a), 4.44 (dd, 1H, *J* = 5.1, 11.5 Hz, H-6b), 4.30 (m, 1H, H-5), 3.66 (br s, 1H, SiO*H*), 2.53 (d, 1H, *J* = 8.6 Hz, OH-5), 2.31 (s, 3H, PhCH_3), 1.08, 1.04 (2s, 18 H, 2 (CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.6, 166.3 (COPh); 138.0, 133.7, 133.2, 132.8, 130.3, 129.9, 129.8, 129.7, 128.9, 128.6, 128.4 (arom.); 91.9 (C-1), 85.1 (C-2), 84.9 (C-4), 77.5 (C-3), 68.8 (C-5), 66.2 (C-6); 27.4, 27.3 ((CH_3)$_3$C); 21.1, 20.4 ((CH_3)$_3$C), 20.5 (PhCH_3); HRMS (ESI) m/z calcd for $C_{35}H_{44}NaO_8SSi$ $[M + Na]^+$ 675.2418, found 675.2427.

*p-Tolyl 5-O-Acetyl-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-1-thio-β-D-galactofuranoside (**11**).* To a solution of **10** (9 mg, 0.014 mmol) in dry pyridine (0.25 mL) cooled to −20 °C was added acetic anhydride (0.25 mL) with stirring. After 72 h, the reaction was quenched with MeOH (0.1 mL) and concentrated in vacuum. The residue was co-evaporated with toluene (3 × 2 mL) to give **11** (9 mg, 93%) as a colorless syrup. R_f 0.43 (5:1 hexane-EtOAc); $[\alpha]_D$ −66.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.); 7.96 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.61−7.52 (m, 2H, arom.), 7.46−7.38 (m, 6H, arom.), 7.10 (d, 1H, *J* = 7.9 Hz, arom.), 5.70 (ddd, 1H, *J* = 3.0, 4.6, 7.4 Hz, H-5), 5.66 (s, 1H, H-1), 5.43 (t, 1H, *J* = 1.4 Hz, H-2), 4.62 (ddd, 1H, *J* = 0.6, 3.0, 5.0 Hz, H-4), 4.58 (dd, 1H, *J* = 7.3, 11.7 Hz, H-6a), 4.55 (dt, 1H, *J* = 1.2, 5.0 Hz, H-3), 4.49 (dd, 1H, *J* = 7.3, 11.7 Hz, H-6b), 3.75 (br s, 1H, SiO*H*), 2.31 (s, 3H, PhCH_3), 1.95 (s, 3H, CH_3CO); 1.07, 1.05 (2s, 18H, 2 (CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.7 (CH_3CO); 166.2, 166.0 (PhCO); 137.9, 133.8, 133.2, 132.7, 130.2, 129.9, 129.8, 129.6, 129.5, 128.8, 128.5, 128.4 (arom); 91.4 (C-1), 85.3 (C-2), 83.7 (C-4), 77.2 (C-3), 69.3 (C-5), 63.4 (C-6); 27.4, 27.3 ((CH_3)$_3$C); 21.1, 20.4 ((CH_3)$_3$C), 21.1 (PhCH_3), 20.7 (CH_3CO); HRMS (ESI) m/z calcd for $C_{37}H_{46}NaO_9SSi$ $[M + Na]^+$ 717.2524, found 717.2520.

*p-Tolyl 2,6-Di-O-benzoyl-3,5-O-(di-tert-butylsilanediyl)-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-1-thio-β-D-galactofuranoside (**12**).* To a suspension of **6** (54 mg, 0.085 mmol), AgOTf (65 mg, 0.25 mmol), and powdered 4 Å molecular sieves in anhyd CH_2Cl_2 (1.6 mL) at −78 °C was added a solution of 4-nitrobenzenesulfenyl chloride[55] (17 mg, 0.089 mmol) in anhyd CH_2Cl_2 (0.20 mL) with vigorous stirring. After 5 min, a solution of acceptor **10** (55 mg, 0.085 mmol) in CH_2Cl_2 (0.21 mL) was added. After 1 h, TLC monitoring indicated that no **10** was left, and the mixture was poured into saturated aq $NaHCO_3$ (20 mL) with vigorous stirring. The organic layer was separated, washed with water (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue (80:1 toluene-EtOAc) gave syrupy **12** (55 mg, 56%) as a colorless syrup. R_f 0.38 (20:1 toluene-EtOAc); $[\alpha]_D$ −50.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10−8.03 (m, 4H, arom.), 7.91 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.84 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.58−7.52 (m, 3H, arom.), 7.45−7.35 (m, 9H, arom), 7.22 (dd, 2H, *J* = 7.6, 8.2 Hz, arom.), 7.09 (d, 1H, *J* = 7.9 Hz, arom.), 5.63 (s, 1H, H-1), 5.53 (t, 1H, *J* = 1.6 Hz, H-2), 5.47 (d, 1H, *J* = 2.7 Hz, H-1′), 5.44 (dd, 1H, *J* = 2.7, 6.9 Hz, H-2′), 4.87 (d, 1H, *J* = 5.1 Hz, H-3), 4.84 (td, 1H, *J* = 3.3, 6.9 Hz, H-5′), 4.72 (dd, 1H, *J* = 3.3, 11.9 Hz, H-6a′), 4.65 (dd, 1H, *J* = 4.6, 11.8 Hz, H-6a), 4.61 (dd, 1H, *J* = 6.9, 10.2 Hz, H-3′), 4.58−4.60 (m, 1H, H-4), 4.55 (dd, 1H, *J* = 6.4, 11.4 Hz, H-6b), 4.52 (dd, 1H, *J* = 7.2, 11.9 Hz, H-6b′), 4.44 (dd, 1H, *J* = 6.9, 10.2 Hz, H-4′), 4.44 (m, 1H, H-5), 3.95 (s, 1H, SiO*H*), 2.31 (s, 3H, PhCH_3); 1.06, 1.04, 0.98, 0.87 (4s, 36H, (CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.7, 166.1, 166.0, 165.4 (PHCO); 137.6, 133.6, 133.0, 132.9, 132.4, 130.0, 129.8, 129.72, 129.67, 129.5, 129.4, 128.6, 128.4, 128.3, 128,2 (arom.); 105.5 (C-1′), 91.4 (C-1), 85.1 (C-2), 84.7 (C-4), 82.7 (C-2′), 76.4 (C-3), 75.4 (C-3′), 75.3 (C-4′), 73.0 (C-5), 71.1 (C-5′), 64.9 (C-6′), 64.1 (C-6); 27.4, 27.3, 26.9 ((CH_3)$_3$C); 21.6, 20.6, 20.5, 20.2 ((CH_3)$_3$C), 21.1 (PhCH_3); HRMS (ESI) m/z calcd for $C_{63}H_{78}NaO_{15}SSi_2$ $[M + Na]^+$ 1185.4492, found 1185.4500.

*p-Tolyl 2,6-Di-O-benzoyl-3,5-O-(di-tert-butylsilanediyl)-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert- butylhydroxysilyl-1-thio-β-D-galactofuranoside (**13**).* To a suspension of disaccharide donor **12** (95 mg, 0.082 mmol), AgOTf (61 mg, 0.24 mmol), and powdered 4 Å molecular sieves in anhyd CH_2Cl_2 (1.6 mL) at −78 °C was added a solution of 4-nitrobenzenesulfenyl chloride (18 mg, 0.095 mmol) in CH_2Cl_2 (0.18 mL) with stirring. After 20 min, a solution of acceptor **10** (59 mg, 0.090 mmol) in CH_2Cl_2 (0.25 mL) was added. After stirring for 18 h at −78 °C, the mixture was poured into saturated aq $NaHCO_3$ (2 mL) with vigorous stirring. Additional CH_2Cl_2 (5 mL) was added to the mixture. The organic phase was separated, washed with water (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. Column chromatography of the residue (40:1 toluene-EtOAc) gave **13** (76 mg, 55%) as a colorless syrup. R_f 0.39 (15:1 toluene-EtOAc); $[\alpha]_D$ −27.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (dd, 3H, *J* = 1.3, 8.4 Hz, arom.), 8.02 (dd, 3H, *J* = 1.3, 8.4 Hz, arom.), 7.93−7.82 (m, 6H, arom.), 7.78 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.58−7.46 (m, 6H, arom.), 7.46−7.31 (m, 16H, arom.), 7.23−7.14 (m, 6H, arom.), 7.06 (d, 2H, *J* = 7.9 Hz, arom.), 5.59−5.56 (m, 3H, H-1, H-1′, H-2), 5.52 (d, 1H, *J* = 2.7 Hz, H-1″), 5.47 (dd, 1H, *J* = 1.2, 2.6 Hz, H-2′), 5.44 (dd, 1H, *J* = 2.7, 7.0 Hz, H-2″), 4.95 (ddd, 1H, *J* = 1.0, 2.4, 5.2 Hz, H-3), 4.85 (dd, 1H, *J* = 2.6, 5.8 Hz, H-3′), 4.82 (dt, 1H, *J* = 3.3, 7.0, H-5″), 4.68 (dd, 1H, *J* = 3.3, 12.0 Hz, H-6a″), 4.66−4.59 (m, 3H, H-3″, H-6a′, H-6b′), 4.52−4.59 (m, 3H, H-6b″, H-6a, H-6b), 4.51−4.43 (m, 4H, H-4, H-5, H-4′, H-4″), 4.36 (m, 1H, H-5′), 4.15, 4.02 (2 br s, 2H, SiO*H*), 2.27 (s, 3H, PhCH_3); 1.03, 1.02, 0.99, 0.97, 0.95, 0.92 (6s, 58H, (CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 128,5 MHz) δ 166.6, 166.01, 165.96, 165.9, 165.4 (PHCO); 137.6, 133.5, 133.4, 133.0, 132.9, 132.6, 129.89, 129.85, 129.73, 129.65, 129.5, 129.4, 128.43, 128.37, 128.3, 128.2; 106.1 (C-1′), 105.7 (C-1″), 90.5 (C-1), 84.9 (C-2′, C-4′), 84.5 (C-2), 84.0 (C-4), 82.8 (C-2″), 76.1 (C-3), 75.8 (C-3′), 75.39 (C-3″), 75.33 (C-4″), 74.2 (C-5), 73.2 (C-5′), 71.1 (C-5″), 65.0 (C-6), 64.8 (C-6″), 64.1 (C-6′); 27.44, 27.40, 27.3, 27.2, 27.0, 26.9 ((CH_3)$_3$C); 21.6, 20.6, 20.5, 20.3, 20.2 ((CH_3)$_3$C), 21.1 (PhCH_3); HRMS (ESI) m/z calcd for $C_{91}H_{114}NaO_{23}SSi_3$ $[M + Na]^+$ 1713.6677, found 1713.6605. Unreacted donor **12** (34 mg) was also recovered.

*p-Tolyl 2,6-Di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-1-thio-β-D-galactofuranoside (**14**).* To a solution of **12** (148 mg, 0.127 mmol) in CH_2Cl_2 (1.5 mL) cooled to −15 °C, a solution of nBu$_4$NF (37 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL) was added in portions during 1.5 h with stirring. After 16 h of stirring at −20 °C, TLC showed that no starting material was left. The mixture was diluted with CH_2Cl_2 (5 mL), washed with water (3 × 3 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by column chromatography (4:1 hexane-EtOAc) to yield **14** (92 mg, 61%) as a colorless syrup. R_f 0.25 (toluene-EtOAc 10:1); $[\alpha]_D$ −45.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (dd, 2H, *J* = 1.3; 8.4 Hz, arom.), 8.00 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.92−7.85 (m, 4H, arom.), 7.59−7.50 (m, 3H, arom.), 7.46−7.34 (m, 9H, arom.), 7.19 (t, 2H, *J* = 7.9 Hz, arom.), 7.09 (d, 2H, *J* = 7.9 Hz, arom.), 5.57 (s, 1H, H-1′), 5.61−5.53 (m, 2H, H-1, H-2), 5.41 (dd, 1H, *J* = 1.0, 2.5 Hz, H-2′), 4.90 (ddd, 1H, *J* = 0.5, 2.6, 5.5 Hz, H-3), 4.73 (dd, 1H, *J* = 2.5, 5.4 Hz, H-3′), 4.60 (dd, 1H, *J* = 4.5, 11.7 Hz, H-6a), 4.53 (dd, 1H, *J* = 6.6, 11.6 Hz, H-6b), 4.50−4.42 (m, 3H, H-6a′, H-4, H-5), 4.40−4.33 (m, 2H, H-6b′, H-4′), 4.17 (m, 1H, H-5′), 4.11 (br s, 1H, SiO*H*), 3.67

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J. Org. Chem. 2016, 81, 9585−9594

(br s, 1H, SiO*H*), 2.72 (br d, 1H, *J* = 5.6 Hz, OH-5′), 2.30 (s, 3H, PhCH_3), 1.03, 1.02, 0.97, 0.95 (4s, 36H, (CH_3)$_3$C). ^{13}C NMR (CDCl$_3$, 125.8 MHz) δ 166.8, 166.03, 165.97, 165.9 (PHCO), 137.7, 133.6, 133.5, 133.2, 132.9, 132.6, 129.9, 129.71, 129.68, 129.6, 129.5, 128.1, 128.8, 128.5, 128.44, 128.37, 128.3 (arom.); 106.6 (C-1′), 90.7 (C-1), 85.4 (C-4), 84.8 (C-2), 84.4 (C-2′), 83.7 (C-4′), 76.6 (C-3′), 76.4 (C-3), 74.8 (C-5), 69.2 (C-5′), 66.5 (C-6′), 64.5 (C-6); 27.42, 27.40, 27.3, 27.2 ((CH$_3$)$_3$C); 21.1, 20.2, 20.1 ((CH$_3$)$_3$C), 20.5 (PhCH$_3$); HRMS (ESI) *m*/*z* calcd for $C_{63}H_{80}NaO_{16}SSi_2$ [M + Na]$^+$ 1203.4598, found 1203.4593.

*p-Tolyl 2,6-Di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-1-thio-β-D-galactofuranoside (**15**).* To a solution of **13** (19 mg, 0.011 mmol) in CH_2Cl_2 (0.5 mL) cooled to −15 °C, a solution of *n*Bu$_4$NF (3.5 mg, 0.013 mmol) in CH_2Cl_2 (0.21 mL) was added in portions during 2.5 h with stirring. The reaction mixture was stirred for 16 h at −20 °C, and a TLC showed no starting material left. The mixture was diluted with CH_2Cl_2 (5 mL), washed with water (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by column chromatography (15:1 toluene-EtOAc) to yield **15** (8 mg, 42%) as a colorless syrup. R_f 0.39 (15:1 toluene-EtOAc); [α]$_D$ +93.3 (*c* 0.8, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.00 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.97 (dd, 2H, *J* = 1.3, 8.4 Hz, arom.), 7.90−7.83 (m, 8H, arom.), 7.59−7.45 (m, 4H, arom.), 7.43 (d, 2H, *J* = 8.1 Hz, arom.), 7.41−7.29 (m, 10H, arom.), 7.19−7.10 (m, 4H, arom.), 7.07 (d, 2H, *J* = 7.9 Hz, arom.), 5.64 (s, 1H, H-1″), 5.61 (d, 1H, *J* = 2.2 Hz, H-1), 5.55 (t, 1H, *J* = 2.2 Hz, H-2), 5.50 (dd, 1H, *J* = 1.7, 3.9 Hz, H-2′), 5.46 (d, 1H, *J* = 1.7 Hz, H-1′), 5.41 (d, 1H, *J* = 1.3 Hz, H-2″), 4.97 (dd, 1H, *J* = 1.7, 5.0 Hz, H-3), 4.88 (dd, 1H, *J* = 3.9, 6.7 Hz, H-3′), 4.70 (dd, 1H *J* = 2.0, 4.6 Hz, H-3″), 4.67 (dd, 1H, *J* = 4.8, 11.6 Hz, H-6a), 4.59 (dd, 1H, *J* = 7.4, 11.9 Hz, H-6a′), 4.56 (dd, 1H, *J* = 3.7, 5.0 Hz, H-4), 4.53 (dd, 1H, *J* = 1.1, 11.6 Hz, H-6b), 4.52 (dd, 1H, *J* = 3.4, 11.9 Hz, H-6b′), 4.49−4.42 (m, 4H, H-6a″, H-6b″, H-4″, H-5), 4.39 (m, 1H, H-5′), 4.33 (dd, *J* = 2.6, 6.7 Hz, H-4′); 4.25, 4.20, 3.80 (3 br s, 3H, SiO*H*), 4.17 (m, 1H, H-5″), 2.82 (bs, 1H, OH-5″), 2.27 (s, 3H, PhCH_3); 1.06, 1.05, 0.97, 0.95, 0.933, 0.931 (6s, 54H, (CH_3)$_3$C); ^{13}C NMR (CDCl$_3$, 125.8 MHz) δ 166.1, 166.0, 165.92, 165.89, 165.8 (PhCO); 133.7, 133.3, 132.8, 132.5, 129.9, 129.7, 129.5, 128.5, 128.4, 128.3 (arom.); 107.1 (C-1″), 106.0 (C-1′), 91.0 (C-1), 86.5 (C-4″), 84.9 (C-2, C-2′), 84.6 (C-4), 84.2 (C-2″), 83.2 (C-4′), 76.7 (C-3″) 76.4 (C-3), 75.5 (C-3′), 74.9 (C-5′), 74.3 (C-5), 69.8 (C-5″), 66.4 (C-6″), 65.3 (C-6′), 63.8 (C-6); 27.5, 27.4, 27.24, 27.17 ((CH$_3$)$_3$C); 21.1 (PhCH$_3$); 20.5, 20.4, 20.3, 20.2, 20.0 ((CH$_3$)$_3$C); HRMS (ESI) *m*/*z* calcd for $C_{91}H_{116}NaO_{24}SSi_3$ [M + Na]$^+$ 1731.6777, found 1731.6789.

*p-Tolyl 2,6-Di-O-benzoyl-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-β-D-galactofuranosyl-(1→5)-2,6-di-O-benzoyl-3-O-di-tert-butylhydroxysilyl-1-thio-β-D-galactofuranoside (**16**).* To a stirred solution of **15** (21.9 mg, 0.0128 mmol) in anhyd DMF (0.160 mL) cooled to 0 °C, AcOH (6.6 μL, mmol, 8.8 equiv) was added followed by a solution of 1 M *n*Bu$_4$NF in anhyd THF (102 μL, 0.102 mmol, 8 equiv). After 4 h at 0 °C, TLC monitoring showed a main spot at R_f 0.53 (4:1 toluene-EtOAc). The mixture was diluted with CH_2Cl_2 (3 mL), washed with water (5 × 2 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by column chromatography (9:1 toluene-EtOAc) to yield **16** (16.8 mg, 85%) as a colorless glassy solid. R_f 0.53 (4:1 toluene-EtOAc); [α]$_D$ −45.4° (*c* 1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.04 (dd, 2H, *J* = 1.4, 8.5 Hz, arom.), 7.97 (dd, 2H, *J* = 1.4, 8.1 Hz, arom.), 7.91−7.88 (m, 7H, arom.), 7.55−7.34 (m, 17H, arom.), 7.29 (t, 2H, *J* = 7.9 Hz, arom.), 7.16 (t, 2H, *J* = 8.0 Hz, arom.), 7.08 (d, 2H, *J* = 8.1 Hz, arom.), 5.69 (s, 1H, H-1′), 5.66 (d, 1H, *J* = 1.2 Hz, H-1″), 5.57 (t, 1H, *J* = 3.6 Hz, H-2), 5.53 (d, 1H, *J* = 3.6 Hz, H-1), 5.19 (dd, 1H, *J* = 1.2, 2.9 Hz, H-2″), 4.95 (dd, 1H, *J* = 6.3, 3.7 Hz, H-3), 4.78 (dd, 1H, *J* = 4.0, 1.6 Hz, H-3′), 4.60 (dd, 1H, *J* = 6.7, 11.6 Hz, H-6a), 4.59−4.52 (m, 3H, H-6a′, H-6b, SiO*H*), 4.52 (dd, 1H, *J* = 3.2, 11.9 Hz, H-6a″), 4.51−4.45 (m, 3H, H-5, H-4′, H-6b′), 4.41 (dd, 1H, *J* = 7.5, 12.0 Hz, H-6b″), 4.39 (dd, 1H, *J* = 2.5, 6.3 Hz, H-4), 4.34 (m, 1H, H-5′), 4.33−4.29 (m, 2H, H-3″, H-4″), 4.21 (br s, 1H, SiO*H*), 4.16 (m, 1H, H-5″), 4.09 (d, 1H, *J* = 5.8 Hz OH-3″), 2.85 (bs, 1H, OH-5″), 2.29 (s, 3H, PhCH_3); 1.00, 0.99, 0.97, 0.95 (4s, 36H, (CH_3)$_3$C); ^{13}C NMR (CDCl$_3$, 125.8 MHz) δ 166.7, 166.5, 166.2, 166.03, 166.00, 165.9 (PhCO); 137.6, 133.6, 133.4, 133.2, 133.0, 132.6, 130.2, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.3, 129.3, 128.8, 128.6, 128.5, 128.4, 128.3, 107.0 (C-1′), 104.6 (C-1″), 89.9 (C-1); 86.2, 86.1 (C-2″, C-4′); 84.5, 84.4, 84.3 (C-4″, C-2′, C-2), 82.8(C-4), 77.1 (C-3″), 76.5 (C-3′), 75.9 (C-3), 74.6 (C-5), 73.1 (C-5′), 70.9 (C-5″), 66.3 (C-6″); 64.3, 64.1 (C-6′, C-6), 27.3, 27.2 ((CH$_3$)$_3$C), 21.1(PhCH$_3$); 20.7, 20.3, 20.2, 19.90 ((CH$_3$)$_3$C); HRMS (ESI) *m*/*z* calcd for $C_{83}H_{98}NaO_{23}SSi_2$ [M + Na]$^+$ 1573.5650, found 1573.5875.

*p-Tolyl β-D-Galactofuranosyl-(1→5)-1-thio-β-D-galactofuranoside (**17**).* To a solution of **14** (20 mg, 0.017 mmol) in anhyd THF (0.2 mL) cooled to 0 °C, a solution of *n*Bu$_4$NF (44 mg, 0.17 mmol, 10 equiv) in THF (0.8 mL) was added with stirring. After 5 h of stirring at 0 °C and additional 16 h at −20 °C, the mixture was evaporated in vacuo. To the residue was added a cold (0 °C) solution of 0.75 M NaOMe in methanol (0.2 mL), and the mixture was stirred for 6 h. TLC examination showed only one compound (R_f 0.40, 5:1 CH_2Cl_2-MeOH). The solution was passed through a cationic interchange column (H$^+$ form) washing with 95:5 MeOH:H_2O. The eluate was neutralized with a solution of TEA-MeOH and concentrated under reduced pressure, and the methyl benzoate was co-evaporated with water (3 × 0.5 mL). The residue was further purified twice through a C18 cartridge, eluting with 75:25 H_2O:CH_3OH and MeOH. Concentration of the fractions at room temperature gave 4.6 mg of **17** (61%) as a colorless syrup. R_f 0.40 (5:1 CH_2Cl_2-MeOH); [α]$_D$ −153.2 (*c* 0.5, MeOH); ^{1}H NMR (CD$_3$OD, 500 MHz) δ 7.39 (d, *J* = 8.3 Hz, 2H), 7.14 (dd, 2H, *J* = 8.3, 0.6 Hz, arom), 5.14 (d, 1H, *J* = 1.1 Hz, H-1′), 5.13 (d, 1H, *J* = 5.3 Hz, H-1), 4.15 (dd, 1H, *J* = 7.5, 5.4 Hz, H-3), 4.06 (m, 1H, H-4′), 4.02 (d, 1H, *J* = 1.1 Hz, H-2′), 4.01 (dd, 1H, *J* = 1.1, 3.0 Hz, H-3′), 4.01 (dd, 1H, *J* = 7.5, 3.0 Hz, H-4), 3.91 (t, 1H, *J* = 5.4 Hz, H-2), 3.91−3.88 (m, 1H, H-5), 3.74 (dd, 1H, *J* = 6.6, 11.6 Hz, H-6a), 3.72 (dd, 1H, *J* = 6.0, 11.6 Hz, H-6b), 3.72−3.69 (m, 1H, H-5′), 3.63 (dd, 1H, *J* = 6.1, 11.2 Hz, H-6a′), 3.60 (dd, 1H, *J* = 6.8, 11.2 Hz, H-6b″), 2.32 (s, 3H, CH$_3$); ^{13}C NMR (126 MHz, CD$_3$OD) δ 139.0, 133.8, 132.1, 130.8 (arom); 109.4 (C-1′), 93.2 (C-1), 84.4 (C-4′), 83.3 (C-4), 83.1 (C-2), 82.6 (C-2′), 78.7(C-3′), 77.9 (C-3), 77.3 (C-5), 72.2 (C-5′), 64.4 (C-6), 62.9 (C-6′), 21.3 (CH$_3$); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{28}NaO_{10}S$ [M + Na]$^+$ 471.1295, found 471.1313.

*p-Tolyl β-D-Galactofuranosyl-(1→5)-β-D-galactofuranosyl-(1→5)-1-thio-β-D-galactofuranoside (**18**).* To a solution of **16** (15 mg, 0.0098 mmol mmol) in anhyd THF (0.2 mL) cooled to 0 °C, a solution of *n*Bu$_4$NF (26 mg, 0.099 mmol, 10 equiv) in THF (0.4 mL) was added with stirring. After 6 h of stirring at 0 °C and an additional 12 h at −20 °C and 3 h at 10 °C, the mixture was evaporated in vacuo. The residue was then treated with a cold (0 °C) solution of 0.75 M NaOMe in methanol (0.2 mL) for 8 h and then processed and purified as described for **17** to yield 3.4 mg of **18** as colorless syrup (58%). R_f 0.46 (3:1 EtOAc-methanol); [α]$_D$ −157.1 (*c* 0.3, MeOH); ^{1}H NMR (CD$_3$OD, 500 MHz) δ 7.40 (d, 2H, *J* = 7.9 Hz, arom), 7.14 (d, 2H, *J* = 7.9 Hz, arom), 5.13 (d, 1H, *J* = 0.7 Hz, H-1′ or H-1″), 5.13 (d, 1H, *J* = 5.3 Hz, H-1), 5.11 (d, 1H, *J* = 1.8 Hz, H-1′or H-1″), 4.14 (dd, 1H, *J* = 5.3, 7.3 Hz, H-3), 4.14−4.10 (m, 2H, H-4′, H-4″), 4.07 (dd, 1H, *J* = 4.0, 6.8 Hz, H-3′), 4.03−3.99 (m, 4H, H-2′, H-2″, H-3″, H-4), 3.91 (t, 1H, *J* = 5.3 Hz, H-2), 3.94−3.85 (m, 2H, H-5, H-5′), 3.75−3.68 (m, 5H, H-5′, H-6a, H-6b, H-6a′, H-6b′), 3.66 (dd, 1H, *J* = 6.2, 11.2 Hz, H-6a″), 3.62 (dd, 1H, *J* = 6.7, 11.2 Hz, H-6b″), 2.32 (s, 3H, CH$_3$); ^{13}C NMR (126 MHz, CD$_3$OD) δ 138.8, 133.7, 131.9, 130.6 (arom.), 109.0 (C-1′, C-1″), 93.0 (C-1), 84.6 (C-4″), 83.6 (C-4, C-2′or C-2″), 83.4 (C-4′), 83.0 (C-4, C-2′or C-2″), 82.9 (C-2), 82.4 (C-4, C-2′or C-2″), 78.7 (C-3″), 78.3 (C-3′), 77.9 (C-3); 77.2′, 76.7 (C-5′, C-5), 64.2 (C-6″); 62.5, 62.0 (C-6, C-6′), 21.1 (CH$_3$); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{38}NaO_{15}S$ [M + Na]$^+$ 633.1824, found 633.1819.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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NMR spectra for all new compounds **7** and **9**−**18** (PDF)

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Notes

The authors declare no competing financial interest.

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