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Glycosylation studies on conformationally restricted 3,5-*O*-(di-*tert*-butylsilylene)-D-galactofuranosyl trichloroacetimidate donors for 1,2-*cis* α-D-galactofuranosylation

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ABSTRACT

Conformationally restricted 3,5-*O*-di-*tert*-butylsilylene-D-galactofuranosyl trichloroacetimidate donors were synthesized from allyl α-D-galactofuranoside for the construction of 1,2-*cis* α-D-galactofuranosyl linkages. Glycosylation reactions were performed with several acceptors, including D-galactono-1,4-lactone, D-rhamnopyranosyl, and D-mannopyranosyl derivatives. The influence of the temperature and the reaction solvents was evaluated, as well as the 6-O-substitution pattern of the donor. The higher α-selectivities were obtained at −78 °C in diethyl ether as solvent. 6-*O*-Acetyl substitution on constrained donor increased the α-selectivity compared to the 6-*O*-benzyl substitution. Almost no selectivities were observed in the non-participating solvent CH_2Cl_2. In contrast, ethereal solvents enhanced the α-selectivity suggesting a participating effect in the reaction intermediate.

1. Introduction

It is recognized that the lack of pure and well-defined carbohydrates and glycoconjugates constitutes a major obstacle in glycobiology,[1,2] in view of the essential role of carbohydrates in biology.[3] Synthetic efforts in the oligosaccharide fields have been pursued mainly focused in the stereoselective preparation of pyranose derivatives,[4,5] whereas studies on stereoselective furanosylation have been more limited.[6–9] Galactofuranose-containing oligosaccharides have deserved much attention since galactofuranose is found in many pathogenic microorganisms such as *Mycobacterium tuberculosis*, *Leishmania*, *Trypanosoma cruzi* and *Klebsiella pneumoniae*, as examples.[6–8,10] Due to the xenobiotic nature of galactofuranose, its metabolism has been proposed as a potential target for antimicrobial chemotherapy[11] and studies on the biosynthesis are currently being pursued.[12,13] Although Gal*f* is commonly found in β-configuration, several examples of α-D-Gal*f*-containing oligosaccharides with 1,2-*cis* configuration have been established also in bacteria and fungi.[6,7] Interesting examples are the pathogenic *Streptococcus pneumoniae* 22F,[14] *Escherichia coli* O167[15] and O85[16] *Salmonella enterica* O53[17] and O17,[16] and *Paracoccidioides brasiliensis*,[18] the etiological agent of paracoccidioidomycosis, the most common systemic mycosis in Latin America. The synthesis of oligosaccharides containing α-D-Gal*f* units would provide tools for the biosynthetic studies.

Whereas β-D-galactofuranosides are readily obtained through neighboring group participation, the synthesis of 1,2-*cis* α-D-galactofuranosides is more difficult to achieve as a single diastereomer, as so far, no general method is available for this purpose.[4,6,7] The trichloroacetimidate method for α-galactofuranosylation[19] allowed the synthesis of α-D-Gal*f*-(1→2)-D-galactitol, isolated by reductive β-elimination from glycoproteins of *Clostridium thermocellum* and *Bacteroides cellulosolvens*, by the use of *O*-(2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl) trichloroacetimidate (**1**).[20] A hexasaccharide repeating unit from a rhizobacteria containing terminal α-D-Gal*f*-(1→2)-α-L-Rha disaccharide was also synthesized using **1** as donor with 7:1 α/β glycosylation ratio.[21] More recently, higher diastereoselectivities have been obtained at low temperature reaction (−78 °C) using 2-OH rhamnopyranoside (10:1 α/β ratio) and 6-OH mannopyranoside (12.6:1 α/β ratio) acceptors derivatives, however, selectivities depended on the acceptor type and protecting group pattern.[22] The thioglycoside method was also evaluated on *galacto* and *gluco* derivatives acceptors, giving better yields but moderate selectivities which depended also on the acceptor used.[23]

The first example of a single diastereomer α-galactofuranosylation was reported by the use of the 2′-carboxybenzyl (CB) glycoside method, formerly developed for the construction of 1,2-*cis* β-D-mannosides. The antineoplastic glycosphingolipid agelagalastatin with α-D-Gal*f*-(1→2)-D-Gal*f* as terminal unit was synthetized.[24]

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More recently, di- and tetrasaccharide subunits of the cell wall polysaccharide of *Talaromyces flavus* were achieved containing α-D-Gal*f*-(1→2)-Man unit.[25]

α-D-Galactofuranosides have been synthetized by the 2,3-anhydrosugar methodology, formerly developed for the construction of 1,2-*cis* β-D-Ara*f* linkages.[26] In this indirect method, the 2,3-anhydro-D-gulofuranosyl thioglycoside or sulfoxide donor reacts with the acceptor by S_N2-like displacement, to form a disaccharide epoxide derivative with a new 1,2-*cis* glycosidic linkage. After the stereoselective opening of the epoxide, the desired α-disaccharide is obtained. The use of 2,3-anhydro-5,6-di-*O*-benzoyl-β-D-gulofuranosyl-*p*-tolyl-(*R*/*S*)-sulfoxide as donor allowed the challenging synthesis of the pentasaccharide repeating unit of varianose, a polysaccharide produced by the fungus *Penicillium varians* which possesses an internal α-Gal*f* unit.[27] Glycosylation reaction afforded one single diastereomer, however, further epoxide opening was not completely regioselective.

Intense research has been performed to understand the factors that affect chemical glycosylation mechanism,[28–30] however, mainly focused on glycopyranosyl donors. Stereoselective furanosylation studies are more limited and this could be due to the flexible ring in which the anomeric effect is less pronounced. Protecting groups play considerable role in the stereochemical control of glycosylation reaction and few examples have been described for 1,2 *cis*-arabinofuranosylation.[31–33]

On studying C-glycosylation of five-member ring oxacarbenium ions, Woerpel et al. had proposed that the nucleophilic attack occurred from inside the envelope (*inside attack*) in order to avoid eclipsing interactions. Mixtures were obtained with arabinofuranose derivatives due to the stereoelectronic influence of C-2 and C-3 substituents in *trans*-relationship, and in conformational equilibrium.[34] Conformationally constrained arabinofuranosyl donors have been designed which produced highly selective 1,2-*cis* β-arabinofuranosylation. The introduction of a 3,5-*O*-di-*tert*-butylsilylene protecting group in L-arabinofuranosyl thioglycoside derivative L-**2** (Fig. 1) locked the oxacarbenium intermediate ring in a E_3 conformation, directing the attack of the acceptor to the β face, giving rise to 1,2-*cis* linkage.[35] Glycosylation studies on the enantiomer analog of **1** (D-**3**) showed that the activation method of glycosylation was crucial for stereoselectivity.[36] Moreover, D-arabinofuranosylation resulted less selectively than L-arabinofuranosylation.[37] The development of donor D-**3**[36,38] allowed the synthesis of the 22-residue arabinan oligosaccharide from mycobacterial arabinogalactan and related compounds.[39] Other donors than thioglycoside such as sulfoxide L-**4**[36] or trichloroacetimidate L-**5**[40] also gave high β-selectivities. Moreover constrained donor L-**5** was used in the synthesis of a hexasaccharide and related fragments of rhamnogalacturonan II, a highly complex pectic oligosaccharide of the primary cell wall of higher plants. In this case, the β-anomer was obtained as a single diastereomer whereas 1-thioarabinofuranoside analog L-**2** gave a slightly reduced anomeric selectivity.

On the other hand, the conformationally constrained donor D-**6** (Fig. 1) with a 3,5-*O*-tetra-*i*-propyldisiloxanyllidene protecting group also gave high β-selectivity[41] and it was employed in the synthesis of docosasaccharide arabinan motif of mycobacterium cell wall.[42] More recently, a novel method for 1,2-*cis* β-selective arabinofuranosylation was developed by the use of 2,3-*O*-xylylene-protected Ara*f* thioglycoside donor which allowed the synthesis of an oligosaccharide fragment of mannose-capped mycobacterial lipoarabinomannan.[43]

In view of the results obtained with constrained arabinofuranosyl donors in selective 1,2-*cis* glycosylation, and considering the stereochemical relationship between arabinose and galactose, the synthesis of a conformationally restricted galactofuranosyl donor was envisioned for the construction of 1,2-*cis* α-D-galactofuranosyl linkages. The 3,5-*O*-di-*tert*-butylsilylene protecting group on galactofuranosyl oxocarbenium would favor the entrance of the nucleophile acceptor from the 'inside' face (α-face) of the rigid conformer avoiding the eclipsing interactions produced by a β-face trajectory (Fig. 2). We here present the scope and limitation of this approach as a contribution to the furanose glycosylation field.

2. Results and discussion

Among the glycosylation methods already employed for galactofuranosyl linkage construction, the trichloroacetimidate method[44] has been extensively used for the synthesis of oligosaccharides of biological significance.[6,7,45–50] In addition, high 1,2-*cis* selectivities have been obtained with constrained arabinofuranosyl imidate L-**5** (Fig. 1).[40] On the other side, a non participating group was required in *O*-2 of the constrained galactofuranosyl donor. For these reasons, we decided to synthesize *O*-(2,6-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranosyl) trichloroacetimidate (**7**, Fig. 2) as conformationally constrained D-galactofuranosyl donor. Several precursors of D-galactofuranose have been used to date; some of them are synthesized in several steps.[7,9]

2.1. Synthesis of constrained D-galactofuranosyl trichloroacetimidate donor

In this case, the synthesis started with allyl α-D-galactofuranoside (**8**)[51,52] which is obtained crystalline by direct O-alkylation of galactose in one step. The anomeric allyl group, orthogonal to the benzyl and di-*tert*-butylsilylene protecting groups, would allow the selective deprotection of the anomeric center and further activation as the trichloroacetimidate derivative. On the other hand, selective 2,6-O-protection has been previously described on pentenyl α-D-galactofuranoside, analog of **8**.[53] Treatment of **8** with 2.2 equiv of benzoyl chloride in pyridine at −10 °C gave the 2,6-di-*O*-benzoyl derivative **9** in 63% yield (Scheme 1). In the ^{1}H NMR spectrum, as expected, the H-1 appeared as a doublet with $J_{1,2}$ 4.8 Hz due to H-1–H-2-*cis* disposition.[20,22] Selective benzoylation occurred as indicated by the H-2 and H-6a,6b resonances that shifted 0.94 and 0.74–0.75 ppm downfield, respectively, compared to the same signals in **8**. In the ^{13}C NMR spectrum of **9**, the resonances of C-2 and C-4 appeared at 80.2 and 82.7 ppm characteristic of the galactofuranosyl compounds. On reaction with *t*-$Bu_2Si(OTf)_2$

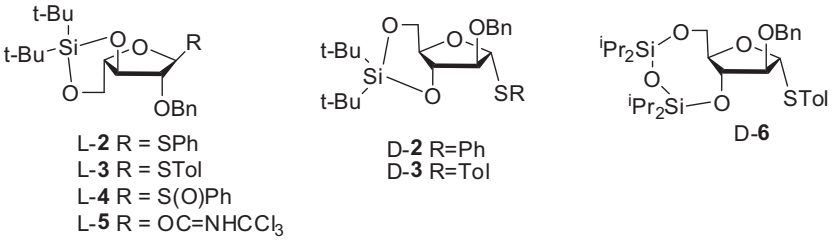


Figure 1. Conformationally constrained donors used for 1,2-*cis* β-Ara*f* linkage construction.

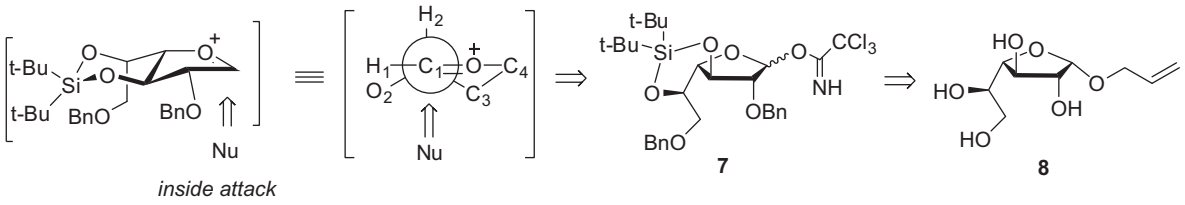
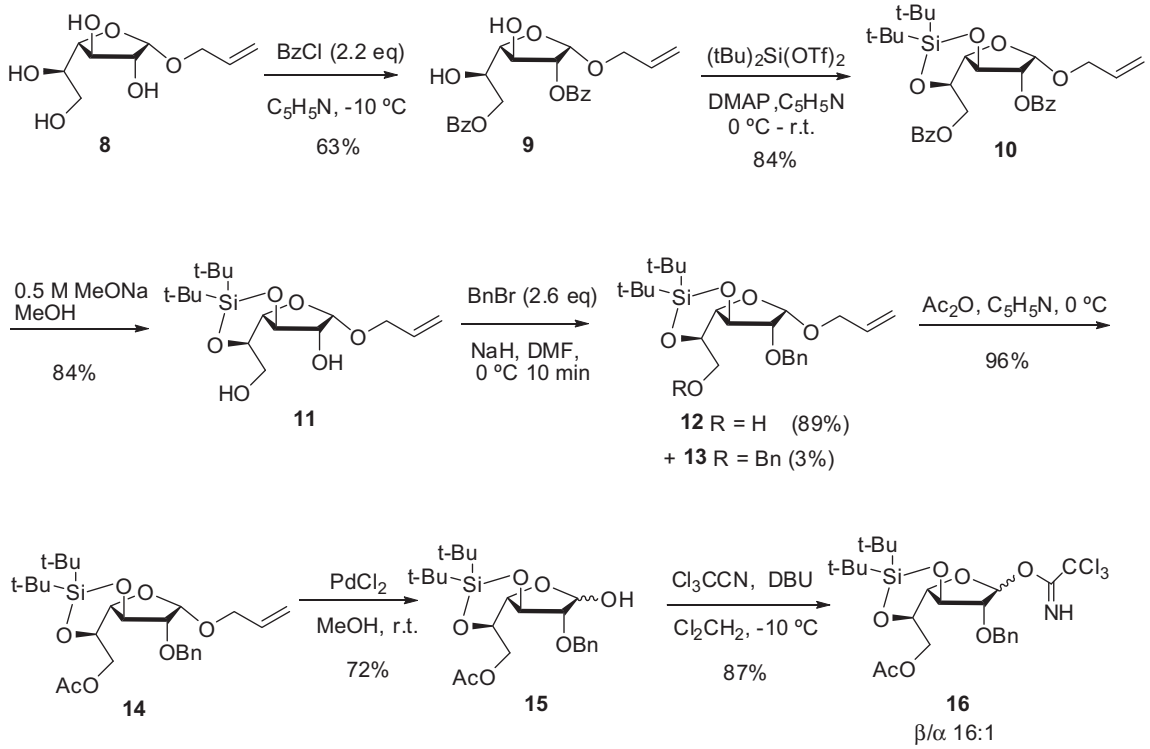


Figure 2.



Scheme 1. Synthesis of constrained D-galactofuranosyl trichloroacetimidate donor **16**.

in pyridine, catalyzed by DMAP afforded the conformationally restricted silylene derivative **10** (84%). Analysis of the coupling constants in the ^{1}H NMR spectrum of **10** indicated that a furanose conformation change occurred. Whereas $J_{1,2}$ remained almost unchanged (5.0 Hz) compared to the precursor **9**, the large coupling constants ($J_{2,3}$ 9.1 and $J_{3,4}$ 9.8 Hz) in constrained derivative **10** are in agreement with almost *trans*-diaxial relationship between H-2 and H-3, and between H-3 and H-4. In the ^{13}C NMR spectrum of **10**, the C-4 and C-2 resonances appeared at 74.7 and 77.2 ppm, respectively, almost 6 ppm and 3 ppm upfield shifted compared to the same signals in **9**. In the arabinofuranosyl series, the furanose ring of thioglycoside donor D-**3** (Fig. 1) adopts a nearly perfect E_4 envelope conformation as indicated by X-ray studies.[38] Interestingly, constrained 3,5-*O*-benzylidene analogous of D-**3**, also adopts the same E_4 conformation.[36]

In order to introduce a non-participating group in O-2, benzoyl groups of **10** were removed by treatment with sodium methoxide in methanol to give **11** in 84% yield. Next step was the 2,6-di-O-benzylation of **10**. On treatment with 2.6 equiv of benzylbromide and 2.6 equiv of NaH in DMF at 0 °C, 2,6-di-*O*-benzyl derivative **13** was obtained in very low yield (2%) together with 2-*O*-benzyl derivative **12** (31%) and low migrating decomposition by-products (data not shown). 2-*O*-Benzyl substitution in **12** was confirmed by standard acetylation to give **14**. In the ^{1}H NMR spectrum of **14**, the H-6a and H-6b resonated 0.5 ppm downfield shifted compared to the same signals in **12** confirming the acetylation in O-6. A careful TLC analysis of the benzylation reaction showed that the 2-*O*-benzyl derivative **12** was rapidly formed as the main product (5–10 min) followed by decomposition as shown by the low migrating by-products. Other milder conditions were assayed. The replacement of DMF by THF as solvent described for the arabinofuranosyl counterpart[36] was not successful for the galactofuranosyl compound. Moreover, by the use of nBu$_4$NI as catalyst or activation with Ag$_2$O instead of NaH[37] the desired 2,6-di-*O*-benzyl derivative **13** was not obtained at all. In these cases, TLC revealed a mixture of 2-*O*-benzyl derivative **12** together with low migrating decomposition by-products. These results showed that primary 6-OH is less reactive than secondary 2-OH, and this could be attributed to steric factors provided by *tert*-butyl groups on silyl atom. At this point, we decided to optimize the synthesis of 2-*O*-benzyl derivative **12** by reduction of the reaction time in order to avoid decomposition. The best results were obtained by reaction of **11** with an excess of benzyl bromide (2.6 equiv) in DMF at 0 °C, followed by addition of NaH (2.6 equiv) and careful quenching of the reaction after 10 min. In this case, **12** was obtained in 89% yield together with 2,6-di-*O*-benzyl derivative **13** in 3% yield. On the other hand, attempts to benzylate the 6-O-position of **12** by reaction of benzyl trichloroacetimidate and TMSOTf[54] was also unsuccessful, for that reason **12** was finally acetylated by standard conditions to give **13** in 96% yield.

In order to activate the anomeric center via trichloroacetimidate, removal of the anomeric function of **14** was performed by reaction with $PdCl_2$ in methanol[52] to afford **15** in 72% yield as an anomeric mixture in 2:13 α/β ratio, as indicated by the integration of the anomeric protons at δ 5.30 ($J_{1,2}$ 3.5 Hz, β anomer) and 5.26 ($J_{1,2}$ = 5.7 Hz, α anomer) in the ^{1}H NMR spectrum. Removal of palladium by washing the reaction with water instead of filtering was required to avoid decomposition. On the other hand, allyl isomerization with hydrogen activated $[Ir(COD)(Ph_2MeP)_2]PF_6$ complex in CH_2Cl_2 of **13**, followed by hydrolysis with *p*-toluensulfonic acid in CH_2Cl_2 of the vinyl glycoside did not improve the yield.[55] Treatment of **15** with acetonitrile and DBU gave imidate **16** in 16:1 β/α anomeric ratio as indicated by the integration of the anomeric signals at 6.33 (H-1α anomer, $J_{1,2}$ 4.6 Hz) and 6.20 ppm (H-1β anomer, J 2.7 Hz) in the ^{1}H NMR spectrum. Imidate **16** could be stored at −20 °C for several weeks.

2.2. Glycosylation reactions

Once **16** was in hand, the next step was the evaluation of the conformationally locked donor for α-galactofuranosylation. All reactions were performed employing 1 equiv of donor (0.04 M) and 1.2 equiv of acceptor using standard trichloroacetimidate activation conditions (TMSOTf 0.3 equiv and 4 Å molecular sieves). For all cases, the diastereomeric α/β ratio of the products of glycosylation was determined from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the signals of each diastereomer and comparison with pure isolated isomers. The α/β ratio was confirmed by weighting the isolated α and β products after purification by column chromatography when possible.

The first solvent of choice was the non-participating CH_2Cl_2, previously used in selective α-arabinofuranosylation with constrained donors of Figure 1. We first evaluated the influence of the temperature in glycosylation reactions with cyclohexanol as acceptor. When the reaction was performed at −10 °C (Table 1, method A, entry 1), unexpectedly, only the 1,2-*trans* β-isomer **17β** was obtained as a single diasteromer in low yield (29%). The ^{13}C NMR spectrum of **17β** showed the anomeric C-1 resonance at 104.9 ppm indicating a β-configuration, whereas in the ^{1}H NMR spectrum, the anomeric H-1 appeared at 5.06 ppm as a doublet with a small coupling constant ($J_{1,2}$ 3.2 Hz), however, larger compared to flexible β-galactofuranosyl derivatives (~1 Hz).[22,45–49] The transposition by-product 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilylene)-1-*N*-trichloroacetyl-α-D-galactofuranosylamine (**18**) was also obtained (35%) suggesting that donor **16** is very reactive probably due to the arming silylene group. *N*-Glycosyl trichloroacetamides as by-products of glycosylation have been obtained on reaction with low nucleophilic or sterically hindered acceptors.[4,20,44,48,56] In the ^{1}H NMR spectrum of **18**, the H-1 appeared as a triplet with a $J_{1,2}$ of 7.0 Hz suggesting a α-configuration confirmed by the H-1–H-4 correlation in the NOESY experiment.

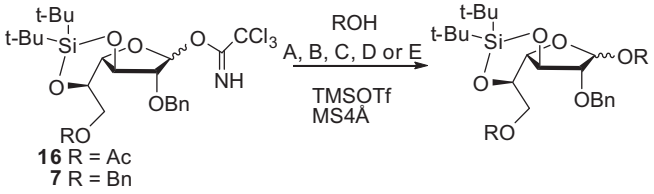
By lowering the temperature reaction to −40 °C (method B, entry 1), the α-product was now also obtained. Analysis of the crude reaction by ^{1}H NMR spectroscopy showed **17** in 1.3:1 α/β ratio, established by the integration of H-2α signal and the superimposed signals of H-1β and H-1α. Purification on column chromatography gave pure **17β** (31%) and a second fraction of **17α** slightly impurified with the transposition byproduct **18** in 10:1 **17α**/**18** ratio as shown by integration of the anomeric protons in the ^{1}H NMR spectrum. When the reaction was conducted at −78 °C (method C), the analysis of the crude reaction mixture showed **17** in 1.7:1 α/β ratio and no signals of transposition by product **18**. Purification of the crude gave **17β** (27%) and pure **17α** (48%). The configuration of the anomeric center of **17α** was established by the coupling constant ($J_{1,2}$ 5.0 Hz) observed for H-1 signal (δ 5.40). In the ^{13}C NMR spectrum, the C-1 appeared at 98.8 ppm confirming the α-configuration. It is interesting to note that by employing 2,3,5,6-tetra-*O*-benzyl-α,β-D-galactofuranosyl trichloroacetimidate (**1**), the flexible equivalent of imidate **16**, and in the same reaction conditions, the corresponding cyclohexyl glycoside was obtained in a similar ratio (2.0:1 α/β ratio).[22] Considering that a moderate diastereoselectivity favoring the α-anomer was obtained at −78 °C, we next evaluated **16** with several acceptors. Based on our experience in the aldonolactone strategy for the synthesis of galactofuranose-containing oligosaccharides,[46,48] we first used 2,3,5-tri-*O*-benzoyl-D-galactono-1,4-lactone (**19**)[57] as acceptor. In this condition, disaccharide **20** was obtained as an inseparable mixture in 87% yield (entry 2, method C). After HPLC separation and full characterization of the anomers, **20α** and **20β** were assigned on the basis of the ^{1}H and ^{13}C NMR spectra. Whereas the H-1′ signal of **20α** appeared as a doublet (δ 5.06) with a coupling constant of 5.1 Hz, the $J_{1,2}$ for the same signal of **20β** (δ 4.96) was smaller (2.9 Hz). On the other hand, in the ^{13}C NMR spectra of **20α** and **20β**, the anomeric carbons appeared at 101.5 (C-1′) and 107.3 (C-1′) ppm, respectively. Analysis of the ^{1}H NMR spectrum of the crude reaction indicated a 1.3:1 α/β ratio shown by the integration of H-4α signal compared to the integration of superimposed H-4′β and H-1′β signals. We next evaluated 3,4-di-*O*-benzyl-α-L-rhamnopyranoside[58] (**21**) as acceptor which is precursor of the disaccharide present in *S. pneumoniae* 22F.[14] Unexpectedly, reaction of **21** with constrained imidate **16** at −78 °C in CH_2Cl_2 (method C, entry 3) gave only the β diastereomer **22β** (66% yield) as indicated by the H-1′ signal at δ 5.28 ($J_{1,2}$ 3.1 Hz) in the ^{1}H NMR spectrum and the C-1′ signal at 108.7 ppm in the ^{13}C NMR spectrum. Interestingly, the opposite selectivity was obtained on reaction of **21** with the flexible tetra-*O*-benzyl trichloroacetimidate analog **1** to give the corresponding disaccharide in 10:1 α/β ratio.[22]

2.3. Influence of the 6-O-substitution on galactofuranosyl constrained donor

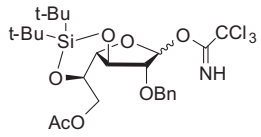
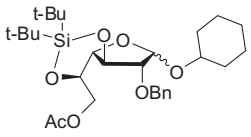
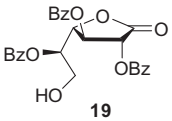
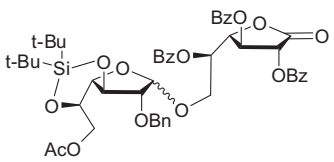
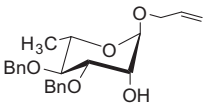
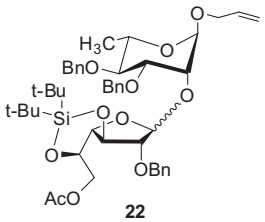
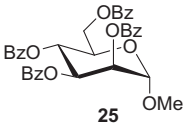
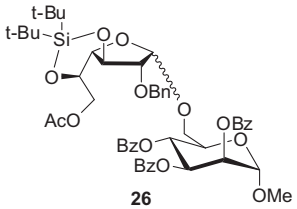
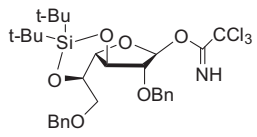
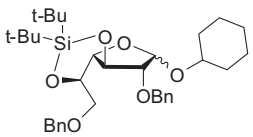
Taking into consideration these unexpected results obtained with constrained galactofuranosyl trichloroacetimidate donor **16** compared to the constrained D-arabinofuranosyl analogs (Fig. 1), we speculated that the 6-*O*-acetyl group may contribute as a remote participating group[29,59] suggested by preliminary molecular modeling calculations on the corresponding oxacarbenium ion. The acetyl group on quasi-axial hydroxymethyl group oriented to the electrophilic positive carbon. For that reason, we synthesized the 6-*O*-benzyl analog of **16**, *O*-(2,6-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranosyl) trichloroacetimidate (**7**), starting from **13** previously obtained as a by-product of the benzylation reaction (Scheme 1). Treatment of **13** with $PdCl_2$ in methanol gave **23** in 82% yield (Scheme 2). Subsequent activation of the anomeric center with Cl_3CCN and DBU gave the β-trichloroacetimidate **7** as a single isomer.

However, on reaction of **7** with cyclohexanol at −78 °C, the separable glycosides **24α** and **24β** were obtained in 1:1 α/β ratio as indicated by the integration of the anomeric hydrogen in the ^{1}H NMR spectrum of the crude reaction (entry 5, method C). No transposition by-product was obtained in this case. No selectivity for the α-anomer was obtained in this glycosylation reaction compared to the previous one, concluding that no remote participation is exerted by the acetyl group in O-6 of **16**. Stereoelectronic effects are involved in the sense that the electron withdrawing group such as acetyl favors the α-anomer on 3,5-*O*-silylene galactofuranosyl donor. The hydroxymethyl and the protecting group pattern on O-6 strongly influenced the stereochemical course of the glycosylation, compared to the D-arabinofuranosyl counterpart.

Table 1
Glycosylation reactions with silylene donors **16** and **7** (methods **A**–**E**)



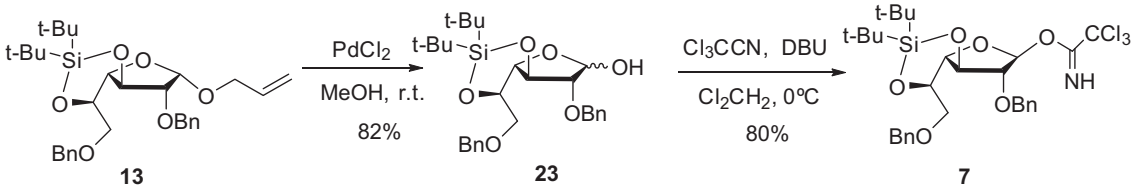
(A) Cl_2CH_2, -10 °C; (B) Cl_2CH_2, -40 °C; (C) Cl_2CH_2, -78 °C
(D) CH_3CN, -40 °C; (E) Et_2O, -78 °C

Entry	Donor	Acceptor	Product	Method	α/β[a] (yield)[b]
1	 **16** β:α 16:1	Cyclohexanol	 **17**	A B C D E	Only β (29%) (**17** 35%)[d] 1.3:1 (71%) (**17** 4%)[d,e] 1.7:1 (75%) 2.0:1 (33%) 3.6:1 (70%)
2		 **19**	 **20**	C E	1.3:1 (87%)[c] 4.5:1 (70%)[c]
3		 **21**	 **22**	C E	Only β (66%) 1.1:1 (66%)
4		 **25**	 **26**	E	7.7:1 (95%)
5	 **7**	Cyclohexanol	 **24**	C E	1.0:1 (94%) 2.0:1 (71%)

[a] α/β ratio established from ^{1}H NMR (500 MHz) spectrum of the crude and confirmed by weights of isolated α and β products.
[b] Yield of isolated products (combined yield of the α- and β-D-isomers).
[c] α/β unseparable mixture.
[d] % of 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-1-*N*-trichloroacetyl-α-D-galactofuranosylamine (**18**) also recovered.
[e] Calculated from the unseparable mixture of **18** and α anomer.

2.4. Influence of the solvent

We next evaluated the influence of the solvent system with low expectation, considering that the best results favoring the 1,2-*cis* glycosylation product with constrained D-arabinofuranosyl donors (Fig. 1) and with the flexible tetra-*O*-benzyl galactofuranosyl trichloroacetimidate **1** were achieved using the non participating solvent CH_2Cl_2. It is accepted that acetonitrile favors the 1,2-*trans* β-glycosylation products in D-*gluco*- and D-galactopyranose derivatives through the formation of an α-nitrilium ion (nitrile effect)



Scheme 2. Synthesis of constrained D-galactofuranosyl thrichloroacetimidate donor **7**.

which is further displaced by the acceptor.[29,44] Glycosylation of **16** with cyclohexanol in acetonitrile (−40 °C, method D, entry 1) gave **17** in 2.0:1 α/β ratio, slightly better compared to that obtained with CH_2Cl_2 at −78 °C (method C) but in very low yield. To our surprise, when the reaction was carried in diethyl ether as solvent at −78 °C (method E), glycoside **17** was obtained in 3.6:1 α/β ratio (70%). Same α/β ratio was obtained with THF as solvent. This ratio was even better than it was obtained using the flexible imidate **1** in ethyl ether (2.4:1 α/β) or CH_2Cl_2 at −78 °C (2.0:1 α/β) in the same reaction conditions.[22] Moreover, reaction of 6-*O*-benzyl constrained imidate **7** with cyclohexanol gave **24** in 2:1 α/β ratio (entry 5, method E) whereas no selection was observed in CH_2Cl_2. With these results, evaluation of method E on acceptors **19** and **21** were also conducted.

On reaction of imidate **16** with lactone **19** the α/β ratio of disaccharide **20** increased from 1.3:1 to 4.5:1 by changing the solvent from CH_2Cl_2 to ethyl ether (entry 2, method E). On the other hand, the reaction with rhamnosyl acceptor **21** gave disaccharide **22** in 1.1:1 α/β ratio (entry 3, method E), whereas only the β anomer was obtained in CH_2Cl_2 at −78 °C (method C). We also evaluated methyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside[60] **25** as acceptor because it is a precursor of the disaccharide constituent of *P. brasiliensis*. In this case, disaccharide **26** was obtained in 95% yield in 7.7:1 α/β ratio (entry 4) as indicated by the integration of the signals corresponding to H-1′ of the α-anomer and H-1 of the β-anomer in the ^1H NMR spectrum of the crude reaction. Compounds **26α** and **26β** were easily purified by column chromatography. By the use of the flexible imidate **1**, the corresponding disaccharide was obtained in 1.5:1 α/β ratio in the same solvent and in 12.6:1 α/β ratio in CH_2Cl_2, however in moderate yield (63%).[22] This disaccharide was obtained also by the carbobenzoxy method of glycosylation in 8:1 α/β ratio without characterization data.[25] Compound **16** could be considered a good precursor for α-D-Gal*f*-(1-6)-D-Man linkage construction, with a galactofuranosyl moiety that could be further functionalized.

It is intriguing why diethylether increased the selectivity toward the α-product in all cases when the 3,5-*O*-silylene moiety locks the conformation of the galactofuranosyl ring. In the pyranose counterpart, diethylether increases the α-anomeric selectivity apparently by the formation of a diethyl oxonium ion intermediate which adopts a β-configuration probably by steric factors, although reverse anomeric effect has been also considered.[4,5,44] We may speculate that ethyl ether could participate from the β-face which is further displaced by the nucleophile leading to the α-product. On the other hand, activation was performed by TMSOTf, thus, a covalent triflate intermediate could be involved. On activation of constrained arabinofuranosyl donors **D-3** and **L-4**, a triflate intermediate in 1,2-*trans* configuration was identified by low variable temperature ^1H NMR studies. If this were the case, after a β-triflate formation in galactofuranosyl constrained donor, the nucleophilic displacement of the acceptor should provide the α-glycoside, at least in non participating solvents such as CH_2Cl_2. Mechanism of glycosylation of furanoses deserves more investigation because many aspects remain unclear.

3. Conclusions

On the basis of the stereochemical relationship between arabinose and galactose, and considering the influence of the 3,5-*O*-silylene group as 1,2-*cis*-directing glycosylation group on arabinofuranose donors derivatives, we have performed glycosylation studies on the galactofuranose counterpart. 3,5-*O*-Silylene-D-galactofuranosyl constrained trichloroacetimidate donors for 1,2-*cis* α-galactofuranosylation were synthesized from allyl D-galactofuranoside. The presence of the 3,5-*O*-silylene-group was not determinant for the α-diastereoselection since almost no α-selectivities were obtained in CH_2Cl_2 as solvent. However, modest to high selectivities toward the α-anomer were achieved using diethylether as solvent at −78 °C suggesting a participating effect in the reaction intermediate. Moreover, 6-*O*-acetyl substitution on constrained donor increased the α-selectivity compared to the 6-*O*-benzyl substitution. α/β ratio of the glycosylation products strongly depended on the acceptor employed. The solvent effects on constrained galactofuranosyl trichoroacetimidate are the opposite to those exerted on the flexible 2,3,5,6-tetra-*O*-benzyl-D-galactofuranosyl trichoroacetimidate and this fact could be due to the change in the conformation on the oxacarbenium intermediate.

The development of conformationally constrained arabinofuranosyl donors allowed the synthesis of challenging and biologically relevant oligosaccharides with 1,2-*cis* linkages. However, stereoselectivity strongly depended on the activation method of glycosylation, as well as on the acceptor.[36,61] In this sense, other methods of glycosylation such as the thioglycoside method should be evaluated on 3,5-*O*-silylene constrained galactofuranosyl donor and this is currently being pursued in our laboratory to bring a better understanding to the furanose glycosylation field.

4. Experimental

4.1. General methods

TLC was performed on 0.2 mm Silica Gel 60 F254 aluminium-supported plates. When TEA was added to the solvent system, a previous TLC elution was performed. 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). High-performance liquid chromatography (HPLC) was performed using Thermo Separation (Spectra Series P100) with a Beckman ultrasphere ODS (5 μm, 250 × 10 mm), employing a variable wavelength UV detector at a rate of 3.00 mL/min in 9:1 acetonitrile/H_2O. Melting points are uncorrected. Optical rotations were measured at 25 °C. NMR spectra were recorded at 500 MHz (^1H) and 125.8 MHz (^{13}C) or, at 200 MHz (^1H) and 50.3 MHz (^{13}C). ^1H and ^{13}C NMR spectra assignments were supported by homonuclear COSY and HSQC-DEPT experiments. High resolution mass spectra (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. Allyl 2,6-di-*O*-benzoyl-α-D-galactofuranoside (9)

To a stirred solution of allyl α-D-galactofuranoside[52] (**8**, 1.18 g, 5.36 mmol) in dry pyridine (36 mL), cooled at −15 °C, benzoyl chloride (1.4 ml, 12.1 mmol) was added during 3 h. After 3 h of stirring, ice (20 g) was added and the stirring was continued for 1 h. The resulting mixture was diluted with water (30 mL) and then extracted with CH_2Cl_2 (3 × 70 mL). The organic layer was sequentially washed with 2.5 M HCl (70 mL), saturated aq $NaHCO_3$ (70 mL), water (3 × 70 mL), dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the mixture (8:1 toluene–EtOAc) gave syrupy **9** (1.45 g, 63%): R_f = 0.76 (9:1 CH_2Cl_2–MeOH), $[\alpha]_D$ +40.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08–7.42 (m, 10H, aromatic), 5.85 (dddd, 1H, *J* = 17.2, 10.4, 5.8, 5.4 Hz, C*H*=CH_2), 5.37 (d, 1H, *J* = 4.8 Hz, H-1), 5.28 (dq, 1H, *J* = 17.2, 1.4 Hz, HC=C*H*$_a$H), 5.18 (dq, 1H, *J* = 10.4, 1.4 Hz, HC=C*H*$_b$H), 5.11 (dd, 1H, *J* = 7.3, 4.8 Hz, H-2), 4.82 (dd, 1H, *J* = 7.3, 6.4 Hz, H-3), 4.49 (dd, 1H, *J* = 11.4, 6.4 Hz, H-6a), 4.41 (dd, 1H, *J* = 11.4, 5.8 Hz, H-6b), 4.27 (ddt, 1H, *J* = 13.1, 5.4, 1.4 Hz, OC*H*$_a$H-CH=), 4.22 (dd, 1H, *J* = 6.2, 3.4 Hz, H-4), 4.11 (ddt, 1H, *J* = 13.1, 5.8, 1.4 Hz, OC*H*$_b$H-CH=), 4.08 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 167.0, 166.6 (*C*OPh); 133.6, 133.1, 129.9, 129.8, 129.7, 129.0, 128.5, 128.4 (aromatic); 133.1 (*C*H=CH_2), 118.2 (CH=*C*H$_2$), 100.0 (C-1), 82.7 (C-4), 80.8 (C-2), 73.5 (C-3), 69.9 (O*C*H$_2$-CH=), 69.3 (C-5), 65.4 (C-6). Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.21; H, 5.48.

4.3. Allyl 2,6-di-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside (10)

To a stirred solution of **9** (5.68 g, 13.3 mmol) and DMAP (85 mg, 0.70 mmol) in dry pyridine (40 mL), cooled to 0 °C, (*t*Bu)$_2$Si(OTf)$_2$ (5.0 mL, 15.3 mmol) was added during 3.5 h. The mixture was allowed to reach room temperature and after 1 h of stirring, the reaction was quenched by addition of MeOH (2 mL). The resulting solution was coevaporated with toluene to dryness. Column chromatography (toluene) of the residue gave **10** (6.37 g, 85%) as a syrup. R_f = 0.66 (hexane–EtOAc 2:1); $[\alpha]_D$ +157.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12–7.42 (m, 10H, aromatic), 5.64 (dddd, 1H, *J* = 17.3, 10.5, 6.0, 5.3 Hz, C*H*=CH_2), 5.40 (d, 1H, *J* = 5.0 Hz, H-1), 5.08 (dd, 1H, *J* = 9.1, 5.0 Hz, H-2), 5.05 (dq, 1H, *J* = 17.3, 1.7 Hz, HC=C*H*$_a$H), 4.97 (dq, 1H, *J* = 10.5, 1.5 Hz, HC=C*H*$_b$H), 4.91 (t, 1H, *J* = 9.5 Hz, H-3), 4.81 (dt, 1H, *J* = 3.9, 6.8 Hz, H-5), 4.71 (dd, 1H, *J* = 11.9, 3.9 Hz, H-6a), 4.53 (dd, 1H, *J* = 11.9, 6.7 Hz, H-6b), 4.21 (dd, 1H, *J* = 9.8, 6.8 Hz, H-4), 4.09 (ddt, 1H, *J* = 13.7, 5.3, 1.5 Hz, OC*H*$_a$H-CH=), 3.91 (ddt, 1H, *J* = 13.7, 6.0, 1.4 Hz, OC*H*$_b$H-CH=), 1.07, 1.04 (2s, 18H, 2(CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 166.5, 166.3 (*C*OPh), 133.5 (*C*H=CH_2); 133.2, 132.9, 130.2, 129.8 (×2), 129.6, 128.4, 128.3 (aromatic); 117.2 (CH=*C*H$_2$), 98.8 (C-1), 77.2 (C-2), 74.7 (C-4), 72.1 (C-3), 72.0 (C-5), 69.6 (O*C*H$_2$-CH=), 64.7 (C-6); 27.2, 27.1 ((*C*H$_3$)$_3$C); 21.7, 20.8 ((CH$_3$)$_3$*C*); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{41}O_8Si$ (M+H$^+$) 569.2571, found 569.2567.

4.4. Allyl 3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside (11)

To a externally cooled (0 °C) flask containing **10** (6.37 g, 11.2 mmol) was added cooled 0.5 M NaOMe in MeOH (75 mL) with stirring and the mixture was sonicated to complete dissolution (2 min). The solution was stirred for 3 h at 0 °C, and then warmed to rt over 0.5 h. After cooling at 0 °C, the reaction was quenched and neutralized with cold 10% m/v HCl (14 mL). The mixture was then extracted with CH_2Cl_2 (3 × 80 ml) and the combined organic layer was successively washed with saturated aq $NaHCO_3$ (50 mL), water (3 × 70 mL), dried (Na_2SO_4), filtered, and concentrated. Methyl benzoate was eliminated by co-evaporation with water and the residue was purified by column chromatography (5:1 hexane–EtOAc) to afford **11** (3.41 g, 84%) as a colorless syrup: R_f = 0.45 (2:1 hexane–EtOAc); $[\alpha]_D$ +137.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, D_2O 500 MHz) δ 5.90 (dddd, 1H, *J* = 17.2, 10.4, 6.2, 5.7 Hz, C*H*=CH_2), 5.30 (dq, 1H, *J* = 17.2, 1.5 Hz, CH=C*H*$_a$H), 5.25 (dq, 1H, *J* = 10.3, 1.2 Hz, CH=C*H*$_b$H), 5.02 (d, 1H, *J* = 5.4 Hz, H-1), 4.46 (m, 1H, H-5), 4.25 (t, 1H, *J* = 9.5 Hz, H-3), 4.24 (ddt, *J* = 12.7, 5.7, 1.4 Hz, OC*H*$_a$HCH=), 4.11 (ddt, *J* = 12.7, 6.2, 1.2 Hz, OC*H*$_b$HCH=), 4.07 (dd, 1H, *J* = 8.8, 5.5 Hz, H-2), 4.06 (dd, 1H, *J* = 9.5, 6.7 Hz, H-4), 3.82 (dd, 1H, *J* = 11.6, 5.9 Hz, H-6a), 3.71 (dd, 1H, *J* = 11.6, 6.6 Hz, H-6b), 1.05, 1.02 (2s, 18H, 2(CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 133.3 (*C*H=CH_2), 118.5 (CH=*C*H$_2$), 99.9 (C-1), 76.0 (C-4), 75.2 (C-2), 74.6 (C-3), 73.2 (C-5), 70.2 (O*C*H$_2$CH=), 62.6 (C-6); 27.2, 27.1 ((*C*H$_3$)$_3$C); 21.7, 20.7 (2(CH$_3$)$_3$*C*).

Anal. Calcd for $C_{17}H_{32}O_6Si$: C, 56.64; H, 8.95. Found: C, 56.36; H, 9.06.

4.5. Allyl 2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside (12)

To a solution of **11** (1.23 g, 3.41 mmol) in dry DMF (30 mL) cooled to 0 °C was added BnBr (1.05 mL, 8.80 mmol) followed by NaH (dispersion in oil 60% , 350 mg, 8.75 mmol) with stirring. After 10 min of stirring, ice (5 g) was added. The reaction mixture was rapidly diluted with CH_2Cl_2 (250 mL), washed with water (3 × 70 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography (12:1 toluene–EtOAc) of the residue afforded a first fraction of syrupy allyl 2,6-di-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside (**13**, 0.053 g, 3%): R_f = 0.74 (2:1 hexane–EtOAc); $[\alpha]_D$ +73.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) 7.47–7.25 (m, 5H, aromatic), 5.88 (dddd, *J* = 16.6, 10.6, 6.0, 5.6 Hz, C*H*=CH_2), 5.23 (dd, *J* = 16.6, 1.4 Hz, CH=C*H*$_a$H), 5.16 (dd, *J* = 10.6, 1.2 Hz, CH=C*H*$_b$H), 4.87 (d, 1H, *J* = 5.2 Hz, H-1), 4.82, 4.74 (2d, 2H, *J* = 12.4 Hz, 4.65–4.55 (m, 3H, H-5, C*H*$_2$Ph), 4.49 (t, 1H, *J* = 9.3 Hz, H-3), 4.12 (dd, *J* = 12.8, 5.2 Hz OC*H*$_a$HCH=), 3.99–3.91 (m, 2H, H-4, OC*H*$_b$HCH=), 3.87 (dd, 1H, *J* = 9.1, 5.2 Hz, H-2), 3.86 (dd, 1H, *J* = 10.2, 3.4 Hz, H-6a), 3.75 (dd, 1H, *J* = 10.2, 7.6 Hz, H-6b), 1.03, 1.00 (2s, 18H, 2(C*H*$_3$)$_3$C)); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 138.0, 137.7 , 134.0, 128.3, 128.2 (×2), 128.0, 127.7,127.6 (aromatics), 117.7 (CH=*C*H$_2$), 99.1 (C-1), 80.5, 75.5, 73.8, 73.7, 71.9, 70.0, 68.9, 27.3, 27.2 ((*C*H$_3$)$_3$C), 21.5, 20.6 ((CH$_3$)$_3$*C*); HRMS (ESI) *m*/*z* Calcd for $C_{31}H_{44}NaO_6Si$ [M+Na]$^+$ 563.2805. Found: [M+Na]$^+$ 563.2799.

The second fraction gave syrupy **12** (1.36 g, 89%): R_f = 0.55 (2:1 hexane–EtOAc); $[\alpha]_D$ +84.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43–7.25 (m, 5H, aromatic), 5.90 (dddd, *J* = 17.2, 10.4, 6.3, 5.5 Hz, C*H*=CH_2), 5.30 (dq, *J* = 17.2, 1.5 Hz, CH=C*H*$_a$H), 5.21 (dq, *J* = 10.4, 1.2 Hz, CH=C*H*$_b$H), 4.92 (d, 1H, *J* = 5.1 Hz, H-1), 4.84, 4.76 (2d, 2H, *J* = 12.3 Hz, C*H*$_2$Ph), 4.62 (t, 1H, *J* = 9.4 Hz, H-3), 4.44 (q, 1H, *J* = 6.3 Hz, H-5), 4.16 (ddt, *J* = 12.9, 5.5, 1.4 Hz, OC*H*$_a$HCH=), 4.05 (ddt, *J* = 12.9, 6.3, 1.2 Hz, OC*H*$_b$HCH=), 4.03 (dd, 1H, *J* = 9.6, 6.5 Hz, H-4), 3.92 (dd, 1H, *J* = 9.1, 5.1 Hz, H-2), 3.86 (m, 1H, H-6a), 3.75 (m, 1H, H-6b), 2.28 (t, *J* = 6.8 Hz, OH), 1.06, 1.01 (2s, 18H, 2(C*H*$_3$)$_3$C)); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 137.7 (Ar); 133.8 (*C*H=CH_2); 128.3, 128.2, 127.5 (aromatics), 118.1 (CH=*C*H$_2$), 99.8 (C-1), 80.3 (C-2), 76.1 (C-4), 73.5 (C-5), 73.3 (C-3), 71.9 (*C*H$_2$Ph), 69.8 (O*C*H$_2$CH=), 62.9 (C-6), 28.0, 27.2 ((*C*H$_3$)$_3$C), 21.6, 20.8 ((CH$_3$)$_3$*C*).

Anal. Calcd for $C_{24}H_{38}O_6Si$: C, 63.97; H, 8.50. Found: C, 63.91; H, 8.72.

4.6. Allyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside (14)

To a solution of **12** (1.56 g, 3.46 mmol) in dry pyridine cooled at 0 °C was added dropwise acetic anhydride (15 mL) with stirring.

After 1.5 h, the reaction mixture was allowed to reach room temperature and the stirring continued for 1 h. The reaction was cooled at 0 °C, quenched with MeOH and concentrated in vacuum. Purification of the residue by column chromatography (15:1 hexane–EtOAc) afforded **14** (1.64 g, 96%) as a syrup: R_f 0.67 (2:1 hexane–EtOAc); $[\alpha]_D$ +77.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44–7.28 (m, 5H, aromatic), 5.89 (dddd, 1H, *J* = 17.2, 10.3, 6.4, 5.4, Hz, C*H*=CH_2), 5.29 (dq, 1H, *J* = 17.2, 1.6 Hz, CH=C*H*$_a$H), 5.19 (ddt, 1H, *J* = 10.3, 1.6, 1.3 Hz, CH=C*H*$_b$H), 4.91 (d, 1H, *J* = 5.1 Hz, H-1), 4.83, 4.78 (2d, 2H, *J* = 12.3 Hz, C*H*$_2$Ph), 4.65 (t, 1H, *J* = 9.4 Hz, H-3), 4.56 (dt, 1H, *J* = 6.6, 3.5 Hz, H-5), 4.36 (dd, 1H, *J* = 11.9, 6.6 Hz, H-6a), 4.27 (dd, 1H, *J* = 11.9, 3.6 Hz, H-6b), 4.17 (dddd, 1H, *J* = 12.8, 5.3, 1.6, 1.3 Hz, OC*H*$_a$HCH=), 3.98 (ddt, 1H, *J* = 12.8, 6.4, 1.3 Hz, OC*H*$_b$HCH=), 3.98 (dd, 1H, *J* = 9.9, 6.7, Hz, H-4), 3.89 (dd, 1H, *J* = 5.1, 9.1 Hz, H-2), 2.09 (s, 3H, C*H*$_3$CO), 1.07, 1.01 (2s, 18H, 2(C*H*$_3$)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.8 (CH_3CO), 137.8 (Ar), 133.9 (*C*H=CH_2); 128.3 (Ar), 128.1 (Ar), 127.7 (Ar), 117.9 (CH=*C*H$_2$), 99.2 (C-1), 80.3 (C-2), 75.4 (C-4), 73.8 (C-3), 71.9 (C-5), 71.7 (*C*H$_2$Ph), 69.1 (O*C*H$_2$CH=), 64.3 (C-6), 27.2, 27.1 (2(*C*H$_3$)$_3$C), 21.7 (*C*H$_3$CO), 21.0, 20.7 (2(CH$_3$)$_3$*C*).

Anal. Calcd for $C_{26}H_{40}O_7Si$: C, 63.38; H, 8.18. Found: C, 63.29; H, 8.24.

4.7. 6-*O*-Acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-D-galactofuranose (15)

To a solution of **14** (876 mg, 1.78 mmol) in MeOH (8 mL), $PdCl_2$ (150 mg, 0.85 mmol) was added at rt and the reaction mixture was sonicated until dissolution of the palladium salt (20 s) and covered from light exposure. After 2.5 h of stirring, CH_2Cl_2 (40 mL) was added and the mixture was washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (4:1 hexane–EtOAc) to afford syrupy **15** (584 mg, 72%) as 2:13 α/β anomeric mixture: R_f = 0.48 (2:1 hexane–EtOAc); $[\alpha]_D$ +19.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) data for the β anomer, diagnostic signal for the α anomer is given δ 7.41–7.27 (m, 5H, aromatic), 5.30 (t, 1H, *J* = 3.5 Hz, H-1), 5.26 (dd, 0.15H, *J* = 8.1, 5.7 Hz, H-1α anomer), 4.79, 4.67 (2d, 2H, *J* = 11.9 Hz, C*H*$_2$Ph), 4.64–4.58 (m, 1H, H-5), 4.36 (dd, 1H, *J* = 10.1, 6.6 Hz, H-4), 4.32–4.29 (m , 3H, H-3, H-6a, H-6b), 3.94 (dd, 1H, *J* = 6.6, 3.1 Hz, H-2), 3.12 (d, 1H, *J* = 3.5 Hz, OH), 2.09 (s, 3H, C*H*$_3$CO), 1.06, 1.02 (2s, 18H, 2(C*H*$_3$)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) data for the β anomer, diagnostic signal for the α anomer is given δ 170.9 (CH_3CO); 137.6, 128.5, 128.4 (×2), 128.2, 128.1, 127.9 (×2), 127.8 (aromatic); 101.4 (C-1), 95.2 (C-1α), 88.6 (C-2), 77.0 (C-3), 75.0 (C-4), 72.0 (*C*H$_2$Ph), 71.0 (C-5), 64.3 (C-6), 27.1, 27.0 (2(*C*H$_3$)$_3$C), 21.6, 20.8 (2(CH$_3$)$_3$*C*), 21.0 (*C*H$_3$CO).

Anal. Calcd for $C_{23}H_{33}O_7Si$: C, 61.03; H, 8.02. Found: C, 61.03; H, 8.15.

4.8. *O*-(6-*O*-Acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α,β-D-galactofuranosyl) trichloroacetimidate (16)

To a stirred solution of **15** (237 mg, 0.52 mmol) and trichloroacetonitrile (380 μl, 3.79 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C, DBU (35 μl, 0.23 mmol) was slowly added. After 40 min of stirring, the solution was concentrated under reduced pressure at rt, and the dark brown residue was purified by column chromatography (15:1 toluene–EtOAc) to give syrupy **16** (270 mg, 87%) as a 1:16 α/β mixture. Compound **16** was stable for 1 month at −20 °C. R_f = 0.61 (6:1:0.05 toluene–EtOAc–TEA); ^{1}H NMR ($CDCl_3$, 500 MHz) data for the β anomer, diagnostic signal for the α anomer is given δ 8.61 (s, 1H, N*H*), 7.40–7.28 (m, 5H, aromatic), 6.33 (d, 0.06H, *J* = 4.6 Hz, H-1α anomer), 6.20 (d, 1H, *J* = 2.7 Hz, H-1β anomer), 4.78, 4.68 (2d, 2H, *J* = 12.0 Hz, C*H*$_2$Ph), 4.67 (dt, 1H, *J* = 6.9, 3.6 Hz, H-5), 4.42 (dd , 1H, *J* = 10.3, 6.6, Hz, H-3), 4.38 (dd, 1H, *J* = 12.0, 3.6 Hz, H-6a), 4.36 (dd, 1H, *J* = 10.3, 6.6 Hz, H-4), 4.33 (dd, 1H, *J* = 12.0, 7.2 Hz, H-6b), 4.22 (dd, 1H, *J* = 6.6, 2.7 Hz, H-2), 2.09 (s, 3H, C*H*$_3$CO), 1.06, 1.02 (2s, 18H, 2(C*H*$_3$)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.8 (CH_3CO), 160.9 (*C*=NH); 137.2, 128.4, 127.8 (aromatic); 104.1 (C-1), 91.0 (CCl_3), 87.1 (C-2), 76.9 (C-3), 76.4 (C-4), 72.2 (*C*H$_2$Ph), 70.7 (C-5), 64.0 (C-6), 27.1, 27.0 (2(*C*H$_3$)$_3$C), 21.6, 20.7 (2(CH$_3$)$_3$*C*), 20.9 (*C*H$_3$CO).

4.9. 2,6-*O*-Benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α,β-D-galactofuranose (23)

To a solution of allyl 2,6-di-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside **13** (120 mg, 0.22 mmol) in MeOH (2.7 mL), $PdCl_2$ (27 mg, 0.15 mmol) was added at rt and the reaction mixture was sonicated until dissolution of the palladium salt (20 s). The mixture was covered from light exposure and stirred. After 2 h of stirring, CH_2Cl_2 (10 mL) was added and the mixture was washed with water (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated at room temperature. The crude product was purified by column chromatography (7:1 hexane–EtOAc) to afford **23** as a colorless syrup (90 mg, 82%): R_f = 0.31 (4:1 hexane–EtOAc); $[\alpha]_D$ +22.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.49–7.19 (m, 10H, aromatic), 5.29 (t, 1H, *J* = 3.0 Hz, H-1), 4.83–4.51 (m, 5H, 2 PhC*H*$_2$, H-5); 4.30 (mAB, 2H, H-3, H-4), 3.90 (dd, 1H, *J* = 3.2, 6.2 Hz, H-2), 3.72 (dd, 1H, *J* = 3.4, 10.2 Hz, H-6a), 3.61 (dd, 1H, *J* = 7.2, 10.2 Hz, H-6b), 2.94 (d, 1H, *J* = 3.4 Hz, OH); 1.03, 1.02 (2s, 18H, 2(C*H*$_3$)$_3$C). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 138.1, 137.6, 128.4 (×2), 128.0, 127.9, 127.8, 127.6 (arom.); 101.3 (C-1), 88.9 (C-2), 77.2 (C-3), 75.2, 73.6, 72.7, 72.0, 70.0, 27.2, 27.1 (2(*C*H$_3$)$_3$C); 21.6, 20.7 (2(CH$_3$)$_3$*C*); HRMS (ESI) Calcd for $C_{28}H_{40}NaO_6Si$ $[M+Na]^+$ 523.2492. Found: $[M+Na]^+$ 523.2503.

4.10. *O*-(2,6-*O*-Benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranosyl) trichloroacetimidate (7)

To a stirred solution of **23** (75 mg, 0.15 mmol) and trichloroacetonitrile (110 μl, 1.10 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C, DBU (11.5 μl, 0.077 mmol) was slowly added. After 40 min of stirring, the solution was concentrated under reduced pressure at rt, and the dark brown residue was purified by column chromatography (20:1 hexane–EtOAc) to give **7** as a colorless syrup (77 mg, 80%). Compound **7** could be stored at −20 °C for 1 month. R_f = 0.68 (4:1:0.05 hexane–EtOAc–TEA); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.60 (s, 1H, N*H*), 7.49–7.19 (m, 10H, aromatic), 6.19 (d, 1H, *J* = 2.6 Hz, H-1), 4.78, 4.65 (2d, 2H, *J* = 11.8 Hz, C*H*$_2$Ph), 4.64, 4.55 (2d, 2H, *J* = 12.2 Hz, C*H*$_2$Ph), 4.70–4.60 (m, 1H, H-5), 4.40 (dd , 1H, *J* = 10.0, 6.0, Hz, H-3), 4.31 (dd, 1H, *J* = 10.0, 6.2 Hz, H-4), 4.20 (dd, 1H, *J* = 6.4, 2.6 Hz, H-2), 3.77 (dd, 1H, *J* = 10.2, 3.0 Hz, H-6a), 3.66 (dd, 1H, *J* = 10.2, 7.3 Hz, H-6b), 1.04, 1.01 (2s, 18H, 2(C*H*$_3$)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 137.3, 128.4 (×2), 128.0, 127.9, 127.6 (aromatic); 104.2 (C-1), 87.5 (C-2), 76.6, 73.6, 72.5, 72.3, 69.8; 27.2 (2(*C*H$_3$)$_3$C); 21.6, 20.7 (2(CH$_3$)$_3$*C*).

4.11. General procedures for glycosylation reactions

4.11.1. Method A

To a solution of trichloroacetimidate donor (1 equiv) and the acceptor (1.2 equiv) in anhyd CH_2Cl_2 (3.0 mL/0.04 M of donor) was added activated powdered 4 Å molecular sieves (150 mg), and the mixture was vigorously stirred at room temperature under argon. After 5 min, the mixture was cooled to −10 °C, TMSOTf (0.3 equiv) was added and the stirring continued for 40 min. The reaction was monitored by TLC, and quenched by the addition of triethylamine (0.3 equiv) after total disappearance of the donor. The mixture was diluted with CH_2Cl_2 (5 mL) and filtered. The

filtrate was concentrated and the residue was purified by silica gel column chromatography, as indicated in each case.

α/β ratio was established from the ^{1}H NMR spectrum of the crude reaction, and then corroborated by weights of isolated α and β products (Table 1).

4.11.2. Method B

Same procedure described for method A was followed at −40 °C.

4.11.3. Method C

Same procedure described for method A was followed at −78 °C.

4.11.4. Method D

Same procedure described for method A was followed, using anhyd CH_3CN as solvent at −40 °C.

4.11.5. Method E

Same procedure described for method A was followed at −78 °C, using anhyd diethylether as solvent.

4.11.6. Cyclohexyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside (17α) and cyclohexyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranoside (17β)

Compounds **17α** and **17β** were obtained according to general procedures (method E) from donor **16** (120 mg, 0.201 mmol) and cyclohexanol (25 μL, 0.241 mmol). The crude was purified by column chromatography (25:1 hexane–EtOAc) to afford **17β** (16 mg, 15%) as a syrup: R_f = 0.53 (15:1 toluene–EtOAc); $[\alpha]_D$ −28.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.25 (m, 5H, arom), 5.06 (d, 1H, *J* = 3.2 Hz, H-1), 4.75, 4.64 (2d, 2H, *J* = 12.0 Hz, PhCH_2), 4.61 (m, 1H, H-5), 4.34 (dd, 1H, *J* = 3.5, 11.9 Hz, H-6a), 4.28 (dd, 1H, *J* = 7.6, 11.9 Hz, H-6b), 4.25 (dd, 1H, *J* = 6.4, 10.2 Hz, H-3), 4.22 (dd, 1H, *J* = 6.4, 9.1 Hz, H-4), 3.91 (dd, 1H, *J* = 3.2, 6.4 Hz, H-2), 3.48 (m, 1H,OC*H*), 2.09 (CH_3CO), 1.88 (m, 2H), 1.71 (m, 2H), 1.52 (m, 1H), 1.42–1.14 (m, 5H); 1.04, 1.01 (2s, 18H, 2(CH_3)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 171.0 (CH_3*C*O); 137.9, 128.3, 127.7, 127.6 (arom.); 104.9 (C-1), 88.3 (C-2), 76.7 ((CH_2)$_5$CHO), 76.4 (C-3), 74.7 (C-4); 71.9, 71.2 (Ph*C*H$_2$, C-5); 64.5 (C-6); 33.8, 31.7, 25.6, 24.2, 24.1 ((CH_2)$_5$CHO); 27.2, 27.0 (2(*C*H$_3$)$_3$C); 21.6, 20.7 (2(CH_3)$_3$*C*); 21.0 (*C*H$_3$CO); HRMS (ESI) Calcd for $C_{29}H_{46}NaO_7Si$ $[M+Na]^+$ 557.2911. Found: $[M+Na]^+$ 557.2915.

Next fraction from the column gave syrupy **17α** (59 mg, 55%): R_f = 0.45 (15:1 toluene–EtOAc); $[\alpha]_D$ +80.3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44–7.24 (m, 5H, arom), 5.05 (d, 1H, *J* = 5.2 Hz, H-1), 4.75 (s, 2H, PhCH_2), 4.55 (t, 1H, *J* = 9.3 Hz, H-3), 4.55 (m, 1H, H-5), 4.32 (dd, 1H, *J* = 6.7, 11.9 Hz, H-6a), 4.28 (dd, 1H, *J* = 4.3, 11.9 Hz, H-6b), 3.93 (dd, 1H, *J* = 6.7, 9.7 Hz, H-4), 3.85 (dd, 1H, *J* = 5.3, 9.0 Hz, H-2), 3.44 (m, 1H, OC*H*), 2.10 (s, 3H, CH_3CO), 1.90 (m, 2H), 1.74 (m, 2H), 1.52 (m, 1H), 1.45–1.12 (m, 5H), 1.05, 1.01 (2s, 18H, 2(CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.9 (CH_3CO); 138.1, 128.3, 127.8, 127.6 (aromatic); 98.9 (C-1), 80.6 (C-2), 77.6 ((CH_2)$_5$*C*HO), 75.0 (C-4), 73.6 (C-3), 72.0 (C-5), 71.5 (Ph*C*H$_2$), 64.5 (C-6); 33.6, 32.0, 25.5, 24.5, 24.3 ((CH_2)$_5$CHO); 27.3, 27.1 (2(*C*H$_3$)$_3$C); 21.6, 20.7 (2(CH_3)$_3$*C*), 21.0 (*C*H$_3$CO); HRMS (ESI) Calcd for $C_{29}H_{46}NaO_7Si$ $[M+Na]^+$ 557.2911. Found: $[M+Na]^+$ 557.2915.

Method A: Compound **16** (27 mg, 0.045 mmol) and cyclohexanol (6.5 μL, 0.054 mmol) gave 7 mg of **17β** (29%) and 9.5 mg of 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-1-*N*-trichloroacetyl-α-D-galactofuranosylamine (**18**, 35%) as a syrup: R_f = 0.45 (15:1 toluene–EtOAc); $[\alpha]_D$ +66.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, 1H, *J* = 8.0 Hz, N*H*), 7.38–7.30 (m, 5H, aromatic), 5.64 (t, 1H, *J* = 7.7 Hz, H-1), 4.80, 4.70 (2d, 2H, *J* = 12.0 Hz, CH_2Ph), 4.65 (dt, 1H, *J* = 6.7, 4.5 Hz, H-5), 4.41 (dd , 1H, *J* = 11.8, 4.5, Hz, H-6a), 4.33 (dd, 1H, *J* = 10.0, 6.7 Hz, H-3), 4.23 (dd, 1H, *J* = 11.8, 6.8 Hz, H-6b), 4.15 (t, 1H, *J* = 7.0 Hz, H-2), 3.91 (dd, 1H, *J* = 10.0, 6.7 Hz, H-4), 2.06 (s, 3H, C*H*$_3$CO), 1.07, 1.02 (2s, 18H, 2(CH_3)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.9 (CH_3*C*O), 161.8 (NH*C*=O); 136.6, 128.5, 128.2, 127.8 (aromatic); 79.9 (C-2), 79.5 (C-1), 76.7 (C-3), 74.0 (C-4), 72.3 (*C*H$_2$Ph), 70.8 (C-5), 63.5 (C-6); 27.2, 27.1 (2(*C*H$_3$)$_3$C); 21.7, 21.0 (2(CH_3)$_3$*C*); 20.7 (*C*H$_3$CO); NOESY H-1–H-4; HRMS (ESI) Calcd for $C_{25}H_{37}Cl_3NO_7Si$ $[M+H]^+$ 596.1405. Found: $[M+H]^+$ 596.1417.

Method B: Compound **16** (43 mg, 0.072 mmol) and cyclohexanol (9.0 μL, 0.086 mmol) gave 12 mg of **17β** (31%), and 17 mg of **17α** (40%) and **18** (4%) as a 10:1 mixture according to ^{1}H NMR spectrum.

Method C: Compound **16** (65 mg, 0.109 mmol) and cyclohexanol (13.6 μL, 0.131 mmol) gave 16 mg of **17β** (27%), and 28 mg of **17α** (48%).

Method D: Compound **16** (60 mg, 0.101 mmol) and cyclohexanol (12.6 μL, 0.121 mmol) gave 6 mg of **17β** (11%), and 12 mg of **17α** (22%).

4.11.7. 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 (20α) 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 (20β)

Compounds **20α** and **20β** were obtained according to general procedures (method E) from donor **16** (86 mg, 0.144 mmol) and 2,3,5-tri-*O*-benzoyl-D-galactono-1,4-lactone (**19**, 85 mg, 0.173 mmol).[57] The crude was purified by column chromatography (25:1 toluene–EtOAc) to afford 93 mg of **20α** and **20β** (70%) in 4.5:1 ratio as indicated by the ^{1}HNMR spectrum. HPLC separation of a fraction was performed only for identification purposes.

Compound **20α**: tr 17.5 min (9:1 CH_3CN–H_2O), R_f = 0.25 (15:1 toluene–EtOAc); $[\alpha]_D$ +51.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12–7.25 (m, 20H, arom.), 5.90 (d, 1H, *J* = 6.4 Hz, H-2), 5.83 (t, 1H, *J* = 6.2 Hz, H-3), 5.67 (ddd, 1H, *J* = 1.9, 5.5, 8.7 Hz, H-5), 5.06 (d, 1H, *J* = 5.1 Hz, H-1′), 5.01 (dd, 1H, *J* = 2.0, 6.1 Hz, H-4), 4.79, 4.69 (2d, 2H, *J* = 12.2 Hz, PhCH_2), 4.58 (t, 1H, *J* = 9.3 Hz, H-3′), 4.49 (dt, 1H, *J* = 3.6, 6.6 Hz, H-5′), 4.37 (dd, 1H, *J* = 6.6, 11.9 Hz, H-6b′), 4.06 (dd, 1H, *J* = 5.6, 10.2 Hz, H-6a), 3.97 (dd, 1H, *J* = 6.7, 9.7 Hz, H-4′), 3.95 (dd, 1H, *J* = 5.1, 9.0 Hz, H-2′), 3.81 (dd, 1H, *J* = 8.9, 10.1 Hz, H-6b), 2.06 (s, 3H, CH_3CO), 1.04, 1.00 (2s, 18H, 2(CH_3)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.9 (CH_3*C*O), 168.9 (C-1); 165.4, 165.1, 164.9 (Ph*C*O); 137.9, 133.8, 133.7, 133.6, 130.1 (×2), 130.0, 128.9, 128.6, 128.5, 128.4 (×2), 128.1, 127.7, 127.5 (arom); 101.5 (C-1′), 81.1 (C-2′), 78.2 (C-4), 75.4 (C-4′), 73.5 (C-3′), 73.5 (C-3), 72.6 (C-2), 71.7 (C-5′), 71.6 (Ph*C*H$_2$), 69.8 (C-5), 65.8 (C-6), 64.1 (C-6′), 27.3, 27.1 (2(*C*H$_3$)$_3$C), 21.7, 20.8 (2(CH_3)$_3$*C*), 20.9 (*C*H$_3$CO); HRMS (ESI) Calcd for $C_{50}H_{56}NaO_{15}Si$ $[M+Na]^+$ 947.3286. Found: $[M+Na]^+$ 947.3244.

Compound **20β**: tr 20.0 min (9:1 CH_3CN–H_2O); R_f = 0.25 (15:1 toluene–EtOAc); $[\alpha]_D$ −3.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08–7.22 (m, 20H, arom.), 6.06 (d, 1H, *J* = 5.6 Hz, H-2), 5.83 (t, 1H, *J* = 5.4 Hz, H-3), 5.82 (td, 1H, *J* = 2.6, 6.4 Hz, H-5), 4.98 (dd, 1H, *J* = 2.6, 5.2 Hz, H-4), 4.96 (d, 1H, *J* = 2.9 Hz, H-1′); 4.63, 4.49 (2d, 2H, *J* = 11.9 Hz, PhCH_2), 4.54 (dt, 1H, *J* = 4.9 Hz, H-5′), 4.30–4.24 (m, 3H, H-6a′, H-6b′, H-3′), 4.19 (dd, 1H, *J* = 6.8, 10.2 Hz, H-4′), 4.02 (dd, 1H, *J* = 6.5, 10.7 Hz, H-6a), 3.90 (dd, 1H, *J* = 2.9, 6.6 Hz, H-2′), 3.88 (dd, 1H, *J* = 6.5, 10.7 Hz, H-6b), 2.09 (s, 3H, CH_3CO), 1.03, 0.98 (2s, 18H, 2(CH_3)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.9 (CH_3*C*O), 169.0 (C-1); 165.4, 165.2, 165.0 (Ph*C*O); 137.5, 133.9, 133.7, 133.6, 130.1, 130.0 (×2), 128.9, 128.6, 128.4, 128.3, 127.9, 127.7 (×2) (arom); 107.3 (C-1′), 87.9 (C-2′), 79.3 (C-4), 76.9 (C-3′), 75.0 (C-4′), 74.3 (C-3), 72.3 (C-2), 72.0 (Ph*C*H$_2$), 70.8 (C-5, C-5′), 65.8 (C-6), 64.2 (C-6′); 27.1, 27.0 (2(*C*H$_3$)$_3$C); 21.6, 20.7 (2(CH_3)$_3$*C*); 21.0 (*C*H$_3$CO); HRMS (ESI) Calcd for $C_{50}H_{56}NaO_{15}Si$ $[M+Na]^+$ 947.3286. Found: $[M+Na]^+$ 947.3250.

Method C: Compound **16** (112 mg, 0.188 mmol) and **19** (111 mg, 0.226 mmol) gave 152 mg of **20α** and **20β** (87%) in 1.3:1 ratio as indicated by ^{1}H NMR spectrum.

4.11.8. Allyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (22α) and allyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (22β)

Compounds **22α** and **22β** were obtained according to general procedures (method E) from donor **16** (58 mg, 0.097 mmol) and allyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**21**, 44 mg, 0.114 mmol).[58] The crude was purified by column chromatography (40:1 toluene–EtOAc) to afford 25 mg of **22β** (31%) as a syrup: R_f = 0.38 (15:1 toluene–EtOAc); $[\alpha]_D$ −40.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.20 (m, 15H, aromatic), 5.82 (dddd, 1H, *J* = 5.3, 6.2, 10.3, 17.2 Hz, C*H*=CH$_2$), 5.28 (d, 1H, *J* = 3.1 Hz, H-1′), 5.22 (dq, 1H, *J* = 1.6, 17.2 Hz, CH=C*H$_a$*H), 5.13 (dq, 1H, *J* = 1.3, 10.3 Hz, CH=C*H$_b$*H), 4.91, 4.53 (2d, 2H, *J* = 10.7 Hz, PhC*H$_2$*), 4.76, 4.61 (2d, 2H, *J* = 10.6 Hz, PhC*H$_2$*), 4.74, 4.64 (2d, 2H, *J* = 12.1 Hz, PhC*H$_2$*), 4.71 (d, 1H, *J* = 1.6 Hz, H-1), 4.54 (m, 1H, H-5′), 4.36 (dd, 1H, *J* = 3.8, 11.9 Hz, H-6a′), 4.30 (m, 2H, H-4′, H-3′), 4.26 (dd, 1H, *J* = 7.3, 11.9 Hz, H-6b′), 4.10 (dd, 1H, *J* = 3.1, 6.6 Hz, H-2′), 4.09 (ddt, 1H, *J* = 1.7, 5.0, 12.9 Hz, OCH*H*-CH=CH$_2$), 3.98 (dd, 1H, *J* = 3.3, 9.5 Hz, H-3), 3.88 (ddt, 1H, *J* = 1.3, 6.2, 12.9 Hz, OCH*H*-CH=CH$_2$), 3.82 (dd, 1H, *J* = 1.6, 3.3 Hz, H-2), 3.69 (dq, 1H, *J* = 6.4, 9.5 Hz, H-5), 3.56 (t, 1H, *J* = 9.5 Hz, H-4), 2.08 (s, 3H, CH_3CO), 1.30 (d, 3H, *J* = 6.4 Hz, H-6); 1.04, 1.00 (2s, 18H, 2(C*H$_3$*)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.9 (CH_3CO); 138.4, 138.3, 137.5, 128.3, 128.2, 128.0 (×2), 127.6, 127.3 (aromatic); 133.7 (CH$_2$*C*H=CH$_2$), 117.4 (CH$_2$CH=*C*H$_2$), 108.7 (C-1′), 96.9 (C-1), 88.2 (C-2′), 80.3 (C-3), 80.0 (C-4), 78.8 (C-2), 77.0 (C-3′), 75.3 (Ph*C*H$_2$), 75.1 (C-4′), 73.3 (Ph*C*H$_2$), 71.9 (Ph*C*H$_2$), 71.0 (C-5′), 67.8 (C-5), 67.7 (*C*H$_2$CH=CH$_2$), 64.2 (C-6′); 27.2, 27.0 (2(*C*H$_3$)$_3$C); 21.0 (*C*H$_3$CO); 21.6, 20.7 (2(CH$_3$)*C*); 17.9 (C-6); HRMS (ESI) Calcd for $C_{46}H_{62}NaO_{11}Si$ [M+Na]$^+$ 841.3959. Found: [M+Na]$^+$ 841.3954.

Next fraction from the column gave syrupy **22α** (28 mg, 35%): R_f = 0.35 (15:1 toluene–EtOAc); $[\alpha]_D$ +5.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.4–7.2 (m, 15H, arom.), 5.80 (m, 1H, C*H*=CH$_2$), 5.19 (dq, 1H, *J* = 1.6, 17.3 Hz, CH=C*H$_a$*H), 5.19 (d, 1H, *J* = 4.9 Hz, H-1′), 5.13 (dq, 1H, *J* = 1.6, 10.4 Hz, HC=C*H$_b$*H), 4.98, 4.54 (2d, 2H, *J* = 10.7 Hz, PhC*H$_2$*), 4.78 (s, 2H, Ph*CH$_2$*), 4.75, 4.64 (2d, 2H, *J* = 12.0 Hz, PhC*H$_2$*), 4.69 (d, 1H, *J* = 1.9 Hz, H-1), 4.59 (m, 1H, H-5′), 4.58 (t, 1H, *J* = 9.0 Hz, H-3′), 4.38 (dd, 1H, *J* = 6.9, 11.9 Hz, H-6a′), 4.32 (dd, 1H, *J* = 4.3, 11.9 Hz, H-6b′), 4.08 (ddt, 1H, *J* = 1.6, 5.5, 13.1 Hz, CH*H*CH=CH$_2$), 4.00 (dd, 1H, *J* = 3.1, 9.1 Hz, H-3), 3.97 (dd, 1H, *J* = 6.7, 9.7 Hz, H-4′), 3.91 (dd, 1H, *J* = 1.9, 2.9 Hz, H-2), 3.90 (dd, *J* = 4.9, 8.8 Hz, H-2′), 3.88 (ddt, 1H, *J* = 1.4, 6.0, 13.1 Hz, CH*H*CH=CH$_2$), 3.66 (dq, 1H, *J* = 6.2, 9.4 Hz, H-5), 3.56 (t, 1H, *J* = 9.1 Hz, H-4), 2.01 (s, 3H, CH_3CO), 1.26 (d, 3H, *J* = 6.2 Hz, H-6), 1.05, 1.04 (2s, 18H, 2(CH$_3$)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.8 (CH_3CO), 138.6, 138.0, 128.3 (×2), 128.2, 127.9, 127.8, 127.6, 127.5 (aromatic); 134.0 (CH$_2$*C*H=CH$_2$), 117.0 (CH$_2$CH=*C*H$_2$), 101.3 (C-1′), 97.5 (C-1), 81.2 (C-2′), 80.3 (C-4), 78.4 (C-3), 76.2 (C-2), 75.2 (C-4′), 74.9 (Ph*C*H$_2$), 74.0 (C-3′), 73.0 (Ph*C*H$_2$), 72.0 (C-5′), 71.7 (Ph*C*H$_2$), 68.1 (C-5), 67.7 (*C*H$_2$CH=CH$_2$), 64.3 (C-6′); 27.2, 27.0 (2(*C*H$_3$)$_3$C); 20.9 (*C*H$_3$CO); 21.7, 20.7 (2(CH$_3$)*C*); 17.81 (C-6); HRMS (ESI) Calcd for $C_{46}H_{62}NaO_{11}Si$ [M+Na]$^+$ 841.3959. Found: [M+Na]$^+$ 841.3945.

Method C: Compound **16** (103 mg, 0.173 mmol) and **21** (80 mg, 0.208 mmol) gave 94 mg of **22β** (66%).

4.11.9. Cyclohexyl 2,6-di-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranoside (24α) and cyclohexyl 2,6-di-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranoside (24β)

Compounds **24α** and **24β** were obtained according to general procedures (method E) from *O*-(2,6-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranosyl) trichloroacetimidate (**7**, 21 mg, 0.033 mmol) and cyclohexanol (4 μL, 0.038 mmol). The crude was purified by column cromatography (25:1 hexane–EtOAc) to give a first fraction of syrupy **24β** (4.5 mg, 24%): R_f = 0.43 (15:1 hexane–EtOAc); $[\alpha]_D$ −15.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.26 (m, 10H, aromatic), 5.05 (d, 1H, *J* = 3.1 Hz, H-1), 4.73, 4.62 (2d, 2H, *J* = 11.9 Hz, PhC*H$_2$*); 4.63, 4.56 (2d, 2H, *J* = 12.2 Hz, PhC*H$_2$*), 4.61 (m, 1H, H-5), 4.19 (mAB, 2H, H-3, H-4), 3.90 (dd, 1H, *J* = 3.1, 6.6 Hz, H-2), 3.72 (dd, 1H, *J* = 2.9, 10.3 Hz, H-6a), 3.63 (dd, 1H, *J* = 7.9, 10.3 Hz, H-6b), 3.48 (m, 1H, OC*H*), 1.87 (m, 2H), 1.71 (m, 2H), 1.51 (m, 1H), 1.39–1.12 (m, 5H); 1.02, 1.01 (2s, 18H, 2(C*H$_3$*)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 138.2, 137.9, 128.3, 127.9, 127.8, 127.7, 127.6 (arom.); 104.8 (C-1), 88.7 (C-2), 76.9 (C-3), 76.2 ((CH$_2$)$_5$*C*HO), 74.9 (C-4), 73.6 (Ph*C*H$_2$), 73.0 (C-5), 72.0 (Ph*C*H$_2$), 70.1 (C-6); 33.8, 31.7, 29.7, 25.6, 24.2, 24.1 ((*C*H$_2$)$_5$CHO); 27.2, 27.1 (2(*C*H$_3$)$_3$C); 21.6, 20.7 (2(CH$_3$)$_3$*C*); HRMS (ESI) Calcd for $C_{34}H_{50}NaO_6Si$ [M+Na]$^+$ 605.3274. Found: [M+Na]$^+$ 605.3257.

Next fraction from the column gave **24α** as a syrup (9 mg, 71%): R_f = 0.29 (15:1 hexane–EtOAc); $[\alpha]_D$ +57.6 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.26 (m, 10H, arom.), 5.00 (d, 1H, *J* = 5.2 Hz, H-1), 4.73 (s, 2H, Ph*CH$_2$*), 4.60 (s, 2H, Ph*CH$_2$*), 4.59 (ddd, 1H, *J* = 2.7, 6.4, 8.7 Hz, H-5), 4.40 (t, 1H, *J* = 9.3 Hz, H-3), 3.90 (dd, 1H, *J* = 6.6, 9.7 Hz, H-4), 3.82 (dd, 1H, *J* = 5.2, 9.0 Hz, H-2), 3.71 (dd, 1H, *J* = 2.9, 10.4 Hz, H-6a), 3.58 (dd, 1H, *J* = 8.6, 10.4 Hz, H-6b), 3.40 (m, 1H, OC*H*), 1.86 (m, 1H), 1.81–1.66 (m, 3H), 1.53 (m, 1H), 1.35–1.08 (m, 5H); 1.03, 1.00 (2s, 18H, 2(C*H$_3$*)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 138.1, 138.0, 128.3 (×2), 128.1, 127.9, 127.7, 127.6 (arom.); 98.7 (C-1), 80.8 (C-2), 77.3 ((CH$_2$)$_5$*C*HO), 75.1 (C-4), 73.9 (C-5), 73.7 (Ph*C*H$_2$, C3), 71.6 (Ph*C*H$_2$), 70.0 (C-6); 33.7, 31.9, 25.5, 24.5, 24.4 ((*C*H$_2$)$_5$CHO); 27.3 (2(*C*H$_3$)$_3$C); 21.5, 20.6 (2(CH$_3$)$_3$*C*); HRMS (ESI) Calcd for $C_{34}H_{50}NaO_6Si$ [M+Na]$^+$ 605.3274. Found: [M+Na]$^+$ 605.3297.

Method C: Compound **7** (20 mg, 0.031 mmol) and cyclohexanol (3.9 μL, 0.037 mmol) gave 8.5 mg of **24β** (47%) and 8.5 mg of **24α** (47%).

4.11.10. Methyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-α-D-galactofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (26α) and methyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-β-D-galactofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (26β)

Compounds **26α** and **26β** were obtained according to general procedure (method E) from **16** (40 mg, 0.067 mmol) and methyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (**25**, 40 mg, 0.079 mmol).[60] The crude was purified by column chromatography (15:1 toluene–EtOAc) to give 7 mg of syrupy **26β** (11%): R_f = 0.61 (6:1 toluene–EtOAc); $[\alpha]_D$ −46.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10–7.23 (m, 20H, arom.), 5.86 (dd, 1H, *J* = 3.3, 10.0 Hz, H-3), 5.81 (t, 1H, *J* = 10.0 Hz, H-4), 5.65 (dd, 1H, *J* = 1.8, 3.3 Hz, H-2), 5.00 (d, 1H, *J* = 3.1 Hz, H-1′), 4.96 (d, 1H, *J* = 1.8 Hz, H-1), 4.72, 4.63 (2d, 2H, *J* = 11.8 Hz, PhC*H$_2$*), 4.56 (dt, 1H, *J* = 3.6, 7.3 Hz, H-5′), 4.29 (dd, 1H, *J* = 3.8, 11.9 Hz, H-6a′), 4.27–4.22 (m, 3H, H-6b′, H-5, H-3′), 4.20 (dd, 1H, *J* = 6.5, 10.2 Hz, H-4′), 3.91 (dd, 1H, *J* = 3.1, 6.7 Hz, H-2′), 3.87 (dd, 1H, *J* = 2.7, 11.5 Hz, H-6a), 3.72 (dd, 1H, *J* = 6.7, 11.5 Hz, H-6b), 3.49 (s, 3H, C*H$_3$*O), 2.07 (s, 3H, C*H$_3$*CO); 1.03, 0.97 (2s, 18H, 2(C*H$_3$*)$_3$C); ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.9 (CH_3CO); 165.5 (×2), 165.4 (Ph*C*=O); 137.8, 133.5, 133.4, 133.1, 129.9, 129.8, 129.7, 129.1, 128.6, 128.5, 128.3 (×2), 127.8, 127.7 (arom.); 107.8 (C-1′), 98.4 (C-1), 88.0 (C-2′), 74.9 (C-4′), 72.0 (Ph*C*H$_2$), 71.0 (C-5′), 70.4 (C-2), 70.1 (C-3), 70.0 (C-3′, C-5), 68.1 (C-6), 67.5 (C-4), 64.3 (C-6′), 55.3 (*C*H$_3$O); 27.1, 27.0 (2(*C*H$_3$)$_3$C); 21.6, 20.6 (2(CH$_3$)$_3$*C*); 21.0 (*C*H$_3$CO); HRMS (ESI) Calcd for $C_{51}H_{60}NaO_{15}Si$ [M+Na]$^+$ 963.3599. Found: [M+Na]$^+$ 963.3612.

Next fraction from the column gave syrupy **26α** (53 mg 84%): R_f = 0.55 (6:1 toluene–EtOAc); $[\alpha]_D$ −29.8 (*c* 1, $CHCl_3$); ^{1}H NMR

($CDCl_3$, 500 MHz) δ 8.12–7.14 (m, 20H, arom.), 5.89 (dd, 1H, J = 3.5, 10.0 Hz, H-3), 5.72 (t, 1H, J = 10.1 Hz, H-4), 5.68 (dd, 1H, J = 1.7, 3.5 Hz, H-2), 5.04 (d, 1H, J = 1.7 Hz, H-1), 4.90 (d, 1H, J = 4.9 Hz, H-1′); 4.80, 4.72 (2d, 2H, J = 12.4 Hz, PhCH_2); 4.62 (t, 1H, J = 9.4 Hz, H-3′), 4.56 (m, 1H, H-5′), 4.46 (dd, 1H, J = 7.6, 12.0 Hz, H-6a′), 4.33 (ddd, 1H, J = 2.0, 7.9, 10.1 Hz, H-5), 4.25 (dd, 1H, J = 3.8, 12.0 Hz, H-6b′), 4.00 (dd, 1H, J = 6.6, 9.7 Hz, H-4′), 3.95 (dd, 1H, J = 7.9, 10.8 Hz, H-6a), 3.90 (dd, 1H, J = 4.9, 9.0 Hz, H-2′), 3.60 (dd, 1H, J = 2.0, 10.8 Hz, H-6b), 3.51 (s, 3H, CH_3O), 1.91 (s, 3H, CH_3CO); 1.02, 0.99 (2s, 18H, 2(CH_3)$_3$C). ^{13}C NMR ($CDCl_3$, 128.5 MHz) δ 170.5 (CH_3CO); 165.6, 165.5, 165.4, (PhCO); 137.9, 133.4, 133.3, 133.0, 129.9, 129.8, 129.7, 129.5, 129.2, 129.0, 128.5, 128.4, 128.2(x2), 128.0, 127.7 (aromatic); 100.0 (C-1′), 98.1 (C-1), 80.5 (C-2′), 75.6 (C-4′), 73.4 (C-3′), 72.0 (C-5′), 71.7 (PhCH_2), 70.6 (C-2), 70.1 (C-3), 69.5 (C-5), 67.7 (C-4), 67.2 (C-6), 64.3 (C-6′), 55.1 (CH_3O); 27.2, 27.0 (2(CH_3)$_3$C); 21.6, 20.7 (2(CH_3)$_3$C); 20.6 (CH_3CO).

HRMS (ESI) Calcd for $C_{51}H_{60}NaO_{15}Si$ $[M+Na]^+$ 963.3599. Found: $[M+Na]^+$ 963.3576.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for new compounds **7**, **9**–**16**, **17α**, **17β**, **18**, **20α**, **20β**, **22α**, **22β**, **23**, **24α**, **24β**, **26α** and **26β**) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.10.004.

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