Carbohydrate Research 346 (2011) 1495–1502

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Influence of the solvent in low temperature glycosylations with *O*-(2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl) trichloroacetimidate for 1,2-*cis* α-D-galactofuranosylation

Gabriel Gola, Mariano J. Tilve, Carola Gallo-Rodriguez *

CIHIDECAR, Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pabellón II, 1428 Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 25 February 2011
Received in revised form 31 March 2011
Accepted 4 April 2011
Available online 8 April 2011

Dedicated to Professor Dr. András Lipták on the occasion of his 75th birthday

Keywords:
Glycosylation
Trichloroacetimidate
1,2-*Cis*
Galactofuranose
Solvents effects
Diastereoselectivity

ABSTRACT

Glycosylation studies for the construction of 1,2-*cis* α-linkages with *O*-(2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl) trichloroacetimidate (**1**) and several acceptors, including D-mannosyl and L-rhamnosyl derivatives were performed. The reactions were conducted at low temperatures using CH_2Cl_2, Et_2O, and acetonitrile as solvents. A non-participating solvent such as CH_2Cl_2 at −78 °C, favored the α-D-configuration. In contrast, acetonitrile strongly favored the β-D-configuration, whereas no selectivities were observed with Et_2O. The use of thiophene as an additive did not enhance the α-D-selectivity as in the pyranose counterpart. Although selectivities strongly depended on the acceptor, trichloroacetimidate **1** constitutes a valuable donor for the synthesis of α-D-Gal*f*-(1→2)-L-Rha and α-D-Gal*f*-(1→6)-D-Man. As these motifs are present in pathogenic microorganisms, these procedures described here are useful for the straightforward synthesis of natural oligosaccharides.

1. Introduction

The synthesis of oligosaccharides is a topic of increasing interest because these molecules are involved in many biological processes and, in consequence, pure samples are required for biological studies.[1] Particularly, galactofuranose-containing oligosaccharides have deserved much attention, since they are present in many pathogenic microorganisms such as *Mycobacterium tuberculosis*, *Leishmania*, *Trypanosoma cruzi,* and *Klebsiella pneumoniae*.[2–5] As Gal*f* is absent in mammals, the metabolism of this sugar has been proposed as a potential target for antimicrobial chemotherapy[6] and studies on the biosynthesis are currently being pursued.[7,8] Although less common in nature, α-D-Gal*f* with 1,2-*cis* configuration, has been found in several bacteria and fungi,[3–5] some of them pathogenic like *Streptococcus pneumoniae* 22F,[9] *Escherichia coli* O167,[10] and *Paracoccidioides brasiliensis*.[11] The latter is the etiological agent of paracoccidioidomycosis, the most common systemic mycosis in Latin America. The biosynthesis of this rather unusual unit has not been studied and the synthesis of oligosaccharides containing α-D-Gal*f* units would provide tools for these studies.

Most of the synthetic efforts have been focused on the construction of β-D-Gal*f* containing oligosaccharides, which are more common in nature than those containing α-D-Gal*f*. The synthesis of the 1,2-*trans* β-D-galactofuranosyl linkage has been accomplished diastereoselectively by neighboring group participation by an acyl group attached to O-2, and many methods of glycosylation have been reported.[3–5] The 1,2-*cis* configuration is more difficult to be achieved as a single diastereomer and so far, no general method is available for this purpose.[12,13] The first requirement for the construction of a 1,2-*cis* α-D-Gal*f* linkage is the presence of a non-participating group in the O-2 of the galactofuranosyl donor. However, the use of the pentenyl method of glycosylation applied to the 2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl derivative gave mainly β-D-products. Moreover, different kinds of solvents did not affect the stereochemical course of the reaction.[14] The trichloroacetimidate method for α-D-galactofuranosylation was first described by Plusquellec et al. using *O*-(2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl) trichloroacetimidate (**1**) with galacto- and glucopyranosyl acceptors having primary 6-OH free, to afford moderate yields and selectivities.[15] By taking advantage of this method, we have synthesized α-D-Gal*f*-(1→2)-D-galactitol, which has been isolated by reductive β-elimination from glycoproteins of *Clostridium thermocellum* and *Bacteroides cellulosolvens*.[16] The thioglycoside method, evaluated on *galacto* and *gluco* acceptors, gave better yields but moderate selectivities which depended on the acceptor used.[17]

The difficulty to construct α-D-Gal*f* linkages has been overcome by means of few approaches. Thus, the 2′-carboxybenzyl (CB)

* Corresponding author. Tel./fax: +54 11 4576 3352.
E-mail address: cgallo@qo.fcen.uba.ar (C. Gallo-Rodriguez).

0008-6215/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2011.04.005

glycoside method, developed for 1,2-*cis* β-D-mannosides, has been successfully applied to the diastereoselective synthesis of the antineoplastic glycosphingolipid agelagalastatin, which presents a terminal α-D-Gal*f*-(1→2)-D-Gal*f* unit.[18] Exclusively the α-D-isomer was formed at −78 °C with high yield and constituted the first example of a single diasteromer in an α-galactofuranosylation. More recently, di- and tetrasaccharide subunits of the cell wall polysaccharide of *Talaromyces flavus* were obtained employing the same method.[19] In this case, the α-D-Gal*f*-(1→2)-Man linkage was obtained as a single diastereomer at −78 °C, after evaluation of several glycosylation methods such as sulfoxide, thioglycosides, and fluoride, as well as protecting groups pattern in the acceptor and the donor.

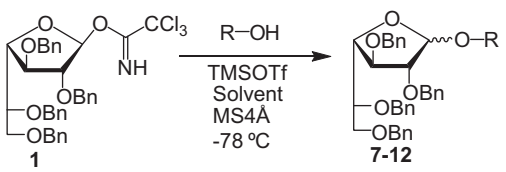
Lowary et al. have applied the 2,3-anhydrosugar methodology, formerly developed for the construction of 1,2-*cis* β-D-Ara*f* linkages, to the synthesis of α-D-galactofuranosides.[20] In this case, the galactofuranosyl precursor is a 2,3-anhydro-D-gulofuranosyl thioglycoside or sulfoxide, which reacts 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 disaccharide was obtained. The use of 2,3-anhydro-5,6-di-*O*-benzoyl-β-D-gulofuranosyl-*p*-tolyl-(*R*/*S*)-sulfoxide as donor allowed the synthesis of the pentasaccharide repeating unit of varianose, a polysaccharide produced by the fungus *Penicillium varians* which possesses an internal α-D-Gal*f*.[21] Glycosylation reaction afforded one single diastereomer, however, further epoxide opening was not completely regioselective.

These two elegant strategies described above have succeeded in complete stereoselective glycosylation, however, the synthesis of the described donors requires many steps, as well as previous evaluation of its reactivity with the desired glycosyl acceptor. Carboxybenzyl galactofuranoside donor is synthesized in four reaction steps, involving the use of mercuric salts from pentaacetylgalactofuranose, which also requires three additional reaction steps from galactose.[18] The 2,3-anhydro-5,6-di-*O*-benzoyl-β-D-gulofuranosyl-*p*-tolyl-(*R*/*S*)-sulfoxide is synthesized in four steps from *p*-tolyl 1-thio-α/β-D-galactofuranoside, which requires additional five steps from galactose.[20]

The trichloroacetimidate method proved to be a very valuable and reliable method of glycosylation, as it was employed for the synthesis of many oligosaccharides.[12] In this sense, we and other groups have synthesized Gal*f*-containing oligosaccharides from *Mycobacterium*, *Leishmania* and *T. cruzi*, as well as the already mentioned α-D-Gal*f*-containing di- and trisaccharides alditol from *B. cellulosolvens*.[3–5,22–28] Particularly, among the donors employed for α-D-galactofuranosylation, *O*-(2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl) trichloroacetimidate (**1**) has been readily synthesized from D-galactose, in four reaction steps via its allyl α-D-glycoside.[16,29] Taking into account the easy access to imidate donor **1** and as a continuation of previous work,[15,16] we now describe a glycosylation study on different acceptors including L-rhamnosyl and D-mannosyl derivatives for the construction of α-D-Gal*f* 1,2-*cis* linkage present in natural oligosaccharides. Low temperature reactions, the influence of the solvent employed, as well as the use of additives like thiophene, have been evaluated.

2. Results and discussion

To explore the diastereoselectivity in glycosylation reactions of Gal*f* we employed trichloroacetimidate **1** (1 equiv) as donor and TMSOTf as catalyst (0.3 equiv) in the presence of molecular sieves (Scheme 1). Four general procedures (methods A–D) were followed involving solvents such as CH_2Cl_2 (method A), Et_2O (method B), CH_3CN (method C), and CH_2Cl_2 with thiophene as additive (method D).



Scheme 1. Glycosylation of acceptors **2–6** with trichloroacetimidate **1**.

Several acceptors were selected as precursors of disaccharide constituents of glycoconjugates in microorganisms. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[30,31] (**2**) and its benzoyl analog **3**[32] (Table 1) were chosen as precursors of disaccharide constituents of *Paracoccidiodes brasiliensis* and allyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside[33] (**4**) for the construction of the disaccharide present in *Streptococcus pneumoniae* 22F. Methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside[34] (**5**) was employed as precursor of disaccharides present in *Talaromyces flavus*. As glycosylation of 2-*O*-benzoyl-5,6-*O*-isopropylidene-D-galactono-1,4-lactone[24] (**6**) with *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl) trichloroacetimidate led stereoselectively to the α-D-Gal*p*-(1→3) linkage,[24] we have also selected acceptor **6** for comparison purposes with its D-Gal*f* counterpart.

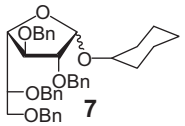
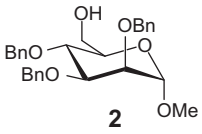
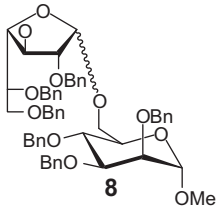
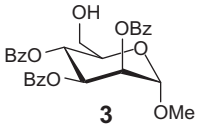
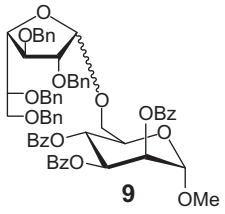
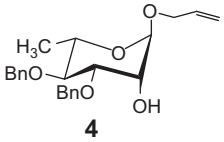
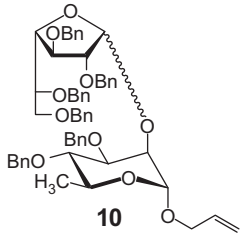
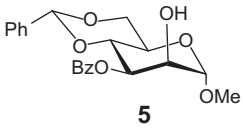
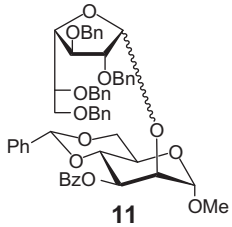
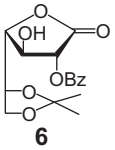
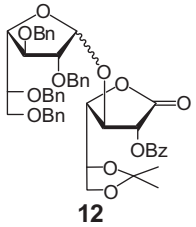
The diastereomeric α/β ratio of the products of glycosylation was determined from the ^1H NMR spectrum of the crude reaction mixture by integration of the signals of each diastereomer and comparison with pure isolated disaccharides. The α/β ratio was confirmed by weighting the isolated α and β products after purification by column chromatography.

The configuration of the new galactofuranosyl linkages of the new products were readily established by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectra, the β-D-Gal*f* anomeric hydrogen resonated as a broad singlet or as a doublet with a small coupling constant (1–1.5 Hz), whereas α-D-Gal*f* H-1 appeared as a doublet with $J_{1,2}$ 4.2–4.5 Hz. In the ^{13}C NMR spectra, β-D-Gal*f* anomeric carbon resonated deshielded (δ 104.0–107.9) compared to the same signal in the α-D-Gal*f* product (δ 97.9–101.0).[16,23–28]

Preliminary results on our synthesis of α-D-Gal*f* disaccharides of *Clostridium thermocellum*, using the imidate method in CH_2Cl_2, indicated that low temperature reaction favored the α-D-stereoselectivity. On the other hand, excellent stereoselectivities were obtained on D-galactopyranoside acceptors having the OH-6 free employing the carboxybenzyl method from −78 °C to 0 °C. Same reaction conditions allowed the formation of the single α-D-isomer when reacted with a D-mannopyranosyl derivative with free OH-2, whereas the thioglycoside and the sulfoxide method gave 3:1 and 8:1 α/β ratios, respectively.[19] These facts, together with the high reactivity previously shown by imidate **1**, prompted us to set the reaction temperature at −78 °C.

We first evaluated CH_2Cl_2 as a non-participating solvent at −78 °C. The simple cyclic alcohol cyclohexanol gave moderate selectivity toward the α-D-isomer (entry 1).[15] We next evaluated the glycosylation reaction on primary OH-6 of D-mannosyl acceptors **2** and **3**. A marked effect was observed depending on the substitution pattern. Interestingly, while the benzyl substituted mannosyl **2** gave separable disaccharides **8α** and **8β** in 3.3:1 α/β ratio (entry 2), the selectivity was significantly increased to 12.6:1 α/β ratio with the less nucleophlilic benzoyl counterpart **3** (entry 3) as shown by the ^1H NMR spectrum of the crude reaction mixture. In this case, only the α-D-product **9α** was recovered in 63% yield after column chromatography. In this sense, donor **1** and benzoyl substituted acceptor **3** constitute a matched pair and a reliable method is now available for the construction α-D-Gal*f*-(1→6)-D-Man, present in the pathogen fungus *Paracoccidiodes brasiliensis*. Compound **9α** was previously obtained by the carbobenzoxy method of glycosylation in 8:1 α/β ratio, however, no characterization data

Table 1
Glycosylation of cyclohexanol and acceptors **2–6** with donor **1** (methods **A**–**D**)

Entry	Acceptor	Product	Method A CH_2Cl_2 −78 °C α/β[a] (yield)[b]	Method B Ether −78 °C α/β[a] (yield)[b]	Method C CH_3CN −40 °C α/β[a] (yield)[b]	Method D CH_2Cl_2 thiophene −78 °C α/β[a] (yield)[b]
1	Cyclohexanol	 **7**	2.0:1.0 (93%)	2.4:1.0 (94%)	1.0:3.9 (69%)	2.5:1.0 (44%)
2	 **2**	 **8**	3.3:1.0 (75%)	2.4:1.0 (89%)	1.0:6.7 (86%)	2.4:1.0 (64%)
3	 **3**	 **9**	12.6:1.0 (63%)	1.5:1.0 (68%)[c]	1.0:12.5 (90%)[c]	4.5:1.0 (66%)[c]
4	 **4**	 **10**	10.0:1.0 (48%) (**13** 24%)[d]	3.0:1.0 (56%) (**13** 31%)[d]	0:1.0 (92%)	10.0:1.0 (63%) (**13** 34%)[d]
5	 **5**	 **11**	3.3:1.0 (36%) (**13** 36%)[d]	0:0 (0%) (**13** 45%)[d]	1.0:1.4 (39%)	1.7:1.0 (7%) (**13** 12%)[d]
6	 **6**	 **12**	2.8:1.0 (27%) (**13** 30%)[d]	1.0:0.0 (8%) (**13** 73%)[d]	1.4:1.0 (60%)	3.7:1.0 (22%) (**13** 33%)[d]

[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 2,3,5,6-tetra-*O*-benzyl-1-*N*-trichloroacetyl-α-D-galactofuranosylamine (**13**) also recovered.

were reported.[19] Glycosylation reaction occurred with inversion of C-1 configuration as expected in CH_2Cl_2, a non-participating solvent. β-D-Imidate **1** afforded 1,2-*cis* glycoside, a S_N2-type reaction, with the nucleophile acceptor attacking from the face of the ring opposite to the leaving group could be proposed. However, as the activator is TMSOTf, a covalent triflate intermediate could be involved.[35–38] In this sense, low-temperature NMR studies of thioarabinofuranosyl constrained donors activation allowed the identification of a triflate arabinofuranosyl intermediate in 1,2-*trans* relationship.[38] Questions also arise on the selectivity obtained because benzyl protected acceptor **2** should be more nucleophilic than the benzoyl counterpart **3**. Thus, higher selectivities should be expected in the S_N2-type reaction, and the opposite situation was experimentally found, indicating that other factors are involved. Many aspects of the mechanism of glycosylation of furanoses remain unclear.

Preliminary results showed that reaction of imidate **1** with 2-OH L-rhamnosyl acceptor **4** at −15 °C led only to the β-D-isomer. Interestingly, the same reaction conducted at −78 °C gave **10** with higher diastereoselectivity in favor of the α-D-isomer (10.0:1 α/β ratio), however, with moderate yield (48%). The transposition by-product 2,3,5,6-tetra-*O*-benzyl-1-*N*-trichloroacetyl-α-D-galactofuranosylamine (**13**)[16] was also obtained (24%). *N*-Glycosyl trichloroacetamides have been observed as by-products in glycosylation reactions when low nucleophilic or sterically hindered acceptors were employed.[12,16,27,39–42] As compounds **10α** and **10β** could be isolated by column chromatography, a straightforward method is now available for the synthesis of disaccharides constituents of *Streptococcus pneumoniae* 22F. The disaccharide methyl α-D-Gal*f*-(1→2)-L-Rha*p* has been previously synthesized by the 2,3-anhydrosugar methodology with high stereoselectivity.[20] The 2-OH mannosyl acceptor **5** afforded the disaccharide **11** with moderate selectivity toward the α product, and in low yield. In this case, **13** was obtained as the main product (36%), and this result is in agreement with the lesser nucleophilicity of mannosyl acceptor **5** compared to deoxysugar acceptor **4**. Similar results in terms of selectivities, yields, and by-product **13** were achieved with lactone **6**.

As next step we evaluated the glycosylation reaction in participating solvents. As it is known, diethylether enhances the α-selectivities on the pyranose counterpart.[12,13,43] In this case, this solvent (method B) had almost no effect for cyclohexanol, or lowered the α-D-selectivities compared to CH_2Cl_2 (entry 2–4). No glycosylation product was obtained with mannosyl acceptor **5** and transposition by-product **13** was mainly formed, suggesting that this solvent lowered the reactivity of the acceptor. Similar results were obtained with the lactone acceptor **6**. As a conclusion, ethyl ether is not suitable for this method of glycosylation. In agreement with this result, no selectivity had been observed by the thioglycoside method using this solvent.[17]

Acetonitrile is a participating solvent which is frequently used for 1,2-*trans* β-linkage construction in galacto- and glucopyranosyl donors lacking a participating group at the vicinal 2-position.[35–38,43] It is accepted that nitrile effect is due to the formation of a α-D-glycopyranosyl nitrilium ion, which is further displaced by the acceptor. Reactions in this solvent at −40 °C (method C) favored the β-D-isomer in almost all cases, with the exception of lactone acceptor **6**. Glycosylation of the benzylated mannopyranoside acceptor **2** gave separable **8α** and **8β** in 1:6.7 α/β ratio in high yield (entry 2). Higher diastereomeric ratio favoring the 1,2-*trans* β-D-isomer **9β** was obtained with the benzoylated analogue **3** (entry 3) also with high yields. It is interesting to note that the use of benzoyl protecting group in **3** instead of benzyl, increased the selectivity toward the β-D-product. Similar result was obtained using CH_2Cl_2 toward the α-D-product.

Interestingly, on glycosylation of rhamnosyl acceptor **4**, disaccharide **10β** was obtained as a single diastereomer in very good yield (entry 4). Thus, donor **1** can be used to construct α- or β-D-Gal*f* with high diastereoselection by varying the solvent reaction (and temperature). Almost no selectivities were observed with mannosyl acceptor **5** (entry 5) and lactone **6** (entry 6). Enhancement of the β-D-selectivity had been also observed by the thioglycoside method with 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside as acceptor in this solvent.[17] Thus, reactive acceptors such as primary 6-OH derivatives or deoxysugar derivative **4** favored the β-selectivity, suggesting that a common nitrilium intermediate is involved.

Recently, thiophene additive in Cl_2CH_2 has been shown to favor 1,2-*cis* α-D-glycopyranosylation of donors lacking a participating group at the 2-position by formation of β-equatorial covalent sulfonium ion-type adducts with the glycopyranosyl cation. Through this procedure, 2-azido-α-D-glucosyl derivatives have been successfully synthesized with high diastereoselectivities.[44] However, in our hands this glycosylation series in Cl_2CH_2 as solvent and thiophene as additive (method D), gave no improvement of the α-D-selectivities compared to the reactions without additive.

The nature of the solvent strongly determined the stereochemical course of glycosylation reaction as demonstrated above. Recently, D-Gal*f* thrichloroacetimidate donors that lack anchimeric assistance by substitution either by 2-*O*-Gal*p* or 2-*O*-Gal*f* have been evaluated with derivatives of 4-OH GlcNAc acceptors. In this case, acetonitrile favored the β-linkage when β-D-Gal*p*-(1→2)-D-Gal*f* was the donor,[27] whereas in contrast with these results dichloromethane favored the β-D-configuration employing the β-D-Gal*f*-(1→2)-D-Gal*f* donor.

3. Conclusions

The glycosylation studies with readily available *O*-(2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl) trichloroacetimidate (**1**) of several selectively protected sugar acceptors show that non-participating solvents as Cl_2CH_2 at −78 °C, favored the α-D-configuration. The inclusion of thiophene as additive did not enhance the α-D-selectivity, as reported in the pyranose counterpart. Glycosylation in acetonitrile strongly favored the formation of glycosidic linkages with β-D-configuration, whereas no substantial differences on selectivities were observed with Et_2O.

Protecting group pattern on the acceptor was decisive for the increment on selectivity. For instance, the α-D-Gal*f*-(1→6)-D-Man linkage was obtained in 12.6:1 α/β ratio when the benzoylated mannosyl acceptor **3** was employed instead of the benzyl counterpart. Moreover, by changing the solvent from CH_2Cl_2 to CH_3CN, the β-disaccharide was obtained in high selectivity. A similar behavior was found with rhamnosyl acceptor **3**.

In conclusion, trichloroacetimidate **1** constitutes a valuable donor for the synthesis of α-D-Gal*f* containing glycoconjugates present in pathogenic microorganisms. Straightforward procedures for the synthesis of linkages found in natural oligosaccharides are reported.

4. Experimental

4.1. General Methods

TLC was performed on 0.2 mm Silica Gel 60 F254 aluminum supported plates. Detection was effected by exposure to UV light, then by spraying with 5% (v/v) sulfuric acid in EtOH and charring. Column chromatography was performed on Silica Gel 60 (230–400 mesh). NMR spectra were recorded with a Bruker AVANCE II 500 spectrometer at 500 MHz (^{1}H) and 125.8 MHz (^{13}C). Chemical shifts are given relative to the signal of internal TMS standard at 0.00 ppm for ^{1}H NMR and the signal for $CDCl_3$ at 77.0 ppm for ^{13}C NMR. ^{1}H and ^{13}C assignments were supported by COSY and HSQC 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. General procedures for glycosylation reactions

4.2.1. Method A

To a solution of *O*-(2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl) trichloroacetimidate[16] (**1**, 1 equiv) and the acceptor (1.3 equiv) in anhyd CH_2Cl_2 (3.0 mL/50 mg of **1**) was added activated powdered 4 Å molecular sieves (150 mg), and the mixture was vigorously stirred at room temperature under argon. After 10 min, the mixture was cooled to −78 °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 **1** or 2,3,5,6-tetra-*O*-benzyl-D-galactofuranose. 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).

4.2.2. Method B

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

4.2.3. Method C

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

4.2.4. Method D[44]

To a solution of donor **1** (1 equiv), the acceptor (1.5 equiv) and thiophene (1 equiv) in anhydr CH_2Cl_2 (3.0 mL/50 mg of **1**) was added activated 4 Å molecular sieves (150 mg) at room temperature under argon. After vigorously stirring for 10 min, the mixture was cooled to −78 °C and TMSOTf (0.1 equiv) was added and the stirring continued for 40 min. The reaction was monitored by TLC, and quenched by the addition of triethylamine (0.1 equiv) after total disappearance of **1** or 2,3,5,6-tetra-*O*-benzyl-D-galactofuranose. The solution 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 weighting the isolated α and β products (Table 1).

4.2.5. Cyclohexyl 2,3,5,6-tetra-*O*-benzyl-α-D-galactofuranoside (7α)

Compound **7α** was obtained according to general procedures, using cyclohexanol as acceptor. The crude was purified by column chromatography (80:1 toluene–EtOAc) to give a syrup; R_f 0.59 (10:1 toluene–EtOAc); $[\alpha]_D$ +35.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.20 (m, 20H, ArH), 5.12 (d, 1H, *J* = 4.4 Hz, H-1), 4.74, 4.48 (2d, 2H, *J* = 11.6 Hz, PhCH_2), 4.74, 4.63 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.65, 4.51 (2d, 2H, *J* = 11.6 Hz, PhCH_2), 4.50, 4.44 (2d, 2H, *J* = 12.1 Hz, PhCH_2), 4.27 (t, 1H, *J* = 7.3 Hz, H-3), 4.03 (dd, 1H, *J* = 4.4, 7.5 Hz, H-2), 3.94 (t, 1H, *J* = 6.9 Hz, H-4), 3.74 (dt, 1H, *J* = 3.8, 6.5 Hz, H-5), 3.66 (dd, 1H, *J* = 3.8, 10.4 Hz, H-6a), 3.62–3.58 (m, 1H, $(CH_2)_5CHO$), 3.56 (dd, 1H, *J* = 6.4, 10.4 Hz, H-6b), 1.93–1.85 (m, 2H), 1.77–1.66 (m, 2H), 1.55–1.48 (m, 1H), 1.43–1.11 (m, 5H), (H-1 signal is in agreement with lit. and was the only physical data described for this compound[45]); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9–127.3 (aromatic), 97.9 (C-1), 83.9 (C-2), 81.3 (C-3), 80.4 (C-5), 80.2 (C-4), 75.6 ($(CH_2)_5CHO$); 73.3, 73.0, 72.2, 72.1 (PhCH_2); 70.4 (C-6), 33.6, 31.6, 25.6, 24.4, 24.2 ($(CH_2)_5CHO$); HRMS (ESI) calcd for (M+Na) $C_{40}H_{46}O_6Na$: 645.3187. Found: 645.3195.

4.2.6. Cyclohexyl 2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranoside (7β)

Compound **7β** was obtained according to general procedures, using cyclohexanol as acceptor. The crude was purified by column chromatography (80:1 toluene–EtOAc) to give a syrup; R_f 0.67 (10:1 toluene–EtOAc); $[\alpha]_D$ −49.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.15 (m, 20H, ArH), 5.21 (d, 1H, *J* = 1.4 Hz, H-1), 4.71, 4.52 (2d, 2H, *J* = 11.8 Hz, PhCH_2), 4.58, 4.48 (2d, 2H, *J* = 11.9 Hz, PhCH_2), 4.50(s, 2H, PhCH_2), 4.47, 4.29 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.15 (dd, 1H, *J* = 3.1, 7.3 Hz, H-4), 4.01 (dd, 1H, *J* = 3.7, 7.1 Hz, H-3), 3.99 (dd, 1H, *J* = 1.6, 3.7 Hz, H-2), 3.77 (ddd, 1H, *J* = 3.1, 5.2, 6.5 Hz, H-5), 3.71 (dd, 1H, *J* = 6.5, 9.9 Hz, H-6a), 3.66 (dd, 1H, *J* = 5.2, 9.9 Hz, H-6b), 3.59–3.53 (m, 1H, $(CH_2)_5CHO$), 1.91–1.82 (m, 2H), 1.75–1.65 (m, 2H), 1.54–1.47 (m, 1H), 1.41–1.14 (m, 5H), (H-1 signal is in agreement with lit. and was the only physical data described for this compound[45]); ^{13}C NMR (125 MHz,$CDCl_3$): δ 138.3–127.5 (aromatic), 104.2 (C-1), 89.0 (C-2), 82.7 (C-3), 80.2 (C-4), 76.4 (C-5), 75.3 ($(CH_2)_5CHO$); 73.4, 73.3, 72.0, 71.8 (PhCH_2); 71.0 (C-6), 33.7, 31.8, 25.7, 24.2, 24.1 ($(CH_2)_5CHO$); HRMS (ESI) calcd for (M+Na) $C_{40}H_{46}O_6Na$: 645.3187. Found: 645.3186.

Method A: Compound **1** (64 mg, 0.093 mmol) and cyclohexanol (12.8 μL, 0.121 mmol) gave 36 mg of **7α** (62%) and 18 mg of **7β** (31%).

Method B: Compound **1** (63 mg, 0.092 mmol) and cyclohexanol (12.6 μL, 0.120 mmol) gave 38 mg of **7α** (66%) and 16 mg of **7β** (28%).

Method C: Compound **1** (54 mg, 0.079) and cyclohexanol (10.8 μL, 0.102 mmol) gave 7 mg of **7α** (14%) and 27 mg of **7β** (55%).

Method D: Compound **1** (39 mg, 0.057 mmol) and cyclohexanol (9.0 μL, 0.086 mmol) gave 11 mg of **7α** (31%) and 4.5 mg of **7β** (13%).

4.2.7. Methyl 2,3,5,6-tetra-*O*-benzyl-α-D-galactofuranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (8α)

Compound **8α** was obtained according to general procedures, using methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**2**) as acceptor. The crude was purified by column chromatography (40:1 toluene–EtOAc) to give a syrup; R_f 0.50 (10:1 toluene–EtOAc); $[\alpha]_D$ +23.8 (*c* 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.16 (m, 35H, ArH), 5.32 (d, 1H, *J* = 4.2 Hz, H-1′), 4.80 (d, 1H, *J* = 11.0 Hz, PhCH_2), 4.74 (d, 1H, *J* = 1.8 Hz, H-1), 4.71, 4.65 (2d, 2H, *J* = 11.8 Hz, PhCH_2), 4.70, 4.47 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.66, 4.37 (2d, 2H, *J* = 11.6 Hz, PhCH_2), 4.64–4.58 (m, 5H, PhCH_2), 4.44, 4.42 (2d, 2H, *J* = 12.0 Hz, PhCH_2), 4.25 (t, 1H, *J* = 7.0 Hz, H-3′), 4.04 (t, 1H, *J* = 9.7 Hz, H-4), 3.99 (dd, 1H, *J* = 4.2, 7.2 Hz, H-2′), 3.97 (t, 1H, *J* = 6.7 Hz, H-4′), 3.88 (dd, 1H, *J* = 3.2, 9.5 Hz, H-3), 3.84–3.81 (m, 2H, H-6a, H-6b), 3.79 (dd, 1H, *J* = 1.8, 3.1 Hz, H-2), 3.74 (dt, 1H, *J* = 3.8, 6.5 Hz, H-5′), 3.65 (m, 1H, H-5), 3.63 (dd, 1H, *J* = 3.8, 10.4 Hz, H-6a′), 3.55 (dd, 1H, *J* = 6.3, 10.4 Hz, H-6b′), 3.27 (s, 3H, OCH_3). ^{13}C NMR (125 MHz,$CDCl_3$): δ 138.9–127.3 (aromatic), 100.1 (C-1′), 98.9 (C-1), 84.0 (C-2′), 81.3 (C-3′), 80.7 (C-4′), 80.0 (C-3, C-5′), 75.03 (PhCH_2), 75.0 (C-2), 74.9 (C-4); 73.3, 73.0, 72.9 (PhCH_2); 72.3 (C-5); 72.0 (x2), 71.9 (PhCH_2); 70.5 (C-6′), 65.1 (C-6), 54.7 (OCH_3); HRMS (ESI) calcd for (M+Na) $C_{62}H_{66}O_{11}Na$: 1009.4497. Found: 1009.4471.

4.2.8. Methyl 2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (8β)

Compound **8β** was obtained according to general procedures, using methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**2**) as acceptor. The crude was purified by column chromatography (40:1 toluene–EtOAc) to give a syrup; R_f 0.44 (10:1 toluene–EtOAc); $[\alpha]_D$ −19.5 (*c* 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.16 (m, 35H, ArH), 5.18 (d, 1H, *J* = 1.3 Hz, H-1′), 4.90 (d, 1H, *J* = 11.1 Hz, PhCH_2), 4.74–4.69 (m, 3H, PhCH_2), 4.70 (br s, 1H, H-1), 4.58–4.41 (m, 9H, PhCH_2), 4.28 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.18 (dd, 1H, *J* = 3.2, 7.2 Hz, H-3′), 4.06 (dd, 1H, *J* = 1.3, 3.6 Hz, H-2′), 4.04–4.01 (m, 2H, H-6a, H-4′), 3.86 (dd, 1H, *J* = 3.1, 8.8 Hz, H-3), 3.81–3.70 (m, 5H, H-4, H-5, H-5′,H-6a′), 3.70–3.64 (m, 2H, H-6b, H-6b′), 3.25 (s, 3H, OCH_3). ^{13}C NMR (125 MHz,$CDCl_3$): δ 138.5–127.4 (aromatic), 106.6 (C-1′), 98.8 (C-1), 88.3 (C-2′), 82.7 (C-4′), 80.9 (C-3′), 80.2 (C-3); 76.4, 75.3 (C-5′, C-4); 75.0 (PhCH_2), 74.6 (C-2); 73.4, 73.3, 72.7, 72.1, 72.0, 71.8 (PhCH_2); 71.6 (C-5), 71.3 (C-6′), 67.1 (C-6), 54.6 (OCH_3); HRMS (ESI) calcd for (M+Na) $C_{62}H_{66}O_{11}Na$: 1009.4497. Found: 1009.4535.

Method A: Compound **1** (48 mg, 0.070 mmol) and **2** (42 mg, 0.090 mmol) gave 40 mg of **8α** (58%) and 12 mg of **8β** (17%).

Method B: Compound **1** (57 mg, 0.083 mmol) and **2** (50 mg, 0.108 mmol) gave 51.5 mg of **8α** (63%) and 21.5 mg of **8β** (26%).

Method C: Compound **1** (58 mg, 0.085 mmol) and **2** (51 mg, 0.110 mmol) gave 9.5 mg of **8α** (11%) and 62.5 mg of **8β** (75%).

Method D: Compound **1** (46 mg, 0.067 mmol) and **2** (47 mg, 0.101 mmol) gave 30 mg of **8α** (45%) and 12.5 mg of **8β** (19%).

4.2.9. Methyl 2,3,5,6-tetra-*O*-benzyl-α-D-galactofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (9α)

Compound **9α** was obtained according to general procedure (method A), using methyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (**3**) as acceptor. The crude was purified by column chromatography (30:1 toluene–EtOAc) to give a syrup; R_f 0.44 (10:1 toluene–EtOAc); $[\alpha]_D$ −33.7 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.03–7.14 (m, 35H, ArH), 5.89 (t, 1H, *J* = 9.4 Hz, H-4), 5.85 (dd, 1H, *J* = 3.3, 9.5 Hz, H-3), 5.67 (dd, 1H, *J* = 1.7, 3.0 Hz, H-2), 4.94 (d, 1H, *J* = 1.7 Hz, H-1), 4.89 (d, 1H, *J* = 4.1 Hz, H-1′), 4.72, 4.47 (2d, 2H, *J* = 11.6 Hz, PhCH_2), 4.58, 4.51 (2d, 2H, *J* = 12.0 Hz, PhCH_2), 4.56–450 (m, 2H, PhCH_2), 4.45, 4.40 (2d, 2H, *J* = 12.3 Hz, PhCH_2), 4.27 (m, 1H, H-5), 4.26 (t, 1H, *J* = 7.3 Hz, H-3′), 4.01 (dd, 1H, *J* = 4.1, 7.3 Hz, H-2′), 3.98 (dd, 1H, *J* = 6.0, 10.9 Hz, H-6a), 3.93 (t, 1H, *J* = 7.1 Hz, H-4′), 3.75 (m, 1H, H-5′), 3.61–3.57 (m, 2H, H-6a′, H-6b), 3.49 (dd, 1H, *J* = 6.2, 10.5 Hz, H-6b′), 3.46 (s, 3H, OCH_3). ^{13}C NMR (125 MHz,$CDCl_3$): δ 165.6, 165.5 (*C*OPh), 138.8–127.3 (aromatic), 100.2 (C-1′), 98.5 (C-1), 84.1 (C-2′), 81.1 (C-3′), 80.8 (C-4′), 80.6 (C-5′); 73.3, 73.1, 72.3, 72.1 (PhCH_2), 70.5 (C-2), 70.3 (C-3, C-6′), 69.7 (C-5), 67.4 (C-4), 66.5 (C-6), 55.4 (OCH_3); HRMS (ESI) calcd for (M+Na) $C_{62}H_{60}O_{14}Na$: 1051.3875. Found: 1051.3869.

4.2.10. Methyl 2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (9β)

Compound **9β** was obtained according to general procedure (method C), using methyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (**3**) as acceptor. The crude was purified by column chromatography (30:1 toluene–EtOAc) to give a syrup. A second column chromatography purification allowed the isolation of **9β** (as a 35:1 β/α mixture according to ^1H NMR spectrum) for identification purposes. R_f 0.44 (10:1 toluene–EtOAc); $[\alpha]_D$ −78.2 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.08–7.16 (m, 35H, ArH), 5.90 (t, 1H, *J* = 9.9 Hz, H-4), 5.86 (dd, 1H, *J* = 3.2, 9.9 Hz, H-3), 5.66 (dd, 1H, *J* = 1.9, 3.2 Hz, H-2), 5.13 (d, 1H, *J* = 1.2 Hz, H-1′), 4.95 (d, 1H, *J* = 1.7 Hz, H-1), 4.68, 4.47 (2d, 2H, *J* = 11.8 Hz, PhCH_2), 4.63, 4.49 (2d, 2H, *J* = 11.8 Hz, PhCH_2), 4.45, 4.28 (2d, 2H, *J* = 11.8 Hz, PhCH_2), 4.43 (br s, 2H, PhCH_2), 4.23 (m, 1H, H-5), 4.16 (dd, 1H, *J* = 3.2, 7.3 Hz, H-4′), 4.06 (dd, 1H, *J* = 1.2, 3.5 Hz, H-2′), 4.01 (dd, 1H, *J* = 3.5, 7.3 Hz, H-3′), 3.93 (dd, 1H, *J* = 2.4, 11.5 Hz, H-6a), 3.74 (m, 1H, H-5′), 3.71 (dd, 1H, *J* = 6.1, 11.5 Hz, H-6b), 3.66 (dd, 1H, *J* = 6.6, 10.1 Hz, H-6a′), 3.60 (dd, 1H, *J* = 4.9, 10.1 Hz, H-6b′), 3.46 (s, 3H, OCH_3). ^{13}C NMR (125 MHz,$CDCl_3$): δ 165.5, 165.4, 163.4 (*C*OPh); 138.3–127.5 (aromatic), 106.8 (C-1′), 98.4 (C-1), 88.4 (C-2′), 82.6 (C-3′), 80.9 (C-4′), 76.2 (C-5′), 73.4, 73.2, 72.0, 71.8 (PhCH_2), 70.9 (C-6′), 70.4 (C-2), 70.1 (C-5), 70.0 (C-4), 67.2 (C-3), 66.5 (C-6), 55.4 (OCH_3); HRMS (ESI) calcd for (M+Na) $C_{62}H_{60}O_{14}Na$: 1051.3875. Found: 1051.3868

Method A: Compound **1** (56 mg, 0.082 mmol) and **3** (54 mg, 0.106 mmol) gave 53 mg (63%) of **9α**

Method B: Compound **1** (61 mg, 0.089 mmol) and **3** (59 mg, 0.116 mmol) gave 62 mg of **9α** and **9β** (68%).

Method C: Compound **1** (50 mg, 0.073 mmol) and **3** (48 mg, 0.095 mmol) gave 68 mg of **9α** and **9β** (90%).

Method D: Compound **1** (42 mg, 0.061 mmol) and **3** (47 mg, 0.093) gave 41.5 mg of **9α** and **9β** (66%).

4.2.11. Allyl 2,3,5,6-tetra-*O*-benzyl-α-D-galactofuranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (10α)

Compound **10α** was obtained according to general procedures, using allyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**4**) as acceptor. The crude was purified by column chromatography (100:0.75 and 80:1 toluene–EtOAc) to give a syrup; R_f 0.45 (10:1 toluene–EtOAc); $[\alpha]_D$ +14.0 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.17 (m, 30H, ArH), 5.78 (dddd, 1H, *J* = 5.2, 6.0, 10.4, 17.1 Hz, OCH_2CH=CH_2), 5.30 (d, 1H, *J* = 4.2 Hz, H-1′), 5.19 (dq, 1H, *J* = 1.6, 17.2 Hz, OCH_2CH=CH_aH), 5.09 (dq, 1H, *J* = 1.4, 10.4 Hz, OCH_2CH=CHH_b), 4.96, 4.54 (2d, 2H, *J* = 11.2 Hz, PhCH_2), 4.84 (d, 1H, *J* = 2.2 Hz, H-1), 4.73–4.60 (m, 6H, PhCH_2), 4.49 (d, 1H, *J* = 11.7 Hz, PhC*H*H), 4.42 (d, 1H, *J* = 11.4 Hz, PhC*H*H), 4.36–4.29 (m, 2H, PhCH_2), 4.27 (dd, 1H, *J* = 3.2, 8.7 Hz, H-3), 4.23 (t, 1H, *J* = 7.0 Hz, H-3′), 4.11–4.06 (m, 2H, H-2′, OC*H*H-CH=CH_2), 4.02 (t, 1H, *J* = 6.9 Hz, H-4′), 3.98 (t, 1H, *J* = 2.7 Hz, H-2), 3.91 (ddt, 1H, *J* = 1.3, 6.1, 13.0 Hz, OCH*H*-CH=CH_2), 3.78 (ddd, 1H, *J* = 4.0, 5.8, 6.8 Hz, H-5′), 3.71 (dq, 1H, *J* = 6.3, 9.2 Hz, H-5), 3.58 (t, 1H, *J* = 8.9 Hz, H-4), 3.48 (dd, 1H, *J* = 4.0, 10.5 Hz, H-6a′), 3.38 (dd, 1H, *J* = 5.8, 10.5 Hz, H-6b′), 1.26 (d, 3H, *J* = 6.3 Hz, H-6). ^{13}C NMR (125 MHz,$CDCl_3$): δ 138.9–127.3 (aromatic), 134.0 (OCH_2*C*H=CH_2), 117.1 (OCH_2CH=*C*H_2), 98.2 (C-1′), 96.7 (C-1), 84.5 (C-2′), 81.0 (C-3′, C-4′), 80.1 (C-4), 79.9 (C-5′), 75.5 (C-3), 75.3 (C-2), 73.2, 73.1, 72.6, 72.0, 71.9 (PhCH_2), 70.0 (C-6′), 68.0 (C-5), 67.9 (OCH_2CH=CH_2), 18.0 (C-6); HRMS (ESI) calcd for (M+Na) $C_{57}H_{62}O_{10}Na$: 929.4235. Found: 929.4207.

4.2.12. Allyl 2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (10β)

Compound **10β** was obtained according to general procedures, using allyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**4**) as acceptor. The crude was purified by column chromatography (100:0.75 and 80:1 toluene–EtOAc) to give a syrup; R_f 0.63 (10:1 toluene–EtOAc); $[\alpha]_D$ −31.1 (*c* 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.07 (m, 30H, ArH), 5.82 (dddd, 1H, *J* = 5.1, 6.0, 10.8, 17.3 Hz, OCH_2CH=CH_2), 5.43 (s, 1H, H-1′), 5.23 (dq, 1H, *J* = 1.7, 17.3 Hz, OCH_2CH=C*H*H), 5.13 (dq, 1H, *J* = 1.5, 10.5 Hz, OCH_2CH=CH*H*), 4.90, 4.66 (2d, 2H, *J* = 11.5 Hz, PhCH_2), 4.77, 4.56 (2d, 2H, *J* = 12.3 Hz, PhCH_2), 4.69, 4.52 (2d, 2H, *J* = 11.9 Hz, PhCH_2), 4.68 (d, 1H, *J* = 1.8 Hz, H-1), 4.45, 4.30 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.43 (s, 2H, PhCH_2), 4.37, 4.28 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.27 (dd, 1H, *J* = 3.8, 6.8 Hz, H-4′), 4.14 (dd, 1H, *J* = 3.1, 9.6 Hz, H-3), 4.13–4.08 (m, 2H, OC*H*H-CH=CH_2, H-2′), 4.02 (dd, 1H, *J* = 2.5, 6.8 Hz, H-3′), 3.88 (ddt, 1H, *J* = 1.4, 5.9, 13.1 Hz, OCH*H*-CH=CH_2), 3.80 (dd, 1H, *J* = 1.8, 3.1 Hz, H-2), 3.77 (m, 1H, H-5′), 3.73 (dq, 1H, *J* = 6.2, 9.5 Hz, H-5), 3.66 (dd, 1H, *J* = 6.3, 9.9 Hz, H-6a′), 3.62 (dd, 1H, *J* = 3.2, 9.8 Hz, H-6b′), 3.61 (dd, 1H, *J* = 7.1, 9.5 Hz, H-4), 1.30 (d, 3H, *J* = 6.2 Hz, H-6). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8–127.1 (aromatic), 133.9 (OCH_2*C*H=CH_2), 116.9 (OCH_2CH=*C*H_2), 107.9 (C-1′), 97.4 (C-1), 88.6 (C-2′), 83.3 (C-3′), 81.6 (C-4′), 80.5 (C-4), 78.7 (C-2), 78.4 (C-3), 76.6 (C-5′); 74.9, 73.4, 73.2, 72.1, 71.5 (PhCH_2); 70.5 (C-6′), 68.2 (C-5), 67.7 (OCH_2CH=CH_2), 17.9 (C-6); HRMS (ESI) calcd for (M+Na) $C_{57}H_{62}O_{10}Na$: 929.4235. Found: 929.4207.

Method A: Compound **1** (62 mg, 0.091 mmol) and **4** (45 mg, 0.117 mmol) gave 36 mg (43.6%) of **10α**, 3.6 mg of **10β** (4%), and 15 mg of 2,3,5,6-tetra-*O*-benzyl-1-*N*-trichloroacetyl-α-D-galactofuranosylamine (**13**) (24%).

Method B: Compound **1** (58 mg, 0.085 mmol) and **4** (41 mg, 0.107 mmol) gave 32 mg of **10α** (42%), 11 mg of **10β** (14%) and 18 mg of **13** (31%).

Method C: Compound **1** (42 mg, 0.061 mmol) and **4** (31 mg, 0.080 mmol) gave 51 mg of **10β** (92%).

Method D: Compound **1** (32 mg, 0.047 mmol) and **4** (27 mg, 0.070 mmol) gave 24.5 mg of **10α** (57%), 2.5 mg of **10β** (6%) and 11 mg of **13** (34%).

4.2.13. Methyl 2,3,5,6-tetra-*O*-benzyl-α-D-galactofuranosyl-(1→2)-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (11α)

Compound **11α** was obtained according to general procedures, using methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**5**) as acceptor. The crude was purified by column chromatography (40:1 toluene–EtOAc) to give a syrup; R_f 0.52 (10:1 toluene–EtOAc); $[\alpha]_D$ −2.7 (*c* 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.03–7.10 (m, 30H, ArH), 5.53 (dd, 1H, *J* = 3.2, 10.5 Hz, H-3), 5.38 (s, 1H, C*H*Ph), 5.14 (d, 1H, *J* = 4.5 Hz , H-1′), 5.04 (d, 1H, *J* = 1.7 Hz, H-1), 4.82, 4.44 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.71, 4.41 (2d, 2H, *J* = 11.6 Hz, PhCH_2), 4.68, 4.52 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.50 (s, 2H, PhCH_2), 4.40 (t, 1H, *J* = 7.7 Hz, H-3′), 4.38 (dd, 1H, *J* = 1.7, 3.2 Hz, H-2), 4.25 (dd, 1H, *J* = 9.0, 10.2 Hz, H-4), 4.23 (dd, 1H, *J* = 4.3, 9.5 Hz, H-6a), 4.02 (dd, 1H, *J* = 4.5, 7.7 Hz, H-2′), 3.93 (dd, 1H, *J* = 4.3, 7.7 Hz, H-4′), 3.89 (m, 1H, H-5), 3.83 (t, 1H, *J* = 10.1 Hz, H-6b), 3.71 (m, 1H, H-5′), 3.65 (dd, 1H, *J* = 4.8, 10.0 Hz, H-6a′), 3.62 (dd, 1H, *J* = 6.3, 10.0 Hz, H-6b′), 3.17 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9 (*C*OPh), 138.5–126.1 (aromatic), 101.5 (*C*HPh), 101.0 (C-1′), 100.8 (C-1), 83.5 (C-2′), 80.1 (C-4′), 79.9 (C-3′), 77.7 (C-5′), 76.3 (C-4), 74.5 (C-2), 73.4, 73.0, 72.4 (PhCH_2), 71.8 (C-3), 71.5 (PhCH_2), 70.5 (C-6′), 68.9 (C-6), 63.9 (C-5), 54.8 (OCH_3); HRMS (ESI) calcd for (M+Na) $C_{55}H_{56}O_{12}Na$: 931.3664. Found: 931.3636.

4.2.14. Methyl 2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranosyl-(1→2)-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (11β)

Compound **11β** was obtained according to generals procedures, using methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**5**) as acceptor. The crude was purified by column chromatography (40:1 toluene–EtOAc) to give a syrup; R_f 0.36 (10:1 toluene–EtOAc); $[\alpha]_D$ −43.9 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.09–7.15 (m, 30H, ArH), 5.61 (s, 1H, C*H*Ph), 5.54 (dd, 1H, *J* = 3.6, 10.4 Hz, H-3), 5.14 (d, 1H, *J* = 1.2 Hz, H-1′), 4.74 (d, 1H, *J* = 1.5 Hz, H-1), 4.59, 4.49 (2d, 2H, *J* = 12.0 Hz, PhCH_2), 4.55, 4.27 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.44, 4.29 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.38 (dd, 1H, *J* = 1.6, 3.6 Hz, H-2), 4.33 (dd, 1H, *J* = 4.5, 9.9 Hz, H-6a), 4.27 (dd, 1H, *J* = 8.7, 9.9 Hz, H-4), 4.23, 4.20 (2d, 2H, *J* = 12.0 Hz, PhCH_2), 4.10 (dd, 1H, *J* = 1.2, 3.2 Hz, H-2′), 4.01 (dd, 1H, *J* = 3.2, 6.7 Hz, H-3′), 3.98 (m, 1H, H-5), 3.95 (dd, 1H, *J* = 2.9, 6.7 Hz, H-4′), 3.90 (t, 1H, *J* = 10.2 Hz, H-6b), 3.45 (m, 1H, H-5′), 3.43 (s, 3H, OCH_3), 3.42 (dd, 1H, *J* = 7.7, 9.5 Hz, H-6a′), 3.10 (dd, 1H, *J* = 2.1, 9.5 Hz, H-6b′). ^{13}C NMR (125 MHz,$CDCl_3$): δ 165.7 (*C*OPh), 138.4–126.1 (aromatic), 104.0 (C-1′), 101.7 (*C*HPh), 98.7 (C-1), 87.8 (C-2′), 82.5 (C3′), 81.9 (C-4′), 76.2 (C-5′, C-4), 73.05, 73.14 (PhCH_2), 72.3 (C-2), 71.9, 71.8 (PhCH_2), 71.7 (C-6′), 69.8 (C-3), 68.9 (C-6), 64.1 (C-5), 55.2 (OCH_3); HRMS (ESI) calcd for (M+Na) $C_{55}H_{56}O_{12}Na$: 931.3664. Found: 931.3627.

Method A: Compound **1** (58 mg, 0.085 mmol) and **5** (51 mg, 0.110 mmol) gave 21 mg of **11α** (28%), 6 mg of **11β** (8%), and 21 mg of **13** (36%)

Method B: Compound **1** (56 mg, 0.082 mmol) and **5** (48 mg, 0.104 mmol) gave 25 mg of **13** (45%).

Method C: Compound **1** (52 mg, 0.076 mmol) and **5** (46 mg, 0.099 mmol) gave 11 mg of **11α** (16%) and 15.5 mg of **11β** (23%).

Method D: Compound **1** (29 mg, 0.042 mmol) and **5** (29 mg, 0.063 mmol) gave 2.6 mg of **11α** and **11β** (7%), and 3.5 mg of **13** (12%).

4.2.15. 2,3,5,6-Tetra-*O*-benzyl-α-D-galactofuranosyl-(1→3)-2-*O*-benzoyl-5,6-*O*-isopropylidene-D-galactono-1,4-lactone (12α)

Compound **12α** was obtained according to general procedures, using 2-*O*-benzoyl-5,6-*O*-isopropylidene-D-galactono-1,4-lactone (**6**) as acceptor. The crude was purified by column chromatography (50:1 toluene–EtOAc) to give a syrup; R_f 0.34 (10:1 toluene–EtOAc); $[\alpha]_D$ +24.8 (*c* 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.03–7.22 (m, 25H, ArH), 6.00 (d, 1H, *J* = 8.0 Hz, H-2), 4.77, 4.60 (2d, 2H, *J* = 11.9 Hz, PhCH_2), 4.73 (d, 1H, *J* = 4.3 Hz, H-1′), 4.70, 4.03 (2d, 2H, *J* = 10.1 Hz, PhCH_2), 4.61, 4.51 (2d, 2H, *J* = 11.7 Hz, PhCH_2), 4.49, 4.41 (2d, 2H, *J* = 11.8 Hz, PhCH_2), 4.36 (t, 1H, *J* = 8.0 Hz, H-3′), 4.35 (t, 1H, *J* = 8.2 Hz, H-3), 4.17 (dt, 1H, *J* = 2.6, 6.9 Hz, H-5), 3.97 (dd, 1H, *J* = 4.2, 8.4 Hz, H-2′), 3.94 (dd, 1H, *J* = 6.8, 8.2 Hz, H-6a), 3.86 (dd, 1H, *J* = 1.1, 8.0 Hz, H-4′), 3.81 (dd, 1H, *J* = 7.0, 8.4 Hz, H-6b), 3.77 (dd, 1H, *J* = 8.8, 12.2 Hz, H-6a′), 3.56–3.50 (m, 2H, H-5′,H-6b′), 3.31 (dd, 1H, *J* = 2.6, 7.9 Hz, H-4), 1.40, 1.37 (2 s, 6H, $(CH_3)_2C$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5 (C-1), 164.8 (*C*OPh), 138.3–127.6 (aromatic), 110.2 $(CH_3)_2C$), 99.8 (C-1′), 83.7 (C-2′), 79.5 (C-4′), 78.3 (C-3′), 77.9 (C-3), 77.3 (C-4), 75.8 (C-5′), 74.2 (C-2), 73.4 (PhCH_2), 73.1 (C-5), 72.7, 72.5 (PhCH_2), 70.2 (C-6′), 65.0 (C-6), 26.0, 25.7 $(CH_3)_2C$); HRMS (ESI) calcd for (M+Na) $C_{50}H_{52}O_{12}Na$: 867.3351. Found: 867.3324.

4.2.16. 2,3,5,6-Tetra-*O*-benzyl-β-D-galactofuranosyl-(1→3)-2-*O*-benzoyl-5,6-*O*-isopropylidene-D-galactono-1,4-lactone (12β)

Compound **12β** was obtained according to general procedures, using 2-*O*-benzoyl-5,6-*O*-isopropylidene-D-galactono-1,4-lactone (**6**) as acceptor. The crude was purified by column chromatography (50:1 toluene–EtOAc) to give a syrup; R_f 0.27 (10:1 toluene–EtOAc); $[\alpha]_D$ −31.2 (*c* 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.10–7.18 (m, 35H, ArH), 5.84 (d, 1H, *J* = 7.0 Hz, H-2), 5.23 (br s, 1H, H-1′), 4.73 (t, 1H, *J* = 6.7 Hz, H-3), 4.63 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.56 (d, 1H, *J* = 11.8 Hz, PhCH_2), 4.47–4.40 (m, 5H, PhCH_2), 4.36 (m, 1H, H-5), 4.28 (dd, 1H, *J* = 2.6, 6.4 Hz, H-4), 4.26 (d, 1H, *J* = 11.7 Hz, PhCH_2), 4.11 (dd, 1H, *J* = 3.5, 7.1 Hz, H-4′), 4.02 (dd, 1H, *J* = 1.2, 3.4 Hz, H-2′), 4.00 (dd, 1H, *J* = 3.4, 7.1 Hz, H-3′), 3.92–3.88 (m, 2H, H-6a, H-6b), 3.70 (m, 1H, H-5′), 3.63–3.59 (m, 2H, H-6a′, H-6b′), 1.41, 1.32 (2 s, 6H, $(CH_3)_2C$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2 (C-1), 133.9–127.5 (aromatic), 106.1 (C-1′), 87.9 (C-2′), 82.6 (C-3′), 81.2 (C-4′), 79.8 (C-4), 76.9 (C-3), 75.9 (C-5′), 74.1 (C-2), 73.9 (C-5), 73.3, 72.1, 72.0 (PhCH_2), 70.1 (C-6′), 65.0 (C-6), 25.9, 25.7 $(CH_3)_2C$); HRMS (ESI) calcd for (M+Na) $C_{50}H_{52}O_{12}Na$: 867.3351. Found: 867.3325

Method A: Compound **1** (51 mg, 0.074 mmol) and **6** (31 mg, 0.096 mmol) gave 12.5 mg of **12α** (20%), 4.5 mg of **12β** (7%), and 15.5 mg of **13** (30%)

Method B: Compound **1** (48 mg, 0.070 mmol) and **6** (29 mg, 0.090 mmol) gave 5 mg of **12α** (8%) and 35 mg of **13** (73%).

Method C: Compound **1** (46 mg, 0.067 mmol) and **6** (28 mg, 0.087 mmol) gave 20 mg of **12α** (35%) and 14 mg of **12β** (25%).

Method D: Compound **1** (53 mg, 0.077 mmol) and **6** (37 mg, 0.115 mmol) gave 11 mg of **12α** (17%), 3 mg of **12β** (5%) and 17.5 mg of **13** (33%).

Acknowledgments

This work was supported by grants from Agencia Nacional de Promoción Científica y Tecnológica, Universidad de Buenos Aires and CONICET. C. Gallo-Rodriguez is a research member of CONICET. M. J. Tilve is a fellow from CONICET.

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for compounds **7α** and **7β**, and new compounds **8α**, **8β**, **9α**, **9β**, **10α**, **10β**, **11α**, **11β**, **12α,** and **12β**) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.04.005.

References

1. Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nat. Chem.* **2009**, *1*, 611–622.
2. Lederkremer, R. M.; Colli, W. *Glycobiology* **1995**, *5*, 547–552.
3. Peltier, P.; Euzen, R.; Daniellou, R.; Nugier-Chauvin, C.; Ferrières, V. *Carbohydr. Res.* **2008**, *343*, 1897–1923.
4. Richards, M. R.; Lowary, T. L. *ChemBioChem* **2009**, *10*, 1920–1938.
5. Houseknecht, J. B.; Lowary, T. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 677–682.
6. Pedersen, L. L.; Turco, S. J. *Cell. Mol. Life Sci.* **2003**, *60*, 259–266.
7. Belanova, M.; Dianiskova, P.; Brennan, P. J.; Completo, G. C.; Rose, N. L.; Lowary, T. L.; Mikusova, K. *J. Bacteriol.* **2008**, *190*, 1141–1145.
8. Tam, P.-H.; Lowary, T. L. *Curr. Opin. Chem. Biol.* **2009**, *13*, 618–625.
9. Richards, J. C.; Perry, M. B.; Kniskern, P. J. *Can. J. Chem.* **1989**, *67*, 1038–1350.
10. Linnerborg, M.; Wollin, R.; Wildmalm, G. *Eur. J. Biochem.* **1997**, *246*, 565–573.
11. Ahrazem, O.; Prieto, A.; San-Blas, G.; Leal, J. A.; Jimenez-Barbero, J.; Bernabé, M. *Glycobiology* **2003**, *13*, 743–747.
12. Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934.
13. Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35–79.
14. Arasappan, A.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 7967–7970.
15. Gelin, M.; Ferrières, V.; Plusquellec, D. *Carbohydr. Lett.* **1997**, *2*, 381–388.
16. Gandolfi-Donadio, L.; Gola, G.; de Lederkremer, R. M.; Gallo-Rodriguez, C. *Carbohydr. Res.* **2006**, *341*, 2487–2497.
17. Guelin, M.; Ferrieres, V.; Plusquellec, D. *Eur. J. Org. Chem.* **2000**, 1423–1431.
18. Lee, Y. J.; Lee, B.-Y.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2006**, *8*, 3971–3974.
19. Baek, J. Y.; Joo, Y. J.; Kim, K. S. *Tetrahedron Lett.* **2008**, *49*, 4734–4737.
20. Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9658–9671.
21. Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9672–9680.
22. Choudhury, A. K.; Roy, N. *Carbohydr. Res.* **1998**, *308*, 207–211.
23. Gallo-Rodríguez, C.; Gandolfi-Donadio, L.; de Lederkremer, R. M. *Org. Lett.* **1999**, *1*, 245–248.
24. Gandolfi-Donadío, L.; Gallo-Rodriguez, C.; Lederkremer, R. M. *J. Org. Chem.* **2002**, *67*, 4430–4435.
25. Gandolfi-Donadío, L.; Gallo-Rodriguez, C.; de Lederkremer, R. M. *J. Org. Chem.* **2003**, *68*, 6928–6934.
26. Gallo-Rodriguez, C.; Gil-Libarona, M. A.; Mendoza, V. M.; Lederkremer, R. M. *Tetrahedron* **2002**, *58*, 9373–9380.
27. Mendoza, V. M.; Kashiwagi, G. A.; de Lederkremer, R. M.; Gallo-Rodriguez, C. *Carbohydr. Res.* **2010**, *345*, 385–396.
28. Gandolfi-Donadío, L.; Santos, M.; de Lederkremer, R. M.; Gallo-Rodriguez, C. *Org. Biomol. Chem.* **2011**, *9*, 2085–2097.
29. Gola, G.; Libenson, P.; Gandolfi-Donadío, L.; Gallo-Rodriguez, C. *ARKIVOC* **2005**, (*xii*), 234–242.
30. Ruiz Contreras, R.; Karmerling, J. P.; Vliegenthart, F. G. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 85–88.
31. Boren, H. B.; Eklind, K.; Garegg, P. J.; Lindberg, B.; Pilotti, A. *Acta Chem. Scand.* **1972**, *26*, 4143.
32. Ziegler, T.; Kovac, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1989**, *194*, 185–198.
33. Westerduin, P.; De Haan, P. E.; Deers, M. J.; van Boom, J. H. *Carbohydr. Res.* **1988**, *180*, 195–205.
34. Buchanan, J. G.; Schwarz, J. C. P. *J. Chem. Soc.* **1962**, 4770–4777.
35. Bohé, L.; Crich, D. *C.R. Chim.* **2011**, *14*, 3–16.
36. Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144–1153.
37. Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497–510.
38. Crich, D.; Pedersen, C. M.; Bowers, A. A.; Wink, D. J. *J. Org. Chem.* **2007**, *72*, 1553–1565.
39. Sadozai, K. K.; Nukada, T.; Ito, Y.; Nakahara, Y.; Ogawa, T.; Kobata, A. *Carbohydr. Res.* **1986**, *157*, 101–123.
40. Kinzy, W.; Schmidt, R. R. *Liebigs Ann Chem.* **1987**, 407–415.
41. Kobayashi, M.; Yamazaki, F.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *201*, 51–67.
42. Lohman, G. J. S.; Seeberger, P. H. *J. Org. Chem.* **2004**, *69*, 4081–4093.
43. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
44. Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J. *Org. Lett.* **2007**, *9*, 1959–1962.
45. Osumi, K.; Enomoto, M.; Sugimura, H. *Carbohydr. Lett.* **1996**, *2*, 35–38.