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Synthesis of D-Galactofuranose-Containing Molecules: Design of Galactofuranosyl Acceptors

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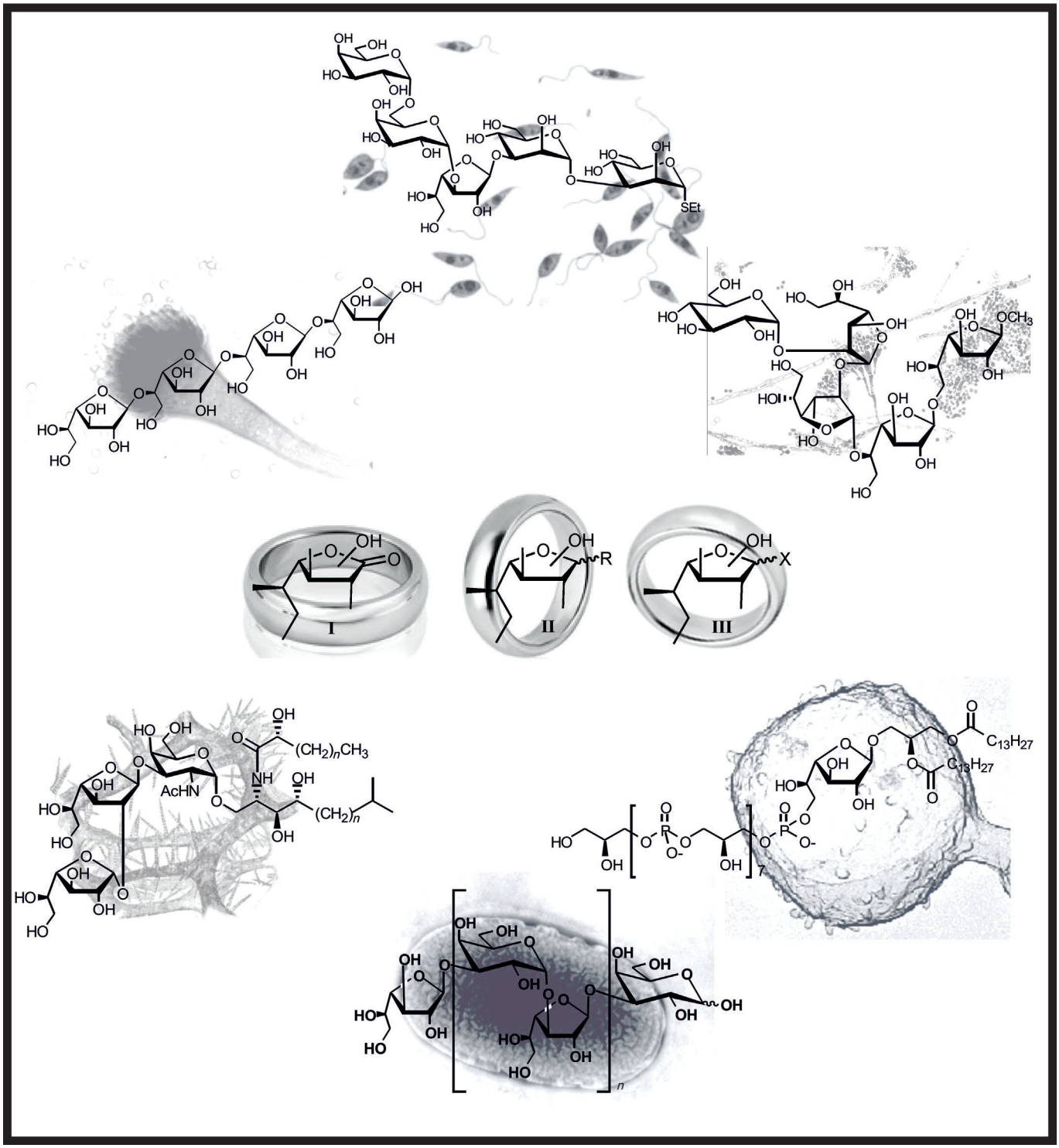
Dedicated to Prof. Rosa M. de Lederkremer in recognition of her pioneering contributions to the glycobiology of galactofuranose.



D-Galactofuranose (D-Gal*f*) is present in glycoconjugates of several pathogenic microorganisms but is absent in mammals, so it is a good target for the development of chemotherapeutic agents for the treatment of microbial infections. This has increased interest in the synthesis of D-Gal*f*-containing molecules for corresponding glycobiological studies. The synthesis of oligosaccharides, glycoconjugates, and mimetics of D-Gal*f* requires specific methods for the preparation of galactose derivatives in the furanosic configuration, the synthesis of appropriate acceptors, and efficient glycosylation methods for the construction of α- and β-D-Gal*f* linkages. This review summarizes the different strategies developed for the preparation of partially protected derivatives of D-Gal*f*, suitable as acceptors for the construction of (1→2), (1→3), (1→5), and (1→6) linkages, and describes recent applications.

Introduction

Among the natural hexoses, D-galactose is the one most extensively found in the furanose configuration. Nevertheless, in mammalian oligosaccharides and glycoconjugates, galactose is present only in the pyranose configuration (D-Gal*p*). The presence of D-galactofuranose (D-Gal*f*) is restricted to low-order organisms such as bacteria,[1–3] protozoa,[4–6] and fungi,[7] as well as certain algae,[8] Archaea,[9] and other invertebrates.[10] Many of these organisms are pathogenic for humans. For example, in *Trypanosoma cruzi*, D-Gal*f* is composed of two types of glycoconjugates, the glycoinositolphospholipids (GIPLs) and the epimastigote mucins of some strains of the parasite.[4] In *Leishmania* spp., D-Gal*f* is present in the lipophosphoglycan (LPG) as an internal unit and in the GIPLs as an external unit.[5,6] In both protozoa, the furanose moiety is vital for the infection.[11,12] In bacteria, the most outstanding example is that of *Mycobacterium tuberculosis* and *Mycobacterium leprae*, in which D-Gal*f* is constituted of a micolyl-arabinogalactan complex, a major component of the cell wall with about 35 D-Gal*f* units.[13] In fungi, the most studied example is *Aspergillus fumigatus,* which produces a galactomannan, two glycoproteins, and glycoinositolphosphoceramides with galactofuranose.[14–16] D-Gal*f* is present in the major antigen circulating in patients with aspergillosis.[7] Recently, D-Gal*f* was found in the encapsulated pathogenic fungus *Cryptococcus neoformans*.[17]

The fact that D-Gal*f* is essential for the survival or virulence of these pathogenic microorganisms and is neither present in nor required by mammals suggests that elucidation of the biosynthetic process by which these glycoconjugates are assembled, as well as inhibition of the related metabolic pathways involved in the biosynthesis of their glycoconjugates, are ideal targets for the development of chemotherapeutic agents. This has triggered a large amount of research directed towards elucidation of the biosynthetic processes by which these glycoconjugates are assembled, as well as inhibition of the related enzymes. The development of effective drugs against tuberculosis[18] and Chagas' disease[19] is still a major challenge.

β-D-Gal*f* residues are formed in nature by ring contraction of UDP-galactopyranose to UDP-galactofuranose, catalyzed by the enzyme UDP-galactopyranose mutase.[20] They are then incorporated into glycans by galactofuranosyl transferases[21–23] and, in some species, β-D-galactofuranosidases are responsible for the degradation of the D-Gal*f*-containing glycoconjugates.[24–26] The biosynthesis and metabolism of α-D-Gal*f*, in contrast, is unknown. The occurrence and biochemistry of D-Gal*f* have been extensively reviewed.[27–32]

Paramount to the study of the biosynthesis of D-Gal*f*-containing polysaccharides and glycoconjugates is the necessity for a ready preparation of renewable quantities of precursors of D-Gal*f*.[32–36] In addition, the synthesis of oligosaccharides, glycoconjugates, and mimetics of this sugar also requires the efficient construction of *O*-galactofuranosidic linkages. Development of these synthetic methodologies matured alongside the general synthesis of pyranosidic oligosaccharides. The synthesis of these molecules,[30–33,37] as well as their conformations,[38] have been carefully reviewed. These reviews were focused mainly on the synthesis of a variety of convenient galactofuranosyl precursors and on the different glycosylation methods used for the construction of α- and β-D-Gal*f* linkages. However, they did not deal with the equally important issue of the preparation of appropriate acceptors that undergo glycosylation at a single site. The purpose of this review is to describe the variety of strategies developed for the synthesis of partially protected D-Gal*f* derivatives as glycosyl acceptors, suitable for the construction of (1→2), (1→3), (1→5), and (1→6) linkages, by glycosylation with D-Gal*f* derivatives or other sugars as donors. In many cases, these acceptors were also prepared to act as donors in a preceding or subsequent glycosylation reaction. The incorporation of specific protecting group patterns and recent applications are also described.

Glycosyl acceptors

The D-Gal*f* derivatives most frequently used as glycosyl acceptors may be classified as one of three types: derivatives of D-galactono-1,4-lactone (type I), derivatives of alkyl glycosides (type II), and derivatives with other anomeric substituents, such as thioglycosides, which are prepared for subsequent activation as glycosyl donors (type III, Scheme 1).

The advantage of using D-galactono-1,4-lactone derivatives (type I) is that selectively substituted derivatives are more easily obtained than for the other types.[39] In addition to steric factors, stereoelectronic effects also operate, increasing the nucleophilicity of the 2-hydroxy group vicinal to the lactone carbonyl.[39,40] Thus, D-Gal*f* acceptors with orthogonal protecting groups at different positions can be obtained in a straightfor-

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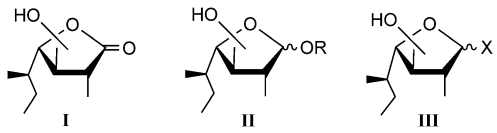


Scheme 1. Galactofuranosyl acceptor types.

ward way. These derivatives can be used as acceptors in glycosylation reactions promoted by different methods, the lactone carbonyl group can later be reduced to the hemiacetal (e.g., with diisoamylborane [DSB]), and the new reducing end can be activated for further glycosylation (Scheme 2). This strategy is the so-called "glycosyl-aldonolactone approach", which was developed by the Lederkremer group and extensively used for the synthesis of oligosaccharide constituents of pathogenic microorganisms. This lactone is usually commercially accessible; otherwise, convenient methods for its preparation are available.[41]

The first task in the synthesis of type II and III D-Gal*f* acceptors is to efficiently synthesize a galactose derivative in the furanose configuration. The more frequently used methodologies are Fischer glycosylation, with varied modifications to favor the furanose configuration, and per-O-benzoylation of galactose at high temperature to give a mixture of anomers of per-*O*-benzoyl-α,β-D-Gal*f*; further glycosylation is carried out by using alcohols or thiols and debenzoylation.[32]

Carla Marino obtained her undergraduate degree in Chemistry from the University of Buenos Aires and her Ph.D. in Organic Chemistry from the same university, under the supervision of Prof. Rosa Muchnik de Lederkremer. After two years at a petrochemical company, she joined CIHIDECAR (Center of Carbohydrate Research), which works together with the National Research Council of Argentina (CONICET) and the University of Buenos Aires. Sine 2004, Carla has been an Assistant Professor in the Department of Organic Chemistry, and her research interest focuses on carbohydrate synthesis and glycobiology.

Luciana Baldoni graduated in Chemistry from the University of Buenos Aires in 2005. In 2012, supervised by Prof. Carla Marino, she obtained a Ph.D. in Organic Chemistry. During her work in the CIHIDECAR–CONICET and in the University of Buenos Aires, she has been involved in the study of the glycosyl iodide glycosylation method, which she has applied to the synthesis of galactofuranose and mannose-containing molecules.

For the preparation of type II and III acceptors, regioselective protection of O- and S-glycosides follows the common rules. Selective protection of the primary 6-OH moiety can be easily achieved with sterically demanding reagents, and exocyclic 5-OH and 6-OH can be involved in an isopropylidene derivative or other 5,6-cyclic derivatives. It is more difficult to differentiate between endocyclic 2-OH and 3-OH in both substitution and glycosylation reactions.

Glycosyl acceptors for (1→2)-D-Gal*f* and (1→3)-D-Gal*f* linkages

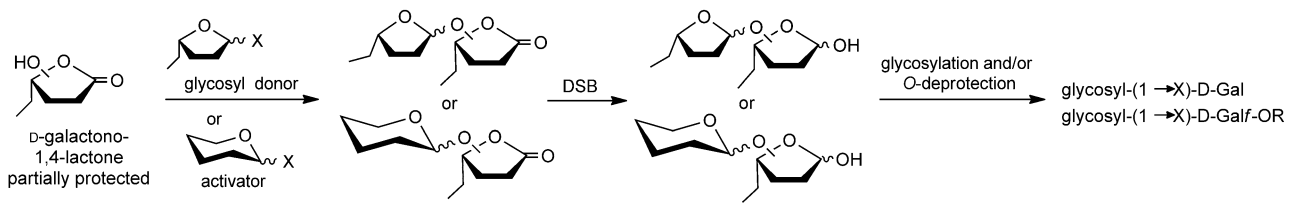
Even though the (1→2)-D-Gal*f* linkage is not the one most frequently found in nature, it is present in glycoconjugates of some organisms, such as fungi from the genera *Penicillium*,[42] *Talaromyces*,[43] and *Fonsecaea*,[44] and in the protozoa *T. cruzi*.[45] Some examples in bacteria have also been reported.[1,46] The (1→3)-D-Gal*f* bond is present in oligosaccharidic structures of *Aspergillus*[14] and in *Renibacterium salmoninarum*[47] besides *Penicillium*[42] and *Talaromyces* spp.[43] It is also found in polyhydroxysteroidal glycosides from the starfish *Anthenea chinensis*.[10]

Often, the strategies used for the synthesis of precursors for the formation of (1→2)-D-Gal*f* linkages are the same as those used for building (1→3) bonds. The usual sequence for preparing (1→2) type I acceptors involves protection of the 5- and 6-OH groups with an isopropylidene,[48] followed by regioselective blocking of the 2-OH moiety, activated by the carbonyl lactone group,[4] and the orthogonal protection of the 3-OH group. Finally, deprotection of the 2-OH moiety leads to type I acceptors that are ready for construction of (1→2)-D-Gal*f* linkages (Scheme 3).

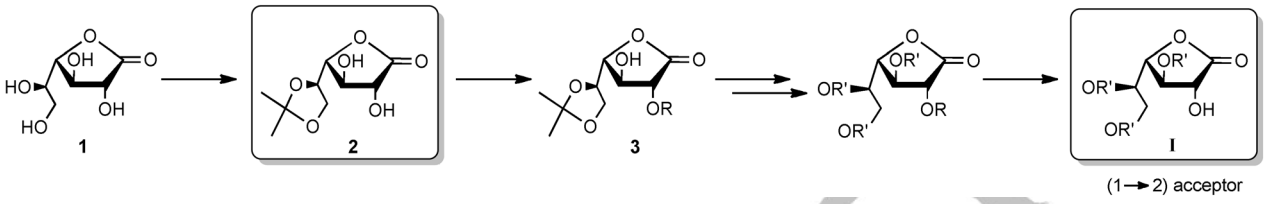
Trisaccharides β-D-Gal*f*-(1→2)-β-D-Gal*f*-(1→4)-D-GlcNA*cp* (**7**) and β-D-Gal*p*-(1→2)-β-D-Gal*f*-(1→4)-D-GlcNA*cp*, isolated as alditols by reductive elimination from mucines of *T. cruzi*,[45] have been synthesized employing the aldonolactone approach to introduce the internal Gal*f* unit substituted at position 2 (Scheme 4).[49] In this case, *tert*-butyldiphenylsilyl was chosen as the protecting group for the 2-OH moiety, due to its resistance to a weak acidic medium. Deprotection of the isopropylidene group to prevent partial hydrolysis during the synthetic sequence, followed by benzoylation and removal of the TBDPS group, yielded the type I Gal*f* acceptor **5** (Scheme 3).

Gallo-Rodriguez and co-workers also attempted to carry out regioselective glycosylation at 2-OH of intermediate **2** using the trichloroacetimidate method, with the aim of reducing the number of steps in the synthesis of oligosaccharide derivatives from *Bacteroides cellulosolvens* glycoproteins.[50] Although the desired product was obtained as the main product in moderate yield, byproducts resulting from 3-O-glycosylation of the lactone were also obtained. On the other hand, by using the glycosyl iodide method developed by Baldoni and Marino, regioselective glycosylation of the 2-OH moiety of compound **2** was achieved, as shown in Scheme 5.[34]

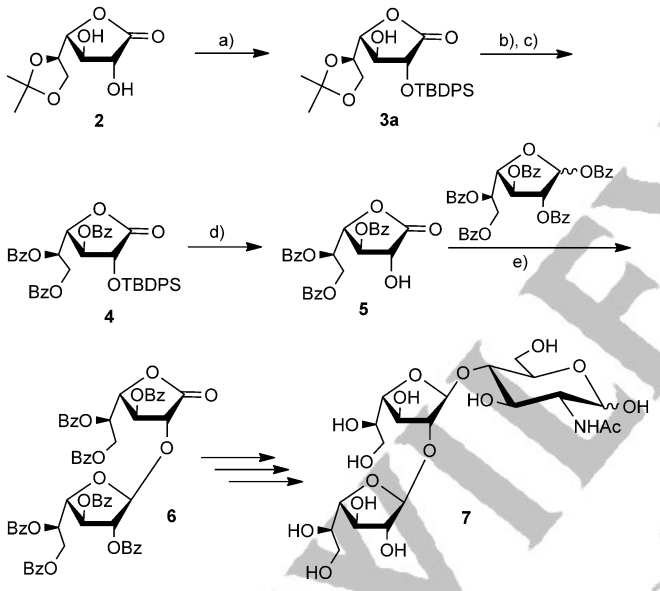
Similarly, regioselective glycosylation of **2** with tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate constituted the key step for a straightforward synthesis of α-D-Glc*p*-(1→2)-D-



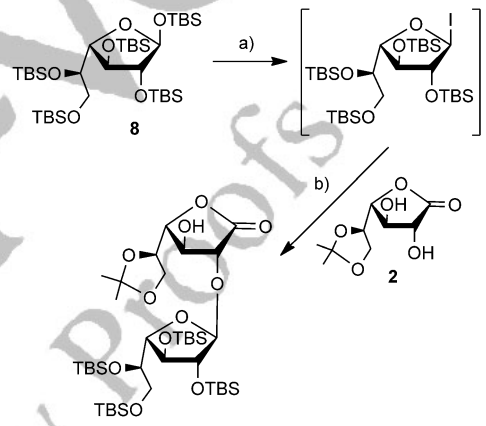
Scheme 2. D-Galactono-1,4-lactone derivatives and the glycosyl–aldonolactone approach.



Scheme 3. Strategy for the synthesis of (1→2) acceptors (type I) involving D-galactono-1,4-lactone (**1**).



Scheme 4. Synthesis of trisaccharide β-D-Gal*f*-(1→2)-β-D-Gal*f*-(1→4)-D-GlcNAc*p* (**7**) by using the aldonolactone approach. a) TBDPSCl (1.2 equiv), imidazole, DMF, 83%; b) AcOH/H_2O, 80 °C; BzCl, py, 0 °C, 68%; d) TBAF, AcOH, DMF, THF, 81%; e) $SnCl_4$, CH_2Cl_2, 92%;

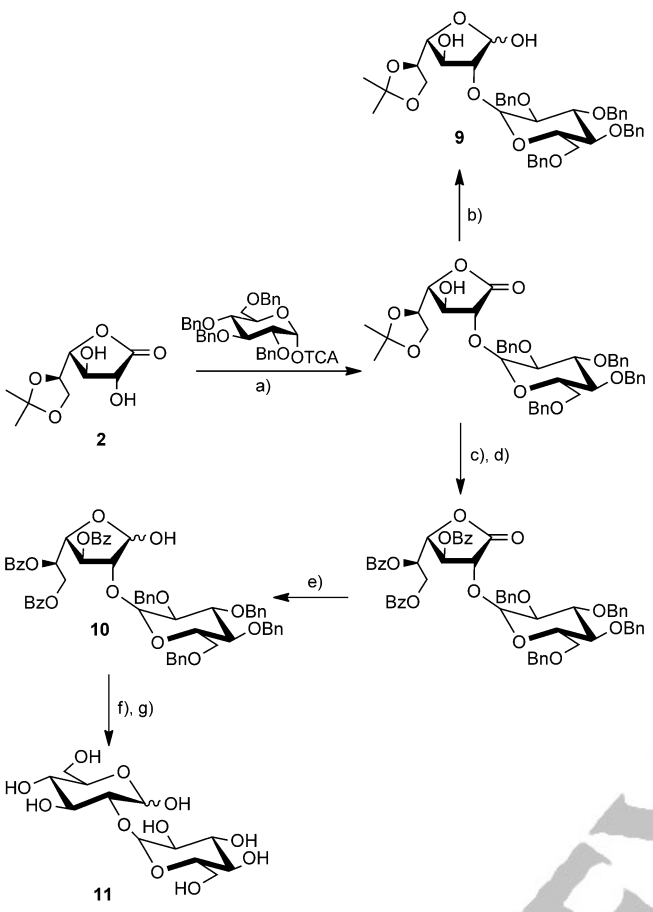


Scheme 5. Regioselective 2-O-glycosylation of isopropylidene **2** by using the galactofuranosyl iodide method.[34] a) TMSI, CH_2Cl_2; b) EtN(*i*Pr)$_2$, 83%.

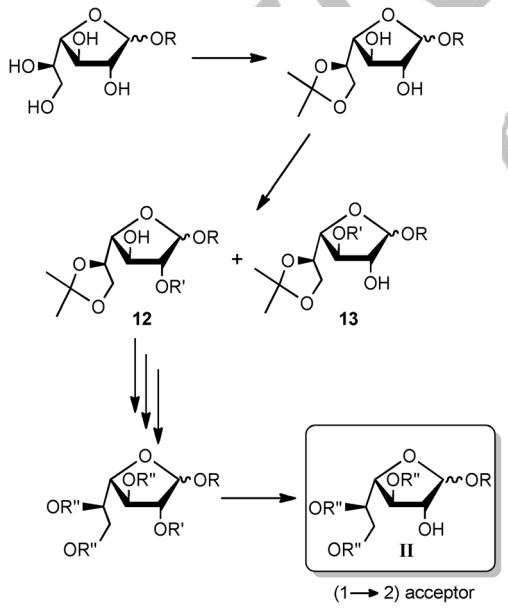
Gal (**11**), a fragment of the polysaccharide varianose useful for biosynthetic studies. In addition, derivatives **9** and **10** are suitable for the synthesis of higher oligosaccharides with internal D-Gal*f* (Scheme 6).[51]

As an alternative to the use of D-galactono-1,4-lactone derivatives (type I acceptors), alkyl D-galactofuranosides were employed as precursors for the synthesis of type II galactofuranosyl acceptors (Scheme 2). The usual strategy is similar to that applied for lactone **1**, which consists of the introduction of an isopropylidene group at the 5- and 6-OH moieties as the first step, then the selective protection of 2-OH by using approximately a one molar equivalent of protecting reagents. However, this step is not regioselective, and a mixture of products with substitutions at 2-OH (**12**) and 3-OH (**13**) are usually obtained (Scheme 7). The subsequent steps (i.e., installation of orthogonal protective groups at the 3-, 5-, and 6-OH groups, depending on the subsequent transformations, and deprotection of the 2-OH group) are also similar to those used for type I acceptors.

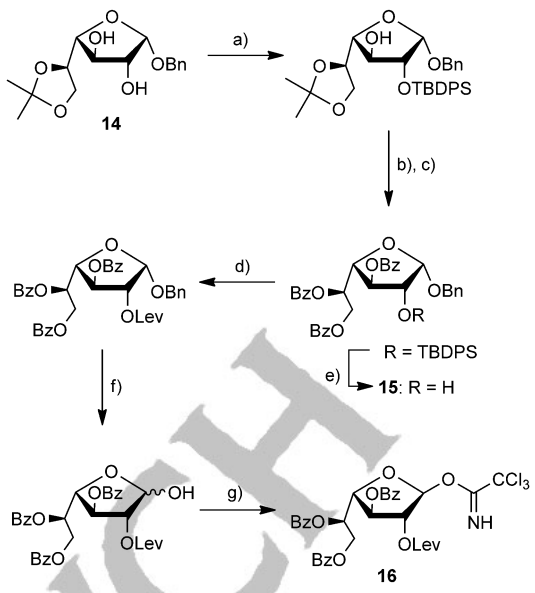
Kashiwagi et al.[52] developed the synthesis of a galactofuranosyl acceptor useful for installing Gal*f*-(1→2)-Gal*f* linkages through a one-step anomeric O-alkylation of galactose.[35,53–55] Selective 2-*O*-benzoyl and 2-*O*-pivaloyl protection were previously described for allyl and pentenyl α-D-galactofuranoside derivatives, which was attributed to the increase in 2-O-nucleophilicity due to the intramolecular hydrogen bond of this hydroxy group with the α-anomeric oxygen.[56] Starting from compound **14**, a levulinoyl group was selectively introduced at the 2-OH by the reaction sequence depicted in Scheme 8. This sequence afforded compound **15** in five steps and 55% yield from **14**. With derivative **15** in hand, glycosyl donor **16** was prepared and used to obtain disaccharide **17** (Scheme 9). De-O-levulinoylation of **17** gave acceptor **18** in 91% yield, which



Scheme 6. Synthesis of α-D-Glc*p*-(1→2)-D-Gal (**11**) by using the aldonolactone approach.[51] a) Et_2O, 71 %; b) DSB, THF; c) $HAcO/H_2O$; d) BzCl, py, CH_2Cl_2, 69%; e) DSB, THF, 76%; f) NaOMe/MeOH; g) H_2, Pd/C, MeOH, 91%.



Scheme 7. Strategy for the synthesis of (1→2) acceptors involving alkyl D-galactofuranoside (type II).

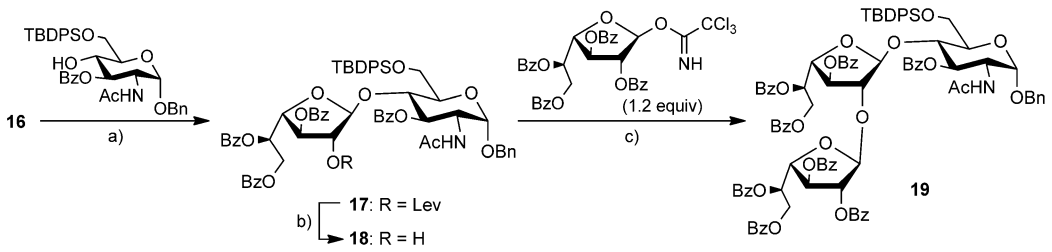


Scheme 8. Synthesis of latent type III acceptor **16**. a) TBDPSCl, imidazole, DMF, 84%; b) $AcOH/H_2O$, 80 °C;) BzCl, py, 0 °C, 81%; d) LevOH (1.3 equiv), DCC (1.3 equiv), DMAP, CH_2Cl_2, 97%; e) TBAF, HAcO, DMF, THF, 83%; f) H_2/Pd(C), AcOEt, 95%; g) Cl_3CCN, DBU, CH_2Cl_2, 90%.

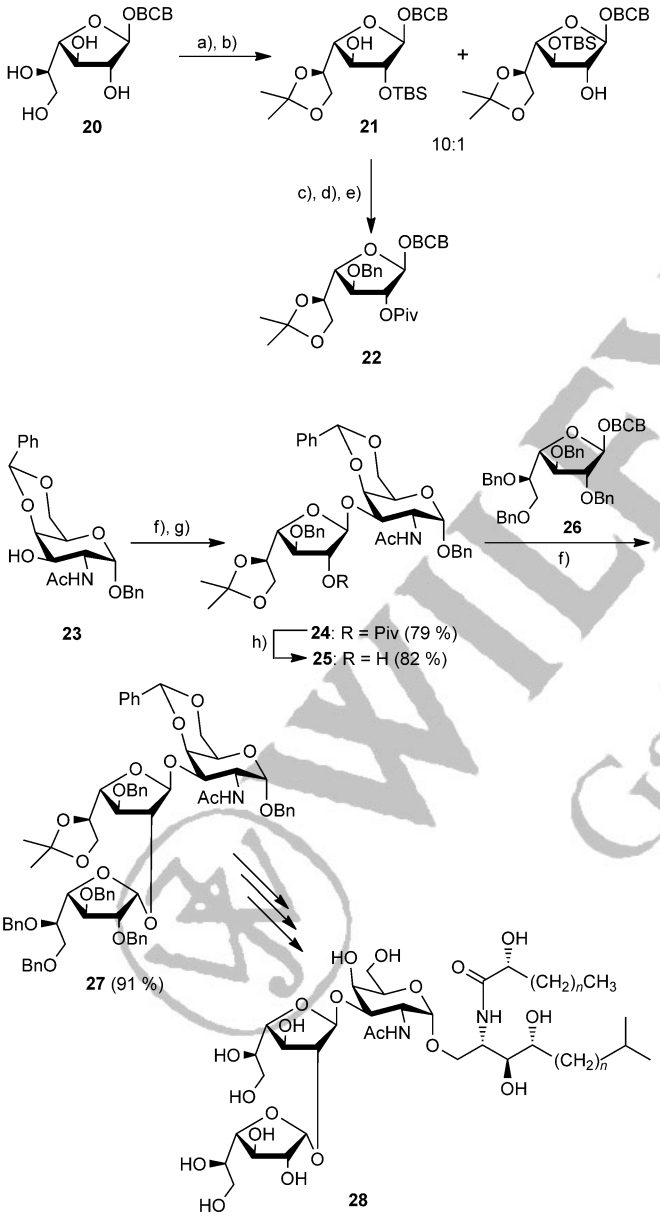
was then ready for trichloroacetimidate glycosylation to diastereoselectively form the β-Gal*f*-(1→2)-Gal*f* linkage of compound **19**. Compound **19** was thus synthesized in eleven steps from benzyl α-D-galactofuranoside in an overall yield of 21%.

A similar strategy was used by Kim et al.[57,58] to introduce the α-D-Gal*f*-(1→2)-D-Gal*f* linkage in the total synthesis of agelagalastatin (**28**, Scheme 10), with the additional challenge presented by the 1,2-*cis* configuration. Building block **22** was designed as a donor for coupling with galactopyranosyl derivative **23** to afford **24** which, upon de-O-pivaloylation, was coupled with galactofuranosyl 2′-(benzyloxycarbonyl)benzyl donor **26** to afford **27**. One of the advantages of this strategy relies on the high regioselectivity of the silylation of ■■isopropylidene *OK?*■■ derivative of compound **20** (90%).

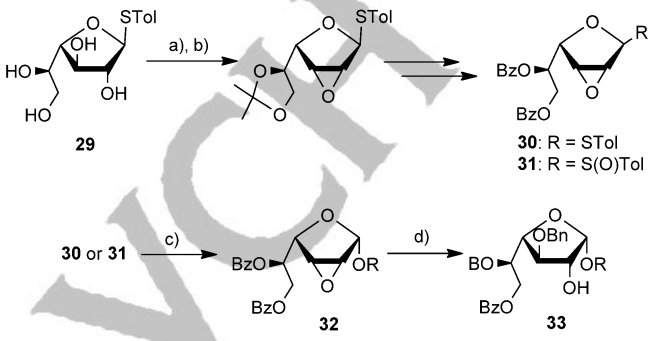
Bai and Lowary developed a method of using 2,3-anhydrosugars for the 1,2-*cis* assembly of glycofuranosides, which was used for the stereocontrolled synthesis of β-D-arabino- and α-D-galactofuranosides.[59] According to this method, the glycosyl donor is a thioglycoside (**30**) or glycosylsulfoxide (**31**) with C-2 and C-3 involved in an epoxide ring. These derivatives can be glycosylated by S_N2-like displacement to give rise to a 1,2-*cis* glycosidic linkage with high diastereoselectivity. Next, the epoxide is regioselectively opened with lithium benzylate in the presence of (−)-sparteine, affording a 3-OH-protected derivative of Gal*f* (Scheme 11). The high selectivity in the epoxide ring opening is probably due to the steric hindrance of the anomeric substituent and the isopropylidene-protected side chain, located at the same face of the furanose as 2-OH, which hinders the attack of the nucleophile at C-2. This novel strategy was used as key feature in the synthesis of a pentasaccharide fragment of varianose (Scheme 12), a cell wall polysaccharide from *Penicillium varians*.[59]



Scheme 9. Installation of the β-D-Gal*f*-(1→2)-D-Gal*f* linkage by using latent acceptor **16**.[52] a) TMSTf, CH_2Cl_2, 66%; b) NH_2NH_2, py, AcOH, 91%; c) TMSOTf, CH_2Cl_2, 81%.



Scheme 10. Total synthesis of agelagalastatin.[57,58] a) $(CH_3)_2C(OCH_3)_2$, CSA, 88%; b) TBSCl, imidazole, 90%; c) BnBr, NaH, 95%; d) Bu_4NF, 98%; e) Piv-ClEt_3N, 99%; f) DTBMP, Tf_2O; g) **22**; h) BnOH, NaH. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, BCB = 2′-benzyloxycarbonyl)benzyl.



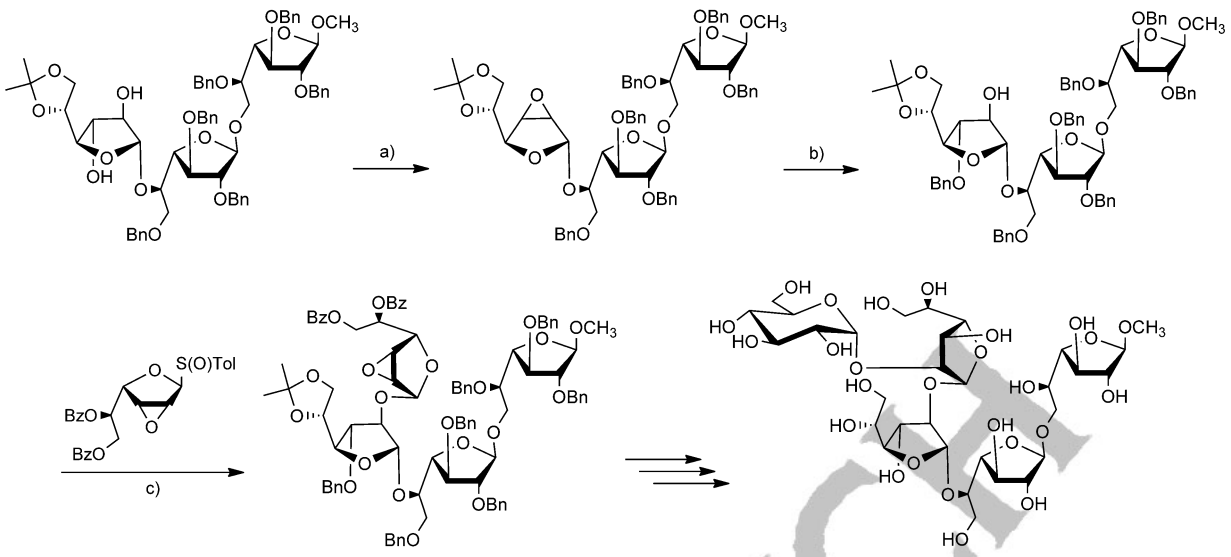
Scheme 11. The 2,3-anhydrosugar method for the synthesis of a (1→2)-α-D-Gal*f* acceptor. a) 2,3-dimethoxypropane, acetone, *p*-TsOH; b) DIAD, Ph_3P, 81%; c) I^+ or Tf^+, ROH, 72–82%; d) BnOLi, BnOH, (−)-sparteine, 75–82%.

For the synthesis of (1→3)-D-Gal*f* linkages, the synthetic strategies generally used arise from those described for building (1→2)-D-Gal*f* linkages, as was mentioned previously. For the aldonolactone approach (type I acceptors, Scheme 13), derivative **3**, regioselectively obtained from **2** by activation of the 2-OH moiety by the lactone carbonyl group, can be used as a galactofuranosyl acceptor in order to install a (1→3)-linkage (Scheme 13). This type of donor was used to prepare β-D-Gal*f*-(1→3)-D-Gal*f* glycoside **35** (Scheme 14),[34] as well as for the synthesis of trisaccharide **36**, present in glycoinositolphospholipids of *Leishmania*, with an internal D-Gal*f* unit (Scheme 15).[40]

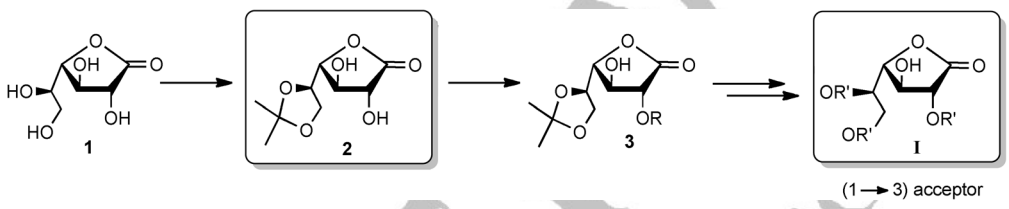
The synthesis of type II and III glycosyl acceptors suitable for the construction of (1→3)-D-Gal*f* linkages is outlined in Scheme 15. Starting either from methyl glycoside **37** or from thioglycoside **29**, benzoylation of isopropylidene derivatives **38** and **41** afforded mixtures of the 2- and 3-substituted derivatives. Thus, the synthesis of methyl β-D-Gal*f*-(1→3)-β-D-Gal*f* was initially accomplished by non-regioselective glycosylation of 5,6-di-*O*-isopropylidene-β-D-galactofuranoside (**41**) with 2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl chloride.[60]

Thioglycoside **39** was obtained in 45% yield and was used for a one-pot procedure to synthesize trisaccharide **42**, present in the capsular polysaccharide antigen of *Streptococcus pneumoniae* (Scheme 17). Interestingly, the reactivity of **39** was efficiently tuned, acting first as a donor with a glucosyl acceptor and later as an acceptor to establish the α-D-Gal*p*-(1→3)-β-D-Gal*f* linkage.[61]

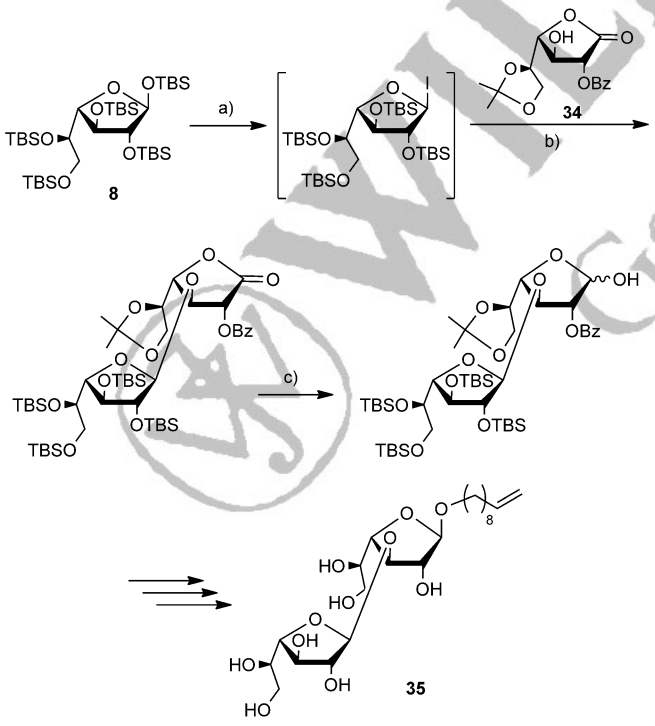
Silylation of thioglycoside **38** under controlled conditions afforded the type III acceptor **40** as a major product (Scheme 16), which was subjected to a sequence of reactions



Scheme 12. Synthesis of a pentasaccharide fragment of varianose.[59] a) DIAD, Ph_3P, THF, 91%; b) LiOBn, BnOH, 87%; c) Tf_2O, DTBMP, CH_2Cl_2, 75%.



Scheme 13. Strategy for the synthesis of (1→3) acceptors (type I) involving D-galactono-1,4-lactone (**1**).

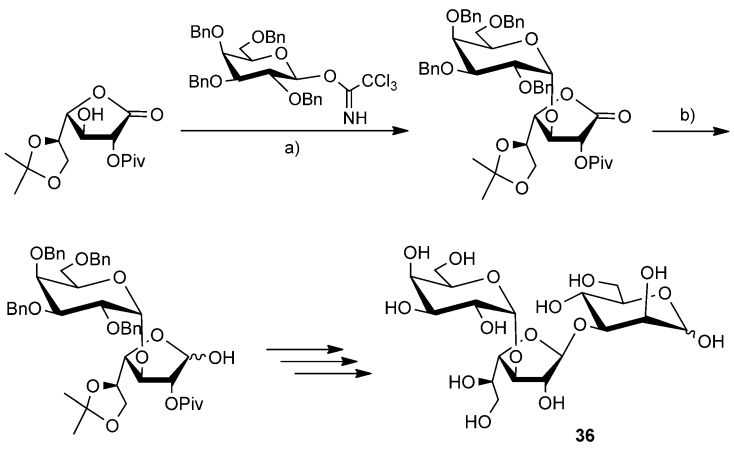


Scheme 14. Installation of the β-D-Gal*f*-(1→3)-D-Gal*f* linkage by the glycosyl iodide method by using acceptor **34**.[34] a) TMSI, CH_2Cl_2; b) EtN(*i*Pr)$_2$, 79%; c) DSB, THF, 93%.

to obtain the derivative **43** (Scheme 18). This thioglycoside was designed to act as a donor by activation with NIS/AgOTf and as an acceptor after delevulinoylation. Compound **43** was a key precursor for the synthesis of oligosaccharides **44** and **45**, containing the repeating unit [→3)-β-D-Gal*f*-(1→3)-α-D-Gal*p*-(1→] present in the lipopolysaccharide of *Klebsiella pneumoniae*.[62]

Another interesting approach for the synthesis of acceptors suitable for (1→3) linkages involved diacetonide **46**, obtained in one step from galactose (Scheme 19). A low-yield procedure was first described for the synthesis of **46**, which was obtained in 22% yield together with 1,2:3,4-di-*O*-isopropylidene-α-D-Gal*p*.[63] Improvements of the procedure were later reported, with the yield of **46** reaching 50% after chromatographic purification and crystallization.[60,64] Derivative **48** was synthesized from **46** by a sequence of reactions comprising benzylation, selective removal of the 5,6-isopropylidene acetal, acetylation, removal of the 1,2-isopropylidene acetal, and acetylation (Scheme 19).

Acceptor **48** was coupled with glycosyl donor **49** to afford trigalactoside **50**. The high reactivity of furanoside donors made it possible to use trisaccharide **50** as donor and to condense **50** with mannose disaccharide **51**, with trimethylsilyltriflate as promoter, without affecting other glycosidic linkages (Scheme 20). Pentasaccharide **52**, obtained in this manner, was crucial for the total synthesis of the *Leishmania* LPG core heptasaccharyl *myo*-inositol.[65]



Scheme 15. Installation of the (1→3)-D-Gal*f* linkage in the terminal trisaccharide of the type 2 glycoinositolphospholipids of *Leishmania* by using a type I acceptor.[52] a) TMSOTf, ether, 0 °C, 74%; b) DSB, THF, 88%.

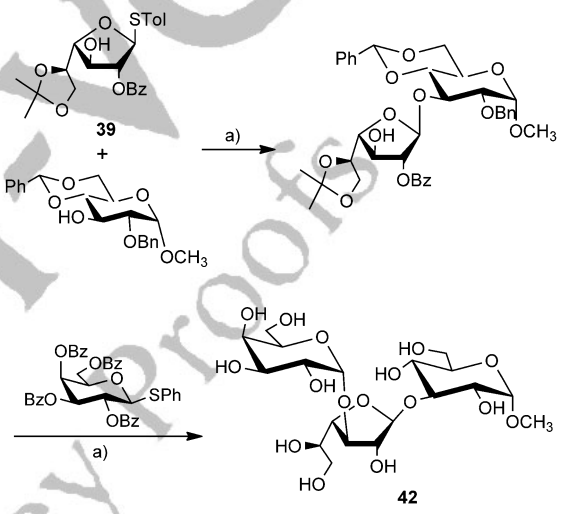
Glycosyl acceptors for (1→5)-D-Gal*f* and (1→6)-D-Gal*f* linkages

β-(1→6)-Linked galactofuranosyl oligosaccharides are constituents of cell wall polysaccharides of bacteria and fungi, such as *Nostoc commune*,[66] *Fusarium* and *Gibberella* spp.,[67] and *Penicillium*.[68] β-(1→5)-Linked galactofuranosyl units are found in some bacteria, such as *Actinobacillus pleuropneumoniae*,[69] and fungi, such as *Helminthosporium sacchari*[70] and *Penicillium fellutanum*.[25] Both linkages are simultaneously present in numerous microorganisms, includign *Mycobacterium*,[13,71] *Bifidobacterium*,[72] *Aspergillius*,[7,73,74] and *Penicillium*,[75] among others.[30–33,37]

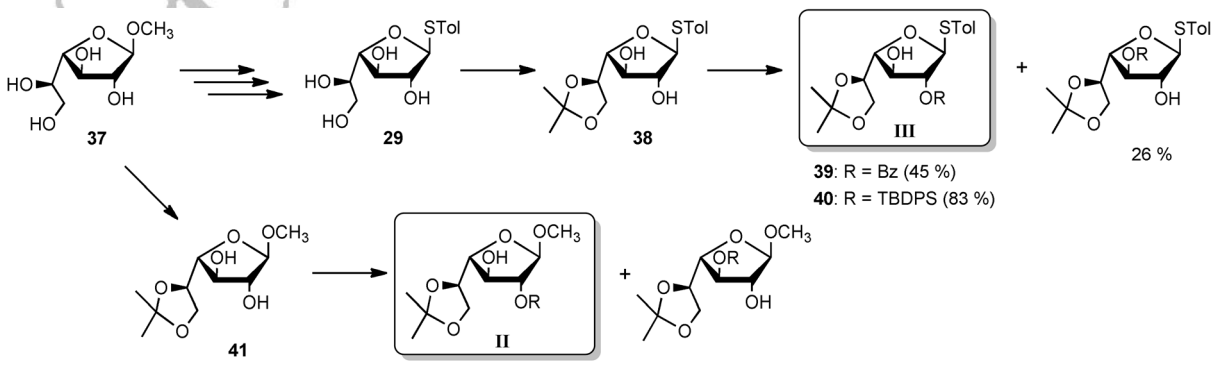
Strategies for the installation of (1→6)-D-Gal*f* linkages are based on the higher reactivity of the primary 6-OH group, which can be selectively protected with sterically demanding protecting groups, orthogonal to substituents of the other hydroxy groups. Upon deprotection, migration of the protecting group from 5-OH to 6-OH could be a problem, but this migration is useful for the installation of (1→5)-D-Gal*f* linkages. The blocking of exocyclic 5-OH and 6-OH groups as an isopropylidene acetal or other cyclic derivatives has also been used to build acceptors for (1→5) linkages.

With regard to D-galactono-1,4-lactone (**1**), type I derivatives are obtained by tritylation, benzoylation of the remaining hydroxyl group, and subsequent de-O-tritylation (Scheme 21). Derivative **54B**, obtained in this manner, has been used for the synthesis of methyl β-D-Gal*f*-(1→6)-D-Gal*f* (**55**) by condensation with per-*O*-benzoyl-D-Gal*f*, with $SnCl_4$ as promoter. Alternatively, precursor **53** was used in the glycosylation step after de-O-tritylation under glycosylation conditions (Scheme 22).[76]

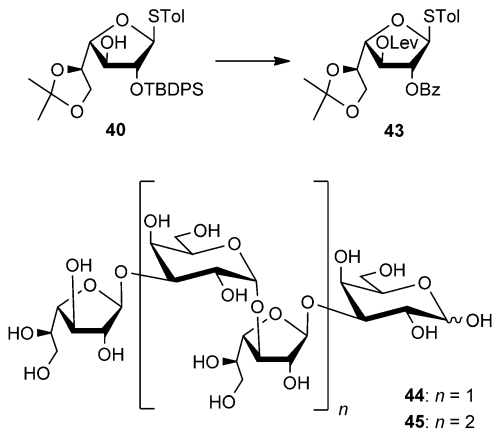
By treating **1** with controlled amounts of acylating agents, 2,6-di-*O*-substituted derivatives were obtained as a result of the higher reactivity of the primary hydroxy group and the hydroxy group vicinal to the lactone (Scheme 21). These derivatives were probed for their suitability as (1→5) acceptors, as the 5-OH located in the lateral chain is less hindered. Derivative **56**, prepared in this manner, was selectively glycosylated at the 5-OH with per-*O*-benzoyl-D-Gal*f*, by using $SnCl_4$ as a promoter. The resulting compound, **58**, was employed as the glycosyl–lactone precursor of disaccharide β-Gal*f*-(1→5)-Gal*f*



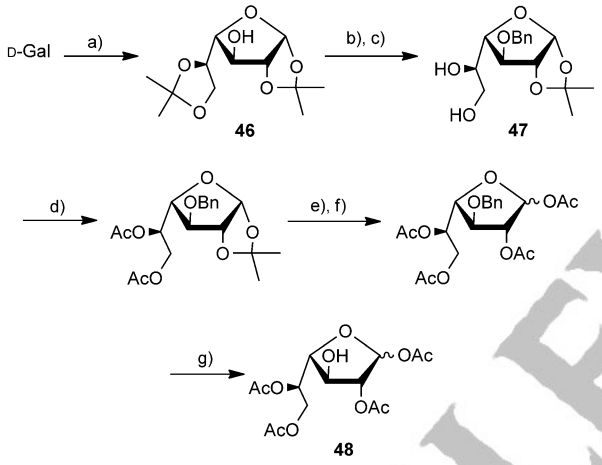
Scheme 17. Synthesis of trisaccharide **42** from partially protected derivative **39**.[61] a) NIS, TfOH, −40 to −20 °C, 79%. ■■*arrows OK?*■■



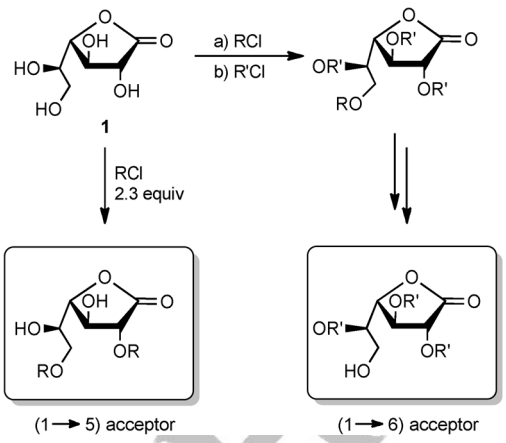
Scheme 16. Strategies for (1→3) acceptors involving alkyl or thiogalactofuranosides.



Scheme 18. Installation of the (1→3)-D-Gal*f* linkage by using latent type II acceptor **43**.[62]



Scheme 19. Strategy for (1→3)-Gal*f* type III acceptors involving di-*O*-isopropylidene derivative **46**. a) DMF/acetone, Dowex 50 [H^+], 50%;[59] b) BnCl, 63%; c) AcOH (aq), 91%; d) Ac_2O, pyridine; e) TFA, $CHCl_3$; f) Ac_2O, pyridine, 76%; g) H_2, Pd/C, 93%.



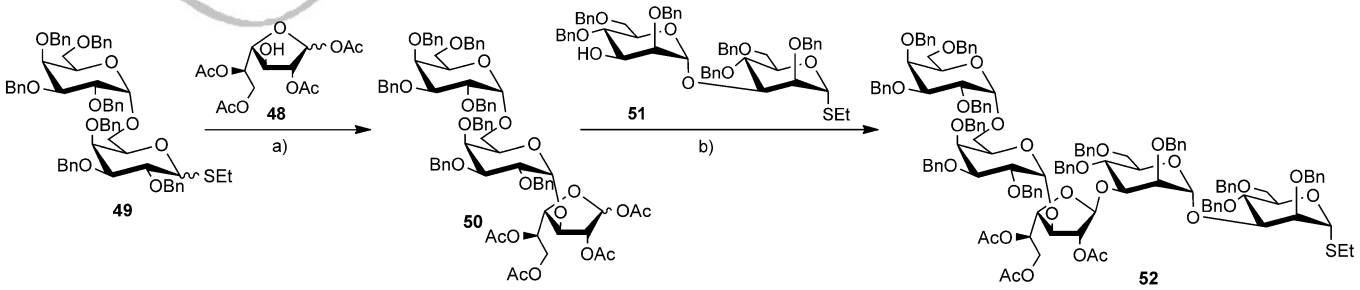
Scheme 21. Strategy for the synthesis of (1→5) and (1→6) acceptors (type I) involving D-galactono-1,4-lactone (**1**).

(**59**, Scheme 23).[77] Similarly, the pivaloylated derivative **57** was suitable for installation of the α-D-Ara*f*-(1→5)-D-Gal*f* linkage in glycoside **61**.[78] The remaining 3-OH group was further glycosylated starting from **58**, or in a one-step procedure from **56**.

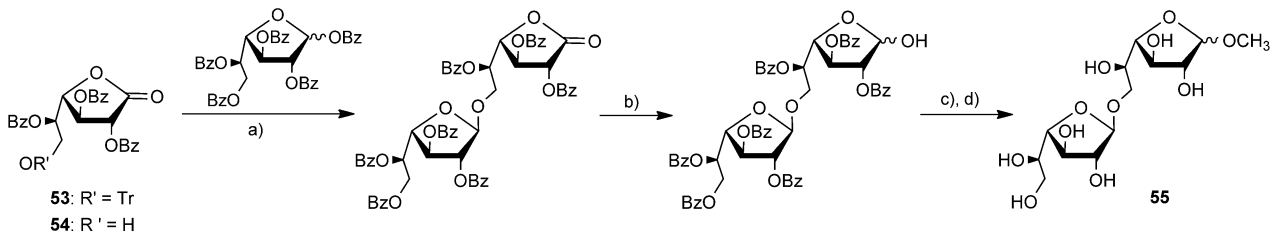
Combining the use of (1→5) (**56**, **57**) and (1→6) (**55**) type I acceptors and the trichloroacetimidate method, the synthesis of trisaccharides **62** (Scheme 24) and **63** (Scheme 25) was developed.[79,80] The same strategy allowed the synthesis of more complex fragments of the mycobacterial arabinogalactan, such as tetrasaccharides **64** and **65** (Scheme 25).[80–82]

As described in Scheme 26, (1→6)-D-Gal*f* type II acceptors are synthesized by blocking the 6-OH of an appropriate galactofuranoside with a bulky protecting group, followed by protection of the remaining hydroxy groups and deprotection of the primary position (step a in Scheme 26). Migration of the protecting group from the 5-OH to the 6-OH affords (1→5)-D-Gal*f* type II acceptors (step b). The same use of protecting groups, but starting from a thiogalactofuranoside, led to (1→6)- and (1→5)-D-Gal*f* type III acceptors. Other strategies involve the simultaneous blocking of the 5- and 6-OH groups with a cyclic derivative, followed by protection of the 2- and 3-OH groups. For example, the sequence of 5,6-isopropylidenation, acylation, de-O-isopropylidenation, and selective substitution of the 6-OH group afforded 1→5 acceptors (step c). Other cyclic derivatives led to 6-O-substituted furanosides through rearrangement reactions; these compounds are (1→5) acceptors (step d).

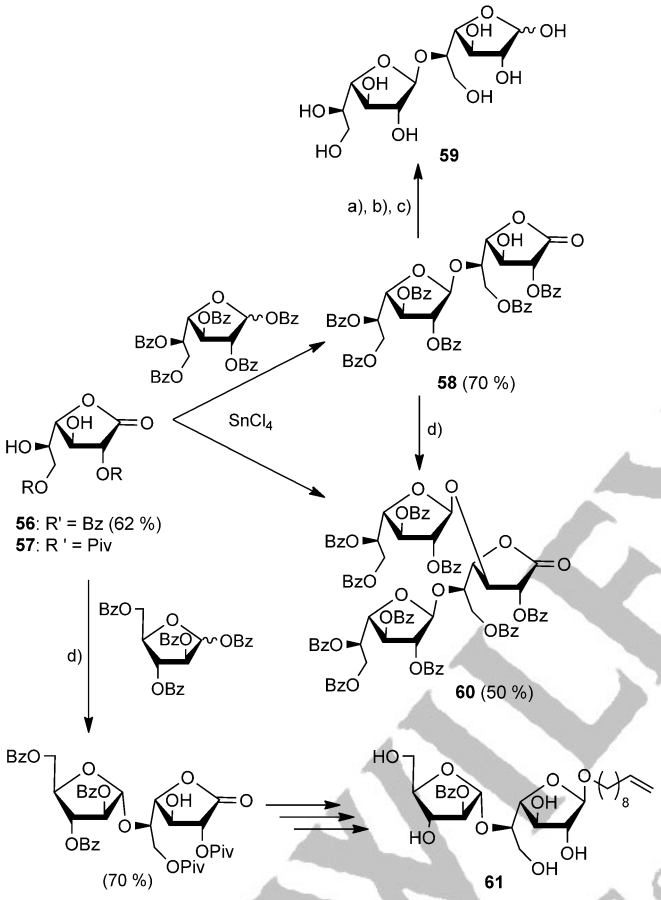
Acceptors **66** and **67** were prepared by tritylation, benzoylation, and de-O-tritylation of octyl β-D-Gal*f*. Glycosylation with a range of glycosyl donors and different activators was studied by Reynolds and co-workers[83,84] to afford **68** and **69**. The free disaccharides obtained from **68** and **69** were employed as sub-



Scheme 20. The use of glycosyl acceptor **48** and subsequent activation of the anomeric acetate.[65] a) DMTST, Et_2O, 67%; b) TMSOTf, CH_2Cl_2, 85%.



Scheme 22. Installation of the β-D-Gal*f*-(1→6)-D-Gal*f* linkage by using the aldono-lactone approach.[76] a) $SnCl_4$, CH_2Cl_2, 92% from **53**, 85% from **54**; b) DSB, THF, 86%; c) CH_2N_2, $BF_3{\cdot}OEt_2$, 77%; d) NaOMe/MeOH, 81%.



Scheme 23. Installation of the (1→5)-D-Gal*f* linkage by using the aldono-lactone approach. a) BzCl, py; b) DSB, THF; c) NaOMe/MeOH; d) $SnCl_4$, CH_2Cl_2;

strates in mycobacterial galactofuranosyltransferase assays (Scheme 27). In some cases, O-5→O-6 migration of the acyl group was also observed during the glycosylation step.[83] The same sequence, but with benzyl instead of benzoyl protecting groups, was used for glycosylation with unprotected 1-thioimidoyl hexofuranosyl donors.[85]

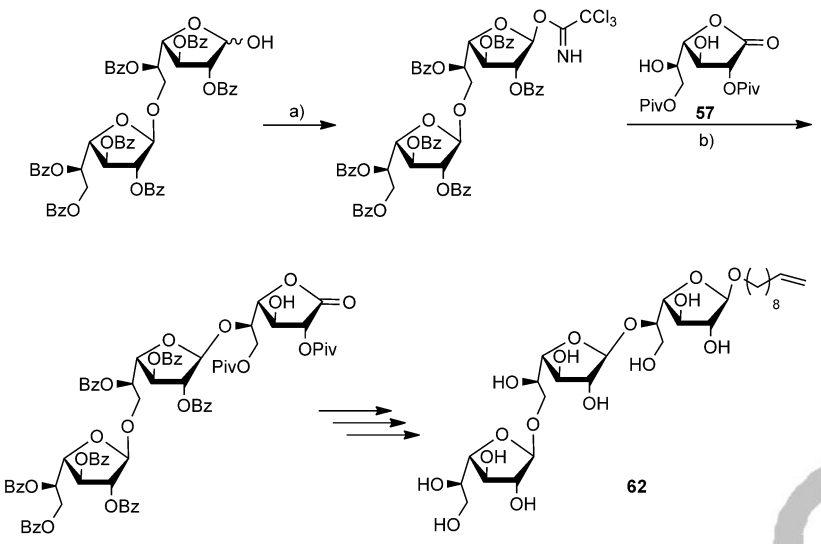
Reynolds and co-workers improved the procedure for the synthesis of disaccharide analogues of **68** and **69** with fluorescent aglycones. In order to prevent migration of the benzoyl groups, the 5- and 6-OH groups of **70** were blocked with an ■■isopropylidene *?*■■ acetal, and the two endocyclic hydroxy groups were converted into 4-methoxybenzyl groups (MPM). Removal of the isopropylidene■■ group gave derivative **71** which, upon tritylation of the primary 6-OH, benzylation of 5-OH, and O-detritylation afforded the (1→6) acceptor **72** (Scheme 28). On the other hand, selective benzylation of **71** in the presence of Bu_2SnO led to the (1→5) acceptor **73**. Glycosylation of **72** and **73** with a thioglycosidic donor afforded disaccharides **74** and **75**, which were later conjugated through reduction of the azide function with dansyl moieties (Scheme 28).[84]

The reaction sequence outlined in Scheme 29 was applied for the synthesis of type II acceptors **76** and **77**. These were iteratively used as acceptors/donors in NIS/AgOTf-promoted glycosylations to achieve the syntheses of **78**–**80**, which are acceptor substrates for mycobacterial galactofuranosyl transferases (Scheme 29).[33]

For the synthesis of the lipoteichoic acid anchor of the *Streptococcus* species DSM 8747 (**83**), a (1→6) glycosyl acceptor was required, though not to install a glycosidic linkage. The glycosyl acceptor **82** was prepared from **81** by using TBS as a sterically demanding protecting group. Silylation was performed after installing the aglycone by using the trichloroacetimidate method, then the 5-OH was benzylated. Removal of the silyl ether led to **82**, which was attached through the 6-OH to the poly(glycerophosphate) backbone by using the phosphoramidite method (Scheme 30).[86] Another approach to **83** and analogues, esterified with fatty acids of varied chain lengths, involved per-*O*-TBS-D-Gal*f* (**8**) as the starting compound. Glycosylation was performed by the glycosyl iodide method (Scheme 5),[34] and selective removal of the 6-O-silyl group was achieved by treatment with trifluoroacetic acid (Scheme 30).[87]

The D-Gal*f* urinate **84**, readily obtained by treatment of D-galacturonic acid with methanol in the presence of a cation (H^+) exchange resin,[88,89] was employed in an interesting strategy to prepare the (1→6)-D-Gal*f* acceptor. Silylation of **84** with TBSCl, followed by reduction with $LiAlH_4$ afforded compounds **85** and **86**, with product distribution of the reduction highly dependent on reaction time.[90] Reduction of **84** for short times led to **85** as the main product, which was subsequently used for the synthesis of **87**, the first example of a thiodisaccharide constituted by two furanose units (Scheme 31).[91] On the other hand, reduction of **84** for longer periods gave the diol **86** as the major product. Compound **86** was selectively substituted at the primary position with bulky protecting groups and used as a precursor for 5,6-thiiranes, useful for the synthesis of other glycomimetics.

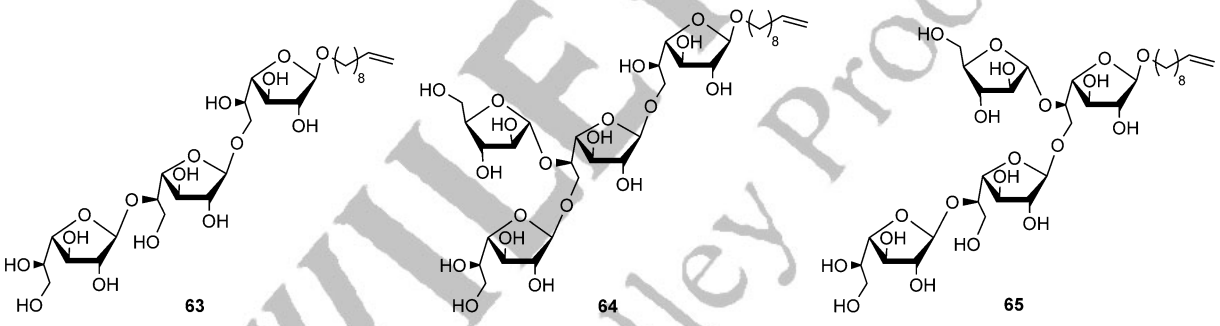
The 1,6-anhydro-α-D-galactofuranose derivative **92** was used as a starting compound for the synthesis of **93**, a latent (1→6)-



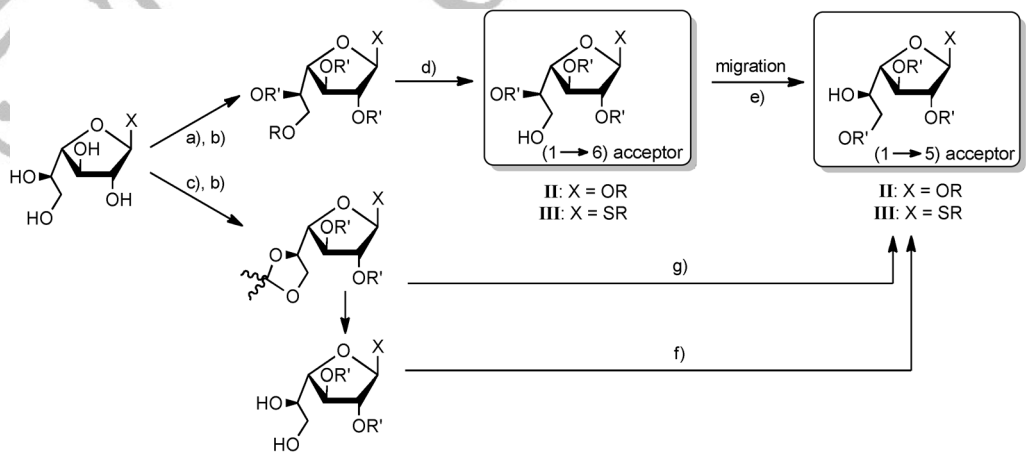
Scheme 24. The use of (1→5) and (1→6) type I acceptors. a) Cl_3CCN, DBU, 97%; b) TMSOTf, CH_2Cl_2, 73%.

D-Gal*f* acceptor. Compound **92** was prepared in six steps from galactose (Scheme 32). The 1,6-ring closure was produced by O-debenzylation of **91** and $SnCl_4$-promoted nucleophilic attack of 6-OH to C-1.[92] The optimized synthesis of **92** by this strategy has been recently described.[93] Glycosylation of **93**, obtained by acetolysis of **92**, was achieved by activation with $BF_3{\cdot}OEt_2$[94] or conversion into donor **94**.[95] The selective removal of the primary acetyl group from the allyl glycoside **95** was accomplished by treatment with acetyl chloride. The extent of the (5→6)-O-migration of the benzoyl group from **96** to **97** increased when a larger amount of acetyl chloride was employed (Scheme 32). These acceptors were employed for the synthesis of β-(1→6)-linked hexasaccharide **98** and galactofuranosyl transferase acceptors **99** and **100** (Scheme 33).[23]

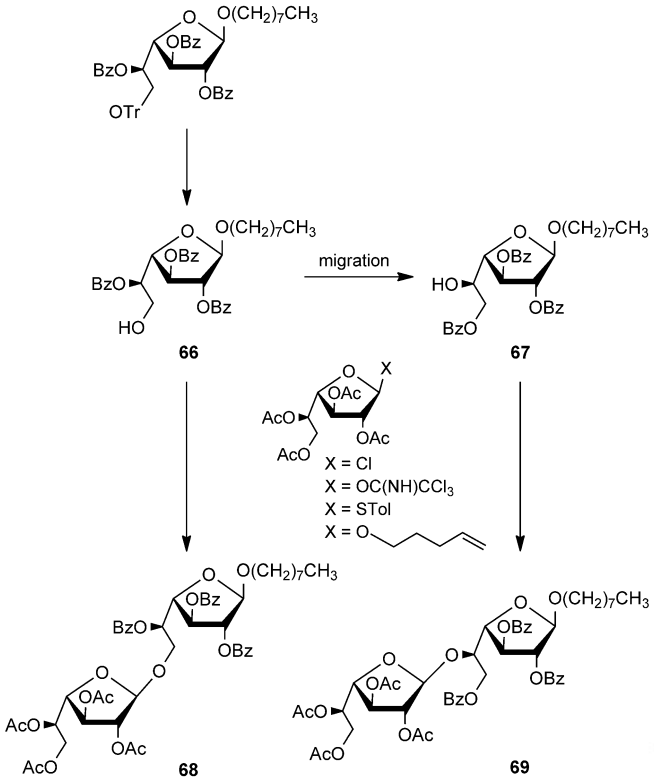
Access to (1→5)-D-Gal*f* acceptors has relied in many cases on diol **101**, obtained after removal of a 5,6-*O*-isopropylidene group, followed by regioselective substitution of the primary position. For example, compound **102**, which contains a bulky silicon group at the 6-OH moiety, was the key acceptor for the synthesis of oligosaccharides fragments of the mycobacterial arabinogalactan synthesized by the aldono-lactone approach.



Scheme 25. Oligosaccharides fragments of the mycobacterial arabinogalactan synthesized by the aldono-lactone approach. a) RCl; b) R′Cl; c) acetalation; d) ?■■; e) ?■■; f) ?■■; g) ?■■.



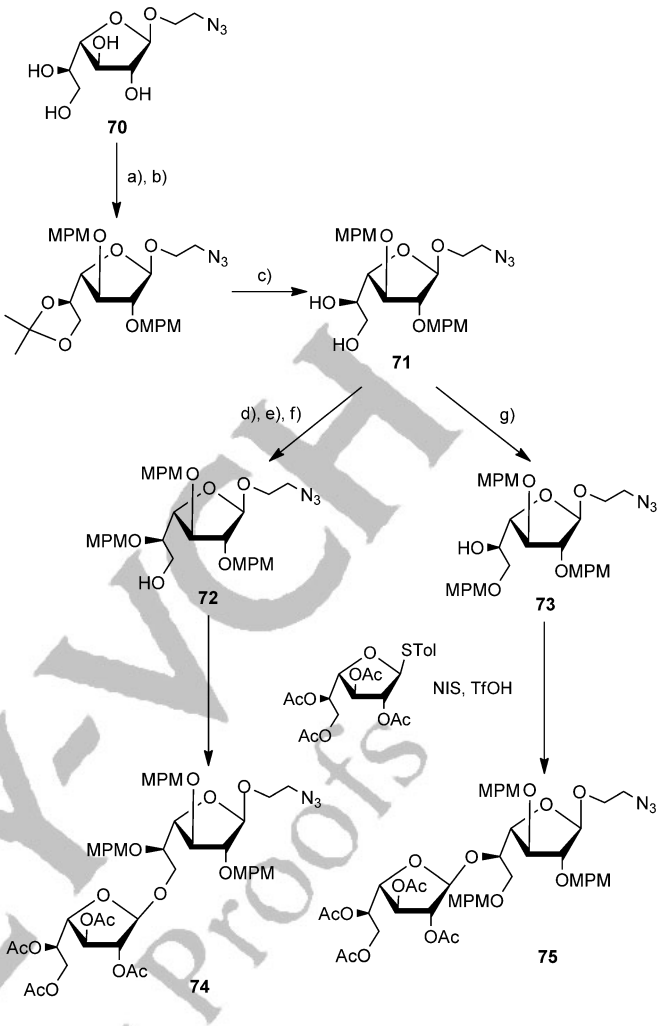
Scheme 26. Strategy for the synthesis of (1→5) and (1→6)-D-Gal*f* acceptors (types II and III).



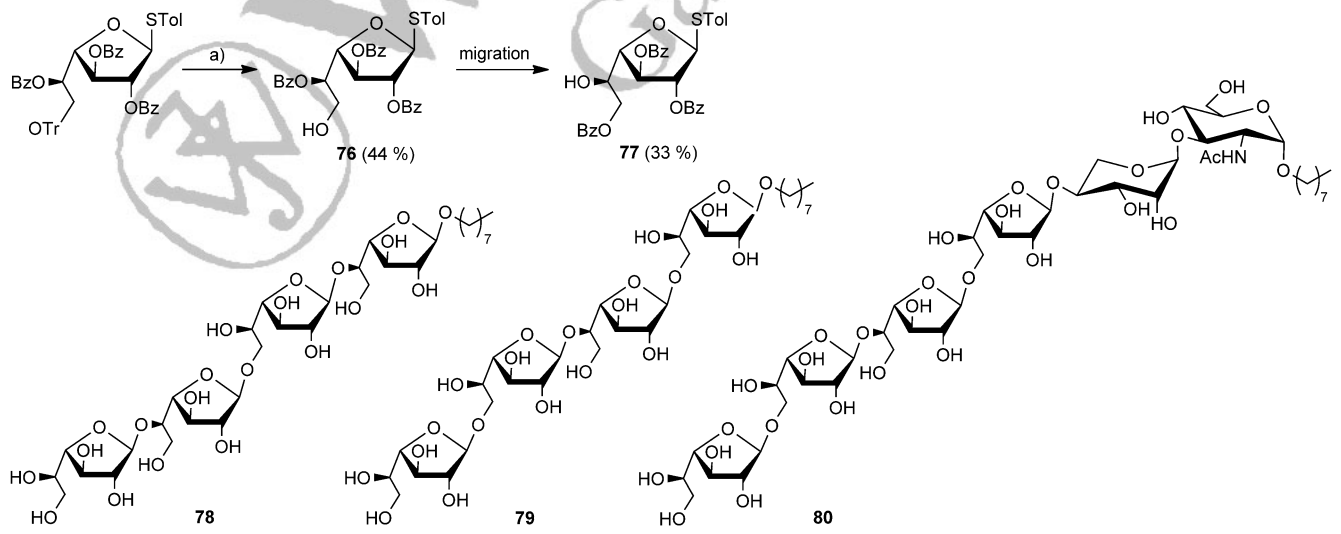
Scheme 27. Synthesis of precursors of disaccharides for mycobacterial galactofuranosyltransferase assays.[83]

ides of motif E of the arabinogalactan of *M. tuberculosis*. Thus, trisaccharide **103** was obtained by a sequence of reactions comprising glycosylation of the 5-OH group, unblocking and glycosylation of the 6-OH group, and complete deprotection (Scheme 34).[96]

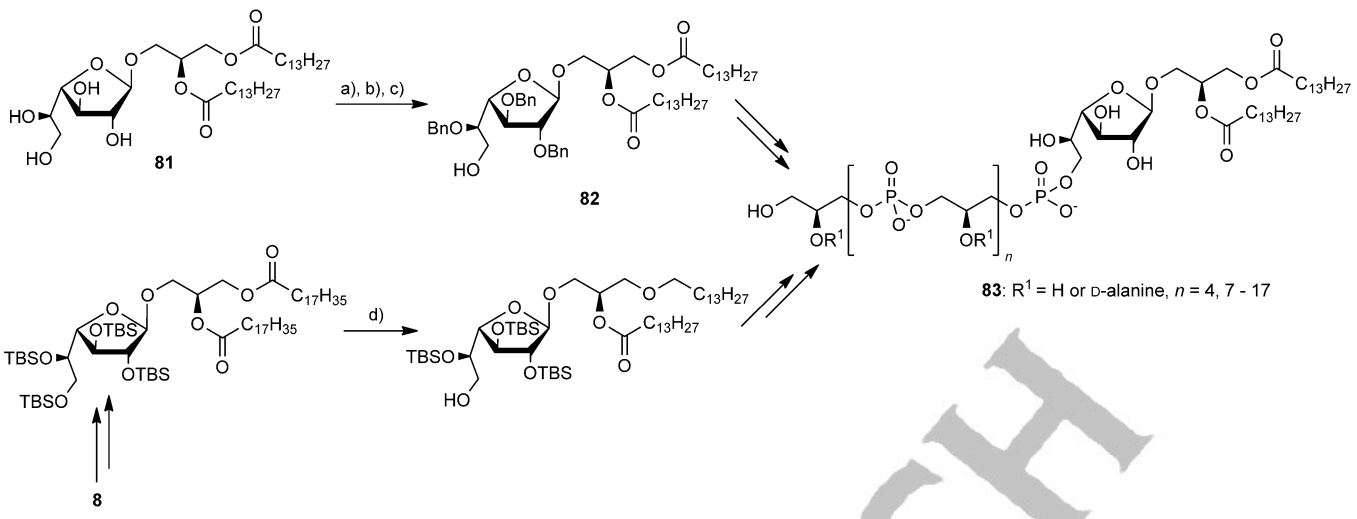
Similarly, type III acceptor **104** was prepared as depicted in Scheme 35 and was iteratively used as a donor by activation with NIS or NBS/TfOH and as an acceptor after removal of the



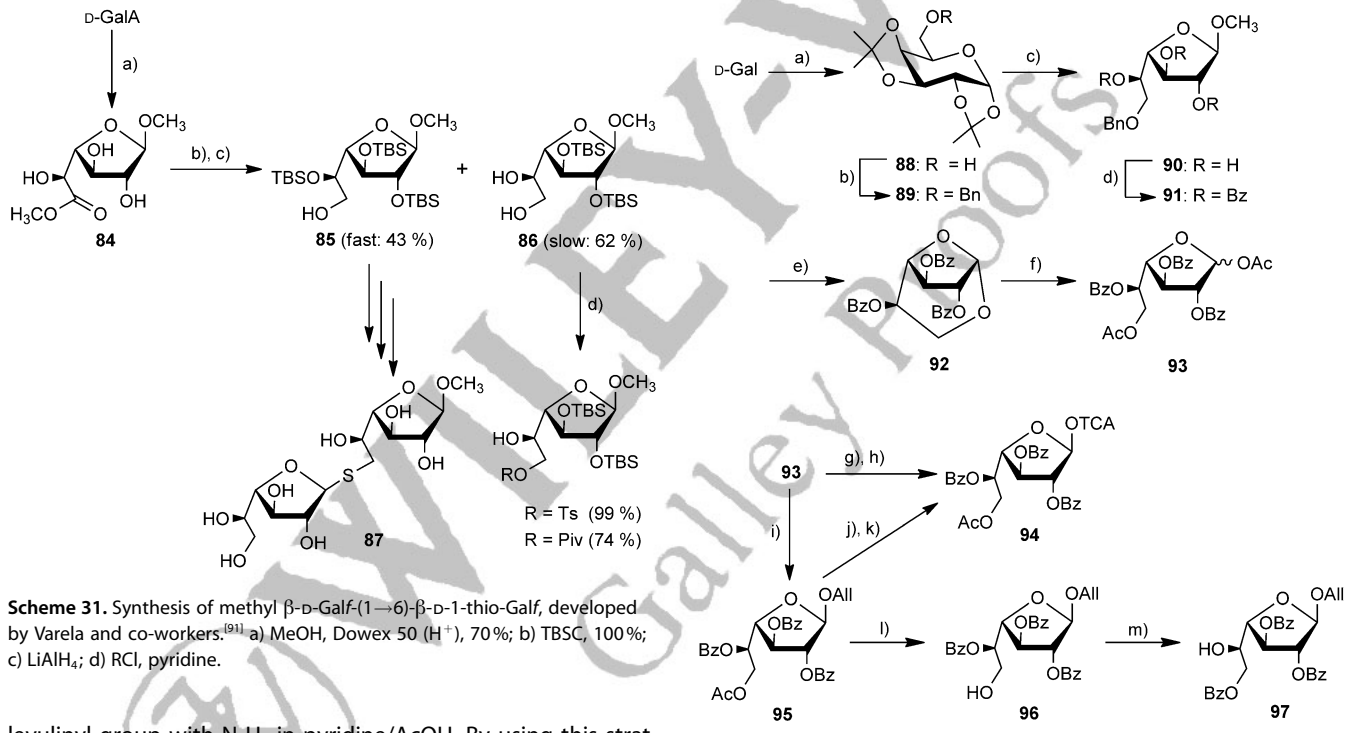
Scheme 28. Synthesis of precursors of fluorescent disaccharides for mycobacterial galactofuranosyltransferase assays.[84] a) 2,2-dimethoxypropane, CSA, 82%; b) MPMCl, NaH, 98%; c) aq AcOH, 77%; d) TrCl, DMAP, 80%; e) MPMCl, NaH, 86%; f) TFA, 70%; g) Bu2SnO, MPMCl, 90%.



Scheme 29. Acceptor substrates for mycobacterial galactofuranosyl transferases synthesized by Completo and Lowary.[33] a) TFA, H_2O, CH_2Cl_2.



Scheme 30. Synthesis of the lipoteichoic acid anchor of the *Streptococcus* species DSM 8747.[86,87] a) TBSCl, DMAP, 63%); b) BnBr, HNa, 90%; c) TBAF, 76%; d) TFA aq., 72%.



Scheme 31. Synthesis of methyl β-D-Gal*f*-(1→6)-β-D-1-thio-Gal*f*, developed by Varela and co-workers.[91] a) MeOH, Dowex 50 (H^+), 70%; b) TBSC, 100%; c) $LiAlH_4$; d) RCl, pyridine.

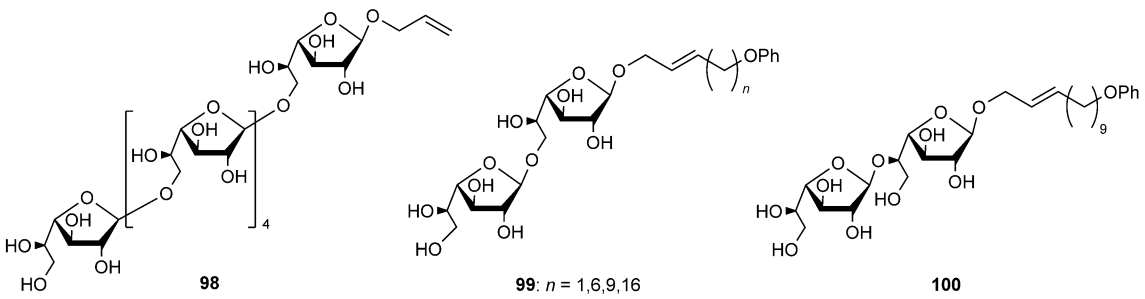
levulinyl group with N_2H_4 in pyridine/AcOH. By using this strategy, the biotin-conjugated tetrasaccharide **105** was synthesized, which was used as a tool for the in vitro diagnosis of aspergillosis.[97]

Alternative approaches for the installation of (1→5)-D-Gal*f* linkages have been based on other 5,6-cyclic derivatives. A pioneering synthesis of D-Gal*f*-(1→5)-D-Gal*f* involved the 5,6-*O*-dimethylaminobenzylidene **106** which, under acidic treatment, afforded the 6-*O*-benzoyl derivative **107** (Scheme 36).[98]

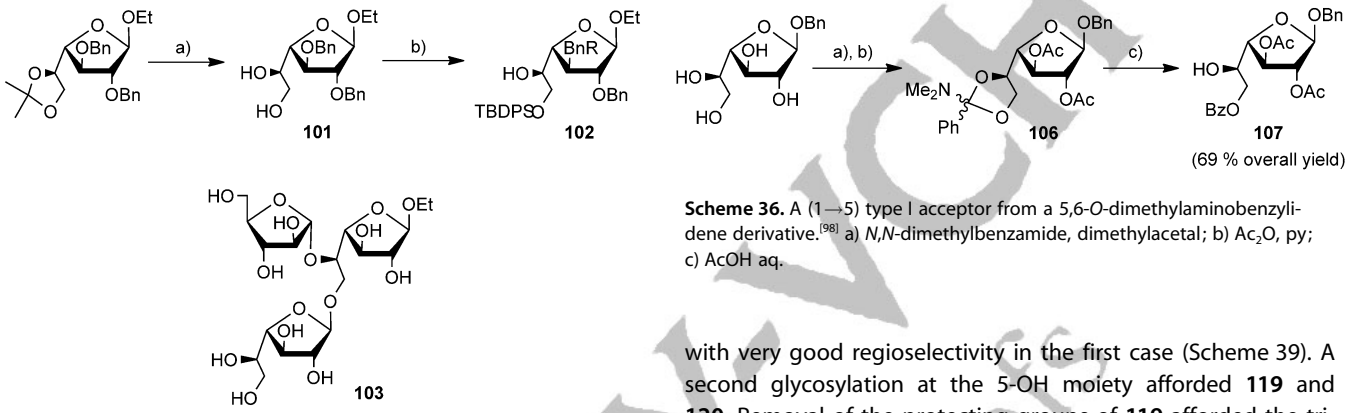
The use of organotin reagents provided useful means to efficiently obtain 6-*O*-substituted derivatives. The 5,6-stannylene acetal **109** was prepared by treatment of **108** with nBu$_2$SnO, and it was selectively benzylated in situ on the 6-OH group to afford **110** (Scheme 37). This (1→5) type II acceptor was used,

Scheme 32. (1→5) and (1→6)-D-Gal*f* acceptors from 2,3,5-tri-*O*-benzoyl-1,6-anhydro-α-D-galactofuranose (**92**). a) acetone/H^+; b) BnBr, NaOHaq, Bu_4NBr, CH_2Cl_2; c) pTsOH, MeOH, reflux, 6 h, 61%; d) BzCl, py; e) $SnCl_4$, CH_2Cl_2, 69%; f) Ac_2O/H_2SO_4, 80%; g) HBr, HOAc; h) CCl_3CN, K_2CO_3, 83%; i) $BF_3{\cdot}OEt_2$, allyl alcohol, 80%; j) $PdCl_2$; k) CCl_3CN, K_2CO_3; l) AcCl, MeOH, CH_2Cl_2, 87%; m) (5→6)-O-migration.

as mentioned above, to improve the synthesis of mycobacterial galactosyltransferase acceptors (Scheme 28) by Reynolds and co-workers,[83] as well as for glycosylation reactions with unprotected 1-thioimidoyl galactofuranosides as donors.[99] Similarly, analogues bearing a methyl (**111**)[83] or a naphthylmethyl (**112**)[99] group at O-6 were prepared (Scheme 37). By levulynation of a 2,3-benzoyl analogue, latent acceptor **113**



Scheme 33. Synthesis of substrates for galactofuranosyl transferase (GlfT2) studies.

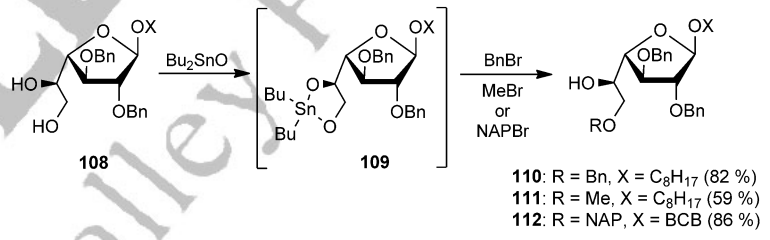


Scheme 34. Synthesis of the motif E trisaccharide of the *M. tuberculosis* arabinogalactan.[96] a) AcOH; b) TBDPSCl, imidazole, 90%.

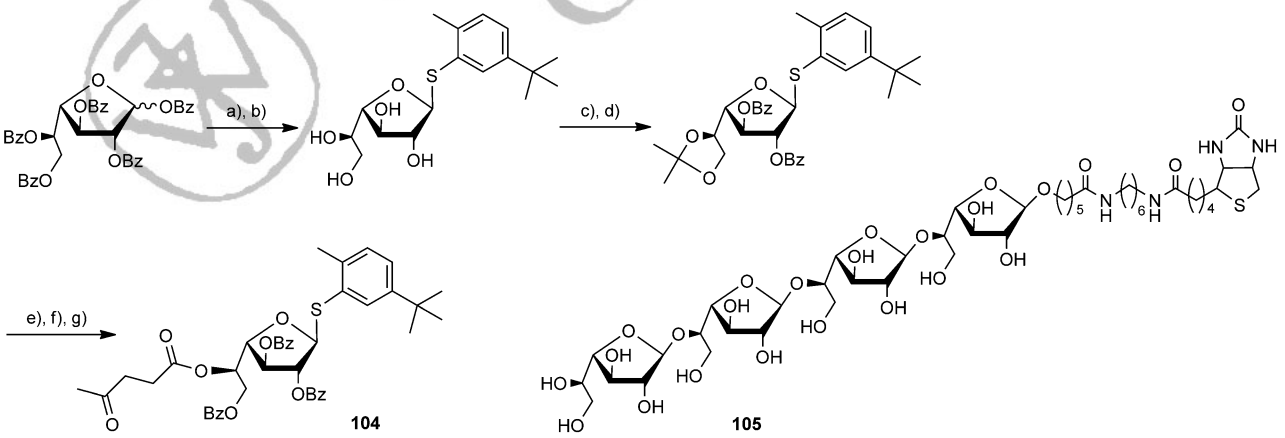
Scheme 36. A (1→5) type I acceptor from a 5,6-*O*-dimethylaminobenzylidene derivative.[98] a) *N,N*-dimethylbenzamide, dimethylacetal; b) Ac_2O, py; c) AcOH aq.

was prepared,[58,100] and combining the use of glycosyl fluorides and carboxybenzyl donors, acceptors **111** and **113** were employed for the synthesis of cyclic galactofuranosides **114** (Scheme 38).[58]

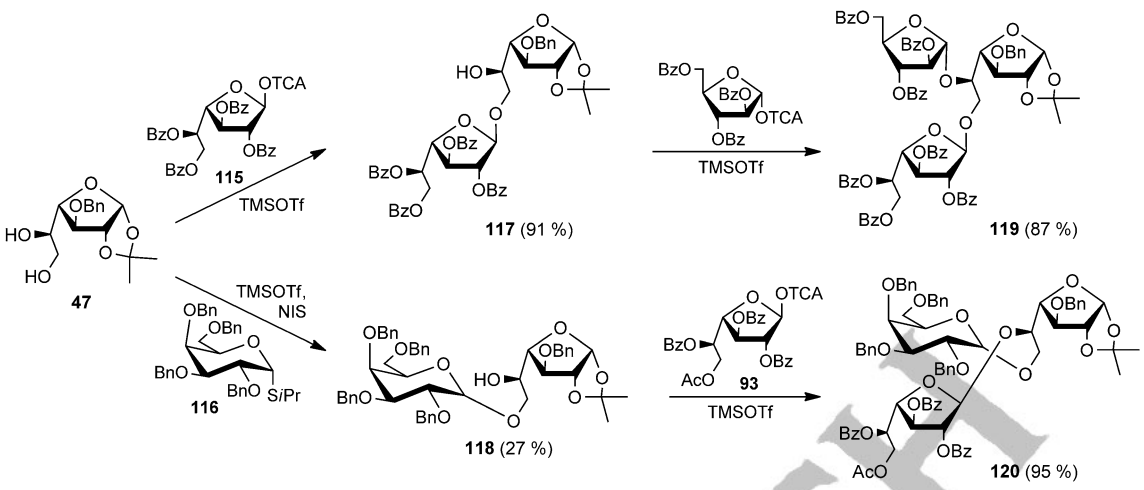
Another interesting approach relied on the regioselective glycosylation of the acetonide **47**, bearing two potentially reactive hydroxy groups (Scheme 19). By condensation with galactosyl donors **115**[101] and **116**,[102] 6-O-glycosides **117** and **118** were obtained, with very good regioselectivity in the first case (Scheme 39). A second glycosylation at the 5-OH moiety afforded **119** and **120**. Removal of the protecting groups of **119** afforded the trisaccharide present in motif E of the *M. tuberculosis* cell wall.[102] Trisaccharide **120** was used for the synthesis of a 5,6-branched



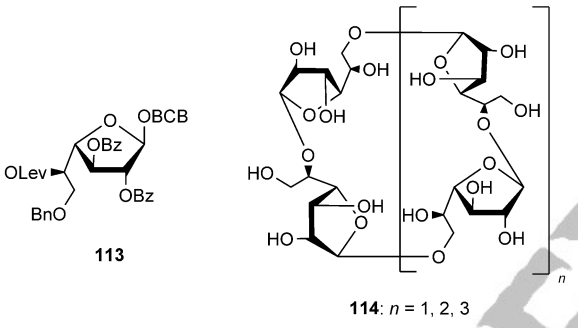
Scheme 37. (1→5) type I and II acceptors from 5,6-stannylene acetals.



Scheme 35. Synthesis of biotinylated tetrasaccharide **105** from type III acceptor **104**.[97] a) $BF_3{\cdot}Et_2O$, RSH, 97%; b) NaOMe, 90%; c) 2,2?■■-dimethoxypropane, CSA, 90%; d) BzCl, DMAP, 99%; e) aq AcOH, 100%; f) BzCl, DMAP −20 °C, 51%; g) LevOH, DCC, DMPA ■■*DMAP?*■■, 78%.



Scheme 39. Strategies involving regioselective glycosylation of acetonide **47**.



Scheme 38. Cyclic galactooligofuranosides synthesized by using latent acceptor **113**.[58]

hexasaccharide of the cell-wall galactans of *Bifidobacterium catenulatum*.[101]

Summary

During the past years, the synthesis of oligosaccharides and glycoconjugates containing D-Gal*f* units has been extensively investigated, due to the fact that this sugar is present in glycoconjugates of low microorganisms and plays a critical role in the survival and pathogenicity of many of them. Extensive developmental work with synthetic substrates has led to elucidation of the pathways involved in the assembly of these glycoconjugates. However, it will take more effort and further research to gain a better insight into the enzymatic mechanisms that operate in each individual case. This will make it possible to develop chemotherapeutic agents.

The efficient synthesis of D-Gal*f*-containing molecules requires the choice of galactose derivatives in the furanosic configuration as precursors of the D-Gal*f* units in the target molecules, as well as appropriate methods for the construction of β- and α-D-Gal*f* linkages. The preparation of partially protected derivatives to be used as glycosyl acceptors is also critical. A number of strategies have been developed for this purpose and have been summarized in this paper. The enormous synthetic work already done will contribute to the synthesis of new D-Gal*f*-containing molecules, that is, substrates analogues and inhibitors, to be used as probes in glycobiology.

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Keywords: carbohydrates · galactofuranosides · galactofuranosyl acceptors · glycosylation · organic synthesis

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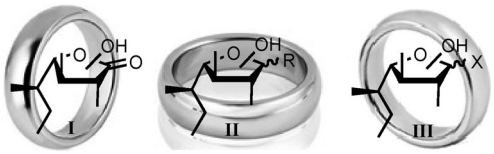

Three rings to rule them all: For the synthesis of D-gal*f* oligosaccharides and glycoconjugates, partially protected derivatives of D-galactofuranose that are suitable as glycosyl acceptors are synthesized mainly from three types of derivatives (type I, II, and III). This review describes the diverse strategies developed for this purpose and recent applications.

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Synthesis of D-Galactofuranose-Containing Molecules: Design of Galactofuranosyl Acceptors