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Synthesis and evaluation of glycosyl donors with novel leaving groups for transglycosylations employing β-galactosidase from bovine testes

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Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—Novel aryl β-D-galactopyranosides were synthesized employing phase-transfer catalysis, and assayed as potential galactose donors in the presence of β-galactosidase from bovine testes using *p*NP-Gal as a reference. The aglycones were represented mainly by nitrophenols containing halogens, hydroxymethyl, aldehyde, carboxyl, ester or amino functions. An unusual intermolecular acetyl migration onto the benzylic alcohol group was observed during galactosylation of hydroxymethylnitrophenols. Pyridyl glycosides were obtained by reaction with the corresponding silver pyridinolates. Glycosides of halo-, hydroxymethyl- or methoxycarbonyl-nitrophenols as leaving groups gave virtually the same yields of transglycosylation products. A minor increase was achieved with nitrosalicylaldehyde as leaving group, whereas carboxy or amino derivatives gave very low or no yield of the transglycosylation product. Commercially available donors such as resorufinyl and 4-methylumbelliferyl β-D-galactopyranosides exhibited a lower transglycosylation potential than these novel *p*NP-Gal derivatives.

Keywords: Glycosidases; Galactosidases; Chemoenzymatic glycosylation; Leaving group

1. Introduction

As part of our ongoing work towards modified sialylated Thomsen–Friedenreich antigen components, we employed β-galactosidases to synthesize the core Galβ1-3GalNAc motif, looking for improvements in yield and regioselectivity.[1] In many cases the optimization of already well known and utilized reaction conditions for the chemoenzymatic glycosylation regarding pH, temperature or buffer system shows only limited implications on the yield.[2,3] Especially, the use of organic cosolvents to reduce water activity and hence hydrolysis might influence enzyme efficiency. Significant improvements have been made by modifications of the enzyme itself. Substitution of the catalytic nucleophile in the binding pocket of a retaining glycosidase by a non-nucleophilic amino acid gave rise to a new group of oligosaccharide synthesizing enzymes, the hydrolytically inactive glycosynthases.[4] However, until to date there have been only a few reports on their use. As long as there will be no greater diversity of glycosynthases available, a simple and more universal method for improving yields in transglycosylation is still sought after.

If a carbohydrate acceptor is bound in the active centre of a retaining glycosidase in such a manner that the transition state is stabilized, the activation energy for transglycosylation is reduced, resulting in the respective oligosaccharide as the kinetic product.[5] Most commonly an extensive excess of acceptor is used to shift the second step of transglycosylation—the transfer of the glycosyl residue from the intermediate glycosyl–enzyme complex

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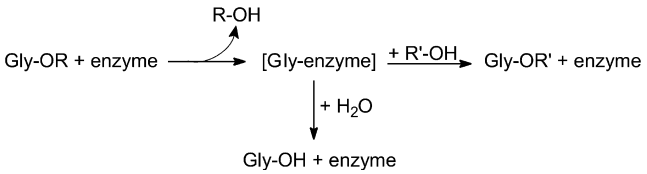


Chart 1. Principle of transglycosylation.

to the acceptor glycoside instead of water—towards the desired oligosaccharide product (Chart 1). The main drawback becomes obvious in the case of not easily available or expensive acceptors, as recovery of the excess acceptor is sometimes quite difficult. Another approach is to increase the concentration of the intermediate glycosyl–enzyme complex, which could already be achieved by employing an oversaturated soln of the most commonly used donor *p*-nitrophenyl β-D-galactopyranoside (*p*NP-Gal).[6] However, under these reaction conditions, the donor may function as an acceptor as well, and thus a considerable amount of the self-glycosylated product was expected and isolated.

Two possible approaches for a faster formation and therefore higher concentration of the intermediate glycosyl–enzyme complex will be examined in this work by varying the leaving group of the glycosyl donor. On the one hand, donors with a better solubility in aqueous solns would allow their use in higher concentrations, and on the other hand, activated donors would show a higher reactivity and therefore reduce hydrolysis of the already formed products. On the latter relies the high transglycosylation activity of *p*NP-Gal, because the released aglycone *p*NP–OH is a poor acceptor itself and can be easily removed during work-up. Although commercially available reducing disaccharides such as lactose or lactulose can be utilized as well, they are less reactive and the released aglycone is a competing acceptor giving rise to product mixtures, which are difficult to separate.[7] In the following sections, the synthesis of novel potential donors is described and their suitability for transglycosylation examined.

2. Results and discussion

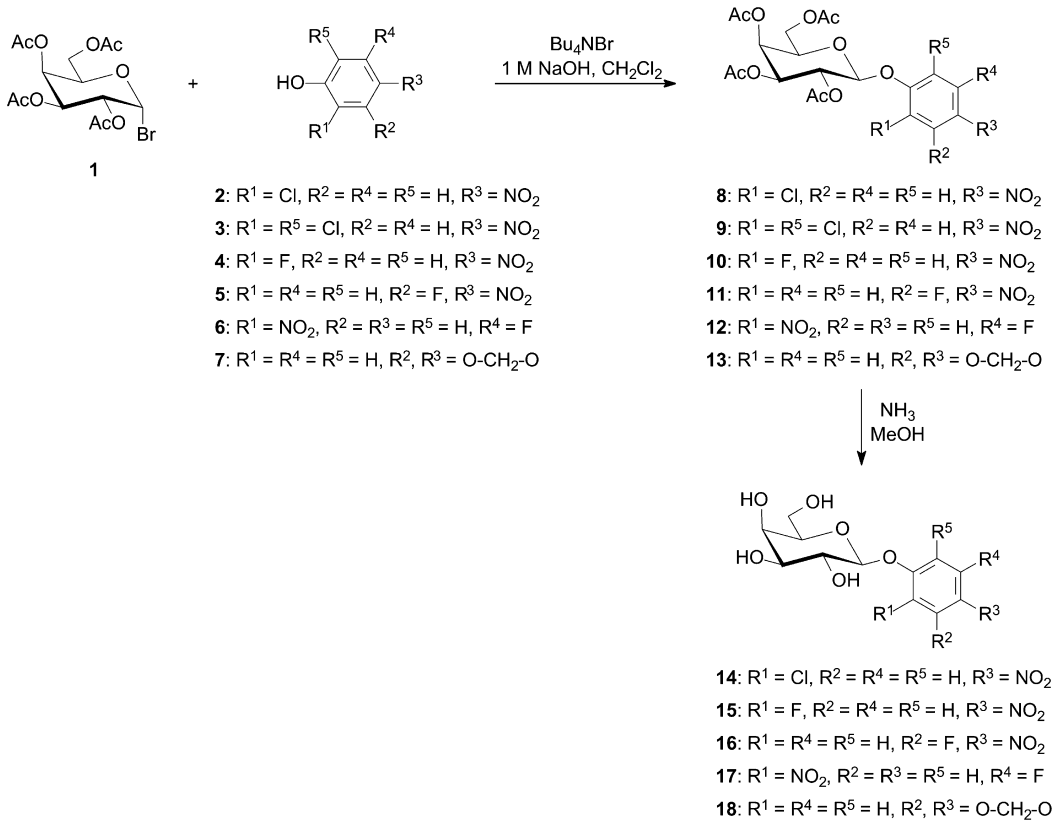
2.1. Synthesis of glycosyl donors

A great diversity of glycosylation methods have been developed and extensively used for the formation of different glycosides.[8–10] The synthesis of aryl β-glycosides could be achieved conveniently and fast under phase-transfer conditions in very good yields.[11] The reaction takes place in an aqueous-organic two-phase system, in which a phase-transfer catalyst forms a lipophilic ion-pair together with the deprotonated phenolate, which migrates into the organic phase. In an aprotic nonpolar solvent such as dichloromethane, the ion-pair is not solvated, and the naked phenolate shows enhanced nucleophilicity and reacts readily with acetobromosugars. Typical phase-transfer catalysts are quaternary ammonium salts or crown ethers, which are soluble in both the organic and aqueous phases.[12]

The phase-transfer-catalyzed (PTC) galactosylation of 2-chloro-4-nitro-(**2**), 2,6-dichloro-4-nitro- (**3**), 2-fluoro-4-nitro- (**4**), 3-fluoro-4-nitro- (**5**) and 5-fluoro-2-nitrophenol (**6**) was achieved in the presence of tetrabutylammonium bromide as phase-transfer catalyst utilizing 3 equiv of the respective phenol in a two-phase system consisting of aqueous sodium hydroxide and dichloromethane in very good yields (Scheme 1). A major advantage of this method is the use of the simple donor 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**1**), which is available in a one-pot reaction from D-galactose.[13] The reaction was stopped by the addition of an excess of EtOAc, in which tetrabutylammonium bromide is not soluble, simplifying work-up significantly. The synthesis of 2-chloro-4-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**8**) reported elsewhere by use of potassium carbonate in acetone under nitrogen could be accelerated (4 h at 35 °C instead of 36 h at 55 °C) while the yield was slightly improved from 76% to 83%.[14] The glycosylation of 3,4-methylenedioxyphenol (sesamol, **7**) gave a somewhat lower yield of **13**, as considerable decomposition of the aglycone occurred.[15] Deprotection of **8** and **10**–**13** to the unprotected donors **14**–**18** used in subsequent chemoenzymatic galactosylation was accomplished in high yield by treatment with catalytic amounts of ammonia in MeOH. Only the removal of the acetyl groups from **9** was not successful, as in our hands even very mild reagents resulted in the cleavage of the activated glycosidic linkage. Thus the treatment of **9** with ammonia in MeOH at pH 8 in the cold gave within 5 min 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose[16] in 93% yield.

The reaction with 3 equiv 4-nitrocatechol (**19**) gave exclusively the undesired bisglycosylated product **20**. Despite an excess of acceptor, no monoglycosylated intermediate could be isolated (Scheme 2). The first glycosylation of the acceptor improves the solubility in the organic phase and seems to enhance the nucleophilicity of the second phenolate, thus apparently bisglycosylation is favoured.

As only phenols react under conditions of phase-transfer catalysis, it is possible to glycosylate a phenolic hydroxy group selectively in the presence of a benzyl alcohol function. Thus 5-hydroxy-2-nitrobenzyl alcohol **21** was galactosylated exclusively at the phenolic position (Scheme 3). Due to partial intermolecular acetyl migration, a mixture of two aryl β-glycosides **22** and **23** was formed in a ratio of 5:2. The derivatives containing either an acetylated or free benzylic alcohol function could easily be separated and severally fully deacetylated, giving the same unprotected glycoside **24**. Since



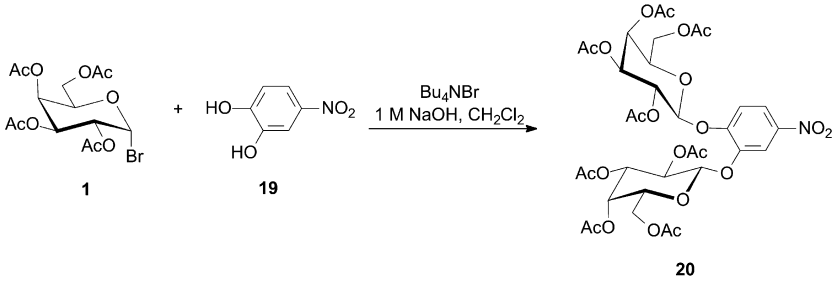
1

2: R^1 = Cl, R^2 = R^4 = R^5 = H, R^3 = NO_2
3: R^1 = R^5 = Cl, R^2 = R^4 = H, R^3 = NO_2
4: R^1 = F, R^2 = R^4 = R^5 = H, R^3 = NO_2
5: R^1 = R^4 = R^5 = H, R^2 = F, R^3 = NO_2
6: R^1 = NO_2, R^2 = R^3 = R^5 = H, R^4 = F
7: R^1 = R^4 = R^5 = H, R^2, R^3 = O-CH_2-O

8: R^1 = Cl, R^2 = R^4 = R^5 = H, R^3 = NO_2
9: R^1 = R^5 = Cl, R^2 = R^4 = H, R^3 = NO_2
10: R^1 = F, R^2 = R^4 = R^5 = H, R^3 = NO_2
11: R^1 = R^4 = R^5 = H, R^2 = F, R^3 = NO_2
12: R^1 = NO_2, R^2 = R^3 = R^5 = H, R^4 = F
13: R^1 = R^4 = R^5 = H, R^2, R^3 = O-CH_2-O

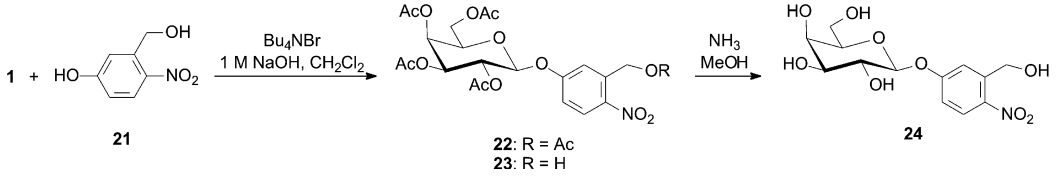
14: R^1 = Cl, R^2 = R^4 = R^5 = H, R^3 = NO_2
15: R^1 = F, R^2 = R^4 = R^5 = H, R^3 = NO_2
16: R^1 = R^4 = R^5 = H, R^2 = F, R^3 = NO_2
17: R^1 = NO_2, R^2 = R^3 = R^5 = H, R^4 = F
18: R^1 = R^4 = R^5 = H, R^2, R^3 = O-CH_2-O

Scheme 1. Phase-transfer catalyzed galactosylations.



1 19 20

Scheme 2. Formation of a bisgalactosylated phenol.

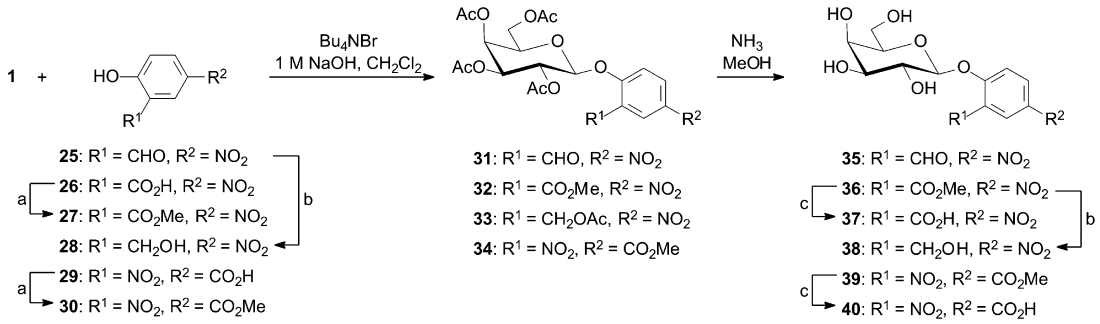


21 **22**: R = Ac **23**: R = H 24

Scheme 3. Intermolecular acetyl migration during glycosylation of 5-hydroxy-2-nitrobenzyl alcohol.

the phenol **21** has a rather good solubility in water, the concentration of the reactive phenolate in the organic phase is reduced, resulting in a somewhat lower yield of glycosylation.

The galactosylation of 2-hydroxy-5-nitrobenzaldehyde (**25**) employing potassium carbonate in acetonitrile was reported in a patent, but the yield was not satisfactory.[17] By means of phase-transfer catalysis the yield could be doubled, giving 59% of the galactopyranoside **31** (Scheme 4). Further, the aldehyde **25** could be reduced to give the corresponding benzyl alcohol **28**. Its glycosylation gave **33** with complete acetylation of the benzylic hydroxy group. Apparently, this was formed by intermolecular migration and no traces of the corresponding glycosylation product with an unprotected benzylic alcohol function could be detected (Scheme 4).



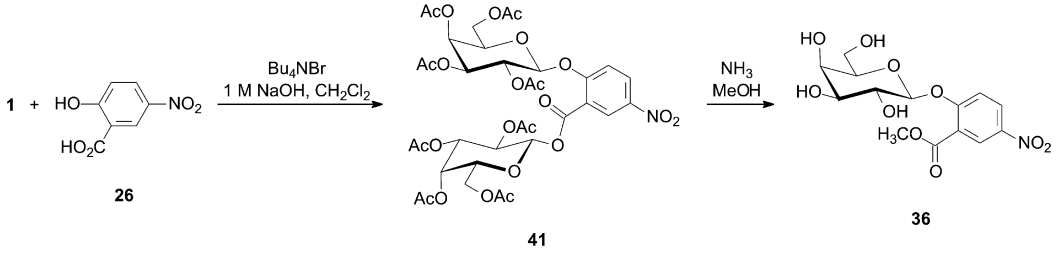
Scheme 4. Glycosylation of phenols containing formyl, methoxycarbonyl, carboxy or hydroxymethyl residues. (a) IR-120 (H^+), MeOH; (b) $NaBH_4$, EtOH; (c) NaOH, MeOH.

Treatment of 5-nitrosalicylic acid (**26**) and 4-hydroxy-3-nitrobenzoic acid (**29**) with MeOH in the presence of a cation-exchange resin (H^+) gave rise to the corresponding methyl esters **27** and **30**, respectively. These methyl esters were readily galactosylated under the standard phase-transfer conditions to give compounds **32** and **34** in high yields.

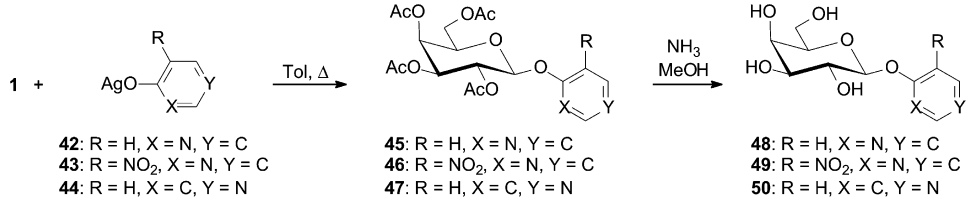
The four galactosides **31**–**34** could be deprotected under standard conditions giving an access to *p*NP-Gal derivatives containing an aldehyde, an ester or an aliphatic alcohol function in the aromatic ring. The aldehyde **35** was shown to have fourfold higher solubility in water than *p*NP-Gal itself.[17] To examine further functionalities and obtain donors with even better solubility in water, methyl esters **36** and **39** were hydrolyzed to give the corresponding free acids **37** and **40**, respectively. An alternative access to the benzylic alcohol derivative **38**, avoiding the cumbersome glycosylation of **28**, was achieved by reduction of methyl ester **36** with sodium borohydride in a substantially higher overall yield (Scheme 4). Another donor with high water solubility is *o*-aminophenyl β-D-galactopyranoside (**51**) described earlier.[18]

Synthesis of the free acid derivatives **37** and **40** had to be conducted *via* the corresponding methyl esters, since treatment of benzoic acid **26** led to an unexpected result. Under PTC glycosylation conditions both the phenolic function as well as the carboxyl group reacted with the formation of unusual β-galactopyranoside-β-galactopyranosyl ester **41** (Scheme 5). The formation of a similar structure has been reported earlier,[19] and despite the use of 4 equiv of the acceptor no formation of a monoglycosylated product could be observed. As expected, removal of the acetyl protecting groups from **41** with ammonia in MeOH resulted in the cleavage of the glycosyl-ester bond as well, giving the known methyl ester derivative **36**.

Hanessian and Lou introduced 2-pyridyl- and 3-methoxy-2-pyridyl glycosides (MOP) as anomeric activation groups, which contain a latent glycosyl-imidate structure and are suitable for very mild glycosylations.[20] Treatment of **1** with 2- or 4-hydroxypyridines under phase-transfer conditions gave a yield of typically less than 25% galactopyranosides, as formation of glycosylamines is a common side reaction. Instead, the syntheses of **45**,[21] **46**[22] and **47** were successfully conducted in



Scheme 5. Glycosylation of 5-nitrosalicylic acid (**26**): formation of an unusual glycosyl ester.



Scheme 6. Synthesis of 2- and 4-pyridyl β-D-galactopyranosides.

refluxing toluene employing the respective silver pyridinolates readily available from hydroxypyridines by treatment with silver nitrate under basic conditions (Scheme 6). Deprotection with ammonia in MeOH gave the 2- and 4-pyridyl β-D-galactopyranosides **48**,[21] **49**[22] and **50**.

2.2. Comparative transglycosylation study of the glycosyl donors

In order to compare the transglycosylation activity of these novel donors, they were made to react on an analytical scale with allyl 2-acetamido-2-deoxy-α-D-galactopyranoside (Allyl-GalNAc) as a reference acceptor under standard conditions of the enzymatic reaction, and the amount of the product, *viz*., allyl 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-α-D-galactopyranoside, was quantified by HPLC.[23]

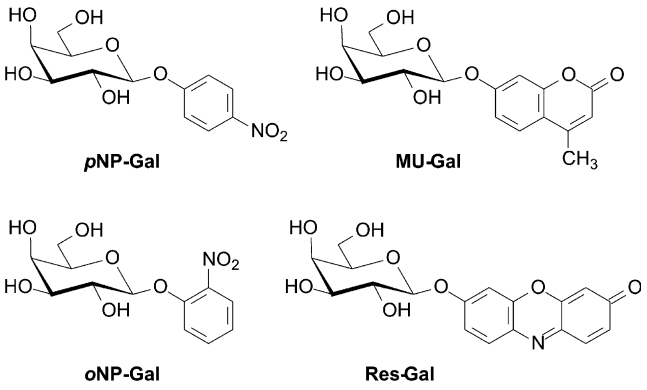
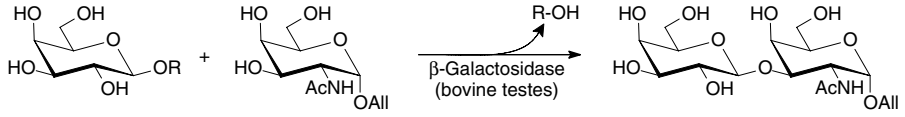


Figure 1. Commercially available donors for galactosylations.

p-Nitrophenyl (*p*NP-Gal) and *o*-nitrophenyl β-D-galactopyranoside (*o*NP-Gal) have found widespread use in transglycosylation reactions, as they are stable in incubation buffers, efficiently recognized by β-galactosidases, and a swift reaction occurs due to their high reactivity. For analytical purposes, the commercially available fluorogenic β-galactosides of 4-methylumbelliferone or resorufine are employed frequently (Fig. 1). Especially, resorufinyl β-D-galactopyranoside (Res-Gal) in only a tenth the concentration of *p*NP-Gal is cleaved at the same rate; nevertheless, no systematic examination has been done to evaluate its potential benefits for transglycosylations.[24]

HPLC-Analysis of the transglycosylation reactions allowed monitoring and quantification of the product formation. *p*NP-Gal and *o*NP-Gal gave the product in approximately the same yield of 67% and 69%, respectively, whereas the substantially less polar donors 4-methylumbelliferyl (MU-Gal) and resorufinyl β-D-galactopyranoside (Res-Gal) were transferred in far lesser amounts onto the acceptor (Table 1). Due to their strong fluorescence and low detection limits, the latter are highly suitable for analytical testing for β-galactosidase activity, but for synthetic purposes their solubility and hence their concentration in aqueous buffers are obviously too low.

Table 1. Influence of different aromatic leaving groups on the yield of transgalactosylation



Donor	R–OH	Yield (%)
*p*NP-Gal	*p*NP–OH	67
*o*NP-Gal	*o*NP–OH	69
MU-Gal	Me-umbelliferone	40
Res-Gal	Resorufine	16
14	**2**	64
15	**4**	70
16	**5**	73
17	**6**	72
18	**7**	75
24	**21**	71
35	**25**	76
36	**27**	64
37	**26**	7
38	**28**	66
39	**30**	71
40	**29**	13
51	*o*NH_2Ph–OH	—
48	**42**	12
49	**43**	—
50	**44**	77

Substitution on the aromatic ring with a halogen (**14**–**17**), having no substantial influence on the solubility in water, shows a small positive effect on the donor activity, but the results were just marginal and should be considered with caution (Table 1). Introduction of a methyl ester (**36**, **39**) or a benzylic hydroxy group (**24**, **38**) had only little influence on the transglycosylation, a positive effect due to a higher donor concentration could not be observed. An intramolecular transglycosylation on the benzylic alcohol moiety, as reported elsewhere,[25] did not occur with this β-galactosidase from bovine testes. The sesamol derivative **18** and aldehyde **35** gave higher yields than *p*NP-Gal.

Despite their high solubility in water, the free benzoic acids **37** and **40** had a low transglycosylation potential; no product formation could be observed from the aniline derivative **51**. These reactive functionalities possibly participate in strong interactions in the binding pocket of the enzyme, as they hydrolyse very slowly. Two carboxyl groups act as catalytic residues in the active centre of the enzyme, which might repel the carboxyl groups in **37** and **40**, preventing a deeper intrusion of the donor into the binding pocket. In donor **51**, not only the anomeric oxygen can be protonated, but the basic amino function as well, hence the formation of the glycosyl–enzyme-complex is apparently hampered (Table 1).

If similar substituents were in different positions of the aromatic ring (compare **36** and **39**, **37** and **40**, **38** and **24**), the donors with the substituent in the ortho-position gave a somewhat lower yield, perhaps due to some steric hindrance during the formation of the transition state. *p*NP-Gal and *o*NP-Gal represent an exception.

Kusumoto et al. introduced nitro-2-pyridyl glycosides into chemoenzymatic glycosylations, as they are chemically more reactive and exhibit a higher solubility in water than the nitrophenyl glycosides.[22] Employing the β-galactosidase from *Escherichia coli*, they used increased concentrations of the donor and were able to obtain the transglycosylation product in higher yields; in contrast, very soluble methoxy-2-pyridyl glycosides gave lower yields. In chemical glycosylations, the ring nitrogen is protonated by the catalyst added. In chemoenzymatic glycosylations, this protonation would be expected to occur by a carboxyl group in the active centre of the enzyme, however, the ring nitrogen is two bond length away from the originally to be protonated anomeric oxygen.

No formation of a transglycosylation product could be observed employing 3-nitro-2-pyridyl galactoside **49** in the presence of β-galactosidase from bovine testes, partial hydrolysis of the donor occurred instead. Utilizing the sterically less hindered 2-pyridyl galactoside **48**, the desired product formed in small amounts (Table 1). The close proximity of the ring nitrogen seems to have a negative effect on the reactive carboxyl groups in the binding pocket. In contrast, the 4-pyridyl donor **50** gave the highest yield of all donors examined. As the ring nitrogen is orientated para to the glycosidic linkage and considerably farther away from the carboxyl groups, it cannot interfere with the normal process of hydrolysis or transglycosylation. The very high yield can be explained by good water solubility, which is sixfold higher than that of *p*NP-Gal, permitting the use of higher concentrations for transglycosylation.

3. Experimental

3.1. General methods

Commercially available starting materials were used without further purification. Solvents were dried according to standard methods. β-Galactosidase from bovine testes was isolated as a crude extract.[26] The enzymatic reaction mixtures were incubated in an Eppendorf thermomixer comfort at 600 rpm. Buffer solns were prepared employing deionized water (Seralpur Pro 90C), containing 0.02% sodium azide. TLC was performed on precoated aluminium plates (Silica Gel 60 F_{254}, E. Merck 5554) employing UV-adsorption and charring with 20% H_2SO_4 in EtOH for visualization. For column flash chromatography (FC), Silica Gel 60, 230–400 mesh, 40–63 μm (E. Merck), was used. For HPLC, LiChrosphere NH_2 column (5 μm, 250 × 4 mm, E. Merck) was used with a E. Merck L-6250 pump and a E. Merck L-3000 DAD detector with DAD-manager-software LiChrograph version 4. For elution, 5% acetonitrile was used at a speed of 1 mL/min. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX-400 MHz (100.62 MHz for ^{13}C) and Bruker DRX-500 (125.83 MHz for ^{13}C) at 300 K. If necessary, assignments were confirmed by ^{1}H^{1}H- and ^{1}H^{13}C-COSY, HMQC or HMBC experiments. Tetramethylsilane or residual nondeuterated solvent was used as internal standards for determination of chemical shifts (Tables 4–7). Melting points were determined with a Büchi apparatus and are not corrected. Optical rotations were measured using a Perkin Elmer 241 instrument at 589 nm and 20 °C. MALDI-TOFMS was performed on a Bruker Biflex III with DHB as a matrix in positive reflector mode. Elemental analyses were performed by the Zentrale Elementanalytik of the Department of Chemistry, Faculty of Science, University of Hamburg.

3.2. General procedures for the synthesis of aryl β-D-galactopyranosides

3.2.1. General procedure (GP1): phase-transfer-catalyzed galactosylation of phenols. 2,3,4,6 Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**1**) was dissolved in CH_2Cl_2 together with 1 equiv of tetrabutylammonium bromide and 3 equiv of the respective phenol. The same vol of 1 M NaOH soln was added and the reaction mixture

was stirred vigorously at 35 °C until the donor was consumed. After dilution with EtOAC, the organic phase was washed three times with a 1 M NaOH soln, twice with water and finally with brine. The organic phase was dried with magnesium sulfate and the solvent removed under diminished pressure. Purification was carried out by chromatography on silica gel. For details, see Table 2 as well.

3.2.2. General procedure (GP2): deacetylation. The acetylated glycoside was dissolved in dry MeOH and treated at ambient temperature with a 7 M soln of ammonia in MeOH (Aldrich) until completion of the reaction. The solvent was removed under diminished pressure and the residue purified by column chromatography on silica gel wherever necessary. For details, see Table 3 as well.

3.3. HPLC assay

The reference acceptor, allyl 2-acetamido-2-deoxy-α-D-galactopyranoside (13.1 mg, 50.1 μmol) and 60.2 μmol (1.2 equiv) of the respective donor were dissolved in the minimal amount (typically 350 μL) of the McIlvain buffer (50 mM, pH 4.3) and warmed to 37 °C. β-Galactosidase from bovine testes (5.6 mU) was added and the reaction mixture was incubated for 50 h at 37 °C. Aliquots (50 μL) were removed, diluted to 500 μL and filtered through a membrane filter (0.45 μL). The filtrate (100 μL) was injected into the HPLC column and eluted with 5% aq MeCN. The yield was estimated by integrating the product peak using the known allyl 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-α-D-galactopyranoside[23] for calibration.

3.4. (2-Chloro-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (8)[14]

Synthesis was carried out according to GP1. FC (1:1 light petroleum (50–70)–EtOAc) gave the product as a yellowish foam: mp 148 °C, lit.[14] 147–149 °C; $[\alpha]_D^{20}$ −29 (*c* 1, $CHCl_3$), lit.[14] −30; MALDI-TOFMS: *m*/*z* 526.1 $[M+Na]^+$, 542.1 $[M+K]^+$.

Table 2. Phase-transfer catalyzed galactosylation of phenols according to general procedure GP1

Phenol	Donor **1**	Bu_4NBr	Volume CH_2Cl_2 1 M NaOH	Time (h)	Product
2 (3.64 g, 21.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	4	**8** (2.92 g, 83%)
3 (4.37 g, 21.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	100 mL, 50 mL	48	**9** (3.24 g, 86%)
4 (2.75 g, 17.5 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	4	**10** (2.64 g, 77%)
5 (1.04 g, 6.62 mmol)	1.35 g, 3.28 mmol	1.06 g, 3.29 mmol	15 mL, 15 mL	5	**11** (1.22 g, 76%)
6 (3.30 g, 21.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	4	**12** (2.69 g, 79%)
7 (2.90 g, 21.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	3	**13** (2.06 g, 63%)
19 (3.26 g, 21.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	4	**20** (2.51 g, 44%)
21 (592 mg, 3.50 mmol)	2.88 g, 7.00 mmol	1.13 g, 3.51 mmol	35 mL, 25 mL	24	**22** (566 mg, 30%) **23** (204 mg, 12%)
25 (2.92 g, 17.5 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	7.5	**31** (2.05 g, 59%)
27 (4.14 g, 21.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	18	**32** (2.65 g, 72%)
28 (90 mg, 530 μmol)	0.66 g, 1.6 mmol	0.17 g, 0.53 mmol	10 mL, 10 mL	6	**33** (153 mg, 53%)
30 (4.14 g, 21.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	50 mL, 50 mL	6.5	**34** (2.47 g, 67%)
26 (5.13 g, 28.0 mmol)	2.88 g, 7.00 mmol	2.26 g, 7.01 mmol	75 mL, 75 mL	6	**41** (2.48 g, 42%)

Table 3. Deacetylation according to general procedure GP2

Acetylated glycoside	MeOH (mL)	Ammonia (mL)	Time (h)	Product
8 (2.78 g, 5.52 mmol)	70	2.5	50	**14** (1.81 g, 98%)
10 (2.63 g, 5.39 mmol)	70	2.5	15	**15** (1.72 g, quant.)
11 (933 mg, 1.91 mmol)	30	0.9	28	**16** (578 mg, 95%)
12 (2.51 g, 5.15 mmol)	200	2.5	6	**17** (1.62 g, 98%)
13 (420 mg, 897 μmol)	35	0.4	5	**18** (234 mg, 87%)
22 (444 mg, 820 μmol)	25	0.4	18	**24** (252 mg, 93%)
23 (153 mg, 306 μmol)	10	0.15	18	**24** (97 mg, 96%)
31 (1.98 g, 3.98 mmol)	150	2.0	5	**35** (1.20 g, 92%)
32 (2.30 g, 4.36 mmol)	130	8.0	12	**36** (1.42 g, 91%)
41 (1.46 g, 1.73 mmol)	50	1.5	28	**36** (430 mg, 69%)
33 (105 mg, 194 μmol)	5	0.1	12	**38** (54 mg, 84%)
34 (1.74 g, 3.30 mmol)	130	2.0	24	**39** (1.04 g, 88%)
45 (190 mg, 447 μmol)	10	0.25	15	**48** (113 mg, 98%)
46 (2.04 g, 4.34 mmol)	100	2.0	8	**49** (1.31 g, quant.)
47 (1.24 g, 2.91 mmol)	70	1.5	6	**50** (717 mg, 96%)

Table 4. ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts (δ in ppm) and coupling constants (J in Hz) for the acetylated aryl β-D-galactopyranosides

Compound	Galactopyranose ring								Aromatic ring					Additional substituents
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	CO–CH_3	H-2′	H-3′	H-4′	H-5′	H-6′	
8	5.06, d $J_{1,2} = 7.6$	5.57, dd $J_{2,3} = 10.7$	5.09, dd $J_{3,4} = 3.1$	5.45, br d	4.08, vt $J_{5,6a} = 7.1$ $J_{5,6b} = 6.1$	4.21, dd $J_{6a/b} = 11.2$	4.14, dd	2.14, 2.05, 2.04, 1.98		8.26, d $J_{3',5'} = 2.5$		8.09, dd $J_{5',6'} = 9.2$	7.08, d	
9	5.25, d $J_{1,2} = 8.1$	5.56, dd $J_{2,3} = 10.7$	5.09, dd $J_{3,4} = 3.6$	5.40, dd $J_{4,5} = 1.0$	3.85, dt $J_{5,6a} = 7.1$ $J_{5,6b} = 6.6$	4.09, dd $J_{6a/b} = 11.2$	4.04, dd	2.19, 2.10, 2.00, 1.96		8.20, br s		8.20, br s		
10	5.09, d $J_{1,2} = 7.6$	5.53, dd $J_{2,3} = 10.7$	5.11, dd $J_{3,4} = 3.1$	5.46, dd $J_{4,5} = 1.0$	4.07, ddd $J_{5,6a} = 7.1$ $J_{5,6b} = 6.1$	4.21, dd $J_{6a/b} = 11.2$	4.15, dd	2.18, 2.08, 2.05, 2.00		8.00, dd $J_{3',5'} = 2.5$ $J_{3',F} = 10.7$		8.02, dd $J_{5',6'} = 9.2$	7.28, dd $J_{6',F} = 7.6$	
11	5.12, d $J_{1,2} = 7.6$	5.49, dd $J_{2,3} = 10.7$	5.11, dd $J_{3,4} = 3.6$	5.46, br d $J_{4,5} = 1.0$	4.10, ddd $J_{5,6a} = 7.1$ $J_{5,6b} = 5.1$	4.19, dd $J_{6a/b} = 11.2$	4.14, dd	2.17, 2.07, 2.06, 2.00	6.89, dd $J_{2',6'} = 2.5$ $J_{2',F} = 12.2$			8.08, dd $J_{5',6'} = 9.2$ $J_{5',F} = 8.1$	6.85, dd	
12	5.06, d $J_{1,2} = 8.1$	5.55, dd $J_{2,3} = 10.7$	5.09, dd $J_{3,4} = 3.6$	5.46, br d $J_{4,5} = 1.0$	4.08, ddd $J_{5,6a} = 7.6$ $J_{5,6b} = 5.1$	4.22, dd $J_{6a/b} = 11.2$	4.16, dd	2.17, 2.11, 2.08, 2.00		7.88, dd $J_{3',4'} = 9.2$ $J_{3',F} = 5.6$	6.89, ddd $J_{4',6'} = 2.5$ $J_{4',F} = 9.2$		7.12, dd $J_{6',F} = 9.7$	
13	4.86, d $J_{1,2} = 7.9$	5.41, m_c $J_{2,3} = 10.4$	5.06, dd $J_{3,4} = 3.3$	5.41, m_c $J_{4,5} = 0.8$	3.99, ddd $J_{5,6a} = 7.1$ $J_{5,6b} = 6.4$	4.21, dd $J_{6a/b} = 11.2$	4.14, dd	2.16, 2.07, 2.04, 1.99	6.58, d $J_{2',6'} = 2.5$			6.68, d $J_{5',6'} = 8.4$	6.45, dd	5.92, s, O–CH_2–O
22	5.17, d $J_{1,2} = 7.9$	5.0, m $J_{2,3} = 10.4$	5.12, dd $J_{3,4} = 3.6$	5.45, dd $J_{4,5} = 1.0$	4.10, dt $J_{5,6a} = 5.6$ $J_{5,6b} = 6.9$	4.19, dd $J_{6a/b} = 9.7$	4.14, dd	2.17, 2.06, 2.05, 2.00	7.13, d $J_{2',6'} = 2.6$			8.15, d $J_{5',6'} = 9.2$	7.00, dd	5.54–5.46, m, Ar–CH_2–OAc
23	5.19, d $J_{1,2} = 7.9$	5.50, dd $J_{2,3} = 10.4$	5.12, dd $J_{3,4} = 3.3$	5.46, br d		4.20–4.10, m		2.17, 2.16, 2.05, 2.04, 2.00	7.37, d $J_{2',6'} = 2.8$			8.14, d	6.98, dd $J_{5',6'} = 9.2$	4.99, s, Ar–CH_2–OH
31	5.26, d $J_{1,2} = 8.1$	5.60, dd $J_{2,3} = 10.7$	5.16, dd $J_{3,4} = 3.6$	5.49, br d	4.18–4.13, m $J_{5,6b} = 9.2$		4.22, dd $J_{6a/b} = 12.7$	2.19, 2.06, 2.05, 2.01		8.70, d $J_{3',5'} = 3.1$		8.40, dd $J_{5',6'} = 9.2$	7.23, d	10.32, s, C*H*O
32	5.15, d $J_{1,2} = 7.6$	5.59, dd $J_{2,3} = 10.2$	5.10, dd $J_{3,4} = 3.1$	5.47, br d		4.23–4.16, m		2.18, 2.07, 2.06, 2.01		8.65, d $J_{3',5'} = 3.1$		8.31, dd $J_{5',6'} = 9.2$	7.23, d	3.89, s, CO_2–CH_3
33	5.15, d $J_{1,2} = 7.9$	5.54, dd $J_{2,3} = 10.4$	5.13, dd $J_{3,4} = 3.6$	5.47, dd $J_{4,5} = 1.0$	4.11, dt $J_{5,6a} = 6.9$ $J_{5,6b} = 5.6$	4.22, dd $J_{6a/b} = 10.9$	4.15, dd	2.18, 2.15, 2.09, 2.06, 2.01		8.22, d $J_{3',5'} = 2.8$		8.16, dd $J_{5',6'} = 9.2$	7.13, d	5.18, d Ar–CH_2-a 5.04, d Ar–CH_2-b $J_{Ar\text{-}CH2\text{-}a/b} = 14.2$

34	5.15, d $J_{1,2} = 7.6$	5.55, dd $J_{2,3} = 10.2$	5.10, dd $J_{3,4} = 3.6$	5.46, dd $J_{4,5} = 1.0$	4.10, ddd $J_{5,6a} = 7.1$ $J_{5,6b} = 5.6$	4.23, dd $J_{6a/b} = 11.2$	4.16, dd	2.17, 2.11, 2.06, 2.00	8.43, d $J_{3',5'} = 2.0$		8.17, dd $J_{5',6'} = 9.2$	7.37, d	3.93, s, CO_2-CH_3
45	6.17, d $J_{1,2} = 8.1$	5.48, dd $J_{2,3} = 10.7$	5.14, dd $J_{3,4} = 3.1$	5.44, br d		4.13–4.11, m		2.14, 1.99, 1.98, 1.95	6.79, d $J_{3',4'} = 8.1$	7.60, ddd $J_{4',5'} = 7.1$ $J_{4',6'} = 1.5$	6.96, dd $J_{5',6'} = 5.1$	8.13, dd	
46	6.14, d $J_{1,2} = 8.1$	5.58, dd $J_{2,3} = 10.2$	5.15, dd $J_{3,4} = 3.6$	5.46, br d		4.18–4.12, m		2.16, 2.03, 2.01, 2.00		8.24, dd $J_{4',5'} = 7.9$ $J_{4',6'} = 1.8$	7.16, dd $J_{5',6'} = 4.8$	8.38, dd	
47	5.18, d $J_{1,2} = 7.6$	5.49, dd $J_{2,3} = 10.7$	5.11, dd $J_{3,4} = 3.6$	5.45, br d		4.20–4.09, m		2.16, 2.05, 2.04, 2.00	8.48, br d $J_{2',3'} = 6.1$	6.92, br d	6.92, br d $J_{5',6'} = 6.1$	8.48, br d	

3.5. (2,6-Dichloro-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (9)

According to GP1. FC (3:2 light petroleum (50–70)–EtOAc) gave the product as white crystals: mp 118 °C; $[\alpha]_D^{20}$ −0.7 (*c* 1, $CHCl_3$); MALDI-TOFMS: *m*/*z* 560.0 $[M+Na]^+$, 576.0 $[M+K]^+$. Anal. Calcd for $C_{20}H_{21}Cl_2NO_{12}$: C, 44.63; H, 3.93; N, 2.60. Found: C, 44.77; H, 3.99; N, 2.27.

3.6. (2-Fluoro-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (10)

According to GP1. FC (2:1 light petroleum (50–70)–EtOAc) gave the product as yellowish crystals: mp 134 °C; $[\alpha]_D^{20}$ −37 (*c* 1, $CHCl_3$); MALDI-TOFMS: *m*/*z* 510.1 $[M+Na]^+$, 526.1 $[M+K]^+$.

3.7. (3-Fluoro-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (11)

According to GP1. FC (chloroform/MeOH 400:1) gave the product as a yellowish foam: mp 143 °C; $[\alpha]_D^{20}$ −19 (*c* 0.4, $CHCl_3$); MALDI-TOFMS: *m*/*z* 510.2 $[M+Na]^+$, 526.2 $[M+K]^+$.

3.8. (5-Fluoro-2-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (12)

According to GP1. FC (2:1 light petroleum (50–70)–EtOAc) gave the product as a yellowish foam: mp 159 °C; $[\alpha]_D^{20}$ −21 (*c* 1, $CHCl_3$); MALDI-TOFMS: *m*/*z* 510.1 $[M+Na]^+$, 526.1 $[M+K]^+$.

3.9. (3,4-Methylenedioxyphenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (13)[15]

According to GP1. FC (3:1 light petroleum (50–70)–EtOAc) gave the product as a brownish glass: $[\alpha]_D^{20}$ +7 (*c* 1, $CHCl_3$), lit.[15] +3; MALDI-TOFMS: *m*/*z* 491.1 $[M+Na]^+$, 507.1 $[M+K]^+$.

3.10. (2-Chloro-4-nitrophenyl) β-D-galactopyranoside (14)[14]

According to GP2. Crystallization from MeOH gave the product as yellowish crystals: mp 211 °C, lit.[14] 213–215 °C; $[\alpha]_D^{20}$ −53 (*c* 1, MeOH), lit.[14] −50.

3.11. (2-Fluoro-4-nitrophenyl) β-D-galactopyranoside (15)

According to GP2. Crystallization from MeOH gave the product as yellowish crystals: mp 172 °C; $[\alpha]_D^{20}$ −60 (*c* 0.6, MeOH); Anal. Calcd for $C_{12}H_{14}FNO_8$: C, 45.15; H, 4.42; N, 4.39. Found: C, 45.29; H, 4.60; N, 4.40.

Table 5. ^{13}C NMR (100.6 MHz, $CDCl_3$) chemical shifts (δ in ppm) and coupling constants (J in Hz) for the acetylated aryl β-D-galactopyranosides

Compound	Galactopyranose ring								Aromatic ring						Additional substituents
	C-1	C-2	C-3	C-4	C-5	C-6	*C*O–CH_3	CO–*C*H_3	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	
8	98.97	66.86	69.35	65.63	70.71	60.35	169.24, 169.07, 169.03, 168.12	19.70, 19.65, 19.60, 19.54	156.34	123.93	125.22	142.21	122.56	115.41	
9	101.80	69.29	70.98	66.97	71.79	61.06	170.63, 170.47, 170.13, 169.78	21.25, 21.14, 21.08, 20.96	153.62	131.24	124.86	144.74	124.86	131.24	
10	100.63	68.58	70.82	67.04	72.08	61.68	170.68, 170.50, 170.45, 169.66	21.05, 21.03, 21.00, 20.96	150.20, d $J_{1',F} = 10.5$	152.55, d $J_{2',F} = 254$	113.39, d $J_{3',F} = 22.9$	147.73, d $J_{4',F} = 7.1$	118.97	120.81, d $J_{6',F} = 3.7$	
11	99.06	68.53	70.93	67.08	72.19	61.91	170.72, 170.46, 170.39, 169.60	21.08, 21.05, 21.01, 20.94	161.93, d $J_{1',F} = 10.2$	106.42, d $J_{2',F} = 24.7$	157.42, d $J_{3',F} = 266$	135.42, d $J_{4',F} = 13.2$	128.24	113.09	
12	101.06	68.04	70.90	67.18	72.28	62.09	170.77, 170.53, 170.48, 169.73	21.05, 21.03, 21.01, 20.97	151.79	137.87	127.89, d $J_{3',F} = 11.0$	111.05, d $J_{2',F} = 23.3$	165.38, d $J_{5',F} = 256$	107.74, d $J_{6',F} = 27.3$	
13	101.53	69.10	71.27	67.31	71.44	61.97	170.81, 170.68, 170.55, 169.79	21.17, 21.12, 21.08, 21.00	152.62	100.98	148.53	144.09	108.39	110.09	101.89, O–*C*H_2–O
22	97.45	67.27	69.59	65.65	70.45	60.28	169.27, 169.18, 169.07, 169.02, 168.27	19.81, 19.73, 19.69, 19.60, 19.52	159.35	115.49	134.50	141.06	126.70	114.11	61.92, Ar–*C*H_2–OAc
23	97.49	67.31	69.62	65.83	70.54	60.49	169.49, 169.16, 169.06, 168.32	19.69, 19.62, 19.58, 19.54	159.74	115.32	139.56	140.94	126.60	114.50	61.40, Ar–*C*H_2–OH
31	97.83	67.03	69.22	65.50	70.79	60.23	169.21, 169.00, 168.94, 168.24	19.63, 19.59, 19.54, 19.51	160.99	124.81	123.45	142.35	129.09	114.71	185.95, *C*HO
32	99.19	66.65	69.40	65.63	70.72	60.39	169.51, 169.44, 169.37, 169.22	19.64, 19.59, 19.55, 19.53	158.97	119.51	126.11	149.56	134.02	128.63	164.07, *C*O_2–CH_3 51.68, CO_2–*C*H_3
33	99.46	68.52	70.83	67.08	72.04	61.76	170.50, 170.41, 170.23, 169.92, 169.74	21.28, 21.17, 21.06, 21.04, 20.94	158.73	127.99	124.65	143.64	125.34	114.78	60.25, Ar–*C*H_2–OAc
34	99.19	66.65	69.40	65.63	70.72	60.39	169.24, 169.08, 168.91, 168.19	19.64, 19.59, 19.55, 19.53	151.45	139.78	125.70	124.61	133.67	117.35	163.53, *C*O_2–CH_3 51.68, CO_2–*C*H_3
45	94.30	69.08	71.55	67.69	71.51	61.68	170.76, 170.70, 170.52, 169.95	21.40, 21.19, 21.10, 21.02		161.74	112.19	139.79	119.27	147.16	
46	95.28	68.19	71.24	67.23	71.92	61.43	170.72, 170.67, 170.58, 170.50	21.07, 21.05, 21.01, 20.92		169.40	154.21	135.64	119.18	151.44	
47	98.29	68.61	71.02	67.08	71.89	61.74	170.71, 170.52, 170.45, 169.66	21.09, 21.05, 21.03, 20.96		151.05	112.27	163.54	112.27	151.05	

Table 6. ^{1}H NMR (400 MHz, MeOH-d_4) chemical shifts (δ in ppm) and coupling constants (J in Hz) for the unprotected aryl β-D-galactopyranosides

Compound	Galactopyranose ring							Aromatic ring					Additional substituents
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-2′	H-3′	H-4′	H-5′	H-6′	
14	5.13, d $J_{1,2} = 8.1$	3.95–3.89, m $J_{2,3} = 9.7$	3.62, dd $J_{3,4} = 3.1$	3.95–3.89, m		3.80–3.73, m			8.31, d $J_{3',5'} = 2.5$		8.18, dd $J_{5',6'} = 9.2$	7.45, d	
15	5.11, d $J_{1,2} = 7.6$	3.89, dd $J_{2,3} = 9.7$	3.61, dd $J_{3,4} = 3.1$	3.92, br d		3.80, m$_c$			8.09–8.04, m		8.09–8.04, m $J_{5',6'} = 8.6$	7.49, vt $J_{6',F} = 8.6$	
16	5.02, d $J_{1,2} = 7.6$	3.83, dd $J_{2,3} = 9.7$	3.61, dd $J_{3,4} = 3.6$	3.91, br d		3.79, m$_c$		7.12, dd $J_{2',6'} = 2.5$ $J_{2',F} = 12.7$			8.12, vt $J_{5',6'} = 9.2$ $J_{5',F} = 8.6$	7.06, dd	
17	5.06, d $J_{1,2} = 7.6$	3.85, dd $J_{2,3} = 9.7$	3.59, dd $J_{3,4} = 3.6$	3.90, br d		3.80–3.72, m			7.93, dd $J_{3',4'} = 9.2$ $J_{3',F} = 6.1$	6.92, ddd $J_{4',6'} = 2.5$ $J_{4',F} = 7.6$		7.27, dd $J_{6',F} = 10.7$	
18[a]	4.74, d $J_{1,2} = 7.6$	3.72, dd $J_{2,3} = 9.7$	3.55, dd $J_{3,4} = 3.3$	3.88, dd $J_{4,5} = 0.7$	3.63, ddd $J_{5,6a} = 5.6$ $J_{5,6b} = 6.6$	3.76–3.73, m		6.76, d $J_{2',6'} = 2.5$			6.78, d $J_{5',6'} = 8.4$	6.63, dd	5.92, s, O–CH_2–O
24	5.03, d $J_{1,2} = 7.9$	3.85, br d $J_{2,3} = 9.7$	3.61, dd $J_{3,4} = 3.3$	3.93, br d		3.80–3.74, m		7.54, d $J_{2',6'} = 2.8$			8.14, d $J_{5',6'} = 9.2$	7.15, dd	4.96, s, Ar–CH_2–OH
35	5.19, d $J_{1,2} = 7.6$	3.94–3.89, m $J_{2,3} = 9.7$	3.61, dd $J_{3,4} = 3.6$	3.94–3.89, m		3.81–3.74, m			8.44, d $J_{3',5'} = 2.8$		8.21, dd $J_{5',6'} = 9.2$	7.39, d	10.52, s, C*H*O
36[a]	5.09, d $J_{1,2} = 7.6$	3.90, dd $J_{2,3} = 9.7$	3.62, dd $J_{3,4} = 3.6$	3.91, br d		3.81–3.74, m			8.62, d $J_{3',5'} = 3.1$		8.40, dd $J_{5',6'} = 9.2$	7.53, d	3.94, s, CO_2–CH_3
37[b]	5.11, d $J_{1,2} = 7.9$	3.89, dd $J_{2,3} = 9.7$	3.67, dd $J_{3,4} = 3.1$	3.92, br d		3.83–3.76, m			8.61, d $J_{3',5'} = 2.8$		8.43, dd $J_{5',6'} = 9.2$	7.60, d	
38	5.13, d $J_{1,2} = 7.9$	3.87, dd $J_{2,3} = 9.7$	3.64, dd $J_{3,4} = 3.3$	3.91, br d		3.81–3.73, m			8.24, d $J_{3',5'} = 2.9$		8.15, dd $J_{5',6'} = 9.2$	7.21, d	4.88, s, Ar–CH_2–OH
39[a]	5.15, d $J_{1,2} = 7.6$	3.86, dd $J_{2,3} = 9.7$	3.60, dd $J_{3,4} = 3.6$	3.91, br d		3.80–3.74, m			8.40, d $J_{3',5'} = 2.5$		8.21, dd $J_{5',6'} = 9.2$	7.55, d	3.93, s, CO_2–CH_3
40[b]	5.13, d $J_{1,2} = 8.1$	3.87, dd $J_{2,3} = 9.7$	3.62, dd $J_{3,4} = 3.6$	3.93, br d		3.81–3.74, m			8.38, d $J_{3',5'} = 2.0$		8.18, dd $J_{5',6'} = 9.2$	7.48, d	3.93, s, CO_2–CH_3
48[a]	5.70, d $J_{1,2} = 8.1$	3.58, dd $J_{2,3} = 9.7$	3.45–3.39, m $J_{3,4} = 3.6$	3.70, br d	3.54–3.48, m		3.45–3.39, m		8.17, dd $J_{3',4'} = 5.1$ $J_{3',5'} = 2.0$	7.03, ddd $J_{4',5'} = 7.1$ $J_{4',6'} = 1.0$	7.75, ddd $J_{5',6'} = 8.1$	6.84, d	
49	6.09, d $J_{1,2} = 7.9$	3.90, dd $J_{2,3} = 9.7$	3.62, dd $J_{3,4} = 3.3$	3.93, br d		3.73–3.71, m				8.35, dd $J_{4',5'} = 7.9$ $J_{4',6'} = 1.5$	7.23, dd $J_{5',6'} = 4.8$	8.43, dd	
50[a]	5.02, d $J_{1,2} = 8.1$	3.60, dd $J_{2,3} = 9.5$	3.41, dd $J_{3,4} = 3.5$	3.72, br d	3.65, vt $J_{5,6a} = 5.7$ $J_{5,6b} = 6.6$	3.55, dd $J_{6a/b} = 11.0$	3.49, dd	8.43, br d $J_{2',3'} = 6.1$	7.04, br d		7.04, br d $J_{5',6'} = 6.1$	8.43, br d	
51	4.69, d $J_{1,2} = 7.6$	3.81, dd $J_{2,3} = 9.7$	3.56, dd $J_{3,4} = 3.6$	3.89, dd $J_{4,5} = 0.8$	3.60, ddd $J_{5,6a} = 5.6$ $J_{5,6b} = 5.3$	3.77, dd $J_{6a/b} = 11.7$	3.74, dd		6.78, dd $J_{3',4'} = 7.9$ $J_{3',5'} = 1.5$	6.84, dt $J_{4',5'} = 7.4$ $J_{4',6'} = 1.3$	6.65, ddd $J_{5',6'} = 8.1$	7.10, dd	

[a] In DMSO-d_6.
[b] In D_2O.

Table 7. ^{13}C NMR (100.6 MHz, MeOH-d_4) chemical shifts (δ in ppm) and coupling constants (J in Hz) for the unprotected aryl β-D-galactopyranosides

Compound	Galactopyranose ring						Aromatic ring						Additional substituents
	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	
14	102.82	72.24	75.30	70.54	77.88	62.79	159.86	125.27	127.09	143.94	125.17	117.28	
15	102.96	72.27	75.21	70.53	77.86	62.78	152.68, d $J_{1',F} = 11.2$	153.21, d $J_{2',F} = 250$	113.58, d $J_{3',F} = 23.4$	143.70, d $J_{4',F} = 8.1$	118.32	122.10, d $J_{6',F} = 4.1$	
16	102.82	72.28	75.06	70.53	77.81	62.81	164.89, d $J_{1',F} = 11.0$	107.29, d $J_{2',F} = 24.5$	158.65, d $J_{3',F} = 263$	133.41, d $J_{4',F} = 6.8$	129.14	114.24	
17	103.40	72.24	75.23	70.53	77.90	62.79	154.07, d $J_{1',F} = 12.2$	138.89	128.84, d $J_{3',F} = 11.4$	110.35, d $J_{4',F} = 24.1$	167.02, d $J_{5',F} = 253$	106.70, d $J_{6',F} = 28.1$	
18[a]	102.61	70.67	73.29	68.53	75.43	60.82	153.04	99.57	147.85	142.55	107.51	108.78	101.05, O–*C*H$_2$–O
24	102.72	72.45	75.17	70.53	77.64	62.75	163.73	116.99	142.14	143.02	128.68	116.26	62.60, Ar–*C*H$_2$–OH
35	103.09	72.31	75.09	70.53	77.82	62.83	161.34	124.60	126.67	147.02	131.78	117.01	189.81, *C*HO
36[a]	101.04	70.27	73.32	68.17	76.08	60.48	161.02	121.68	126.61	141.18	128.85	116.69	164.77, *C*O$_2$–CH$_3$ 52.95, CO$_2$–*C*H$_3$
37[b]	102.13	70.30	73.27	68.14	75.89	60.49	160.86	117.34	127.07	141.62	128.52	116.47	169.93, *C*O$_2$H
38	103.24	73.19	75.98	71.32	78.07	62.51	163.47	136.73	125.76	144.21	127.96	116.68	61.83, Ar–*C*H$_2$–OH
39[a]	103.05	72.22	75.26	70.52	77.95	62.78	155.24	141.98	127.74	125.51	136.13	118.81	166.71, *C*O$_2$–CH$_3$ 53.40, CO$_2$–*C*H$_3$
40[b]	103.15	72.34	75.23	70.58	77.79	62.78	154.13	141.78	127.70	115.84	136.31	118.36	170.64, *C*O$_2$H
48[a]	96.85	70.30	73.81	68.43	76.01	60.57		162.59	147.22	118.48	139.90	111.44	
49	98.02	71.30	74.78	69.84	77.09	61.84		135.70	155.48	136.03	119.15	152.03	
50[a]	100.14	70.35	73.56	68.43	76.06	60.66		151.30	111.97	163.59	111.97	151.30	
51	104.19	71.33	73.78	69.16	75.91	61.35	146.14	138.27	116.38	123.66	118.51	119.93	

[a] In DMSO-d_6.
[b] In D_2O.

3.12. (3-Fluoro-4-nitrophenyl) β-D-galactopyranoside (16)

According to GP2. Crystallization from MeOH gave the product as yellowish crystals: mp 174 °C; $[\alpha]_D^{20}$ −81 (*c* 0.6, MeOH); MALDI-TOFMS: *m*/*z* 342.1 $[M+Na]^+$, 358.0 $[M+K]^+$. Anal. Calcd for $C_{12}H_{14}FNO_8$: C, 45.15; H, 4.42; N, 4.39. Found: C, 45.36; H, 4.63; N, 4.40.

3.13. (5-Fluoro-2-nitrophenyl) β-D-galactopyranoside (17)

According to GP2. Crystallization from MeOH gave the product as yellowish crystals: mp 151 °C; $[\alpha]_D^{20}$ −89 (*c* 0.7, MeOH); MALDI-TOFMS: *m*/*z* 342.2 $[M+Na]^+$, 358.1 $[M+K]^+$. Anal. Calcd for $C_{12}H_{14}FNO_8$: C, 45.15; H, 4.42; N, 4.39. Found: C, 45.32; H, 4.63; N, 4.36.

3.14. (3,4-Methylenedioxyphenyl) β-D-galactopyranoside (18)[27]

According to GP2 at 0 °C. Crystallization from MeOH gave the product as a glass: $[\alpha]_D^{20}$ +19 (*c* 0.3, DMSO).

3.15. 1,2-Bis-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-4-nitrobenzene (20)

According to GP1. FC (2:1 light petroleum (50–70)–EtOAc) gave the product as white crystals: mp 211 °C (decomp.); $[\alpha]_D^{20}$ −32 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 1H, $J_{Ar\text{-}3,5}$ 2.5 Hz, Ar-3), 7.90 (dd, 1H, $J_{Ar\text{-}5,6}$ 9.2 Hz, Ar-5), 7.11 (d, 1H, Ar-6), 5.44–5.42 (m, 2H, H-4, H-4′), 5.40 (dd, 1H, $J_{1',2'}$ 7.6 Hz, $J_{2',3'}$ 10.2 Hz, H-2′), 5.38 (dd, 1H, $J_{1,2}$ 7.6 Hz, $J_{2,3}$ 10.7 Hz, H-2), 5.16 (d, 1H, H-1′), 5.10 (d, 1H, H-1), 5.08 (dd, 1H, $J_{3,4}$ 3.6 Hz, H-3), 5.07 (dd, 1H, $J_{3',4'}$ 3.6 Hz, H-3′), 4.17–4.06 (m, 5 H, H-6a,b, H-5′, H-6′a,b), 4.04 (vt, 1H, $J_{5,6a} = J_{5,6b}$ 7.1 Hz, H-5), 2.13, 2.12, 2.05, 2.04, 2.02, 2.00, 1.95, 1.94 (8s, 24H, $8COCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.65, 169.21, 169.13, 169.05, 168.99, 168.37, 167.84, 167.76 (8C, $8COCH_3$), 150.76 (Ar-1), 145.75 (Ar-2), 142.20 (Ar-4), 118.45 (Ar-5), 115.77 (Ar-6), 112.11 (Ar-3), 98.96 (C-1), 98.37 (C-1′), 70.97 (C-5′), 70.61 (C-5), 69.68 (C-3), 69.66 (C-3′), 67.48 (C-2), 67.40 (C-2′), 66.14 (C-4′), 65.86 (C-4), 60.91 (C-6′), 60.27 (C-6), 19.64, 19.61, 19.60, 19.58, 19.56, 19.55, 19.53, 19.52 (8C, $8COCH_3$); MALDI-TOFMS: *m*/*z* 838.6 $[M+Na]^+$, 854.5 $[M+K]^+$. Anal. Calcd for $C_{34}H_{41}NO_{22}$: C, 50.06; H, 5.07; N, 1.72. Found: C, 48.49; H, 5.01; N, 1.88.

3.16. (3-Acetoxymethyl-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (22) and (3-hydroxymethyl-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (23)

According to GP1. The products were separated by FC (CH_2Cl_2/acetone 30:1).

3.16.1. (3-Acetoxymethyl-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (22).

White crystals: mp 137 °C; $[\alpha]_D^{20}$ +7.4 (*c* 0.2, $CHCl_3$); MALDI-TOFMS: *m*/*z* 564.3 $[M+Na]^+$, 580.2 $[M+K]^+$.

3.16.2. (3-Hydroxymethyl-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (23).

White crystals: mp 156 °C; $[\alpha]_D^{20}$ −3.5 (*c* 0.25, $CHCl_3$); MALDI-TOFMS: *m*/*z* 522.1 $[M+Na]^+$, 538.0 $[M+K]^+$.

3.17. (3-Hydroxymethyl-4-nitrophenyl) β-D-galactopyranoside (24)

By deprotection of **22** according to GP2. FC (ethyl acetate/MeOH 6:1).

By deprotection of **23** according to GP2. FC (6:1 EtOAc–MeOH). Glass; $[\alpha]_D^{20}$ −11 (*c* 0.13, MeOH); MALDI-TOFMS: *m*/*z* 354.1 $[M+Na]^+$, 370.1 $[M+K]^+$.

3.18. Methyl 5-nitrosalicylate (27)[28]

5-Nitrosalicylic acid (9.16 g, 50.0 mmol) and Amberlite IR-120 (4 g, H^+-form) were stirred in MeOH (80 mL) for 7 days. The ion-exchange resin was removed by filtration and the filtrate concentrated to dryness. The residue was dissolved in $CHCl_3$ and washed with satd aq $NaHCO_3$ soln and water. After drying with magnesium sulfate, the solvent was removed to give **27** as yellow needles (8.39 g, 85%): mp 116 °C, lit.[28] 117 °C; ^1H NMR (400 MHz, DMSO): δ 8.72 (d, 1H, $J_{4,6}$ 2.5 Hz, H-6), 8.36 (dd, 1H, $J_{3,4}$ 9.2 Hz, H-4), 7.13 (d, 1H, H-3), 4.03 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, Me_2SO): δ 170.22 (CO_2CH_3), 167.15 (C-2), 141.39 (C-5), 131.42 (C-4), 127.44 (C-6), 119.64 (C-3), 113.84 (C-1), 53.63 (CO_2CH_3).

3.19. Methyl 4-hydroxy-3-nitrobenzoate (30)[29]

4-Hydroxy-3-nitrobenzoic acid (11.0 g, 60.1 mmol) and Amberlite IR-120 (5 g, H^+-form) were stirred in MeOH (100 mL) for 7 days. The reaction mixture was worked up as described above to give **30** as yellow rhombic crystals (11.0 g, 93%): mp 76 °C, lit.[29] 117 °C; ^1H NMR (400 MHz, MeOD): δ 8.62 (d, 1H, $J_{2,6}$ 2.6 Hz, H-2), 8.15 (dd, 1H, $J_{5,6}$ 9.2 Hz, H-6), 7.20 (d, 1H, H-5), 3.91 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, MeOD): δ 166.80 (CO_2CH_3), 158.87 (C-4), 138.09 (C-6), 136.46 (C-3), 128.56 (C-2), 123.65 (C-1), 121.53 (C-5), 53.32 (CO_2CH_3).

3.20. (2-Formyl-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (31)

According to GP1. FC (2:1 light petroleum (50–70)–EtOAc) gave the product as white crystals: mp 178 °C; $[\alpha]_D^{20}$ −23 (*c* 0.5, $CHCl_3$); MALDI-TOFMS: *m*/*z* 520.1

$[M+Na]^+$, 536.1 $[M+K]^+$. Anal. Calcd for $C_{21}H_{23}NO_{13}$: C, 50.71; H, 4.66; N, 2.82. Found: C, 50.81; H, 4.86; N, 2.98.

3.21. (2-Methoxycarbonyl-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (32)

According to GP1. FC (3:2 light petroleum (50–70)–EtOAc) gave the product as white crystals: mp 192 °C (decomp.); $[\alpha]_D^{20}$ −42 (*c* 0.2, $CHCl_3$); MALDI-TOFMS: *m*/*z* 550.0 $[M+Na]^+$, 566.0 $[M+K]^+$.

3.22. (2-Acetoxymethyl-4-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (33)

According to GP1. FC (CH_2Cl_2/acetone 30:1) gave the product as a glass: $[\alpha]_D^{20}$ +13 (*c* 0.11, $CHCl_3$); MALDI-TOFMS: *m*/*z* 564.2 $[M+Na]^+$, 580.2 $[M+K]^+$.

3.23. (4-Methoxycarbonyl-2-nitrophenyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (34)

According to GP1. FC (1:1 light petroleum (50–70)–EtOAc) gave the product as white crystals: mp 163 °C; $[\alpha]_D^{20}$ +57 (*c* 0.5, $CHCl_3$); MALDI-TOFMS: *m*/*z* 550.1 $[M+Na]^+$, 566.1 $[M+K]^+$. Anal. Calcd for $C_{22}H_{25}NO_{14}$: C, 50.10; H, 4.78; N, 2.66. Found: C, 50.25; H, 4.80; N, 2.29.

3.24. (2-Formyl-4-nitrophenyl) β-D-galactopyranoside (35)[17]

According to GP2. Crystallization from MeOH gave the product as yellowish crystals: mp 203 °C; $[\alpha]_D^{20}$ −60 (*c* 0.5, MeOH).

3.25. (2-Methoxycarbonyl-4-nitrophenyl) β-D-galactopyranoside (36)

By deprotection of **32**. Synthesis according to GP2. Precipitation from MeOH.

By deprotection of **41** according to GP2 at 0 °C. Precipitation from MeOH. Glass; $[\alpha]_D^{20}$ −61 (*c* 0.4, MeOH); MALDI-TOFMS: *m*/*z* 382.1 $[M+Na]^+$, 398.0 $[M+K]^+$. Anal. Calcd for $C_{14}H_{17}NO_{10}$: C, 46.80; H, 4.77; N, 3.90. Found: C, 46.65; H, 4.74; N, 4.03.

3.26. (2-Carboxy-4-nitrophenyl) β-D-galactopyranoside (37)

A soln of **36** (179 mg, 498 μmol) in 3:1 water–methanol (6 mL) was treated for 7 h with 1 M aq NaOH (1 mL). After neutralization with Amberlite IR-120 (H^+-form) and filtration, the residue was codistilled with MeOH. FC (2:1 EtOAc–MeOH) gave **37** as a glass (136 mg, 79%): $[\alpha]_D^{20}$ −31 (*c* 0.1, MeOH).

3.27. (2-Hydroxymethyl-4-nitrophenyl) β-D-galactopyranoside (38)

By deprotection of **33** according to GP2. FC (6:1 EtOAc–MeOH).

By reduction of **36**. A suspension of **36** (500 mg, 1.39 mmol) in ethanol (35 mL) was treated for 6 h with sodium borohydride (210 g, 5.55 mmol). The reaction was stopped by the addition of 2 M aq HCl and neutralized with satd aq $NaHCO_3$ soln. The solvent was removed in vacuo and the residue was purified by FC (6:1 EtOAc–MeOH) to give **38** as a glass (372 mg, 81%): $[\alpha]_D^{20}$ −17 (*c* 0.1, MeOH); MALDI-TOFMS: *m*/*z* 354.0 $[M+Na]^+$, 370.0 $[M+K]^+$.

3.28. (4-Methoxycarbonyl-2-nitrophenyl) β-D-galactopyranoside (39)

According to GP2. Precipitation from MeOH gave the product as a glass: $[\alpha]_D^{20}$ −90 (*c* 0.4, MeOH); MALDI-TOFMS: *m*/*z* 382.3 $[M+Na]^+$, 398.4 $[M+K]^+$. Anal. Calcd for $C_{14}H_{17}NO_{10}$: C, 46.80; H, 4.77; N, 3.90. Found: C, 46.35; H, 4.84; N, 3.98.

3.29. (4-Carboxy-2-nitrophenyl) β-D-galactopyranoside (40)[30]

A soln of **39** (179 mg, 498 μmol) in 3:1 water–methanol (6 mL) was treated for 7 h with 1 M aq NaOH (1 mL). After neutralization with Amberlite IR-120 (H^+-form) and filtration, the residue was codistilled with MeOH. FC (2:1 EtOAc–MeOH) gave **40** as a glass (149 mg, 87%): $[\alpha]_D^{20}$ −12 (*c* 0.1, MeOH).

3.30. (2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl) 2-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy)-5-nitrobenzoate (41)

According to GP1. FC (1:1 light petroleum (50–70)–EtOAc) gave the product as a white foam: mp 129 °C; $[\alpha]_D^{20}$ −18 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, 1H, $J_{Ar\text{-}3,5}$ 2.5 Hz, Ar-3), 8.36 (dd, 1H, $J_{Ar\text{-}5,6}$ 9.2 Hz, Ar-5), 7.32 (d, 1H, Ar-6), 5.89 (d, 1H, $J_{1,2}$ 8.1 Hz, H-1), 5.61 (dd, 1H, $J_{1',2'}$ 7.6 Hz, $J_{2',3'}$ 10.7 Hz, H-2′), 5.49 (dd, 1H, $J_{2,3}$ 10.2 Hz, H-2), 5.47–5.44 (m, 2H, H-4, H-4′), 5.19 (d, 1H, H-1′), 5.15 (dd, 1H, $J_{3,4}$ 3.6 Hz, H-3), 5.11 (dd, 1H, $J_{3',4'}$ 3.1 Hz, H-3′), 4.21–4.11 (m, 6 H, H-5, H-6a/b, H-5′, H-6′a/b), 2.19, 2.18, 2.07, 2.06, 2.05, 2.01, 2.00, 1.99 (8s, 24 H, $8COCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.81, 170.73, 170.67, 170.63, 170.52, 170.40, 169.66, 169.44 (8C, 8*C*OCH$_3$), 161.36 (Ar–*C*O), 160.59 (Ar-1), 142.97 (Ar-4), 129.67 (Ar-5), 128.38 (Ar-3), 120.65 (Ar-2), 117.47 (Ar-6), 99.92 (C-1′), 93.44 (C-1), 72.39, 72.17 (2C, C-5, C-5′), 71.11, 71.04 (2C, C-3, C-3′), 68.53 (C-2′), 68.17 (C-2), 67.16, 67.10 (2C, C-4, C-4′), 61.81,

61.47 (2C, C-6, C-6′), 21.65, 21.46, 21.16, 21.08, 21.06, 21.01, 20.83, 20.72 (8C, 8CO*C*H$_3$); MALDI-TOFMS: *m*/*z* 866.2 [M+Na]$^+$, 882.2 [M+K]$^+$. Anal. Calcd for $C_{35}H_{41}NO_{23}$: C, 49.83; H, 4.90; N, 1.66. Found: C, 49.90; H, 4.99; N, 1.59.

3.31. (3-Nitro-2-pyridyl) 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (46)[22]

A soln of **1** (2.88 g, 7.00 mmol) and **43**[22] (1.99 g, 8.06 mmol) in toluene (30 mL) was kept under reflux for 1 h. After cooling to rt and filtration though a pad of Celite, the filtrate was washed with satd aq $NaHCO_3$ soln and water, dried with magnesium sulfate and evaporated to dryness. FC (3:1 toluene–acetone) gave **46** as a glass (2.33 g, 71%): $[\alpha]_D^{20}$ +128 (*c* 0.4, $CHCl_3$); MALDI-TOFMS: *m*/*z* 493.3 [M+Na]$^+$, 509.3 [M+K]$^+$.

3.32. 4-Pyridyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (47)

A soln of **1** (2.88 g, 7.00 mmol) and **44**[21] (1.63 g, 8.07 mmol) in toluene (30 mL) was kept under reflux for 1 h. After cooling to rt and filtration though a pad of Celite, the filtrate was washed with satd aq $NaHCO_3$ soln and water, dried over magnesium sulfate and evaporated to dryness. FC (3:1 light petroleum (50–70)–EtOAc) gave **47** as a glass (1.96 g, 66%): $[\alpha]_D^{20}$ +54 (*c* 0.5, $CHCl_3$).

3.33. (3-Nitro-2-pyridyl) β-D-galactopyranoside (49)[22]

According to GP2 gave **49** as a glass: $[\alpha]_D^{20}$ +37 (*c* 0.1, MeOH).

3.34. 4-Pyridyl β-D-galactopyranoside (50)

According to GP2 gave **50** as a glass: $[\alpha]_D^{20}$ +94 (*c* 0.1, MeOH).

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