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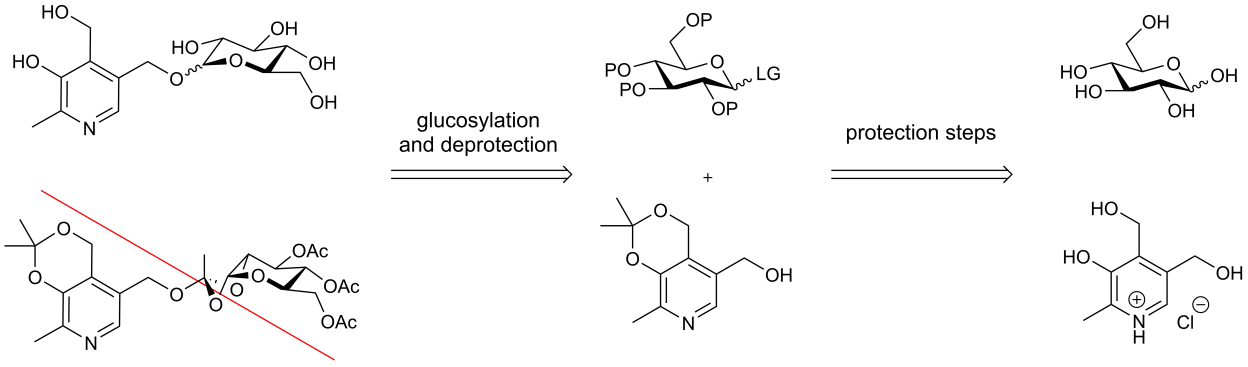

Chemical glucosylation of pyridoxine

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Abstract: The chemical synthesis of pyridoxine-5'-*β*-D-glucoside (5'-*β*-PNG) was investigated using various glucoside donors and promoters. Hereby, the combination of *α*4,3-*O*-isopropylidene pyridoxine, glucose vested with different leaving and protecting groups and the application of stoichiometric amounts of different promoters was examined with regards to the preparation of the twofold protected PNG. Best results were obtained with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl fluoride and boron trifluoride etherate (2.0 eq.) as promoter at 0 °C (59 %). The deprotection was accomplished stepwise with potassium/sodium hydroxide in acetonitrile/water followed by acid hydrolysis with formic acid resulting in the chemical synthesis of 5'-*β*-PNG.

Keywords: Pyridoxine; Vitamin B_6; Chemical Glycosylation; Chemical Synthesis

1. Introduction

The group of vitamin B_6 consists of the three vitamers pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM) and their respective phosphorylated compounds pyridoxine 5'-phosphate (PNP), pyridoxal 5'-phosphate (PLP) and pyridoxamine 5'-phosphate (PMP) (Figure 1).[1]

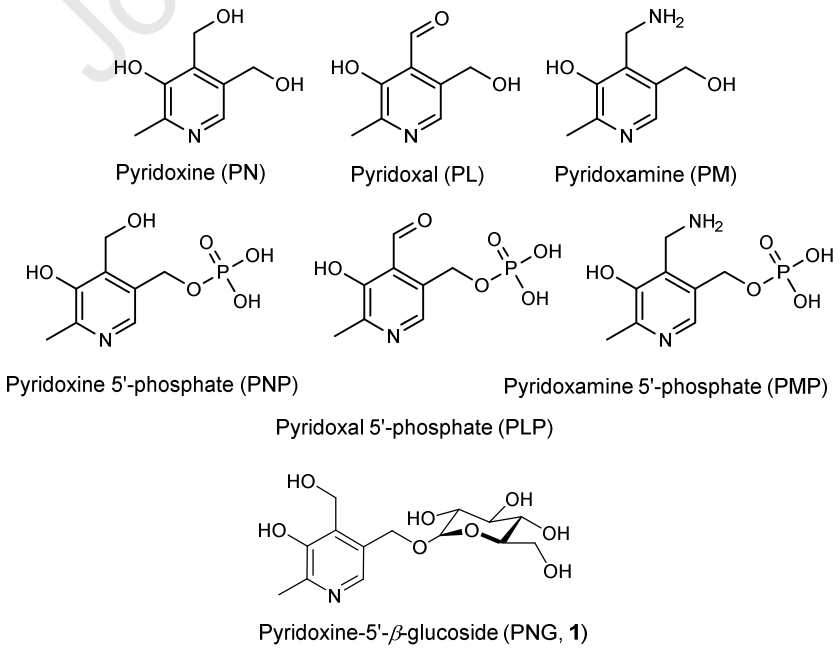


Figure 1. The group of vitamin B_6 unites six substrates sharing a 2-methyl 3-hydroxypyridine structure.

Furthermore, a glucosylated derivative, pyridoxine-5'-*β*-D-glucoside (5'-*β*-PNG, **1**), can be found in plants as a major fraction of the total vitamin B_6 content (Figure 1).[2-4] The substance was first identified in 1968 during investigations regarding the metabolism of pyridoxine in microorganisms.[5] In this study, the transglucosylation of glycosyl-moieties - sucrose was found to be the most efficient as carbon-donor amongst other tested saccharides - to pyridoxine using intact cells of *Sarcina lutea* and the isolated enzyme of *Micrococcus* resulted in mainly 5'-*α*-PNG and small amounts of 4'-*α*-PNG. The molecules were verified *via* enzymatic hydrolysis and comparison to a chemically synthesized sample.[6-10] The latter was prepared and isolated as a hexaacetate derivative according to KOENIGS-KNORR reaction using *α*4,3-*O*-isopropylidene pyridoxine, 2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranosyl chloride and silver carbonate followed by subsequent acetylation.[9] The application of purified *α*-glucosidase from *Mucor javanicus* with dextrin has been reported in 1996 to result in the formation of 4'- and 5'-*α*-PNG in an equimolar ratio with 14 % yield.[11] Also, a marine exo-*α*-glucosidase from the anaspidean mollusc *Aplysia fasciata* was tested regarding transglucosylation properties towards pyridoxine and showed high selectivity towards the 5' position for both mono- (*α*-D-glucose) and disaccharide (*α*-isomaltose) formation resulting in specifically the *α*-glycoside.[12]

Next to these microorganisms and isolated enzymes, also fungi of the genus *Verticillium dahliae* were found to catalyze a highly selective (99 %) transglucosylation towards 5'-*α*-PNG with moderate yield (34 %) from maltodextrin using borate as complexing agent.[13]

Although the *α*-epimer of 5'-PNG also exhibits nutritional value, the main fraction (5 - 70 %) of the total vitamin B_6 content in plant-derived foods consists of the *β*-epimer.[14, 15] After their first identification in 1977 through isolation from rice bran, Yasumoto et al. also pioneered in the chemical synthesis of 5'-*β*-PNG preparing the molecule *via* KOENIGS-KNORR synthesis with a yield of 3 % using *α*4,3-*O*-isopropylidene pyridoxine, 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide and silver carbonate.[16] Additionally, pyridoxine glycosides were prepared from various glycosyl donors (e.g. *p*-nitrophenyl-*β*-glucoside) utilizing a *β*-glucosidase, which has been isolated and purified from rice bran[17] or sweet almond[18] beforehand. With the latter, a mixture of 4'-*α*/5'-*α*/5'-*β*-PNG (20/39/41) was obtained in 36 % (± 10 %) yield.[18] Transglycosylating properties towards 4'- and 5'-*β*-PNG were also detected incubating cellobiose and pyridoxine with *β*-glucosidase (cellobiase) from wheat bran and using an isolated glucosyltransferase from popped pea (*Pisum sativum*) along with UDP-Glucose and PN.[4, 19] In this regard a

variety of glycosidases were tested in glycosylation reactions using pyridoxine as substrate.[20]

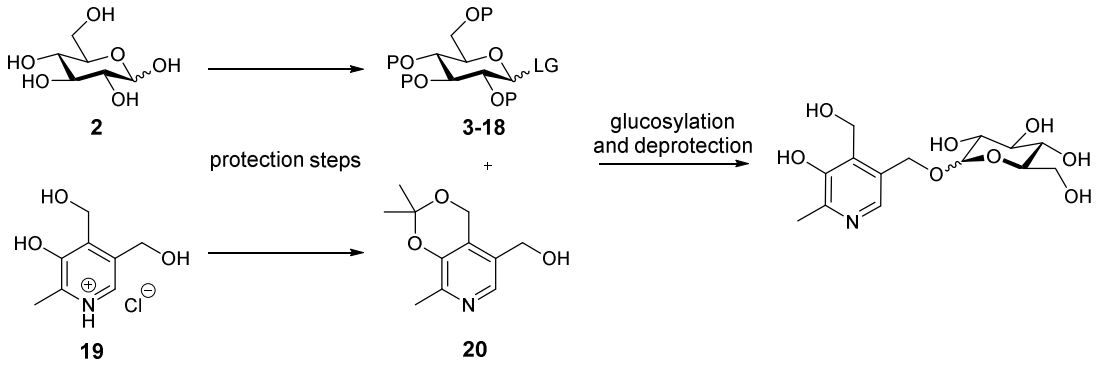
Various plant seeds, *i.e.* soybean, cow pea, jack bean, japanese radish, chinese cabbage, spinach, rice, corn, wheat, trefoil and alfalfa produce PNG during germination.[19, 21-25] While investigating the formation of *β*-PNGs in germinating seeds of wheat, barley and rice, the regioselective preference regarding the 4' and 5'-position of pyridoxine in certain seeds was noticed. Seeds of wheat and barley produced both the 4' and 5'-*β*-PNG in the same molar ratio during the germination. In contrast, rice seeds mainly contained the 5'-glucoside, while the 4'-glucoside was formed only in small amounts at later stages of germination.[11] Soybean seeds formed only 5'-*β*-PNG.[24] Furthermore, alfalfa seeds were reported to create unlabeled PNG - the yields ranged from 35-60 % -, [^{2}H]- and [^{3}H]-*β*-PNG.[25-29]

Although there exists a manifold of different methods with regard to the biotechnological preparation of pyridoxine glycosides, the chemical pathway towards this substrate is not explored well to this day. Hereby, main approaches rely on the preparation *via* KOENIGS-KNORR reaction conditions, but result in rather unsatisfying yields. The aim of this study was to establish a fundament comprising of various methods regarding the chemical preparation of *β*-PNG in order to suggest opportunities in the field of the chemical synthesis of this molecule as an alternative to the commonly utilized preparation *via* biotechnological pathways. To achieve this objective, a strategy was required that would not only compete in the yield and selectivity of the reaction towards the desired molecule, but also in the simplicity of the preparation steps and time needed therefor.

2. Results & Discussion

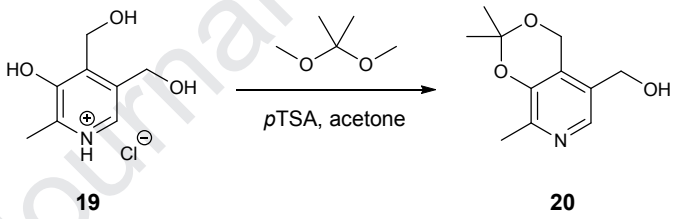
2.1. Synthesis of the glucosyl donors and protection of PN

In order to establish this methodology, this study focused on investigations regarding the chemical glucosylation of pyridoxine. Therefore, the starting materials for the glucosylation reaction, namely the glucosyl donors (**3**-**18**) and acceptor (**20**), were prepared starting from glucose (**2**) and pyridoxine hydrochloride (**19**) and subsequently implemented in a glucosylation reaction (Scheme 1).



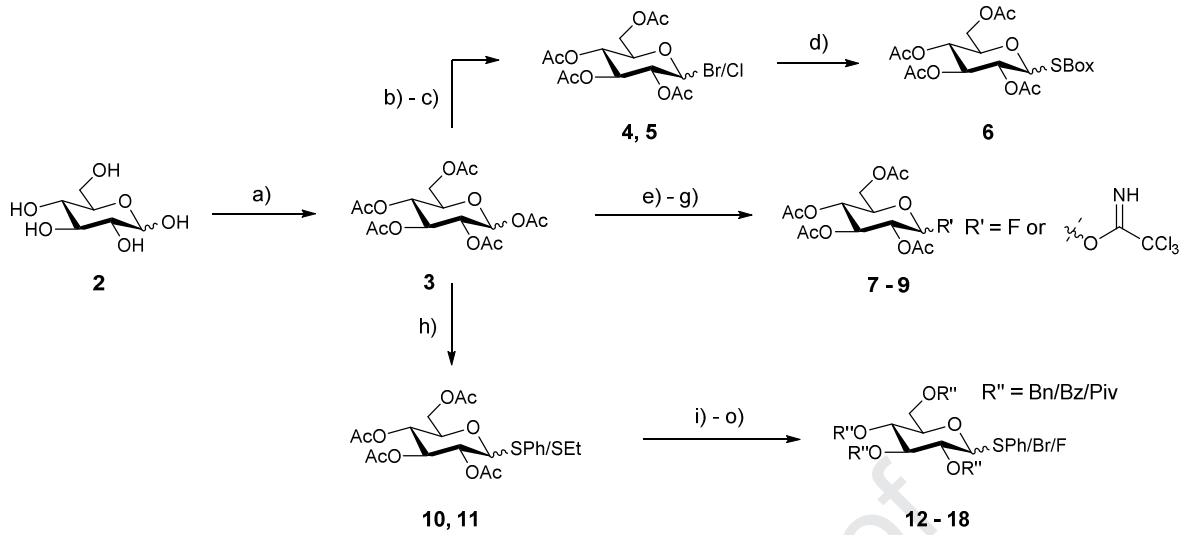
Scheme 1. General depiction outlining the strategy for the chemical glucosylation of pyridoxine. P = protecting group (Ac, Bz, Bn, Piv), LG = leaving group (F, Cl, Br, SEt, SPh, SBox, Imidate).

The hydrophilicity of pyridoxine (PN) shackles the vitamin to its solubility in water - and somewhat ethanol -, a solvent not favorable for glycosylation reactions. In order to enhance its solubility in organic solvents and to improve the selectivity towards 5'-position, the hydroxyl-groups in 3'- and 4'-position were protected using *p*-toluenesulfonic acid (*p*TSA) and 2,2-dimethoxypropane resulting in the protected pyridoxine (**20**, 96 %, Scheme 2).[30] The introduction of the acetonide group in the right position was verified by 2D-NMR measurements.



Scheme 2. The protection of PN proceeded selectively with *p*TSA and 2,2-dimethoxypropane.

The synthesis of the glucosyl donors started with the peracetylation of glucose (**2**, **3**; Scheme 3).[31] Implementation of bromine (**4**) and chlorine (**5**) leaving groups was accomplished with hydrogen bromide (HBr) or thionyl chloride and tin tetrachloride ($SOCl_2/SnCl_4$).[32-34] Deprotection of the anomeric acetate group was achieved with ethylene diamine and acetic acid.[35] The utilization of benzyl amine as selective anomeric-deprotection reagent[36] required a longer reaction time and higher effort with regards to the purification of the product. Continuing from the free hydroxyl functionality (**7**) either trichloroacetimidate-glucose (**8**) could be obtained using trichloroacetonitrile and DBU or a fluorine leaving group (**9**) could have been installed using diethylaminosulfur trifluoride (DAST).[35, 37]



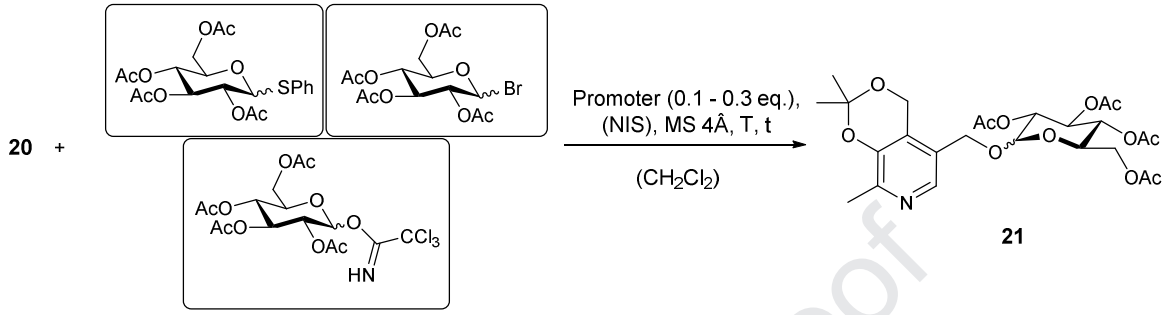
Scheme 3. Preparation of the glucosyl donors. a) Ac_2O, pyridine; b) HBr; c) $SOCl_2$, $SnCl_4$; d) 2-Mercaptobenzoxazole, K_2CO_3; e) Ethylene diamine, HOAc; f) DBU, $NCCl_3$; g) DAST; h) EtSH/EtPh, $BF_3 \cdot OEt_2$; i) NaOMe, MeOH; j) BnBr, NaH; k) BzCl, pyridine; l) PivCl, pyridine; m) NBS; n) $C_2O_2Br_2$; o) DAST.

Thioglycosylation (**10**, **11**) of a peracetylated saccharide can be accomplished with a variety of Lewis acids *e.g.* $SnCl_4$, trimethylsilyl trifluoromethanesulfonate (TMSOTf) or boron trifluoride etherate ($BF_3 \cdot OEt_2$).[38-40] Furthermore, a SBox-leaving group (**6**) was furnished using 2-mercapto-benzoxazole and potassium carbonate.[41] In order to investigate the influence of other protecting groups on the glucosylation of PN, the remaining acetate groups had to be cleaved while leaving the thiol-group intact. Deacetylation (**12**) was undertaken according to ZEMPLÉN using sodium methoxide in methanol followed by application of cation exchange resin (Dowex, H^+-form) during workup.[42] Next, the molecule could be modified with benzyl-protecting groups (**15**) using benzyl bromide (BnBr) and sodium hydride (NaH) or benzoyl-groups (**13**) and pivaloyl-groups (**14**) using the respective chlorides (BzCl/PivCl) as starting material with pyridine. After hydrolysis (**16**) of the thiol group with *N*-bromosuccinimide (NBS), a bromine leaving group could be introduced with oxalyl bromide resulting in the 2,3,4,6-tetra-*O*-benzyl-*α*-D-glucopyranoside bromide (**18**). DAST aided in the synthesis of the fluorinated benzyl glucoside **17**.

2.2. Glucosylation reactions

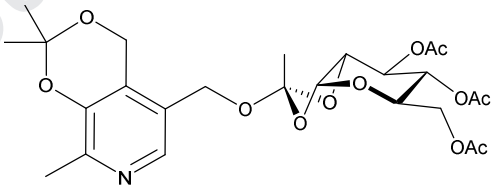
As part of a first approach, a promoting system consisting of the combination of *N*-iodosuccinimide (NIS) and different acidic/Lewis-acidic reagents, namely TMSOTf, triflic acid (TfOH), $BF_3 \cdot OEt_2$, or various silver or rather copper salts, in particular silver triflate (AgOTf), silver carbonate (Ag_2CO_3), silver oxide (Ag_2O) and copper triflate ($Cu(OTf)_2$), was examined (Scheme 4). As for the glucosyl donors, thio, imidate and

bromoglucosides were chosen because of their versatile scope of application, good stability and simple preparation (Scheme 3).[40, 43-45] In order to enhance the selectivity towards the *β*-product, acetate protecting groups represented the first choice due to their neighbouring group participation.[46-48]



Scheme 4. General reaction scheme for the first glucosylation-approaches involving KOENIGS-KNORR- and SCHMIDT-conditions as well as glucosylations with thioglucosides and depiction of the expected product (**21**).

Variations regarding the reaction conditions focused not only on switching the leaving groups and promoter systems, *i.e.* different amounts (0.1 - 0.3 eq.) of promoter with or without the addition of NIS, but - as further dimensions of variation - additionally on temperature (− 78, − 30, 0 °C or rt) and time. Unfortunately, this set of experiments ended exclusively in the formation of the orthoester-structure **22** when NIS was added regardless of the chosen glucosylation method and reaction conditions (Figure 2, Scheme 5).



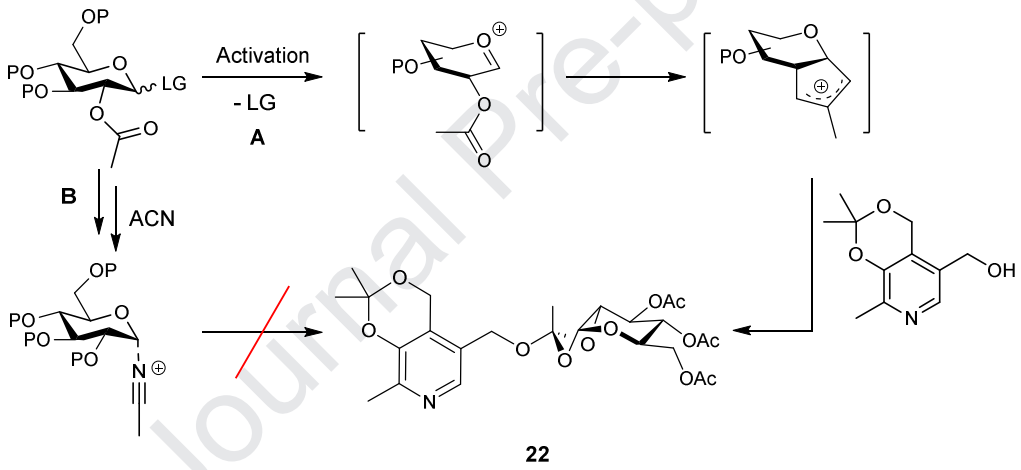
22

Figure 2. First reaction approaches ended exclusively in the formation of the orthoester **22**.

On the other hand, no conversion of the starting material took place using a promoter-system without NIS. This was especially salient in the case of KOENIGS-KNORR conditions, where the acetylated glycopyranosyl bromide **4** was reacted under the addition of silver triflate (0.3 eq.) at 0 °C. Hereby, the orthoester was isolated with a yield of 48 % while adding NIS (3.0 eq.). On the other hand, no conversion occurred without NIS, suggesting a NIS-mediated formation of the orthoester. The structural discrepancy was verified *via* the number of carbon-signals related to the acetate-groups in the ^{13}C-NMR spectra - three in case of the

orthoester versus four in the desired product - and an erroneous m/z (= 414 vs. the sought-after 371) after the following basic deprotection of the acetate groups.

The study of orthoesters is profoundly entrenched in the chemistry of glycosylation reactions, especially in the preparation of 1,2-trans-glycosides where the anchimeric assistance is utilized in the enhancement of *β*-selectivity. Furthermore, orthoesters themselves were already pictured as either intermediates on the way to a desired glycoside or used as starting materials directly.[49-52] Contrarily, their formation was connected to an undesired reaction outcome, too.[53, 54] Their origination can be traced to the activator-assisted heterolytic fission of the C-LG bond with formation of an oxonium ion leading to the generation of a more stable acyloxonium ion through neighbouring group participation of the C-2 acyl group and the subsequent attack of the glycosyl acceptor towards this new electrophilic center (Path **A**, Scheme 5).[55-57]

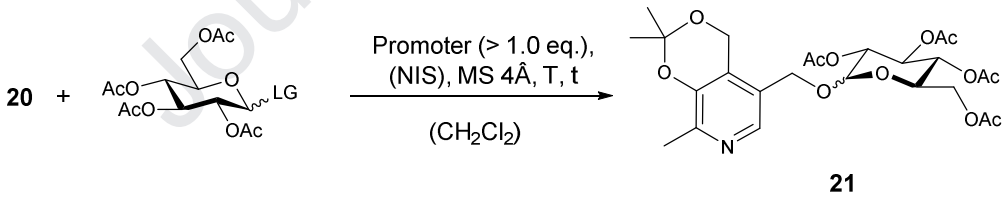


Scheme 5. The formation of orthoesters occurs through neighbouring group participation.

In this regard, the originally planned utilization of the neighbouring group effect to enhance the selectivity towards the *β*-product resulted in an undesired reaction outcome bearing only the orthoester structure, despite the variation of the reaction conditions and use of Lewis acids as promoters. In order to circumvent this problem, either the impact of the neighbouring group effect had to be diminished or a potential transformation of the orthoester into the desired glucosidic structure evaluated. Regarding the latter, especially Lewis-acidic reagents such as TMSOTf are commonly applied as aid in the rearrangement towards the desired product.[49, 50, 58-61] Unfortunately, no procedures helped in our case resulting either in no conversion of PNG while applying mild conditions (0 °C - rt, 0.1 - 1 eq. of acidic catalyst) or cleavage of the glucosidic bond in the case of harsh conditions (> rt, > 1 eq. of acidic catalyst, multiple days).

In order to bypass the neighbouring group effect, a further option that was explored involved the utilization of the nitrilium effect of acetonitrile (ACN). Through selective coordination towards the α-face according to the solvent coordination hypothesis, the nucleophilic attack of the acetate groups can be obviated (Path **B**, Scheme 5).[62-64] Although this strategy being useful with regards to the selectivity of the reaction towards the β-product, the complete substitution of dichloromethane as the reaction solvent was not possible due to reduction in solubility of the starting materials, making the addition of ACN in stoichiometric amounts inevitable. Nevertheless, no orthoester formation was observed with this procedure (AgOTf 0.3 eq./NIS 3.0 eq., − 78 °C) and the desired product could be isolated, even though in low yields (20 %).

Glycosylation reactions involving pyridine based derivatives show either a scarce appearance in the literature[65-67] or are mostly studied in conjunction with nucleotide synthesis.[68-73] Their utilization as part of a protection strategy was also an aspect of research.[74-76] Optimally, application of low amounts of promoter (0.1 – 0.3 eq.) suffices with regards to glycosylation reactions, but since the activation is mostly performed in an acid driven approach, the basicity of pyridine derivatives could exhibit a competing effect under such conditions.[77, 78] In order to explore this hypothesis, the introductory experiments leading to the orthoester were revised with a stoichiometric amount of promoter added to the reaction (Scheme 6).



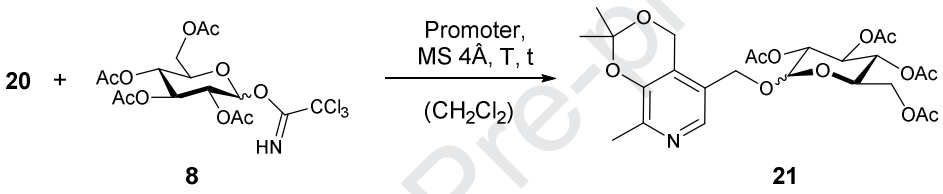
Scheme 6. The initial experiments were repeated with an increased amount of promoter.

Interestingly, this shifted the reaction outcome not only completely from the formation of the orthoester (**22**) to the desired PNG (**21**), but also resulted in a high β-selectivity of the reaction. Since the mechanism proposedly proceeds *via* the departure of the leaving group and the stabilization of the resulting oxonium ion through formation of an acyloxonium ion, a higher amount of promoter - hereby especially triflate substrates - could have an impact not only with regards to countering the basicity of PN, but also providing a shielding effect of the acyloxonium ion, allowing a selective attack of PN on the anomeric position from the β-side.[46, 79-83] A similar outcome, where an increase (0.1 to 0.25 eq.) of promoter helped with the conversion of the starting material - although with non-pyridine moieties -, was

observed with TMSOTf and AgOTf.[58, 84] Furthermore, a dependence of the orthoester formation on the temperature was described while preparing DON-glycosides under SCHMIDT conditions.[85] It additionally has to be noted, that acetonide protecting groups are unstable against Brønsted acids. Due to the Lewis-acidic properties of the promoters used in this study, an increase of promoter showed no harm to the acetonide group.

Having found a method for the synthesis of the desired PNG, the process of optimization was addressed next. For this task, halogen, thio or imidate glucosideswere utilized in analogy to the introductory tests (Scheme 6).

First, reactions revolving around the activation of trichloroacetimidate functionalities (**8**) with Lewis acids in dichloromethane as solvent were investigated (Scheme 7, table 1).[86, 87]



Scheme 7. First glucosylation reactions were performed with trichloroacetimidate donors.

Hereby, no formation of PNG was observed with either TMSOTf (1.0 eq.) or $Sc(OTf)_3$ (1.0 eq.) at 0 °C (entry 1/2). Better conversion was obtained with TfOH (1.0 eq., 33 %, entry 3) and $BF_3 \cdot OEt_2$ (1.0 eq., 40 %, entry 4), indicating a superior activation of trichloroacetimidate groups using $BF_3 \cdot OEt_2$ rather than TMSOTf.[84]

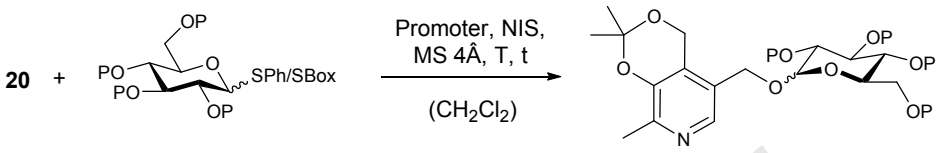
Table 1. Reaction conditions for the imidate glucosides.

entry	substrate	promoter [eq.]	T [°C]	yield [%]
1	**8**	TMSOTf 1.0	0	-
2	**8**	$Sc(OTf)_3$ 1.0	0	-
3	**8**	TfOH 1.0	0	33
4	**8**	$BF_3 \cdot OEt_2$ 1.0	0	40
5	**8**	$BF_3 \cdot OEt_2$ 1.0	rt	11
6	**8**	$BF_3 \cdot OEt_2$ 1.0	− 78	32
7	**8**	$BF_3 \cdot OEt_2$ 1.5	0	42

Lowering (− 78 °C) and raising (rt) the reaction temperature led to lower yields (32 resp. 11 %, entries 5/6). Furtherly increasing the amount of promoter stimulated no higher reaction outcome (42 %, entry 7). All performed reactions led selectively to the β-anomer and no formation of the α-anomer could be detected. Furthermore, monitoring the reactions *via* TLC

indicated that most of the reaction took place during the first 12 hours and a prolonged reaction time did not result in a further change of the reaction mixture.

Thiol derivatives are established leaving groups in chemical glycosylations, having gone through extensive research and thus making them powerful tools in carbohydrate chemistry.[88] Hence, they were included in this survey (Scheme 8).



Scheme 8. Thioglucosides were investigated next as part of this survey.

While applying the same reaction conditions ($BF_3 \cdot OEt_2$ 1.0 eq., entry 3, table 2) as with imidate groups, the glucosylation of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside (**10**) proceeded in approximately the same yield (38 %), whereas TfOH (1.0 eq., entry 4) increased the outcome of the reaction (48 %). Also, both raising (rt, entry 5) and lowering (− 78 °C, entry 6) the temperature led to lower yields (29 and 19 %, respectively) in accordance to imidate donors outlined above and no activation of the donor was achieved with TMSOTf (1.0 eq., entry 1) or AgOTf (1.0 eq., entry 2) at 0 °C.

Table 2. Reaction conditions for the thioglucosylations.

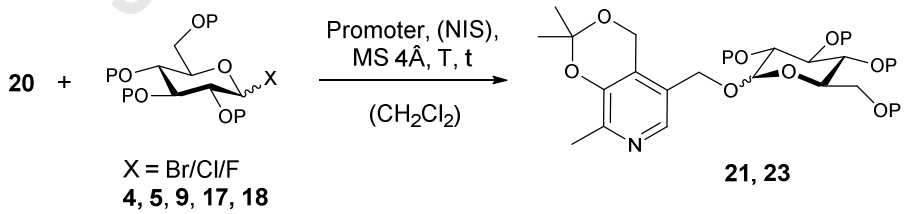
entry	substrate	promoter [eq.][a]	T [°C]	yield [%]	*α*/*β*
1	**10**	TMSOTf 1.0	0	-	-
2	**10**	AgOTf 1.0	0	-	-
3	**10**	$BF_3 \cdot OEt_2$ 1.0	0	38	*β*
4	**10**	TfOH 1.0	0	48	*β*
5	**10**	TfOH 1.0	rt	29	*β*
6	**10**	TfOH 1.0	− 78	19	*β*
7	**10**	TfOH 1.0	0	-	-
8	**15**	TfOH 1.0	− 78	40	76/24
9	**15**	TfOH 1.0	0	55	74/26
10	**13**	TfOH 1.0	0	15	*β*
11	**14**	TfOH 1.0	0	16	*β*
12	**6**	TMSOTf 1.0	0	-	-
13	**6**	$BF_3 \cdot OEt_2$ 1.0	0	-	-
14	**6**	AgOTf 3.0	rt	35	*β*
15	**6**	TfOH 1.0	0	47	*β*

[a] all reactions (except 7) were carried out with 3.0 eq. NIS.

Furthermore, no product could have been isolated utilizing IBr as alternative iodine source (entry 7).[89] All reactions were carried out with and without the addition of NIS (3.0 eq.) as additive as part of this survey, although no conversion occurred in the latter case (table 2). In addition to the electron-withdrawing acetate-groups, also the influence of benzyl- (**15**), benzoyl- (**13**) and pivaloyl-groups (**14**) in combination with TfOH/NIS as promoter was examined. In comparison, benzoyl- (15 %, entry 10) and pivaloyl-groups (16 %, entry 11) hampered the glycosidic bond formation, while the application of benzyl groups, although generating a bigger amount of PNG at 0 °C (55 %, entry 9), resulted in an anomeric mixture of approximately α/β = 3/1 independent of the reaction temperature (− 78 / 0 °C).

A modern approach regarding the aspect of versatility in glycosylation reactions was undertaken by Demchenko introducing SBox-leaving groups, which combine the electronic effects and activation properties of thiol and imidate groups.[90-95] When integrating them (**6**) into this study, the addition of 3.0 eq. AgOTf (35 %, entry 14) at rt and 1.0 eq. TfOH at 0 °C (47 %, entry 15) both formed the product, while no conversion of the starting material was observed with TMSOTf (1.0 eq., entry 12) or $BF_3 \cdot OEt_2$ (1.0 eq., entry 13) at 0 °C. Although being frequently found in the literature as promoter for SBox-leaving groups, the lack of reactivity utilizing TMSOTf states a common agreement with the reactions involving imidate and thioglycosides. In this regard, the insufficiency of $BF_3 \cdot OEt_2$ stands in contrast to the previous experiments.

After scoping imidate and thiol substrates, halogens represented the third party of leaving groups investigated during this study (Scheme 9).



Scheme 9. Halogen glucosides were investigated as last part of this study.

The first experiments were built around the variation of reaction conditions with bromine (**4**) as leaving group. Since a higher amount of promoter hindered the formation of the orthoester, a preliminary reaction was performed with AgOTf (1.0 eq.) and NIS (3.0 eq.) as promoter system at 0 °C, resulting in sparse amounts of product (21 %, entry 1, table 3). Again, in analogy to the activation of the thiol groups, no reaction was observed without NIS while utilizing bromine as leaving group. On the other hand, a trial using solely NIS as promoter resulted in no conversion of the starting material, making this reaction type

interesting, since the addition of NIS as co-promoter is mostly known for thioglycosylations. Increasing the amount further to three equivalents of promoter led to nearly a duplication of the obtained yield (40 %, entry 2). Variation of the temperature both to a lower (− 78 °C, 30 %, entry 3) and higher (rt, 32 %, entry 4) degree led to less product in comparison.

Table 3. Reaction conditions for the glucosylations with a bromine leaving group.

entry	substrate	promoter [eq.][c]	T [°C]	yield [%]	*α*/*β*
1	**4**	AgOTf 1.0	0	21	*β*
2	**4**	AgOTf 3.0	0	40	*β*
3	**4**	AgOTf 3.0	− 78	30	*β*
4	**4**	AgOTf 3.0	rt	32	*β*
5[a]	**4**	AgOTf 3.0	rt	48	*β*
6[b]	**4**	AgOTf 3.0	− 78	-	-
7	**4**	Ag_2CO_3 3.0	0	-	-
8	**4**	Ag_2O 3.0	0	-	-
9	**4**	$Cu(OTf)_2$ 1.0	0	-	-
10	**4**	AgOTf 3.0	0	-	-
11	**18**	AgOTf 3.0	0	37	75/25
12	**18**	AgOTf 3.0	rt	56	75/25

[a] 2 eq. substrate; [b] THF used as solvent; [c] all reactions (except 10) were carried out with 3.0 eq. NIS

No formation of the glucoside occurred by switching to tetrahydrofuran (THF) as solvent (entry 5) and increasing the amount of substrate (2.0 eq.) gave a slightly higher outcome compared to 1.2 equivalents (48 %, entry 6). In a trial of different promoters, silver oxide (Ag_2O, entry 8), silver carbonate (Ag_2CO_3, entry 7) and also copper triflate ($Cu(OTf)_2$, entry 9) all led to no conversion of the starting material at 0 °C. IBr as alternative additive resulted, corresponding to the thiol experiments, in no PNG formation (entry 10). Switching from acetate to benzyl protecting groups (**18**) expectedly increased the yield (56 %, entry 12), but led in a similar manner as the benzylated thiol donors to an anomeric mixture (*α*/*β* = 75/25). Lowering the temperature (0 °C) decreased the yield contrarily to the obtained results using 'deactivating' groups (37 %, entry 11).

Applications of a chloride leaving group in glucosylation reactions are seldom and often considered less powerful in comparison to the other halogens. In order to compare them to the 'classic' KOENIGS-KNORR leaving group (table 3), a few experiments were performed within this study (table 4). Amongst the tested promoters, only AgOTf (37 %, 0 °C, entry 4) in combination with NIS worked out leading to a reaction outcome in the same range as the bromoglucoside (entry 2, table 3). Lowering the temperature (− 78 °C) resulted in nearly the same yield (36 %, entry 5), while increasing the temperature (40 °C, entry 6) and substitution

with IBr (1.1 eq., entry 7) led to no product formation. Tests with TfOH, $BF_3 \cdot OEt_2$ and TMSOTf showed no conversion of the starting material (entries 1-3).

Table 4. Reaction conditions for the glucosylations with chlorine as leaving group.

entry	substrate	promoter [eq.][a]	T [°C]	yield [%]	*α/β*
1	**5**	TfOH 2.0	0	-	-
2	**5**	$BF_3 \cdot OEt_2$ 2.0	0	-	-
3	**5**	TMSOTf 2.0	0	-	-
4	**5**	AgOTf 3.0	0	37	*β*
5	**5**	AgOTf 3.0	− 78	36	*β*
6	**5**	AgOTf 3.0	40	-	-
7	**5**	AgOTf 3.0	0	-	-

[a] all reactions (except 7) were carried out with 3.0 eq. NIS

Since the first introduction of fluorine as leaving groups in order to enhance stereoselectivity during glycosylation reactions due to assumed lower reactivity compared to thioglycosides, their application in the field of chemical glycosylations rose constantly.[96]

Table 5. Reaction conditions for the optimization of the fluoroglucosylation.

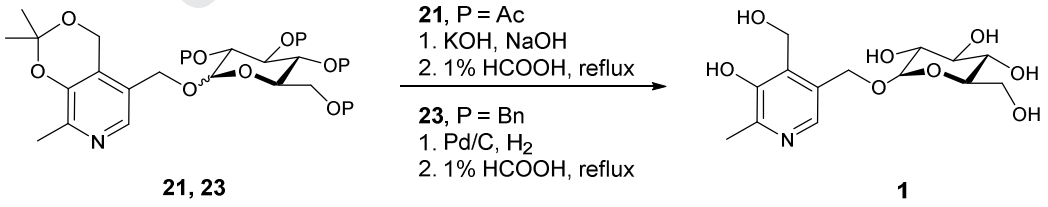
entry	substrate	promoter [eq.]	T [°C]	yield [%]	*α/β*
1[c]	**9**	TMSOTf 2.0	0	-	-
2[a]	**9**	$SnCl_2$ 2.0	0	-	-
3[c]	**9**	AgOTf 3.0	0	-	-
4	**9**	TfOH 2.0	0	-	-
5	**9**	$BF_3 \cdot OEt_2$ 1.0	0	-	-
6[c]	**9**	$BF_3 \cdot OEt_2$ 1.0	0	-	-
7	**9**	$BF_3 \cdot OEt_2$ 2.0	0	59	*β*
8	**9**	$BF_3 \cdot OEt_2$ 6.0	0	59	*β*
9	**9**	$BF_3 \cdot OEt_2$ 6.0	− 78	40	*β*
10	**17**	$BF_3 \cdot OEt_2$ 2.0	0	65	71/29
11	**17**	$BF_3 \cdot OEt_2$ 2.0	− 78	63	75/25
12[b]	**17**	$BF_3 \cdot OEt_2$ 2.0	0	58	46/54
13	**17**	$BF_3 \cdot OEt_2$ 0.5	0	-	-
14	**17**	TMSOTf 0.5	0	-	-
15	**17**	TfOH 0.5	0	-	-
16	**17**	$SnCl_2$ 2.0, $AgClO_4$	0	48	71/29

[a] the reaction was also performed with NIS, but resulted in the same yield; [b] ACN as solvent; [c] reactions were carried out with 3.0 eq. NIS.

The first reactions with the fluoroglucoside **9** were performed with acetate protecting groups and a stoichiometric amount of various promoters. Among the latter were TMSOTf[97] (2.0 eq., entry 1, table 5), $SnCl_2$ (2.0 eq., entry 2), AgOTf (3.0 eq., entry 3) and TfOH (2.0 eq., entry 4), which all led to no formation of product. Also, first experiments with $BF_3 \cdot OEt_2$

(1.0 eq., entry 5), with and without (entry 6) the addition of NIS, bore no fruits. Only with the further increase of the amount of promoter to two equivalents, the reaction with $BF_3 \cdot OEt_2$ resulted in the desired glucoside in good yield (59 %, entry 7). A further increase of $BF_3 \cdot OEt_2$ (6.0 eq., entry 8) did not improve the amount of obtained product (59 %). Carrying out the reaction at − 78 °C gave less PNG (40 %, entry 9). In analogy to the thiol and bromine experiments, benzyl groups were tested in combination with fluorine as leaving group (**17**). Likewise, the reaction outcome grew in comparison to acetate groups using two equivalents of $BF_3 \cdot OEt_2$ at 0 °C and − 78 °C (65 resp. 63 %, entry 10 / 11), but resulted in an anomeric mixture of approximately α/β = 3/1 due to the lack of the neighbouring effect and the anomeric effect taking over. Utilizing acetonitrile as solvent shifted the reaction slightly towards the β-anomer (58 %, α/β = 46/54, entry 12). Furthermore, low amounts of the promoters TfOH, TMSOTf and $BF_3 \cdot OEt_2$ (0.5 eq., entries 13 – 15) were tested with fluorobenzyl donors, but led to no conversion of the starting material. Lastly, stannous chloride in combination with silver perchlorate was examined, but resulted in a lower yield compared to the other experiments (48 %, entry 16).

After scoping various pathways towards the formation of the glyosidic bond, the last step of this study revolved around the deprotection of the acetonide and acetate/benzyl groups. Because of the stability of acetate groups in acidic medium and the stability of the acetonide group under alkaline conditions, a two-step deprotection procedure had to be applied to the acetate protected PNG (**21**). Benzyl groups (**23**) could be cleaved with the aid of palladium and hydrogen (Scheme 10).



Scheme 10. The deprotection of PNG involved a two-step procedure.

Application of a mild procedure involving pH-control with aqueous solutions of potassium and sodium hydroxide followed by cleaving the acetonide group in a slightly acidic media at higher temperatures led to the deprotected PNG (**1**) in quantitative yield. Also, the hydrogenation with palladium and hydrogen followed by the acid deprotection proceeded with the same excellent yield. The validity of the anomeric outcome was verified by NMR-spectroscopy and the transformation with β-glycosidase from almonds was followed by HPLC-analysis.

Closing the circle back to the requirements the proposed method should feature, the arrangement with the literature regarding aspects like yield and working effort seems adequately comparable, since biotechnological methods, *e.g.* utilizing Alfalfa seeds, result also in yields ranging from 35 – 60 %.[29] Furthermore, biotechnological methods for the preparation of *β*-PNG suffer from the detriment of arduous upscaling, limiting the methods to microgram batches, whereas the proposed method can be scaled up quite simply, especially since the starting materials are cheap and easy accessible, making it an interesting alternative for the synthesis of isotopically labeled standards. Also, with this study, only a first glance of the chemistry behind the glycosylation of pyridoxine is given, providing the opportunity to increase the yield even further by testing other leaving groups or modifying the reactivity of the substrates.[98] Additionally, this method can be used to further scout the influence of pyridine-based derivatives in glycosylation reactions and their influence on the mechanism.

3. Conclusions

The catalog of procedures entitled ‘chemical glycosylations’ contains a manifold of various methods and hereby, every known strategy also inherits numerous variables for the specific adaptation towards the particularly investigated substrate. As part of this study, a small part of well-known strategies was examined in order to develop an alternative preparation of pyridoxine glycosides to the common biotechnological procedures and furthermore open avenues for additional investigations regarding the glycosylation of vitamin B_6. Hereby, best conversions of the acetonide-protected pyridoxine were obtained using fluoroglucosides in combination with acetate protection groups and $BF_3 \cdot OEt_2$ (2.0 eq.) as promoter generating the twofold protected PNG in 59 % yield. Thereupon, the deprotection was accomplished stepwise through change of basic and acid milieu to obtain the desired 5'-*β*-PNG.

4. Materials and Methods

4.1. Experimental procedures

Reactions sensitive to air or moisture were carried out in dried glassware under a positive pressure of argon using standard *Schlenk* techniques. Solvents were distilled and stored over molecular sieves prior to use. Chemicals received from commercial sources (*Acros, Sigma-Aldrich, Fluka, Fisher Scientific*) were used without further purification unless stated otherwise. *β*-Glucosidase from almonds was purchased from Sigma-Aldrich. Column chromatography was performed on silica gel 60 (Merck, 230-240 mesh) with the eluent mixtures given for the corresponding procedures. Thin-layer Chromatography (TLC) was performed using silica-coated aluminium plates (silica gel 60). The substances were detected

by UV (λ = 254 nm, 366 nm) or after visualization with CAM (cerium ammonium molybdate)/potassium permanganate ($KMnO_4$) solution. NMR spectra were recorded either on a *Bruker* AV III system (400 MHz, Bruker, Rheinstetten, Germany) or on a Bruker AV III system (500 MHz, Bruker, Rheinstetten, Germany). ^{1}H- and ^{13}C NMR spectra were recorded at 400 or 500 MHz and at 101 or 126 MHz, respectively. ^{1}H and ^{13}C NMR spectroscopic chemical shifts δ are reported in parts per million (ppm) relative to residual proton signal. All coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet. LC-MS/MS was carried out on a Shimadzu LC-30A Prominence system (Shimadzu, Kyoto, Japan) with the mobile phase combinations water/acetonitrile or water/methanol. The injection volume was 1 µL. The LC was interfaced with a triple quadrupole ion trap mass spectrometer (LCMS-8050, Shimadzu, Kyoto, Japan). Data acquisition was performed with LabSolutions software 5.80 (Shimadzu, Kyoto, Japan). The optical rotation was measured on a P3000 polarimeter by Kruess. All preparations of the sugar donors can be found in the supplementary information.

*4.1.1. General procedure for glucosylation reactions (**A1**)*

A mixture of *α*4,3-*O*-isopropylidene pyridoxine, the respective saccharide and molecular sieves (4 Å) was stirred under argon atmosphere in dry solvent (5 mL) at rt for 1 h before it was cooled to the respective temperature T. The promoter was added and the reaction mixture allowed to reach rt overnight. The mixture was diluted with dichloromethane (10 mL) and filtered through a pad of celite. Afterwards, the filtrate was washed with $Na_2S_2O_3$ (10 % in water, 30 mL) and the aqueous phase was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with distilled water (1 × 50 mL), brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product subjected to column chromatography using SiO_2 (pentane/ethyl acetate 1/1 to 1/4, gradient elution) followed by C18 (methanol, isocratic) to afford the glucoside.

*4.1.2. General procedure for deprotection reactions (**A2**)*

A solution of potassium hydroxide (1 M) was added dropwise to a solution of protected glucoside in acetonitrile/water (8 mL, v/v = 1/1) until the pH reached 11. After 1 h at pH = 11, 0.5 mL of a 2 M NaOH-solution were added and the mixture stirred at rt until completion of the reaction (ESI-MS). The solvent was evaporated under reduced pressure, the residue suspended in a solution of abs. EtOH / 1% HCOOH (5 mL, v/v = 0.6 mL/4.4 mL) and the reaction heated to reflux for 1.5 h. The solvent was evaporated under reduced pressure and

the crude product purified *via* column chromatography using Sephadex (methanol, isocratic) and preparative HPLC (C18, water/acetonitrile 90/10, isocratic) to obtain the glucoside.

*4.1.3. 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide (**4**)*

HBr (33 % wt in acetic acid, 8.88 g, 6.25 mL, 109.7 mmol, 86 eq.) was added dropwise to a cooled solution (0 °C) of 1,2,3,4,6-penta-*O*-acetyl-*α*/*β*-D-glucopyranoside (**3**, 0.50 g, 1.28 mmol, 1.00 eq.) in dichloromethane (10 mL) and stirred for 3 h at rt. Ice water (50 mL) was added to the mixture and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with 0.5 % $Na_2S_2O_3$ (1 × 75 mL), sat. $NaHCO_3$ (3 × 75 mL), brine (1 × 75 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product crystallized from diethylether/pentane to afford the halogenated substrate (0.44 g, 1.12 mmol, 88 %). ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) *α*-Anomer *δ* (ppm) = 6.61 (d, J = 4.0 Hz, 1 H), 5.56 (t, J = 9.7 Hz, 1 H), 5.16 (t, J = 9.8 Hz, 1 H), 4.84 (dd, J = 10.0, 4.1 Hz, 1 H), 4.35-4.27 (m, 2 H), 4.15-4.10 (m, 1 H), 2.10 (s, 3 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) *α*-Anomer *δ* (ppm) = 170.6, 170.0, 169.9, 169.6, 86.7, 72.3, 70.8, 70.3, 67.3, 61.1, 20.81, 20.8, 20.8, 20.7; ESI-MS m/z 411.2 $[M + H]^+$; Anomeric ratio *α*/*β* = 100/0.[99]

*4.1.4. 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl chloride (**5**)*

Thionyl chloride (1.22 g, 0.74 mL, 10.2 mmol, 2.00 eq.) and Tin(IV)chloride (1.33 g, 0.59 mL, 5.12 mmol, 1.00 eq.) were added dropwise to a solution of 1,2,3,4,6-penta-*O*-acetyl-*α*/*β*-D-glucopyranoside (**3**, 2.00 g, 5.12 mmol, 1.00 eq.) in dichloromethane (30 mL) and stirred for 2 h at rt. The mixture was added to a cold solution of sat. $NaHCO_3$ and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine (1 × 75 mL) and dried over Na_2SO_4 The solvent was evaporated under reduced pressure and the crude product purified *via* column chromatography (hexane/ethyl acetate = 3/2) to obtain the desired product (1.83 g, 4.99 mmol, 97 %). ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) *α*-Anomer *δ* (ppm) = 6.29 (d, *J* = 4.0 Hz, 1 H), 5.55 (t, *J* = 9.7 Hz, 1 H), 5.13 (t, *J* = 9.7 Hz, 1 H), 5.01 (dd, *J* = 10.1, 4.0 Hz, 1 H), 4.31 (d, *J* = 11.8 Hz, 2 H), 4.13 (d, *J* = 10.5 Hz, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) *α*-Anomer *δ* (ppm) = 170.6, 170.0, 170.0, 169.6, 90.2, 70.8, 70.5, 69.5, 67.5, 61.2, 20.8, 20.7, 20.7, 20.6; ESI-MS m/z 388.8 $[M + Na]^+$; Anomeric ratio *α*/*β* = 100/0; R_f 0.43 (pentane/diethyl ether 1/1) [CAM].[32]

*4.1.5. Benzoxazolyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (**6**)*

A solution of 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide (**4**, 1.00 g, 2.43 mmol, 1.00 eq.) in dry acetone (2.5 mL) was added to a suspension of 2-mercaptobenzoxazole (0.51 g, 3.40 mmol, 1.40 eq.) and potassium carbonate (0.47 g, 3.40 mmol, 1.40 eq.) in acetone (7.5 mL) at 40 °C. The reaction was stirred at the elevated temperature for 2.5 h and at rt overnight. Dichloromethane (30 mL) was added, the mixture washed with 1 % NaOH (25 mL) and dist. water (2 × 25 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure yielding the product, which could be used without further purification (1.07 g, 2.22 mmol, 91 %). ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) δ (ppm) = 7.68 – 7.58 (m, 1 H), 7.50 – 7.44 (m, 1 H), 7.35 – 7.27 (m, 2 H), 5.70 (d, *J* = 10.4 Hz, 1 H), 5.36 (t, *J* = 9.3 Hz, 1 H), 5.31 – 5.13 (m, 2 H), 4.28 (dd, *J* = 12.5, 4.7 Hz, 1 H), 4.14 (dd, *J* = 12.5, 2.2 Hz, 1 H), 3.96 (ddd, *J* = 10.1, 4.7, 2.3 Hz, 1 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) δ (ppm) = 170.7, 170.1, 169.5, 169.5, 161.0, 152.1, 141.6, 124.7, 124.7, 119.0, 110.3, 83.5, 76.5, 73.8, 69.7, 68.0, 61.8, 20.8, 20.7 (3x); ESI-MS m/z 504.10 $[M + Na]^+$.[92]

*4.1.6. 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl fluoride (**9**)*

A cooled (0 °C) solution of 2,3,4,6-tetra-*O*-acetyl-*α*/*β*-D-glucopyranoside (**7**, 0.51 g, 1.46 mmol, 1.00 eq.) in dry dichloromethane (12 mL) was stirred for 20 min with molecular sieves (4 Å) before diethylaminosulfur trifluoride (DAST) (0.27 g, 0.22 mL, 1.68 mmol, 1.15 eq.) was added and the solution was allowed to warm to rt over 2.5 h. After dilution with dichloromethane (20 mL) and filtration through a pad of silica gel, the organic phase was washed with sat. $NaHCO_3$ (2 × 50 mL), dist. water (3 × 50 mL), brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product crystallized from diethyl ether/pentane to afford the halogenated product (0.35 g, 0.99 mmol, 68 %). ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) *β*-Anomer δ (ppm) = 5.36 (dd, *J* = 52.0, 6.0 Hz, 1 H), 5.27 – 5.16 (m, 2 H), 5.16 – 5.05 (m, 1 H), 4.31 – 4.18 (m, 2 H), 3.90 (ddt, *J* = 7.6, 4.7, 2.3 Hz, 1 H), 2.10 (d, *J* = 2.7 Hz, 6 H), 2.04 (d, *J* = 2.8 Hz, 6 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) *β*-Anomer δ (ppm) = 170.7, 170.1, 169.4, 169.2, 106.3 (d, *J* = 219.7 Hz), 72.2 (d, *J* = 3.9 Hz), 71.9 (d, *J* = 8.3 Hz), 71.3 (d, *J* = 28.7 Hz), 67.5, 61.9, 20.8, 20.7, 20.7, 20.7; ESI-MS m/z 373.3 $[M + Na]^+$.[35]

*4.1.7. Phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (**10**)*

$BF_3 \cdot Et_2O$ (16.6 mL, 130.7 mmol, 3.00 eq.) was added to a cooled (0 °C) solution of peracetylated glucose (**3**, 17.0 g, 43.6 mmol, 1.00 eq.) in dichloromethane (150 mL) in one portion. Thiophenol (PhSH, 6.67 mL, 65.3 mmol, 1.50 eq.) was added dropwise to the

reaction mixture at 0 °C, followed by stirring at rt until completion of the reaction (TLC). The mixture was diluted with dichloromethane (50 ml) and successively washed with sat. $NaHCO_3$ (100 ml) and brine (100 ml). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Purification *via* column chromatography (pentane/ethyl acetate = 3/2) gave the desired product (13.7 g, 31.1 mmol, 71 %). ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) δ (ppm) = 7.46 (m, 2 H), 7.29 (m, 3 H), 5.20 (t, J = 9.3 Hz, 1 H), 5.01 (t, J = 9.8 Hz, 1 H), 4.94 (t, J = 9.5 Hz, 1 H), 4.69 (d, J = 10.1 Hz, 1 H), 4.30 – 4.01 (m, 2 H), 3.70 (m, 1 H), 2.05 (s, 3 H), 2.05 (s, 3 H), 1.99 (s, 3 H), 1.96 (s, 3 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) δ (ppm) = 170.5, 170.1, 169.4, 169.2, 133.1, 131.6, 128.9, 128.4, 85.7, 75.8, 73.9, 69.9, 68.2, 20.7, 20.7, 20.6, 20.6; R_f 0.30 (pentane/ethyl acetate 3/2) [$KMnO_4$].[100]

*4.1.8. Ethyl 2,3,4,6-tetra-O-benzoyl-1-thio-α/β-D-glucopyranoside (**13**)*

Benzoyl chloride (BzCl, 0.28 g, 0.23 mL, 1.96 mmol, 4.40 eq.) was added dropwise to a solution of ethyl 1-thio-*α*/*β*-D-glucopyranoside (**12**, 103 mg, 0.46 mmol, 1.00 eq.) in pyridine (5 mL) over 15 min and the mixture was stirred at rt for 12 h. Distilled water (5 mL) was added to the reaction at 0 °C and it was diluted with dichloromethane (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with sat. $CuSO_4$ (3 × 50 mL), dist. water (2 × 50 mL), brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated and the crude product subjected to column chromatography (pentane/ethyl acetate = 6/1) to obtain the desired product (285 mg, 0.41 mmol, 89 %) as colorless oil. ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) *α*-Anomer δ (ppm) = 8.11-7.80, 7.62-7.27 (m, 20 H), 6.07 (t, J = 9.87 Hz, 1 H), 5.94 (d, J = 4.2 Hz, 1 H), 5.68 (t, J = 8.00 Hz, 1 H), 5.50 (dd, J = 10.2, 5.78 Hz, 1 H), 4.89-4.88 (m, 1 H), 4.59 (d, J = 2.81 Hz, 1 H), 4.53 (d, J = 5.45 Hz, 1 H), 2.67-2.58 (m, 2 H), 1.25 (t, J = 6.00 Hz, 3 H); *β*-Anomer δ (ppm) = 8.11-7.80, 7.62-7.27 (m, 20 H), 5.93 (t, J = 9.57 Hz, 1 H), 5.67 (t, J = 9.79 Hz, 1 H), 5.57 (t, J = 9.72 Hz, 1 H), 4.86 (d, J = 9.96 Hz, 1 H), 4.63 (dd, J = 12.2, 3.16 Hz, 1 H), 4.50 (dd, J = 12.2, 5.44 Hz, 1 H), 4.19-4.16 (m, 1 H), 2.83-2.70 (m, 2 H), 1.26 (t, J = 7.46 Hz, 3 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) *β*-Anomer δ (ppm) = 166.3, 166.0, 165.4, 165.3, 130.3, 130.0, 130.0, 129.9, 129.9, 129.8, 129.3, 129.0, 128.9, 128.6, 128.6, 128.5, 128.5, 128.4, 84.1, 76.5, 74.3, 70.8, 69.8, 63.5, 24.6, 15.1; ESI-MS m/z 663.3 $[M + Na]^+$; R_f 0.39 (*α*), 0.25 (*β*, dichloromethane/methanol 9/1) [CAM].[101]

*4.1.9. Ethyl 2,3,4,6-tetra-O-pivaloyl-1-thio-β-D-glucopyranoside (**14**)*

Pivaloyl chloride (PivCl, 0.44 g, 0.45 mL, 3.65 mmol, 7.80 eq.) was added dropwise to a solution of ethyl 1-thio-*α*/*β*-D-glucopyranoside (**12**, 0.11 g, 0.47 mmol, 1.00 eq.) in pyridine (0.50 mL). The reaction mixture was stirred at 75 °C for 48 h. Methanol (5 mL) was added and the mixture was diluted with dichloromethane (10 mL). The mixture was washed with sat. $CuSO_4$ (4 × 50 mL), dist. water (2 × 50 mL), brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product objected to column chromatography (pentane/ethyl acetate = 10/0.1 to 9/1) to obtain the desired product (198 mg, 0.35 mmol, 75 %) as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) *β*-Anomer *δ* (ppm) = 5.33 (t, *J* = 9.4 Hz, 1 H), 5.12 (t, *J* = 9.8 Hz, 1 H), 5.07 (t, *J* = 9.7 Hz, 1 H), 4.51 (d, *J* = 10.1 Hz, 1 H), 4.22 (dd, *J* = 12.3, 1.9 Hz, 1 H), 4.05 (dd, *J* = 12.4, 5.5 Hz, 1 H), 3.73 (ddd, *J* = 10.2, 5.5, 1.9 Hz, 1 H), 2.84 – 2.56 (m, 2 H), 1.26 (m, 3 H), 1.22 (s, 9 H), 1.17 (s, 9 H), 1.15 (s, 9 H), 1.11 (s, 9 H); ^{13}C-NMR (101 MHz, $CDCl_3$) *β*-anomer *δ* (ppm) = 178.2, 177.3, 176.7, 176.6, 83.6, 76.6, 73.4, 69.7, 68.0, 62.3, 39.0, 38.9, 38.9, 38.8, 27.3, 27.3, 27.2, 24.0, 15.1; ESI-MS m/z 583.4 $[M + Na]^+$, 599.4 $[M + K]^+$; R_f 0.83 (*α*), 0.75 (*β*, pentane/ethyl acetate 9/1) [CAM].[102]

*4.1.10. Phenyl 1,2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (**15**)*

A solution of sodium methoxide (NaOMe, 30 % in MeOH, 0.78 mL) was added to a solution of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside (**10**, 5.00 g, 11.3 mmol, 1.00 eq.) in dry methanol at rt and stirred until complete conversion of starting material (TLC). Afterwards the reaction mixture was neutralized using Dowex 5W (H^+-Form), filtered and the solvent evaporated under reduced pressure. The obtained glucopyranoside (3.06 g, 11.2 mmol, 1.00 eq.) was dissolved in dry DMF (150 mL) and the reaction mixture cooled to 0 °C. Sodium hydride (NaH, 60 %, 4.49 g, 112 mmol, 10.0 eq.) was added portionwise and the resulting slurry mixed for additional 30 min at low temperature while warming up. Benzyl bromide (BnBr, 19.2 g, 13.3 mL, 112 mmol, 10 eq.) was added at room temperature and the mixture stirred for 22 h. The solution was cooled to 0 °C and cold dist. water (100 mL) was added slowly. The aqueous phase was extracted with dichloromethane (3 × 50 mL). The collected organic phases were washed with dist. water (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified *via* column chromatography (pentane/ethyl acetate = 10/0.5) to obtain the desired product as white solid (6.09 g, 9.62 mmol, 85 % over two steps). ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) *β*-Anomer *δ* (ppm) = 7.60 (m, 2 H), 7.41 – 7.19 (m, 23 H), 4.92 – 4.81 (m, 4 H), 4.74 (d, *J* = 10.3 Hz, 2 H), 4.68 (d, *J* = 9.7 Hz, 1 H), 4.64 – 4.54 (m, 3 H), 3.80 (dd, *J* =

10.9, 2.1 Hz, 1 H), 3.76 – 3.63 (m, 3 H), 3.52 (m, 2 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) β-Anomer δ (ppm) = 138.5, 138.4, 138.1, 133.9, 132.0, 129.0, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 87.5, 86.9, 80.9, 79.2, 77.9, 75.9, 75.5, 75.2, 73.5, 69.1; ESI-MS m/z 654.1 $[M + Na]^+$; R_f 0.61 + 0.69 (pentane/diethyl ether 2/1) [$KMnO_4$].[100]

*4.1.11. 2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl fluoride (**17**)*

Diethylaminosulfur trifluoride (0.28 g, 1.74 mmol, 1.20 eq.) was added to a cooled (0 °C) solution of 2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-glucopyranose (**16**, 0.78 g, 1.45 mmol, 1.00 eq.) in dichloromethane (10 mL) and stirred for 1.5 h. The reaction mixture was diluted with dichloromethane (10 mL) and filtrated through a pad of Celite. The filtrate was washed with sat. $NaHCO_3$ (2 × 20 mL), dist. water (3 × 20 mL) and brine (1 × 20 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified *via* column chromatography (pentane/ethyl acetate 9/1) to obtain the desired product as as white solid containing both the *α*- and *β*-anomer (0.72 g, 1.33 mmol, 92 %) ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) *α*+*β*-Anomer *δ* (ppm) = 7.38 – 7.25 (m, 18 H), 7.15 (dd, *J* = 6.7, 2.8 Hz, 2 H), 5.56 (dd, *J* = 53.2, 2.7 Hz, 1 H, *α*-anomer), 5.26 (dd, *J* = 52.8, 6.7 Hz, 1 H, *β*-anomer), 4.97 – 4.46 (m, 8 H), 4.01 – 3.53 (m, 6 H); ^{13}C-NMR (101 MHz, $CDCl_3$, 292 K) *α*+*β*-Anomer *δ* (ppm) = 138.6, 138.4, 138.5, 138.0, 137.9, 137.8, 137.8, 137.8, 128.7, 127.8, 110.0 (d, *J* = 215.9 Hz), 105.7 (d, *J* = 227.1 Hz), 83.6, 83.5, 81.7, 81.5, 81.5, 79.5, 79.3, 77.3, 77.0, 76.7, 75.9, 75.6, 75.3, 75.1, 75.0, 74.9, 74.6, 74.5, 73.7, 73.6, 73.6, 72.8, 72.7, 68.5, 67.9; ESI-MS m/z 560.1 $[M + NH_4]^+$, 565.1 $[M + Na]^+$; Anomeric ratio *α*/*β* = 32/68; R_f 0.82 (pentane/ethyl acetate 4/1) [CAM].[103]

*4.1.12. 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl bromide (**18**)*

Oxalyl bromide (0.71 g, 0.46 mL, 3.39 mmol, 2.00 eq.) was added dropwise to a cooled (0 °C) solution of 2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-glucopyranose (**16**, 0.91 g, 1.70 mmol, 1.00 eq.) in dichloromethane/dimethyl formamide (10 mL/0.15 mL) and was allowed to reach rt. After complete conversion of the starting material (TLC), the reaction was cooled (0 °C) and ice water (20 mL) was added dropwise. The layers were separated and the aqueous phase extracted with dichloromethane (3 × 15 mL). The collected organic phases were washed with brine, dried over Na_2SO_4 and the solvent evaporated under reduced pressure to obtain the bromide (0.87 g, 1.44 mmol, 85 %) as yellow oil, which was used without further purification; ^{1}H-NMR (360 MHz, $CDCl_3$, 292 K) *δ* (ppm) = 7.45 – 7.20 (m, 18 H), 7.20 – 7.09 (m, 2 H), 6.43 (d, *J* = 3.7 Hz, 1 H), 4.97 (d, *J* = 10.8 Hz, 1 H), 4.83 (dd, *J* = 10.8, 8.9

575 Hz, 2 H), 4.71 (s, 2 H), 4.44 – 4.60 (m, 3 H), 4.07 – 4.01 (m, 2 H), 3.77 (m, 2 H), 3.65 (dd, *J*
576 = 11.0, 2.0 Hz, 1 H), 3.53 (dd, *J* = 9.3, 3.8 Hz, 1 H); R_f 0.88 (pentane/ethyl acetate 4/1)
577 [CAM].[104]

578 *4.1.13. α4,3-O-Isopropylidene pyridoxine (**20**)*

579 *Para*-toluenesulfonic acid monohydrate (11.1 g, 58.3 mmol, 4.00 eq.) was added to a
580 solution of pyridoxine hydrochloride (19, 3.00 g, 14.6 mmol, 1.00 eq.) and
581 2,2-dimethoxypropane (25.5 g, 30.0 mL, 245 mmol, 16.8 eq.) in acetone (60 mL). The
582 mixture was stirred at rt for 23 h. After neutralization with sat. $NaHCO_3$, the solvent was
583 evaporated under reduced pressure and the aqueous residue was extracted with
584 dichloromethane (3 × 50 mL). The combined organic layers were washed with dist. water (1
585 × 75 mL), brine (1 × 75 mL) and dried over Na_2SO_4. The solvent was evaporated under
586 reduced pressure and the crude product crystallized from diethyl ether/pentane to afford the
587 title compound (2.92 g, 13.9 mmol, 96 %) as a yellowish solid. ^{1}H-NMR ($CDCl_3$, 360 MHz)
588 δ (ppm) 7.83 (s, 1 H), 4.93 (s, 2 H), 4.55 (s, 2 H), 2.37 (s, 3 H), 1.54 (s, 6 H); ^{13}C-NMR
589 ($CDCl_3$, 101 MHz) δ 148.0, 146.2, 138.9, 129.4, 126.0, 99.9, 60.4, 58.7, 24.9, 18.5; ESI-MS
590 m/z 210.6 $[M + H]^+$.[105]

591 *4.1.14. Tetraacetyl-β-D-glucopyranosyl isopropylidene pyridoxine (**21**)*

592 Prepared according to **A1** with *α*4,3-*O*-isopropylidene pyridoxine (**20**, 50.0 mg, 0.24 mmol,
593 1.00 eq.), 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl fluoride (**9**, 1.2 eq.) and $BF_3 \cdot OEt_2$ (68.0
594 mg, 61.0 µL, 0.48 mmol, 2.00 eq.) in dichloromethane (5 mL) at 0 °C to obtain the product as
595 colorless oil (77.0 mg, 0.14 mmol, 59 %). ^{1}H-NMR ($CDCl_3$, 360 MHz, *β*-Anomer) δ 7.89 (s,
596 1 H, H6), 5.13 (t, 1 H, H12), 5.06 (t, 1H, H13), 4.99 (t, 1 H, H11), 4.80 (d, *J* = 1.7 Hz, 2 H,
597 H8), 4.64 (dd, *J* = 82.2, 12.1 Hz, 2 H, H7), 4.46 (d, *J* = 7.9 Hz, 1 H, H_β10), 4.22 (dd, *J* = 12.3,
598 4.9 Hz, 1 H, H15), 4.13 (dd, *J* = 12.3, 2.4 Hz, 1 H, H15), 3.64 (ddd, *J* = 9.8, 4.9, 2.4 Hz, 1 H,
599 H14), 2.39 (s, 3 H, $CH_3$9), 2.09 (s, 3 H, H17), 2.00 (s, 3 H, H19), 1.98 (s, 3 H, H23), 1.97 (s,
600 3 H, H21), 1.53 (s, 3 H, $CH_3$25/$CH_3$26), 1.51 (s, 3 H, $CH_3$25/$CH_3$26); ^{13}C-NMR ($CDCl_3$, 101
601 MHz, *β*-Anomer) δ 170.7 (C16), 170.3 (C20), 169.4 (C22), 169.3 (C18), 149.0 (C2), 146.2
602 (C3), 139.9 (C6), 126.3 (C5), 124.6 (C4), 99.9 (C24), 98.7 (C10), 72.9 (C12), 72.0 (C14),
603 71.3 (C11), 68.3 (C13), 66.0 (C7), 61.9 (C15), 58.5 (C8), 25.0 (C25/C26), 24.6 (C25/C26),
604 20.8 (C17), 20.6 (C19, C21, C23), 18.6 (C9); TLC R_f 0.29 (pentane/ethyl acetate 1/4)
605 [CAM]; ESI-MS m/z 540.2 $[M + H]^+$.

606 *4.1.15. Tetrabenzyl-β-D-glucopyranosyl isopropylidene pyridoxine (**23**)*

Prepared according to **A1** with *α*4,3-*O*-isopropylidene pyridoxine (**20**, 50.1 mg, 0.24 mmol, 1.00 eq.), 2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-glucopyranosyl fluoride (**17**, 0.15 g, 0.29 mmol, 1.2 eq.) and $BF_3 \cdot OEt_2$ (68.0 mg, 61.0 µL, 0.48 mmol, 2.00 eq.) in dichloromethane (5 mL) at 0 °C to obtain the product as a colorless oil in a mixture of anomers (0.11 mg, 0.15 mmol, 65 %, *α*/*β* = 71/29). ^{1}H-NMR ($CDCl_3$, 360 MHz, *β*-Anomer) δ 8.00 (s, 1 H, H6), 7.39 – 7.22 (m, 18 H, Bn-H), 7.15 (m, 2 H, Bn-H), 4.95 - 4.86 (m, 3 H, H8, H19), 4.87 - 4.76 (m, 4 H, H19, H7, H11, H17/H18), 4.69 (d, 1H, H17/H18), 4.62 (d, 1H, H16), 4.58 - 4.50 (m, 3 H, H7, H16, H17/H18), 4.40 (d, *J* = 7.7 Hz, 1 H, $H_{\beta}10$), 3.73 - 3.67 (m, 2 H, H15), 3.64 - 3.59 (m, 2 H, H13, H12), 3.49 - 3.42 (m, 2 H, H11, H14), 2.41 (s, 3 H, $CH_3$9), 1.47 (s, 3 H, $CH_3$25/$CH_3$26), 1.44 (s, 3 H, $CH_3$25/$CH_3$26); ^{13}C-NMR ($CDCl_3$, 101 MHz, *β*-Anomer) δ 148.5 (C2), 146.1 (C3), 140.2 (C6), 138.7 - 138.0 (C_{Bn}), 126.2 (C5), 125.6 (C4), 128.5 - 127.7 (C_{Bn}), 102.1 (C10), 99.9 (C24), 84.9 (C12/C13), 82.2 (C11/C14), 77.9 (C12/C13), 75.8 (C19), 75.0 (3C: C11/C14, C17, C18), 73.6 (C16), 68.9 (C15), 66.0 (C7), 58.7 (C8), 18.7 (C9), 25.0 (C25/C26), 24.6 (C25/C26); TLC R_f 0.36 (pentane/ethyl acetate 1.5/1) [CAM]; ESI-MS m/z 732.4 $[M + H]^+$.

*4.1.16. Tetrapivaloyl-β-D-glucopyranosyl isopropylidene pyridoxine (**24**)*

Prepared according to **A1** with *α*4,3-*O*-isopropylidene pyridoxine (**20**, 51.0 mg, 0.24 mmol, 1.00 eq.), ethyl 2,3,4,6-tetra-*O*-pivaloyl-1-thio-*β*-D-glucopyranoside (**14**, 0.16 g, 0.29 mmol, 1.2 eq.) and TfOH (37.0 mg, 22.0 µL, 0.24 mmol, 1.00 eq.) in dichloromethane (5 mL) at 0 °C to obtain the product as colorless oil (27.8 mg, 39.2 µmol, 16 %). ^{1}H-NMR ($CDCl_3$, 360 MHz, *β*-Anomer) δ 7.87 (s, 1 H, H6), 5.30 (t, *J* = 9.5 Hz, 1 H, H12), 5.12 (t, *J* = 9.7 Hz, 1 H, H13), 5.03 (dd, *J* = 9.6, 8.0 Hz, 1 H, H11), 4.92 – 4.77 (m, 2 H, H8), 4.72 (d, *J* = 11.5 Hz, 1 H, H7), 4.56 (d, *J* = 8.0 Hz, 1 H, $H_{\beta}10$), 4.44 (d, *J* = 11.5 Hz, 1 H, H7), 4.22 (dd, *J* = 12.3, 1.9 Hz, 1 H, H15), 4.04 (dd, *J* = 12.3, 5.4 Hz, 1 H, H15), 3.71 (ddd, *J* = 10.1, 5.4, 1.9 Hz, 1 H, H14), 2.39 (s, 3 H, $CH_3$9), 1.53 (s, 3 H, $CH_3$25, $CH_3$26), 1.52 (s, 3 H, $CH_3$25, $CH_3$26), 1.23 (s, 9 H, CH_3Piv), 1.14 (s, 9 H, CH_3Piv), 1.09 (s, 9 H, CH_3Piv), 1.07 (s, 9 H, CH_3Piv); ^{13}C-NMR ($CDCl_3$, 101 MHz, *β*-Anomer) δ 178.1 (C16), 177.2 (C20), 176.6 (C22), 176.5 (C18), 148.7 (C2), 146.2 (C3), 139.7 (C6), 126.3 (C5), 125.0 (C4), 99.9 (C10, C24), 72.5 (C14), 72.2 (C12, C13), 71.1 (C11), 68.0 (C12, C13), 66.1 (C7), 61.9 (C15), 58.6 (C8), 39.0 (C17), 38.8 (C19), 38.8 (C21), 38.8 (C23), 27.2 (CH_3Piv x2), 27.1 (CH_3Piv), 27.1 (CH_3Piv), 24.9 (C25, C26), 24.8 (C25, C26), 18.7 (C9); TLC R_f 0.64 (pentane/ethyl acetate 1/1) [CAM]; ESI-MS m/z 708.1 $[M + H]^+$.

*4.1.17. Tetrabenzoyl-β-D-glucopyranosyl isopropylidene pyridoxine (**25**)*

Prepared according to **A1** with *α*4,3-*O*-isopropylidene pyridoxine (**20**, 49.4 mg, 0.24 mmol, 1.00 eq.), ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-*α*/*β*-D-glucopyranoside (**13**, 0.18 g, 0.28 mmol, 1.2 eq.) and TfOH (35.0 mg, 21.0 µL, 0.24 mmol, 1.00 eq.) in dichloromethane (5 mL) at 0 °C to obtain the product as colorless oil (28.2 mg, 35.8 µmol, 15 %). ^{1}H-NMR ($CDCl_3$, 360 MHz, *β*-Anomer) δ 8.10 – 7.22 (m, 21 H, H_{Bz}, H6), 5.87 (t, *J* = 9.7 Hz, 1 H, H12), 5.68 (t, *J* = 9.7 Hz, 1 H, H13), 5.54 (dd, *J* = 9.7, 7.8 Hz, 1 H, H11), 4.85 (d, *J* = 7.9 Hz, 1 H, H_{β}10), 4.80 (d, *J* = 12.0 Hz, 1 H, H7), 4.68 (d, *J* = 1.5 Hz, 2 H, H8), 4.67 – 4.63 (m, 1 H, H15), 4.60 – 4.49 (m, 2 H, H7, H15), 4.15 (ddd, *J* = 10.0, 5.3, 3.2 Hz, 1 H, H14), 2.35 (s, 3 H, $CH_3$9), 1.32 (s, 3 H, $CH_3$21/$CH_3$22), 1.29 (s, 3 H, $CH_3$21/$CH_3$22); ^{13}C-NMR ($CDCl_3$, 101 MHz, *β*-Anomer) δ 166.2 (C16), 165.8 (C18), 165.2 (C17), 165.1 (C19), 148.9 (C2), 146.2 (C3), 139.9 (C6), 134.0 – 133.3 (m, C_{Bz}), 130.5 – 128.3 (m, C_{Bz}), 126.4 (C5), 124.7 (C4), 99.8 (C20), 99.3 (C10), 72.9 (C12), 72.5 (C14), 71.8 (C11), 69.7 (C13), 66.2 (C7), 63.0 (C15), 58.5 (C8), 24.7 (C21, C22), 24.4 (C21,C22), 18.6 (C9); TLC R_f 0.61 (pentane/ethyl acetate 1/2) [CAM]; ESI-MS m/z 788.1 $[M + H]^+$.

*4.1.18. Pyridoxine-5'-β-D-glucoside (5'-β-PNG, **1**)*

Prepared according to **A2** with **23** (50.0 mg, 0.09 mmol, 1.00 eq.) to obtain the glucoside as white solid in quantitative yield. ^{1}H-NMR (D_2O, 360 MHz, *β*-Anomer) δ 7.65 (s, 1 H, H6), 4.93 (d, *J* = 12.5 Hz, 1 H, H7), 4.78 – 4.70 (m, 3 H, H7, H8), 4.43 (d, *J* = 7.9 Hz, 1 H, H_{β}10), 3.83 (d, *J* = 11.4 Hz, 1 H, H15), 3.65 (m, *J* = 6.0 Hz, 1 H, H15), 3.41 - 3.35 (m, 1 H, H12, H14), 3.32 (m, 1 H, H13), 3.22 (t, *J* = 8.5 Hz, 1 H, H11), 2.38 (s, 3 H, $CH_3$9); ^{13}C-NMR (D_2O, 101 MHz, *β*-Anomer) δ 159.7 (C3), 145.0 (C2), 139.2 (C5), 131.8 (C4), 126.9 (C6), 101.3 (C10), 75.9 (C12/C14), 75.6 (C12/C14), 73.0 (C11), 69.5 (C13), 66.1 (C7), 60.6 (C15), 56.1 (C8), 15.6 (C9); ESI-MS m/z 331.8 $[M + H]^+$, 353.9 $[M + Na]^+$, 330.2 $[M - H]^-$.

*4.1.19. Pyridoxine-5'-β-D-glucoside (5'-β-PNG, **1**)*

Starting from **24**. Palladium/Coal (5.30 mg, 15.0 µmol, 0.30 eq.) was added to a solution of protected pyridoxine glucoside (**24**, 36.0 mg, 50.0 µmol, 1.00 eq.) in dry ethanol. A pressure of 1 atm H_2 was applied to the reaction vessel and uphold until complete conversion of the starting material (ESI-MS). The mixture was filtered, the solvent evaporated under reduced pressure, the residue suspended in a solution of abs. EtOH / 1% HCOOH (5 mL, v/v = 0.6 mL/4.4 mL) and the reaction heated to reflux for 1.5 h. The solvent was evaporated under reduced pressure and the crude product purified *via* column chromatography using Sephadex (methanol, isocratic) and preparative HPLC (C18, water/acetonitrile 90/10, isocratic) to obtain the glucoside as white solid in quantitative yield.

Supplementary Materials: Experimental procedures and NMR-spectra of the new substances are available online.

Author Contributions: T.B. and M.R. conceived and designed the experiments; T.B. performed the experiments and analyzed the data; T.B. and M.R. wrote the paper.

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Abbreviations: Bn, benzyl; Bz, benzoyl; LG, leaving group; P, protecting group; Piv, pivaloyl; PN, pyridoxine; PL, pyridoxal; PM, pyridoxamine; PLP, pyridoxal phosphate; PMP, pyridoxamine phosphate; PNG, pyridoxine glucoside.

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Chemical glucosylation of pyridoxine

Highlights

- New strategies for the chemical glucosylation of pyridoxine were investigated.
- Multiple leaving groups, protecting groups and promoters were tested.
- The synthesis gave best results with fluorine leaving groups.
- Formation of othoesters can be reduced drastically by increased amounts of promotor.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: