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Regioselective Reductive Opening of Benzylidene Acetals with Dichlorophenylborane/Triethylsilane: Previously Unreported Side-Reactions and How to Prevent Them.

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In memory of Hugues Driquez

Arylidene acetals are widely used protecting groups, not only for the high regioselectivity of their introduction, but also for the possibility to perform further regioselective reductive opening in the presence of a hydride donor and acid catalyst. In this context, the Et₃SiH-PhBCl₂ system present several advantages: silanes are efficient, environmentally benign, and user-friendly hydride donors, while PhBCl₂ open the way to unique regioselectivity with regards to all other Brønsted or Lewis acids used with silanes. This system has been extensively used by several groups and we have demonstrated its high regioselectivity in the reductive opening of 4,6 and 2,4-*O*-*p*-methoxybenzylidene moieties in protected disaccharides. Surprisingly, its use on the 4,6-*O*-benzylidene containing substrates **1** and **2** led to unreproducible yields due to the unexpected formation of several side products. Their characterizations allowed us to identify different pitfall potentially affecting the outcome of reductive opening of arylidenes with the Et₃SiH-PhBCl₂ reagent system: alkene hydroboration, azide reduction and/or Lewis acid promoted cleavage of the arylidene. With this knowledge, we optimized reproducible and high yielding reaction conditions that secure and extend the scope of the Et₃SiH-PhBCl₂ system as reagent for the regioselective opening of arylidenes in complex and multifunctional molecules.

Keywords: Acetals • Ring opening • Reductive cleavage • Regioselectivity • Allyl • Hydroboration • Carbohydrates • Polyols

Introduction

Natural substances, including carbohydrates, are multi-functional molecules whose chemical transformations quasi-inevitably require the use of protecting groups that, beside isolation of the desired reactive center, also influence the kinetic and the stereochemical outcome of many reactions, especially glycosylations.^[1,2] Atom economy and sustainability legitimate concerns give priority to protecting groups that are introduced with high chemo- and regioselectivities and ideally amenable to further regioselective manipulations. In this regard, arylidene acetals gained immense importance and widespread use: they are readily installed in mildly acidic conditions, with a strong preference for 1,3-diols over 1,2-*cis*-diols leaving 1,2-*trans*-diols unprotected.^[3] They are efficiently removed by hydrolysis or transacetalization in mild acidic conditions compatible with a vast majority of other protecting groups. Moreover, a key advantage of arylidenes is their ability to be reductively opened in a regioselective manner exposing a free hydroxyl and an arylmethyl ether enabling the opportunity for further site-specific transformations.^[4] As representative example, the widely used 4,6-*O*-benzylidene acetal can be selectively opened under reductive conditions to yield either 4-OH/6-OBn or 4-OBn/6-OH regioisomers depending on the hydride, acid and solvent used (Fig. 1).^[5]

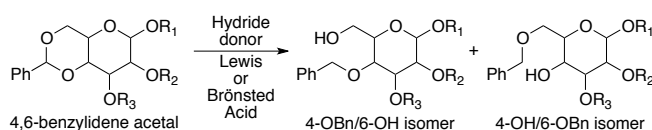


Figure 1. Regioselective reductive opening of 4,6-benzylidene acetals.

Acetal reduction was first performed by Doukas and Fontaine in 1951 to open the acetal moiety present in the ring F of diosgenin, using LiAlH_4 and HCl in anhydrous diethylether.^[6] A couple of years later Eliel and Rerick established AlCl_3 as the active Lewis acid, by performing the reduction of acetal and ketal using the $\text{LiAlH}_4\text{-AlCl}_3$ reagent combination in Et_2O .^[7,8] This reaction was then thoroughly explored by Brown *et al.* that showed that 1,3-dioxolane were more reactive than 1,3-dioxane rings and that 2-phenyl substituents considerably speed up the reaction.^[9,10] Bhattacharjee and Gorin were the first to apply it in carbohydrate chemistry,^[11] while the Lipták group further demonstrated the 4-OBn/6-OH regioselectivity of the $\text{LiAlH}_4\text{-AlCl}_3$ promoted reaction on 3-O-benzyl-4,6-O-benzylidenehexopyranosides.^[12] Searching for more chemoselective conditions for the reductive opening of benzylidene, Garegg *et al.* identified the $\text{NaBH}_3\text{CN-HCl}$ system, previously introduced by Horne and Jordan,^[13] and demonstrated its ability to chemoselectively reduce benzylidene acetals in the presence of *O*-benzoyl or *N*-acetyl moieties.^[14] Most interestingly, they could establish that this reagent combination gives mainly 6-OBn ethers, being thus complementary to the $\text{LiAlH}_4\text{-AlCl}_3$ procedure. Shortly after, the same group introduced the highly chemoselective $\text{BH}_3\cdot\text{NMe}_3\text{-AlCl}_3$ system and found that the regioselectivity of the reductive opening was highly solvent dependent: in THF, the reaction yields 6-OBn ethers while 4-OBn ones are obtained when toluene is used as solvent.^[15] DIBALH^[16] or other boranes ($\text{BH}_3\cdot\text{THF}$,^[17] $\text{BH}_3\cdot\text{SMe}_2$ ^[18]) in conjunction with various Lewis acids have also proved their efficiency as reagents for chemo and regioselective opening of arylidenes. The underlying principles for the regioselectivity of reductive benzylidene opening using boranes as reductant have recently been understood with the extensive kinetic studies conducted by the Ellervik's group^[19-21] and completed by Hung's one.^[22] Silanes, that are environmentally benign and user friendly reagents, have been introduced in 1995 as efficient hydride sources for the reductive openings of benzylidene acetals.^[23] Originally, Et_3SiH was used in conjunction with the protic acid TFA, leading selectively to the 4-OH/6-OBn regioisomer in high yields, although with a limited substrate range. Later on, TfOH ,^[24] $\text{BF}_3\cdot\text{OEt}_2$,^[25] $\text{Cu}(\text{OTf})_2$ ^[26] and more recently I_2 ^[27] were shown to allow the efficient reductive opening of arylidenes, using silanes as reducing agent, on a broad substrates range with excellent regioselectivities. PhBCl_2 , disclosed in 2000, is the sole Lewis acid identified until now, that, in combination with a silane, results in formation of 4-OBn/6-OH regioisomer.^[24] The efficiency and full regioselectivity of the $\text{Et}_3\text{SiH-PhBCl}_2$ combination is attested in more than 35 publications (Table 1) describing high isolated yields: above 90% in one third of them, between 80 and 90% in a second third and between 70 and 80% in most of the remaining ones. Although some variations can be found, especially regarding concentrations, most of the authors perform the reactions in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$ for 1 h, using Et_3SiH (3 equiv), PhBCl_2 (3.4 equiv) and 4 Å molecular sieve as initially described by Sakagami and Hamana.^[24] In these conditions, a complete chemoselectivity is observed for a vast majority of functional and protecting groups: ethers (benzyl, 4-acetamidobenzyl, 2-naphtylmethyl, 4-methoxyphenyl, allyl), silyl ethers (*tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, thexyldimethylsilyl), esters (acetate, benzoate, pivaloate as well as methyl, ethyl and benzylesters), carbonates (allyloxycarbonyl, fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl), carbamates (allyloxycarbonyl, fluorenylmethoxycarbonyl, *N*-methyloxazolidinone), alkyl fluorides, alkyl bromides, alkyl azides (Table 1). Although fucoside cleavage^[28] or endocyclic cleavage of pyranosides^[29,30] have been observed in a very limited number of cases, oligosaccharides, alkyl, allyl, benzyl, 2-trimethylsilylethyl and *tert*-butyldiphenylsilyl glycosides as well as alkyl, phenyl and tolyl thioglycosides are generally stable in the canonical reaction conditions (Table 1). Furthermore, the use of the $\text{Et}_3\text{SiH-PhBCl}_2$ reagent system has been extended with great success to naphthylidenes^[31,32] and functionalized benzylidenes (2-nitro,^[29] 4-bromo,^[33] 4-*tert*-butyl,^[34] fluorously tagged^[30,35]), leading to the 6-OH regioisomer with high regioselectivity. For 4-methoxybenzylidene acetals, more conflicting results, ranging from excellent isolated yields and regioselectivities^[36,37] to substrate degradation,^[38] have been described and may be explained by the instability of PMB ethers towards PhBCl_2 when non-coordinating solvents, such as CH_2Cl_2 , are used.^[28,39-42] In this regard, we demonstrated that full chemo- and regioselectivities with high reproducible yields, up to multi-gram scales, can be obtained when Et_2O is used as solvent for the $\text{Et}_3\text{SiH-PhBCl}_2$ promoted reductive opening of 4,6-*O*-(4-methoxybenzylidene).^[42] These reaction conditions also apply to 2,4-*O*-(4-methoxybenzylidenes)- α -L-iduronyl moieties, leading selectively to the 2-OH/4-OPMB regioisomer, a key step in the synthesis of bioactive heparan sulfate fragments and conjugates developed by our group.^[44,45] However, despite all those positive reports on the use of the $\text{Et}_3\text{SiH-PhBCl}_2$ reagent system for arylidene reductive opening, its widespread use has been hampered by reports on substrate degradation,^[38] poor efficiency,^[46] lower regioselectivity than expected^[47] and by cost consideration for large scale process.^[48] We herein describe how the identification of previously unreported side-reactions, when performing $\text{Et}_3\text{SiH-PhBCl}_2$ promoted 4,6-*O*-benzylidene reductive opening on monosaccharide **1** and trisaccharide **2**, allowed us to optimize new reaction

conditions with greatly improved chemoselectivity that open the way to the use of the Et₃SiH-PhBCl₂ reagent system on a broader range of multifunctional molecules.

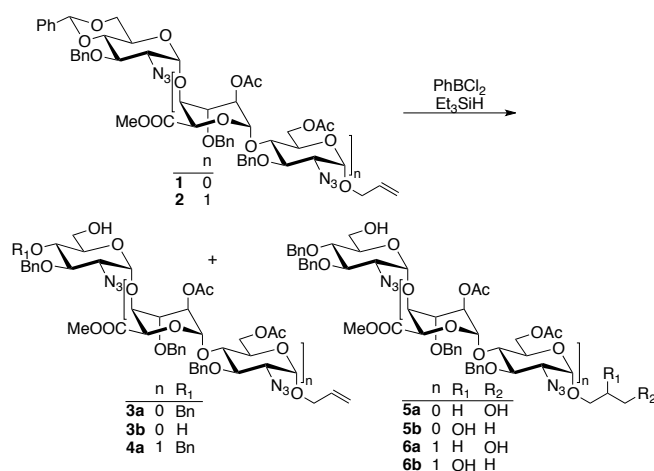
Table 1. Protecting group compatibility with the Et₃SiH-PhBCl₂ reagent system for benzylidene reductive opening.

BnO^a	pAcNHBnO^a	NapO^a	PMPO^a	AlIO^a
24, 28-31, 40-43, 47, 49-59	56	31, 57, 60, 66	33	42, 43, 49, 51
TESO^a	TBDMSO^b	TBDPSO^b	TDSO^b	AcO^c
61	36, 38, 52, 55	41	65	24, 35, 43, 53, 61, 62
BzO^c	PivO^c	CO₂Me/Et^c	CO₂Bn^c	AllocO^d
48, 52-54, 56, 61, 63	54	36, 43, 48, 53, 54, 56, 59, 64	51	65
FmocO^d	TrocO^d	AcNH^e	TCANH^e	PhthN^e
57	34	24, 54, 58, 64		28, 40
AllocNH^f	TrocNH^f	Oxazolidinone^f	N₃	C-F
36	34, 49, 52, 57	50	40, 42, 43, 53, 54, 60, 61, 63, 65	30, 33
C-Br	OH	SAlkyl^g	SPh^g	STol^g
24, 33	43	36, 51	52, 60, 66	28

^aEthers; ^bSilylethers; ^cEsters; ^dCarbonates; ^eAmides; ^fCarbamates; ^gThioglycosides.

Results and Discussion

Within the frame of a structure-activity relationship study on oligosaccharide type inhibitors of Human endosulfatases (HSulf),^[67,68] a class of enzymes catalyzing the regioselective hydrolysis of 6-O-sulfates within heparan sulfate chains, we devised a synthetic route that relied on a Et₃SiH-PhBCl₂ promoted regioselective reductive opening of a 4,6-O-benzylidene moiety (Scheme 1).



Scheme 1. Reductive opening of 4,6-O-benzylidenes, using the Et₃SiH-PhBCl₂ reagent system, as key step towards structure-activity relationship studies on HSulf inhibitors.

Monosaccharide **1** (Scheme 1) was first used as a model and treated with Et₃SiH (5 equiv) and PhBCl₂ (2.4 equiv) in CH₂Cl₂. No conversion was observed at -78 °C. The reaction started at -50 °C leading to the expected 4-OBn/6-OH isomer **3a** along with several side-products with low R_f. We decided to evaluate the effect of the solvent coordinating ability and of the temperature onto the reaction outcome. We thus performed reactions in CH₂Cl₂, CH₂Cl₂/Et₂O mixture (9/1) and Et₂O with temperatures rising from -50 to -15 °C and found that: i. In CH₂Cl₂, conversion of benzylidene **1** started at -50 °C, side-products appeared at -30 °C and became major at -15 °C (Figure 2); ii. In CH₂Cl₂/Et₂O (9/1), the reaction started at -40 °C but unfortunately the formation of side-products was not much retarded with respect to pure CH₂Cl₂; iii. In Et₂O, the reaction started at -20 °C and full conversion of **1** was observed after 3 h at -15 °C, while the formation of side-products remained insignificant. The reactions performed in CH₂Cl₂ and CH₂Cl₂/Et₂O (9/1) were quenched and pooled together. After extractive workup and flash chromatography, two major side-products were isolated and identified, by HRMS and NMR analyses, as a 95/5 mixture of the regiomer alcohols **5a** and **5b** (Scheme 1). To our knowledge, such side-products have never been described when Et₃SiH-PhBCl₂ promoted benzylidene reductive opening were performed on substrates containing allyl ethers or allyl carbonates or allyl carbamates protecting groups (see Table 1).

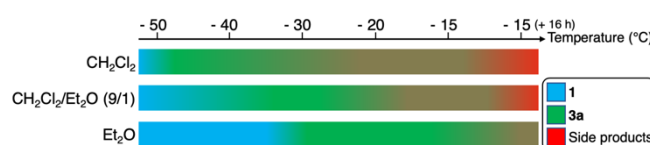
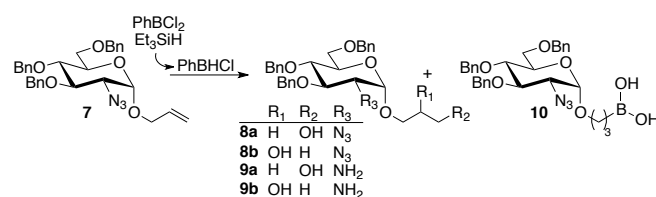


Figure 2. Solvent and temperature effects on the outcome of the reductive opening of compound **1** with the Et₃SiH-PhBCl₂ reagent system. PhBCl₂ was added at -50 °C and the temperature raised to -15 °C over 6 h and kept at this temperature for additional 16 h.



Scheme 2. Side-reactions driven by *in situ* generated PhBHCl.

Table 2. Compound **7** as model to study side-products formations.

Entry	Solvent	Et ₃ SiH (equiv)	7 (%) ^a	8a + 8b (%) ^{a,b}	10 (%) ^a
1	CH ₂ Cl ₂	5	traces	84	-
2 ^c	CH ₂ Cl ₂	5	traces	61	15
3	CH ₂ Cl ₂	1.1	40	44	-
4	Et ₂ O	5	85	traces	-

Compound **7** (0.12 M) was treated at -30 °C with PhBCl₂ (2.4 equiv) and Et₃SiH. After 16 h at -30 °C, the reaction was quenched (NEt₃, then MeOH) followed by oxidative treatment (H₂O₂). ^a Isolated yields. ^b **8b** is a 6/4 mixture of two diastereoisomers. ^c The oxidative treatment with H₂O₂ was omitted.

From these exploratory experiments, Et₂O appears a better solvent than CH₂Cl₂ for the reductive opening of 4,6-*O*-benzylidene with the Et₃SiH-PhBCl₂ system. However, many 4,6-*O*-benzylidene protected sugars are poorly soluble in Et₂O, while highly soluble in CH₂Cl₂. We thus undertook a thorough study to understand how alcohols **5a** and **5b** are formed and how to avoid it. Based on the reaction conditions and the observed anti-Markovnikov regioselectivity, we reasoned that **5a** and **5b** could be formed by a hydroboration/oxidation sequence. Indeed, trialkylsilanes are known to reduce alkyldichloroboranes into alkylchloroboranes which are efficient hydroboration reagents.^[69,70] In the present case, Et₃SiH would reduce PhBCl₂ into PhBHCl, that would readily hydroborate the

allyl moiety. Further oxidation of the boron-carbon bond with dioxygen^[71] would lead to the alcohols **5a** and **5b**. To test this hypothesis and potentially identify additional side-products, we treated allyl-2-azido-3,4,6-O-benzyl- α -D-glucopyranoside **7** (Scheme 2) with 2.4 equiv PhBCl₂ and a 5.0 equiv of Et₃SiH (Table 2, entry 1). The reaction was performed at -30 °C in CH₂Cl₂ since, as described above, such reaction conditions are suitable for the formation of side-products. After 16 h, TLC analysis indicated the total consumption of compound **7**. The reaction was then quenched by sequential addition of NEt₃ then MeOH, then treated with an excess of hydrogen peroxide to accelerate the boron-carbon bond oxidation. After flash chromatography, we isolated the two regioisomers **8a** and **8b** in 74/26 ratio and 84% combined yields. In addition, we could isolate small amounts of a mixture of two ninhydrin reactive compounds with much lower R_f than **8a** and **8b**. The presence of an amino group was further confirmed by NMR analyses of the mixture in which the H-2 protons resonated at $\delta = 3.10$ ppm, thus ≈ 0.32 ppm upfield with respect to H-2 in **7**. Further HRMS analyses allowed assigning the structure **9a** and **9b** to these amino compounds, indicating that azide reduction represent an additional, although slow, side-reaction (see the Supporting Information). Interestingly, azides R¹N₃ are known to react at 20 °C with alkyl or aryldichloroboranes R²BCl₂ to give the secondary amine R¹R²NH after hydrolysis,^[72] but we could not detect any side product that could result from such a transformation. When following the course of the reaction by TLC, we observed other side-products with intermediate polarity, that disappeared slowly upon air exposure and could correspond to alkylboron intermediates. We thus repeated this reaction without oxidative treatment and taking care to avoid prolonged air exposure during treatment and flash-chromatography (Table 2, entry 2). In these conditions, we could isolate the alkylboronic derivative **10** as major compound that proved to be stable enough, under Ar atmosphere, for unambiguous characterization by ¹H, ¹³C and ¹¹B NMR and HRMS. The ¹H NMR spectrum of **10** was very similar to the one of alcohol **8a**, excepted for a strong 2.87 ppm upfield shift of the signal corresponding to the γ methylene protons of the propyl chain (Figure 3a-b), as previously observed in alkylboronic acids.^[73] The 3/2 spin of ¹¹B nucleus and its nuclear quadrupole relaxation result preclude the observation of the ¹³C NMR signal of carbons linked to boron in standard acquisition conditions for ¹³C-¹H or ¹H-¹³C HSQC experiments. Fortunately, by taking advantage of the short transverse relaxation time of C _{γ} , that allows reducing acquisition times and recycling delays, we could increase the number of scans in ¹³C-¹H experiments and the number of experiments in ¹H-¹³C HSQC ones (see SI for details). As a result, a broad signal between 11.0 and 13.0 ppm was clearly distinguished from the background in the ¹³C-¹H spectrum of compound **10** and shown to correlate with the two H- γ in the ¹H-¹³C HSQC spectrum (Figure 3c), thus confirming the covalent binding of a boron to C _{γ} in compound **10**. The ¹¹B NMR spectra, displayed two broad signals between 20 and 50 ppm, close to the signal of the ¹¹B of the borosilicate NMR tube (Fig. 2d), as expected for an alkylboronic acid in different oligomerization states.^[73,74] In the HR-MS spectrum of a methanolic solution of **10**, peaks at *m/z* 598.2737 and 612.2680, corresponding respectively to the sodium adducts of the monomethyl and dimethyl esters of boronic acid **10**, definitely confirmed its structure (see SI). Taken together, the isolation of alcohols **8a** and **8b** as well as alkylboronic acid **10**, definitely establish PhBCl₂ reduction/hydroboration as cascade side-reactions when performing an Et₃SiH-PhBCl₂ promoted benzylidene reductive opening on alkene containing substrates in CH₂Cl₂.

The reduction of the B-Cl bond by trialkylsilanes is known to be the rate limiting step of reduction/hydroboration sequences and it has been established that BCl₃ reduction is nearly instantaneous at -78 °C, while the ones of alkylidichloroboranes needs 25 °C to proceed at a reasonable rate.^[69] Our results (Fig. 2 and Table 2) indicate that, in CH₂Cl₂, the reduction of PhBCl₂ by Et₃SiH is already effective at -30 °C. However, when performing a reaction in CH₂Cl₂ on substrate **7** with 2.4 equiv PhBCl₂ and only 1.1 equiv Et₃SiH, we isolated after 16 h at -30 °C only 44% **8a** and **8b** along with 40% unreacted starting material (Table 2, entry 3). This demonstrates that, at -30 °C in CH₂Cl₂, PhBHCl formation remains a rather slow process compared to hydroboration and, most likely, to the reductive opening of 4,6-O-arylidene moieties. This assumption is strengthened by the fact that we never observed the formation of hydroboration derived side-products still containing the 4,6-O-benzylidene moiety. Therefore, the use of only a slight excess of Et₃SiH, instead of 5 equiv, should prevent the formation of hydroboration derived side products for reductive opening performed in non-coordinating solvent such as CH₂Cl₂ (see below). When the coordinating solvent Et₂O was used as a solvent (Table 2, entry 4), only traces of alcohols **8a** and **8b** could be detected by TLC and 85% of the starting material were recovered. This confirms that the reduction/hydroboration cascade is strongly inhibited when Et₂O is used as solvent and coherent with the reported need to free BHCl₂ from Et₂O, with a Lewis acid such as BCl₃, when using BHCl₂·OEt₂ as hydroborating agent.^[75]

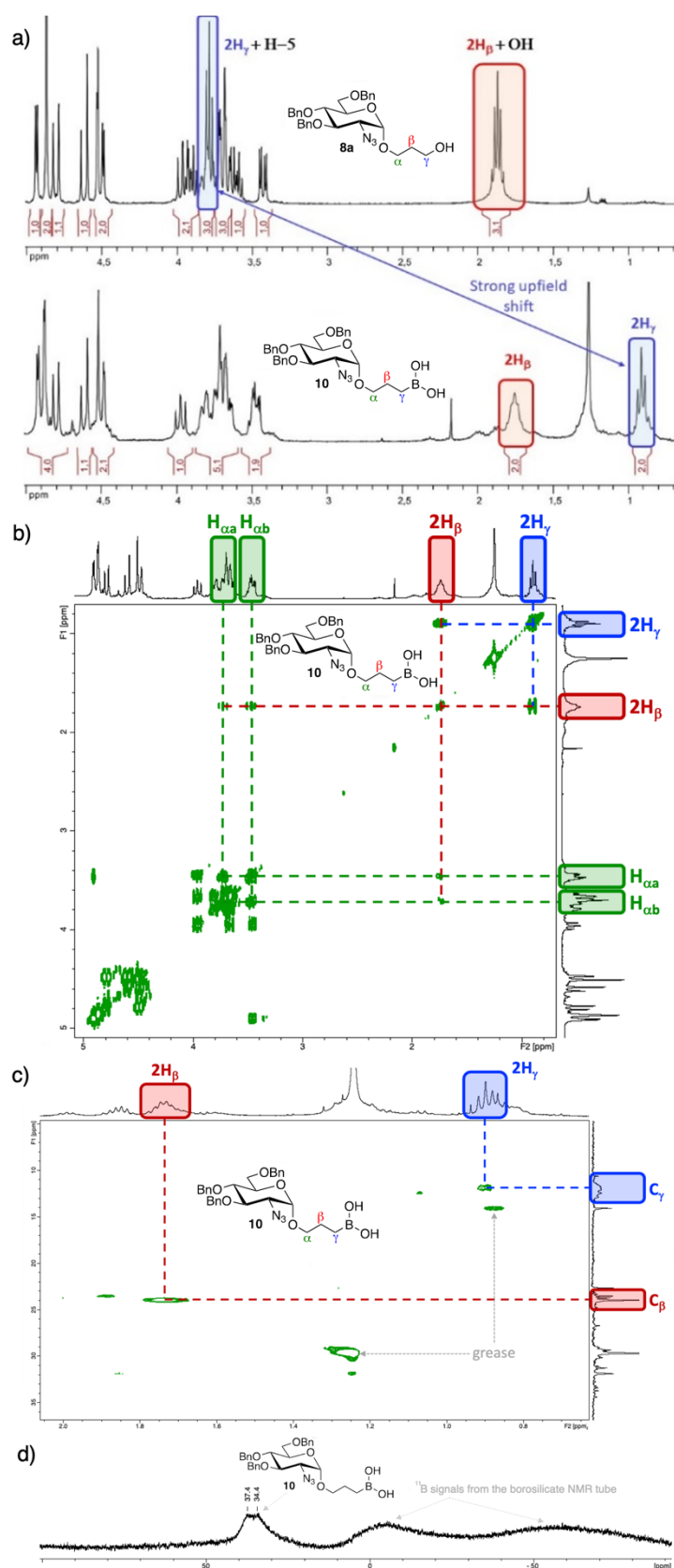


Figure 3. NMR spectrum of side product **10** in CDCl_3 to ascertain its chemical structure. (a) Comparison of ^1H NMR spectrum of **8a** and **10** in CDCl_3 showing the strong upfield of the two $\text{H}-\gamma$ of **10**. (b) 2D COSY spectrum of **10** showing the ^1H - ^1H correlation of the propyl chain protons. (c) ^1H - ^{13}C HSQC spectrum of **10** confirming that the broad signal observed between 11.1 and 12.4 ppm on the ^{13}C - $\{^1\text{H}\}$ NMR spectra of **10** corresponds to $\text{C}-\gamma$. (d) ^{11}B NMR spectra of **10** attesting the presence of alkyl boronic moieties in different oligomerization states.^[73,74]

Having identified how side-products **8a**, **8b**, **9a**, **9b** and **10** are formed in CH₂Cl₂, we looked for secure reaction conditions to avoid it, even at higher temperature and longer reaction time. To this aim, compound **1** was treated for 16 h at -30 °C in CH₂Cl₂ with different amounts of PhBCl₂ and Et₃SiH (Table 3). As expected, with 2.4 equiv PhBCl₂ and 5.0 equiv Et₃SiH, we only isolated 24% of **3a** and already 67% of hydroboration/oxidation products **5a** and **5b** in 95/5 ratio (Table 3, entry 1). Similarly, when trisaccharide **2** was treated in the same conditions we isolated alcohols **6a** and **6b** in 63/37 ratio and in 32% combined yields (*nb.*: H₂O₂ oxidation was omitted in the treatment of this reaction). Since we assumed that the kinetic of the reductive opening is faster than the PhBCl₂ reduction and/or hydroboration reaction, we diminished to 2.0 equiv the quantity of silane used. After 16 h at -30 °C, the formation of **5a** and **5b** was reduced to 35% combined yields, while the one of **3a** increased to 50% (Table 3, entry 2). Reducing further the quantity of Et₃SiH to 1.1 equiv allowed isolating the 6-OH regioisomer **3a** in quantitative yield, even after 16 h of reaction at -30 °C (Table 3, entry 3). To further explore the minimum requirements for the reaction, we reduced the amount of PhBCl₂ to 1.1 equiv, but the reaction did not proceed to completion and we recovered 43% of starting material **1** along with 54% of compound **3a** (Table 3, entry 4). When omitting the silane, we observed a partial cleavage of the 4,6-*O*-benzylidene moiety (Table 3, entry 5), presumably resulting from nucleophilic attack of chloride onto the PhBCl₂ activated acetal, as already observed with B-chlorocatecholborane.^[76] This last experiment establish that it is important to add Et₃SiH prior to PhBCl₂ to avoid such side-reaction. Taken together, these results confirm that, when using the PhBCl₂/Et₃SiH reagent system in CH₂Cl₂, the kinetic of the reductive opening reaction is much faster than both chlorosilane reduction/hydroboration cascade and 4,6-*O*-benzylidene cleavage.

Table 3. Optimizing reductive opening in CH₂Cl₂ on monosaccharide **1**.

Entry ^a	Et ₃ SiH (equiv)	PhBCl ₂ (equiv)	1 (%) ^b	3a (%) ^b	3b (%) ^b	5a + 5b (%) ^b
1	5.0	2.4	-	24	-	67
2	2.0	2.4	-	50	-	35
3	1.1	2.4	-	98	-	-
4	1.1	1.1	43	54	-	-
5	0	2.4	64	-	20	-

Compound **1** (0.15 mmol) in 1.25 mL solvent was treated at -30 °C by PhBCl₂ and Et₃SiH. After 16 h at this temperature, the reaction was quenched by addition of NEt₃, then MeOH, followed by oxidative treatment with excess of H₂O₂. ^b Isolated yields.

The above results allowed us to define reaction conditions to perform Et₃SiH-PhBCl₂ promoted reductive opening of 4,6-*O*-benzylidene in both CH₂Cl₂ and Et₂O, while staying on the safe side for reactions on substrates containing allyl type protecting groups and/or azido moieties. In CH₂Cl₂ the key point is to use only 1.1 equiv of Et₃SiH to avoid PhBCl₂ reduction and subsequent hydroboration of alkene moiety. In such conditions, the reactions are high yielding and reproducible: compound **3a** was obtained from **1** in 93 % isolated yield at 500 mg scale (Table 4, entry 1), while trisaccharide **4a** was obtained from **2** in 82% isolated yield (Table 4, entry 3). Surprisingly, the reaction on trisaccharide **2** proved to be much faster than on monosaccharide **1**: full conversion of the former was achieved in 1 h at -60 °C, while no reaction was observed below -50 °C and 16 h of reaction at -30 °C were needed for the later (Table 4, entry 1 and 3). In Et₂O an excess of Et₃SiH can be used (5 equiv) with temperatures ranging from -15 to 0 °C. However, it is crucial to add the Lewis acid as a 2 M solution in Et₂O (freshly prepared by dropwise addition of PhBCl₂ to Et₂O at 0 °C). Indeed, the PhBCl₂ acid-base reaction with Et₂O is exothermic and direct addition of PhBCl₂ to the reaction causes uncontrolled temperature variations leading to unreproducible yields. In these conditions, the reactions in Et₂O proceeds smoothly with 2.4 equiv PhBCl₂, leading regioselectively to monosaccharide **3a** and trisaccharide **4b** in 90 and 84% isolated yields respectively (Table 4 entry 2 and 4).

Table 4. Optimized conditions for the reductive opening of saccharides **1** and **2** with the PhBCl₂/Et₃SiH system in CH₂Cl₂ or Et₂O.

Entry ^a	Substrate -> Product	Solvent	Temp. (°C)	Time (h)	Et ₃ SiH (equiv)	Yield (%) ^b
1	1 -> 3a	CH ₂ Cl ₂	-30	16	1.1	93
2	1 -> 3a	Et ₂ O	0	2.5	5.0	90
3	2 -> 4a	CH ₂ Cl ₂	-60	1	1.1	82
4	2 -> 4a	Et ₂ O	-15	3.5	5.0	84

^a 2.4 equiv PhBCl₂ were used in each case. ^b Isolated yields.

Finally, we would like to highlight the importance of the quality of the PhBCl₂ to obtain high and reproducible yields. Indeed, we experienced dramatic drops in the yield and/or regioselectivity depending on the provider and the production batches. To solve this issue, we prepare PhBCl₂ following a slightly modified version of the protocol described by Kaufmann^[77] (see Experimental Section). In this way, batches of about 65 g of PhBCl₂ (73% yield) can be obtained in two days' work from commercial 1 M solution of BCl₃ in CH₂Cl₂ (800 mL) and PhSiMe₃ (86 g). It is important to note that the conventional distillation apparatus we used to purify PhBCl₂ did not allowed us to separate the Lewis acid from unreacted PhSiMe₃. We thus obtained PhBCl₂/PhSiMe₃ mixtures, in reproducible ≈ 65/35 molar ratio, that can be further used without additional purification for reductive opening reactions and can be stored for at least five years in sealed ampules. In addition to sustained quality, cost reduction represents an additional advantage of "home-made" PhBCl₂.

Conclusion

We have identified different pitfall potentially affecting the outcome of regioselective reductive opening of 4,6-*O*-benzylidenes with the Et₃SiH-PhBCl₂ reagent system and optimized protocols allowing to stay on the safe side of reactions performed in CH₂Cl₂ or in Et₂O. For reactions in dichloromethane, we identified three potential side-reactions: alkene hydroboration and/or azide reduction, when excess Et₃SiH is used, and Lewis acid promoted cleavage of the benzylidene, when the silane is omitted or added after PhBCl₂. These side-reactions can be efficiently prevented by using 1.1 equiv of Et₃SiH and adding it prior to the Lewis acid. In Et₂O, we did not observe the formation of the side-products resulting from allyl hydroboration or azide reduction, even in the presence of an excess silane relative to PhBCl₂. Et₂O could thus appear as a "safer" solvent for reductive opening of 4,6-*O*-benzylidenes with the Et₃SiH-PhBCl₂ reagent system, but, since the acid-base reaction of PhBCl₂ with Et₂O is exothermic, it is crucial to add the Lewis acid as a 2 M solution in Et₂O to avoid uncontrolled rising of the reaction temperature leading to unreproducible yields. The reaction conditions disclosed in this work allowed us to obtain 4-OBn/6-OH regioisomers of mono and trisaccharides in high yield, full regioselectivity and up to several hundreds of milligram. We anticipate that they should be easily applied to any substrate containing alkene moieties, or other chemical functionalities sensitive to hydroboration or acidic conditions, thus extending greatly the scope of the use of the Et₃SiH-PhBCl₂ reagent system for the regioselective opening of 4,6-*O*-benzylidenes in complex and multifunctional molecules.

Experimental Section

General experimental procedure. All starting materials were of commercial grade and were used without further purification. Anhydrous dichloromethane and diethyl ether were obtained using Glass Technology GT S100 device. Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using 5% sulfuric acid with orcinol for visualization. Column chromatographies were performed on silica gel 60 (15-40 μm , Merck). Evaporation of solvents was conducted under reduced pressure at temperatures less than 40°C. Nuclear magnetic resonance (NMR) data were acquired on different spectrometers: Bruker AVANCE I 300 and 360 and Bruker AVANCE III 400 operating respectively at 300/360/400 MHz for ^1H , at 75/90/100 MHz for ^{13}C and 96 MHz for ^{11}B . Chemical shifts (δ) are reported in parts per million (ppm), using solvent signals as internal standards (chloroform- d_1 : 7.26 ppm for ^1H and 77.15 ppm for ^{13}C ; methanol- d_4 : 3.31 ppm for ^1H and 49.0 ppm for ^{13}C). Splitting patterns for ^1H NMR and ^{13}C NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), broad signal (br) or m (multiplet). Coupling constants (J) are reported in Hz. Carbon multiplicities were determined by DEPT135 experiments. In NMR data, H₁ and C₁ refer respectively to anomeric proton and carbon at the reducing unit; di- and trisaccharide units are identified alphabetically (capital letters) from the reducing end. The aglycone moiety is identified alphabetically (Greek letters) from the acetal. – High-resolution mass spectrometry (HRMS) data were recorded using a Bruker Daltonics microTOF-Q instrument equipped with an electrospray ionization source either in positive or negative mode as appropriate.

Dichlorophenylborane stock solution preparation.

Adapted from the protocol described by D. Kaufman:^[77] Trimethylphenylsilane (85.88 g, 98.6 mL, 0.57 mol, 1 equiv) was added dropwise over 15 min to a stirred commercial 1 M solution of BCl_3 in dichloromethane (800 mL, 0.8 mol, 1.4 equiv) under argon at -78 °C. The resulting solution was stirred at -78 °C for 1 h and then allowed to warm to room temperature over 12 h. CH_2Cl_2 , TMSCl and excess BCl_3 were then distilled at atmospheric pressure. Further distillation of the residue under reduced pressure (64 °C/14 mbar) gave 100 g of a colorless PhBCl_2 and PhSiMe_3 azeotrope in 64/36 molar ratio, *i.e.* 66.5 wt % PhBCl_2 (66.5 g, 0.42 mol, 73%, see Supporting Information for titration details). The presence of a single boron specie was assessed by ^{11}B NMR of the distillate in anhydrous CDCl_3 that displayed a single peak at $\delta = 55$ ppm as described.^[78] This PhBCl_2 - PhSiMe_3 mixture can be used without additional purification for reductive opening reactions and can be stored for at least five years in sealed ampules. ^1H NMR (CDCl_3 , 300 MHz): δ 8.22 (br d, $J = 8.0$ Hz, 2H, H-*o*); 7.72 (tt, $J = 7.5$, $J = 1.5$ Hz, 1H, H-*p*); 7.54 (dd, $J = 8.0$, $J = 7.5$ Hz, 2H, H-*m*). ^{11}B NMR (CDCl_3 , 96 MHz): δ 55.5. ^{13}C - $\{^1\text{H}\}$ NMR (CDCl_3 , 90 MHz): δ 137.0 (2CH-*o*); 135.3 (CH-*p*); 128.3 (2CH-*m*). The C_q bearing the B atom is not visible due to the quadrupolar relaxation mechanism of ^{11}B nucleus.

General procedure A: reductive opening of 4,6-benzylidene acetals in CH_2Cl_2 . Triethylsilane (1.1 equiv) was added to a solution of 4,6-*O*-benzylidene substrate (1 equiv) and 4 Å molecular sieve (0.5 g/g of substrate) in anhydrous CH_2Cl_2 (8.33 mL/mmol of substrate, *i.e.* 0.12 M initial concentration) and the mixture was stirred for 15 min under argon at room temperature. The mixture was cooled to the appropriate temperature and dichlorophenylborane (2.4 equiv) was added dropwise. The reaction mixture was stirred at the same temperature until completion by TLC analysis. The reaction was then quenched by addition of Et_3N (1.5 mL/mmol of substrate, 11 equiv), MeOH (1.5 mL/mmol of substrate 35 equiv) and saturated NaHCO_3 solution (3 mL/mmol of substrate) successively. The resulting suspension was warmed to room temperature, diluted with Et_2O (100 mL/mmol of substrate), washed with 0.1 M NaOH solution (2 x 50 mL/mmol of substrate), 5 % KH_2PO_4 solution (50 mL/mmol of substrate) and water (3 x 50 mL/mmol of substrate). The organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the expected compound **3a** or **4a**.

General procedure B: reductive opening of 4,6-methoxybenzylidene acetals in Et_2O . CAUTION: the reaction between PhBCl_2 and Et_2O is exothermic. To avoid uncontrolled temperature variations of the reaction media, PhBCl_2 must be added as a freshly prepared solution in Et_2O (2 M, prepared at 0 °C by dropwise addition of PhBCl_2 to Et_2O). Triethylsilane (5.0 equiv) was added to a solution of 4,6-*O*-benzylidene substrate (1 equiv) and 4 Å molecular sieve (0.5 g/g of substrate) in anhydrous Et_2O (7.13 mL/mmol of substrate, *i.e.* 0.12 M initial concentration) and the mixture was stirred for 15 min under argon at room temperature. The mixture was cooled to -15 °C and the PhBCl_2 solution in Et_2O (2 M, 2.4 equiv, 1.2 mL/mmol of substrate) was added dropwise. The reaction mixture was stirred at the same temperature until completion (*ca.* 3 h), then quenched and treated as described in General procedure A.

Allyl 2-azido-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranoside (3a). Prepared from **1** following general procedure A (485 mg, 1.146 mmol, 16 h at -30 °C) or B (150 mg, 0.354 mmol, 2.5 h at 0 °C). Purification by flash column chromatography on silica gel (toluene/acetone, 95:5 to 8:2 gradient) gave **3a** as a colourless oil (procedure A: 450 mg, 1.058 mmol, 93% yield; procedure B: 135 mg, 0.212 mmol, 90% yield). R_f = 0.65 (toluene/acetone, 8:2). ^1H NMR data were in agreement with those reported in the literature;^[79] ^1H NMR (CDCl_3 , 360 MHz): δ 7.45-7.28 (m, 10H, Ph), 7.20 – 7.12 (m, 2H, Ph), 5.93 (dddd, $J_{\beta,\gamma\text{a}} = 17.5$, $J_{\beta,\gamma\text{b}} = 10.5$, $J_{\beta,\alpha\text{a}} = 6.0$, $J_{\beta,\alpha\text{b}} = 5.5$ Hz, 1H, H- β), 5.35 (dddd, $J_{\gamma\text{a},\beta} = 17.5$, $J_{\gamma\text{a},\gamma\text{b}} = J_{\gamma\text{a},\alpha\text{a}} = J_{\gamma\text{a},\alpha\text{b}} = 1.5$ Hz, 1H, H- γa), 5.25 (dddd, $J_{\gamma\text{b},\beta} = 10.5$, $J_{\gamma\text{b},\gamma\text{a}} = J_{\gamma\text{b},\alpha\text{a}} = J_{\gamma\text{b},\alpha\text{b}} = 1.5$ Hz, 1H, H- γb), 4.96 (d, $J_{1,2} = 3.5$ Hz, 1H, H-1), 4.91 (s, 2H, - CH_2Ph), 4.89 (d, $J = 11.5$ Hz, 1H, - CH_2Ph), 4.68 (d, $J = 11.5$ Hz, 1H, - CH_2Ph), 4.20 (dddd, $J_{\alpha\text{a},\alpha\text{b}} = 13.0$, $J_{\alpha\text{a},\beta} = 5.5$, $J_{\alpha\text{a},\gamma\text{a}} = J_{\alpha\text{a},\gamma\text{b}} = 1.5$ Hz, 1H, H- αa), 4.06 (dd, $J_{3,2} = 10.0$, $J_{3,4} = 9.0$ Hz, 1H, H-3), 4.04 (dddd, $J_{\alpha\text{b},\alpha\text{a}} = 13.0$, $J_{\alpha\text{b},\beta} = 6.0$, $J_{\alpha\text{b},\gamma\text{a}} = J_{\alpha\text{b},\gamma\text{b}} = 1.5$ Hz, 1H, H- αb), 3.85 – 3.71 (m, 3H, H-5 & H-6), 3.67 (dd, $J_{4,3} = J_{4,5} = 9.0$ Hz, 1H, H-4), 3.37 (dd, $J_{2,3} = 10.0$, $J_{2,1} = 3.5$ Hz, 1H, H-2). ^{13}C - $\{^1\text{H}\}$ NMR (CDCl_3 , 90 MHz): δ 138.0 (C_q), 137.9 (C_q), 133.3 (CH- β), 128.7 (2CH_{arom}), 128.6 (2CH_{arom}), 128.2 (2CH_{arom}), 128.1 (CH_{arom}), 128.0 (3CH_{arom}), 118.2 (C- γ), 96.9 (C-1), 80.3 (C-3), 78.0 (C-4), 75.6 (- CH_2Ph), 75.2 (- CH_2Ph), 71.5 (C-5), 68.7 (C- α), 63.7 (C-2), 61.6 (C-6). HRMS (ESI/Q-TOF) m/z : [M+Na]⁺ Calcd for C₂₃H₂₇N₃O₅Na 448.1843; Found 448.1823.

Allyl (2-azido-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 \rightarrow 4)-(methyl 2-O-acetyl-3-O-benzyl-2-deoxy- α -L-idopyranuronyl)-(1 \rightarrow 4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranoside (4a). Prepared from **2** following general procedure A (50 mg, 47 μmol , 1 h -60 °C) or B (46 mg, 43 μmol , 3 h at -15 °C). Purification by flash column chromatography on silica gel (gradient toluene/acetone, 95:5 to 8:2) gave **4a** as a white foam (procedure A: 42 mg, 40 μmol , 84 % yield; procedure B: 38 mg, 35 μmol , 82% yield). R_f = 0.5 (toluene/acetone, 80:20). ^1H NMR (CDCl_3 , 300 MHz): δ 7.45-7.17 (m, 20H, Ph), 5.95 (dddd, $J_{\beta,\gamma\text{a}} = 17.0$, $J_{\beta,\gamma\text{b}} = 10.5$, $J_{\beta,\alpha\text{a}} = 6.0$, $J_{\beta,\alpha\text{b}} = 5.5$ Hz, 1H, H- β), 5.36 (dddd, $J_{\gamma\text{a},\beta} = 17.0$, $J_{\gamma\text{a},\gamma\text{b}} = J_{\gamma\text{a},\alpha\text{a}} = 1.5$, $J_{\gamma\text{a},\alpha\text{b}} = 1.0$ Hz, 1H, H- γa), 5.27 (dddd, $J_{\gamma\text{b},\beta} = 10.5$, $J_{\gamma\text{b},\gamma\text{a}} = J_{\gamma\text{b},\alpha\text{a}} = 1.5$, $J_{\gamma\text{b},\alpha\text{b}} = 1.0$ Hz, 1H, H- γb), 5.21 (d, $J_{1,2} = 3.5$ Hz, 1H, H-1^B), 4.96-4.91 (m, 3H, H-1^A, H-1^C & H-2^B), 4.85 (d, $J = 11.5$ Hz, 1H, - CH_2Ph), 4.84 (d, $J = 10.5$ Hz, 1H, - CH_2Ph), 4.83 (d, $J = 10.5$ Hz, 1H, - CH_2Ph), 4.79 (d, $J = 10.5$ Hz, 1H, - CH_2Ph), 4.77 (d, $J = 11.0$ Hz, 1H, - CH_2Ph), 4.75 (d, $J = 3.0$ Hz, 1H, H-5^B), 4.72 (d, $J = 11.0$ Hz, 1H, - CH_2Ph), 4.68 (d, $J = 10.5$ Hz, 1H, - CH_2Ph), 4.65 (d, $J = 11.5$ Hz, 1H, - CH_2Ph), 4.39 (d, $J_{6\text{a},6\text{b}} = 12.5$ Hz, $J_{6\text{a},5} = 1.0$ Hz, 1H, H-6a^A), 4.25 (dd, $J_{6\text{b},6\text{a}} = 12.5$, $J_{6\text{b},5} = 2.5$ Hz, 1H, H-6b^A), 4.21 (dddd, $J_{\alpha\text{a},\alpha\text{b}} = 13.0$, $J_{\alpha\text{a},\beta} = 5.5$, $J_{\alpha\text{a},\gamma\text{a}} = J_{\alpha\text{a},\gamma\text{b}} = 1.5$ Hz, 1H, H- αa), 4.06 (dddd, $J_{\alpha\text{b},\alpha\text{a}} = 13.0$, $J_{\alpha\text{b},\beta} = 6.0$, $J_{\alpha\text{b},\gamma\text{a}} = J_{\alpha\text{b},\gamma\text{b}} = 1.0$ Hz, 1H, H- αb), 4.03 (dd, $J_{4,3} = 4.5$, $J_{4,5} = 3.0$ Hz, 1H, H-4^B), 3.94 (dd, $J_{3,4} = J_{3,2} = 4.5$ Hz, 1H, H-3^B), 3.92-3.86 (m, 3H, H-3^A, H-4^A, H-5^A), 3.83 (dd, $J_{3,2} = 10.5$, $J_{3,4} = 9.0$ Hz, 1H, H-3^C), 3.78 – 3.69 (m, 2H, H-5^C & H-6a^C), 3.62 (dd, $J_{6\text{b},6\text{a}} = 12.5$, $J_{6\text{b},5} = 4.5$ Hz, 1H, H-6b^C), 3.57-3.46 (m, 4H, - COOCH_3 & H-4^C), 3.39 (dd, $J_{2,3} = 9.5$, $J_{2,1} = 4.0$ Hz, 1H, H-2^A), 3.21 (dd, $J_{2,3} = 10.5$, $J_{2,1} = 3.5$ Hz, 1H, H-2^C), 2.13 (s, 3H, - COCH_3), 2.08 (s, 3H, - COCH_3). ^{13}C - $\{^1\text{H}\}$ NMR (CDCl_3 , 76 MHz): δ 170.8 (- COCH_3), 170.1 (- COCH_3), 169.5 (- COOMe), 138.0 (2C_q), 137.7 (C_q), 137.4 (C_q), 133.2 (CH- β), 128.6 (5CH_{arom}), 128.3 (3CH_{arom}), 128.2 (3CH_{arom}), 128.1 (3CH_{arom}), 128.0 (CH_{arom}), 127.9 (2CH_{arom}), 127.8 (2CH_{arom}), 127.6 (CH_{arom}), 118.5 (C- γ), 98.3 (C-1^B), 97.9 (C-1^C), 96.7 (C-1^A), 79.8 (C-3^C), 78.6 (C-3^A), 77.9 (C-4^C), 75.5 (C-4^A), 75.4 (- CH_2Ph), 75.0 (- CH_2Ph), 74.9 (- CH_2Ph), 74.3 (C-3^B), 74.4 (- CH_2Ph), 73.1 (C-4^B), 72.6 (C-5^C), 69.3 (C-5^A), 69.2 (C-5^B), 68.9 (C-2^B & C- α), 63.5 (C-2^A), 63.4 (C-2^C), 62.4 (C-6^A), 61.5 (C-6^C), 52.1 (- COOCH_3), 21.0 (2- COCH_3). HRMS (ESI/Q-TOF) m/z : [M+Na]⁺ Calcd for C₅₄H₆₂N₆O₁₇Na 1089.4064; Found 1089.4027.

3-hydroxypropyl 2-azido-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranoside (5a) and 2-hydroxypropyl 2-azido-3,4-di-O-benzyl-2-deoxy- α -D-glucopyranoside (5b). Obtained from **1** (100 mg, 0.236 mmol) as side products when using general procedure A with 5.0 equiv Et₃SiH. After 16 h at -30 °C, the reaction was quenched by addition of Et₃N (350 μL , 1.240 mmol, 11 equiv), MeOH (350 μL , 8.640 mmol, 35 equiv), saturated NaHCO₃ solution (750 μL , aq. H₂O₂ (35%, 200 μL , 10 equiv) and aq. NaOH (0.1 M, 2.5 mL, 10 equiv). Aqueous workup, as described in general procedure A, followed by flash column chromatography on silica gel (toluene/acetone, 95:5 to 7:3 gradient) gave an inseparable mixture of **5a:5b** (95:5) as a colourless oil (70 mg, 0.158 mmol, 67% yield). R_f = 0.175 for **5a:5b** (toluene/acetone, 80:20). NMR data for **5a**: ^1H NMR (CDCl_3 , 360 MHz): δ 7.50 – 7.27 (m, 10H, Ph), 4.90 (d, $J_{1,2} = 3.5$ Hz, 1H, H-1), 4.89 (s, 2H, - CH_2Ph), 4.87 (d, $J = 11.0$ Hz, 1H, - CH_2Ph), 4.67 (d, $J = 12.0$ Hz, 1H, - CH_2Ph), 3.99 (dd, $J_{3,2} = 10.0$, $J_{3,4} = 9.0$ Hz, 1H, H-3), 3.89 (dt, $J_{\alpha\text{a},\alpha\text{b}} = 10.0$, $J_{\alpha\text{a},\beta} = 6.0$ Hz, 1H, H- αa), 3.82 (dd, $J_{6\text{a},6\text{b}} = 11.0$, $J_{6\text{a},5} = 3.5$ Hz, 1H, H-6a), 3.79 (t, $J_{\gamma,\beta} = 6.0$ Hz, 2H, H- γ), 3.76 – 3.68 (m, 2H, H-5 & H-6b), 3.59 (dd, $J_{4,5} = 10.0$, $J_{4,3} = 9.0$ Hz, 1H, H-4), 3.58 (dt, $J_{\alpha\text{b},\alpha\text{a}} = 10.0$, $J_{\alpha\text{b},\beta} = 6.0$ Hz, 1H, H- αb), 3.38 (dd, $J_{2,3} = 10.0$, $J_{2,1} = 3.5$ Hz, 1H, H-2), 1.97 (br s, 2H, OH), 1.87 (tdd, $J_{\beta,\gamma} = J_{\beta,\alpha\text{a}} = J_{\beta,\alpha\text{b}} = 6.0$ Hz, 2H, H- β). ^{13}C - $\{^1\text{H}\}$ NMR (CDCl_3 , 90 MHz): δ 137.8 (2C_q), 128.7 (2CH_{arom}), 128.6 (2CH_{arom}), 128.2 (3CH_{arom}), 128.1 (3CH_{arom}), 97.8 (C-1), 80.5 (C-3), 78.1 (C-4), 75.7 (- CH_2Ph), 75.3 (- CH_2Ph), 71.6 (C-5), 66.2 (C- α), 63.7 (C-2), 61.7 (C-6), 60.6 (C- γ), 31.9 (C- β). HRMS (ESI/Q-TOF)

m/z: [M+Na]⁺ Calcd for C₂₃H₂₉N₃O₆Na 466.1949; Found 466.1921. NMR data for **5b**: the 2 diastereoisomers of **5b** can be identified on ¹H NMR spectrum by the presence of characteristic signals of -CH₃ groups at 1.18 (d, *J* = 6.5 Hz, 3 H-γ) and 1.17 ppm (d, *J* = 6.5 Hz, 3 H-γ).

3-hydroxypropyl (2-azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 2-O-acetyl-3-O-benzyl-2-deoxy-α-L-idopyranuronyl)-(1→4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranoside (6a) and 2-hydroxypropyl (2-azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 2-O-acetyl-3-O-benzyl-2-deoxy-α-L-idopyranuronyl)-(1→4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranoside (6b). Obtained from **2** (40 mg, 37.5 μmol) as side products as described for **5a:5b**. Purification by flash column chromatography on silica gel (toluene/acetone, 80:20 to 40:60 gradient) gave **6a** as a colourless oil (8 mg, 7.4 μmol, 20% yield) and **6b** as a colourless oil (5 mg, 4.6 μmol, 12% yield). *R*_f = 0.1 for **6a** (toluene/acetone, 80:20); *R*_f = 0.16 for **6b** (toluene/acetone, 80:20). NMR data for **6a**: ¹H NMR (CDCl₃, 400 MHz): δ 7.50 – 7.17 (m, 20H, Ph), 5.22 (d, *J*_{1,2} = 3.5 Hz, 1H, H-1^B), 4.93 (dd, *J*_{2,3} = 4.0, *J*_{2,1} = 3.5 Hz, 1H, H-2^B), 4.93 (d, *J*_{1,2} = 3.5 Hz, 1H, H-1^A), 4.89 (d, *J*_{1,2} = 4.0 Hz, 1H, H-1^C), 4.85 (d, *J* = 11.5 Hz, 1H, -CH₂Ph), 4.83 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.83 (d, *J* = 10.5 Hz, 1H, -CH₂Ph), 4.80 (d, *J* = 10.5 Hz, 1H, -CH₂Ph), 4.77 (d, *J* = 11.5 Hz, 1H, -CH₂Ph), 4.73 (d, *J*_{5,4} = 3.5 Hz, 1H, H-5^B), 4.72 (d, *J* = 11.5 Hz, 1H, -CH₂Ph), 4.68 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.66 (d, *J* = 11.5 Hz, 1H, -CH₂Ph), 4.40 (dd, *J*_{6a,6b} = 12.0, *J*_{6a,5} = 1.0 Hz, 1H, H-6a^A), 4.25 (dd, *J*_{6b,6a} = 12.0, ³*J*_{6b,5} = 3.5 Hz, 1H, H-6b^A), 4.04 (dd, *J*_{4,3} = 5.0, ³*J*_{4,5} = 4.0 Hz, 1H, H-4^B), 3.94 (dd, *J*_{3,4} = 5.0, *J*_{3,2} = 4.0 Hz, 1H, H-3^B), 3.92-3.78 (m, 7H, H-αa, H-4^A, H-5^A, H-3^A, H-3^C & 2 H-γ), 3.78 – 3.68 (m, 2H, H-5^C & H-6a^C), 3.59 (dd, *J*_{4,5} = 10.0, ³*J*_{4,3} = 9.0 Hz, 1H, H-4), 3.65-3.55 (m, 2H, H-6b^C & H-αb), 3.54-3.49 (m, 4H, -COOCH₃ & H-4^C), 3.41 (dd, *J*_{2,3} = 9.5, *J*_{2,1} = 3.5 Hz, 1H, H-2^A), 3.21 (dd, *J*_{2,3} = 10.0, *J*_{2,1} = 3.5 Hz, 1H, H-2^C), 2.12 (s, 3H, -COCH₃), 2.08 (s, 3H, -COCH₃), 1.90 (tdd, *J*_{β,γ} = *J*_{β,αa} = *J*_{β,αb} = 6.0 Hz, 2H, H-β). ¹³C-{¹H} NMR (CDCl₃, 90 MHz): δ 170.9 (CH₃C=O), 170.1 (CH₃C=O), 169.6 (CH₃C=O), 138.0 (C_q), 137.9 (C_q), 137.7 (C_q), 137.4 (C_q), 128.6 (6CH_{arom}), 128.3 (3CH_{arom}), 128.2 (2CH_{arom}), 128.1 (3CH_{arom}), 128.0 (CH_{arom}), 127.9 (2CH_{arom}), 127.8 (2CH_{arom}), 127.6 (CH_{arom}), 98.2 (C-1^B), 97.9 (C-1^C), 97.6 (C-1^A), 79.7 (C-3^C), 78.7 (C-3^A), 77.8 (C-4^C), 75.6 (C-4^A), 75.4 (-CH₂Ph), 75.0 (2x-CH₂Ph), 74.3 (C-3^B), 73.5 (-CH₂Ph), 73.1 (C-4^B), 72.6 (C-5^C), 69.3 (C-5^A), 69.1 (C-2^B), 66.6 (C-α), 63.6 (C-2^A), 63.4 (C-2^C), 62.4 (C-6^A), 61.5 (C-6^C), 60.7 (C-γ), 52.2 (-COOCH₃), 31.9 (C-β), 21.0 (2-COCH₃). HRMS (ESI/Q-TOF) m/z: [M+Na]⁺ Calcd for C₅₄H₆₄N₆O₁₈Na 1107.4169; Found 1107.4199. NMR data for **6b**: inseparable mixture of diastereoisomers (1:1 ratio); ¹H NMR (CDCl₃, 360 MHz): δ 7.43 – 7.17 (m, 20H, Ph); 5.24 (m, 1H, H-1^B); 4.98-4.89 (m, 3H, H-2^B, H-1^A & H-1^C); 4.87-4.60 (m, 4x-CH₂Ph & H-5^B); 4.46-4.35 (m, 1H, H-6a^A); 4.28-4.20 (m, 1H, H-6b^A); 4.08-3.99 (m, 2H, H-4^B & H-β); 3.98-3.36 (m, 5H, H-3^A, H-3^B, H-3^C, H-4^A, H-5^A); 3.78 – 3.68 (m, 2.5H, H-5^C, H-6a^C & H-αa dia 1); 3.65-3.45 (m, 6H, H-6b^C, H-4^C, -COOCH₃ & H-αa dia 2); 3.44-3.38 (m, 1H, H-2^A); 3.28 (dd, *J*_{αb,αa} = 10.0 Hz, *J*_{αb,β} = 8.0 Hz, 0.5 H, H-αb dia 1); 3.21 (dd, *J*_{2,3} = 10.5, *J*_{2,1} = 3.5 Hz, 1H, H-2^C); 2.65-2.57 (br, 1H, -OH dia 1 or dia 2); 2.65-2.48 (br, 1H, -OH dia 1 or dia 2); 2.12 (s, 3H, -COCH₃); 2.08 (s, 3H, -COCH₃); 1.80-1.70 (br, 1H, -OH); 1.21-1.17 (m, 3H, H-γ). ¹³C-{¹H} NMR (CDCl₃, 90 MHz): δ 170.8 (CH₃C=O); 170.1 (CH₃C=O); 169.6 (CH₃C=O); 138.0 (C_q); 137.9 (C_q); 137.7 (C_q); 137.4 (C_q); 128.6 (6CH_{arom}); 128.4 (2CH_{arom}); 128.3 (2CH_{arom}); 128.2 (CH_{arom}); 128.1 (3CH_{arom}); 128.0 (CH_{arom}); 127.9 (2CH_{arom}); 127.8 (2CH_{arom}); 127.7 (CH_{arom}); 98.9 (C-1^A); 98.1 (C-1^B); 97.9 (C-1^C); 79.8 (C-3^C); 78.5 (C-3^A); 77.8 (C-4^C); 75.6 (C-4^A); 75.4 (C-α dia 1 & -CH₂Ph); 75.0 (2x-CH₂Ph); 74.6 (C-α dia 2); 74.5 (C-3^B); 73.5 (-CH₂Ph); 73.1 (C-4^B); 72.6 (C-5^C); 69.6 (C-5^A); 69.4 (C-5^B); 69.2 (C-2^B); 66.7 (C-β dia 1); 66.7 (C-β dia 2); 63.8 (C-2^A dia 1); 63.7 (C-2^A dia 2); 63.4 (C-2^C); 62.3 (C-6^A); 61.5 (C-6^C); 52.2 (-COOCH₃); 21.0 (2xCH₃C=O); 19.0 (C-γ dia 2); 18.5 (C-γ dia 1). HRMS (ESI/Q-TOF) m/z: [M+Na]⁺ Calcd for C₅₄H₆₄N₆O₁₈Na 1107.4169; Found 1107.4177.

3-hydroxypropyl 2-azido-3,4,6-tri-O-benzyl-2-deoxy-α-D-glucopyranoside (8a) and 2-hydroxypropyl 2-azido-3,4,6-tri-O-benzyl-2-deoxy-α-D-glucopyranoside (8b). Obtained from **7** (72 mg, 140 μmol) as described for **5a:5b**. Purification by flash column chromatography on silica gel (toluene/acetone, 100:0 to 85:15 gradient) gave **8a** as a colourless oil (46 mg, 86 μmol, 62% yield) and **8b** as colourless oil (16 mg, 30 μmol, 22 % yield). *R*_f = 0.2 for **8a** (toluene/Acetone 85:15); *R*_f = 0.35 for **8b** (toluene/acetone 85:15). NMR data for **8a**: ¹H NMR (CDCl₃, 300 MHz): δ 7.41 – 7.27 (m, 13H, Ph), 7.20 – 7.12 (m, 2H, Ph), 4.94 (d, *J*_{1,2} = 3.5 Hz, 1H, H-1), 4.88 (s, 2H, -CH₂Ph), 4.81 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.62 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 4.52 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.51 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 3.97 (dd, *J*_{3,2} = 10.0, *J*_{3,4} = 9 Hz, 1H, H-3), 3.91 (dt, *J*_{αa,αb} = 10.0, *J*_{αa,β} = 5.5 Hz, 1H, H-αa), 3.83 (ddd, *J*_{5,4} = 10.0, *J*_{5,6a} = 3.5, *J*_{5,6b} = 2.0 Hz, 1H, H-5), 3.79 (t, *J*_{γ,β} = 6.0 Hz, 2H, H-γ), 3.74 (dd, *J*_{6a,6b} = 11.0, *J*_{6a,5} = 3.5 Hz, 1H, H-6a), 3.69 (dd, *J*_{4,5} = 10.0, *J*_{4,3} = 9.0 Hz, 1H, H-4), 3.67 (dd, *J*_{6b,6a} = 11.0, *J*_{6b,5} = 2.0 Hz, 1H, H-6b), 3.61 (dt, *J*_{αb,αa} = 10.0, *J*_{αb,β} = 6.0 Hz, 1H, H-αb), 3.43 (dd, *J*_{2,3} = 10.0, *J*_{2,1} = 3.5 Hz, 1H, H-2), 1.87 (tdd, *J*_{β,γ} = *J*_{β,αa} = *J*_{β,αb} = 6.0 Hz, 3H, H-β et OH). ¹³C-{¹H} NMR (CDCl₃, 75 MHz): δ 137.9 (2C_q), 137.8 (C_q), 128.6 (4CH_{arom}), 128.5 (2CH_{arom}), 128.2 (2CH_{arom}), 128.0 (4CH_{arom}), 127.9 (3CH_{arom}), 97.8 (C-1), 80.7 (C-3), 78.3 (C-4), 75.6 (-CH₂Ph), 75.2 (-CH₂Ph), 73.7 (-CH₂Ph), 70.9 (C-5), 68.4 (C-6), 66.3 (C-α), 63.7 (C-2), 60.7 (C-γ), 31.9 (C-β). HRMS (ESI/Q-TOF) m/z: [M+Na]⁺ Calcd for C₃₀H₃₅N₃O₆Na 556.2418; Found 556.2396. NMR data for **8b**: mixture of 2 diastereoisomers (6:4 ratio). Major

diastereoisomer: ¹H NMR (CDCl₃, 300 MHz): δ 7.41 – 7.27 (m, 13H, Ph), 7.21 – 7.10 (m, 2H, Ph), 4.96 (d, *J*_{1,2} = 3.5 Hz, 1H, H-1), 4.88 (s, 2H, -CH₂Ph), 4.80 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.62 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 4.51 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.49 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 4.04 – 3.94 (m, 2H, H-3 & H-β), 3.86 (ddd, *J*_{5,4} = 10.0, *J*_{5,6a} = 4.0, *J*_{5,6b} = 2.0 Hz, 1H, H-5), 3.78-3.61 (m, 2H, H-6a & H-4), 3.57 (dd, *J*_{αa,αb} = 10.5, *J*_{αa,β} = 4.0 Hz, 1H, H-αa), 3.52 (dd, *J*_{αb,αa} = 10.5, *J*_{αb,β} = 7.5 Hz, 1H, H-αb), 3.42 (dd, *J*_{2,3} = 10.0, *J*_{2,1} = 3.5 Hz, 1H, H-2), 1.17 (d, *J*_{γ,β} = 6.5 Hz, 3H, H-γ). ¹³C-{¹H} NMR (CDCl₃, 75 MHz): δ 137.9 (2C_q), 137.8 (C_q), 128.6 (6CH_{arom}), 128.2 (2CH_{arom}), 128.0 (4CH_{arom}), 127.9 (3CH_{arom}), 98.3 (C-1), 80.4 (C-3), 78.3 (C-4), 75.7 (-CH₂Ph), 75.2 (-CH₂Ph), 74.6 (C-α), 73.7 (-CH₂Ph), 71.2 (C-5), 68.3 (C-6), 66.3 (C-β), 63.7 (C-2), 18.9 (C-γ). Minor diastereoisomer: ¹H NMR (CDCl₃, 300 MHz): δ 7.41 – 7.27 (m, 13H, Ph), 7.21 – 7.10 (m, 2H, Ph), 4.96 (d, *J*_{1,2} = 3.5 Hz, 1H, H-1), 4.88 (s, 2H, -CH₂Ph), 4.80 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.61 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 4.51 (d, *J* = 11.0 Hz, 1H, -CH₂Ph), 4.50 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 4.04 – 3.94 (m, 2H, H-3 & H-β), 3.86 (ddd, *J*_{5,4} = 10.0, *J*_{5,6a} = 4.0, *J*_{5,6b} = 2.0 Hz, 1H, H-5), 3.78 – 3.61 (m, 3H, H-6a & H-4 & H-αa), 3.41 (dd, *J*_{2,3} = 10.0, *J*_{2,1} = 3.5 Hz, 1H, H-2), 3.29 (dd, *J*_{αb,αa} = 10.0, *J*_{αb,β} = 8.0 Hz, 1H, H-αb), 1.16 (d, *J*_{γ,β} = 6.5 Hz, 3H, H-γ). ¹³C NMR (CDCl₃, 75 MHz): δ 137.9 (2C_q), 137.8 (C_q), 128.6 (6CH_{arom}), 128.2 (2CH_{arom}), 128.0 (4CH_{arom}), 127.9 (3CH_{arom}), 99.1 (C-1), 80.4 (C-3), 78.3 (C-4), 75.7 (-CH₂Ph), 75.2 (-CH₂Ph), 75.1 (C-α), 73.7 (-CH₂Ph), 71.1 (C-5), 68.4 (C-6), 66.7 (C-β), 63.8 (C-2), 18.6 (C-γ). HRMS (ESI/Q-TOF) *m/z*: [M+Na]⁺ Calcd for C₃₀H₃₅N₃O₆Na 556.2418; Found 556.2396).

3-(dihydroxybonyl)propyl 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-*D*-glucopyranoside (**10**). Obtained from **7** (74 mg, 144 μmol) as described for **5a,5b** but omitting the oxidative treatment with H₂O₂/NaOH. Purification by flash column chromatography on silica gel (toluene/acetone, 100:0 to 80:20 gradient) gave **10** as a yellowish oil (12 mg, 21 μmol, 15% yield) in addition to **8a** (37 mg, 69 μmol, 48% yield) and **8b** (14 mg, 26 μmol, 18% yield) and. *R*_f = 0.14 for **10** (toluene/acetone 85:15). ¹H NMR (CDCl₃, 300 MHz): δ 7.43 – 7.27 (m, 13H, Ph), 7.20 – 7.10 (m, 2H, Ph), 4.93 (d, *J*_{1,2} = 3.5 Hz, 1H, H-1), 4.92-4.83 (m, 2H, -CH₂Ph), 4.81 (d, *J* = 10.5 Hz, 1H, -CH₂Ph), 4.62 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 4.52 (d, *J* = 10.5 Hz, 1H, -CH₂Ph), 4.51 (d, *J* = 12.0 Hz, 1H, -CH₂Ph), 3.98 (dd, *J*_{3,2} = 10.0, *J*_{3,4} = 9 Hz, 1H, H-3), 3.82 (ddd, *J*_{5,4} = 10.0, *J*_{5,6a} = 3.5, *J*_{5,6b} = 2.0 Hz, 1H, H-5), 3.74 (dt, *J*_{αa,αb} = 10.0, *J*_{αa,β} = 6.0 Hz, 1H, H-αa), 3.74 (dd, *J*_{6a,6b} = 11.0, *J*_{6a,5} = 3.5 Hz, 1H, H-6a), 3.68 (dd, *J*_{4,5} = 10.0, *J*_{4,3} = 9.0 Hz, 1H, H-4), 3.66 (dd, *J*_{6b,6a} = 11.0, *J*_{6b,5} = 2.0 Hz, 1H, H-6b), 3.49 (dt, *J*_{αb,αa} = 10.0, *J*_{αb,β} = 6.5 Hz, 1H, H-αb), 3.43 (dd, *J*_{2,3} = 10.0, *J*_{2,1} = 3.5 Hz, 1H, H-2), 1.76 (m, 3H, H-β), 0.91 (t, *J*_{γ,β} = 7.0 Hz, 2H, H-γ). ¹¹B NMR (CDCl₃, 96 MHz): δ 32.2. ¹³C-{¹H} NMR (CDCl₃, 75 MHz): δ 138.0 (C_q), 137.9 (C_q), 137.8 (C_q), 128.6 (3CH_{arom}), 128.5 (2 CH_{arom}), 128.2 (CH_{arom}), 128.1 (2CH_{arom}), 128.0 (4CH_{arom}), 127.9 (2CH_{arom}), 97.9 (C-1), 80.7 (C-3), 78.3 (C-4), 75.7 (-CH₂Ph), 75.2 (-CH₂Ph), 73.7 (-CH₂Ph), 71.0 (C-5), 70.5 (C-α), 68.4 (C-6), 63.8 (C-2), 24.1 (C-β), 12.9-11.2 (m, C-γ). HRMS were obtained by infusion of methanolic solutions of boronic acid **10** leading to the spontaneous formation of mono and dimethyl ester: HRMS monomethyl ester (ESI/Q-TOF) *m/z*: [M+Na]⁺ Calcd for C₃₁H₃₈BN₃O₇Na 598.2695; Found 598.2746; HRMS dimethyl ester (ESI/Q-TOF) *m/z*: [M+Na]⁺ Calcd for C₃₂H₄₀BN₃O₇Na 612.2852; Found 612.2884.

Supporting Information

- PhBCl₂ ¹H NMR titration and NMR data for PhBCl₂/PhSiMe₃ mixture.
 - ¹H and ¹³C-{¹H} NMR data for compounds **3a**, **4a**, **5a**, **5b**, **6a**, **6b**, **8a** and **8b**
 - HRMS data for compound **9**
 - ¹H, ¹³C-{¹H}, COSY, ¹H-¹³C HSQC, ¹H-¹³C HMBC and HRMS data for compound **10**
- FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: **3a**, **4a**, **5a** + **5b**, **6a**, **6b**, **8a**, **8b** and **10**, as well as for PhBCl₂ and the titration of the PhBCl₂/PhSiMe₃ mixture. See FID for Publication for additional information.

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References

- [1] Jensen, H. H.; Nordstrom, M.; Bols, M. The disarming effect of the 4,6-acetal group on glycoside reactivity: torsional or electronic? *J. Am. Chem. Soc.* **2004**, *126*, 9205–9213.
- [2] Adero, P. O.; Amarasekara, H.; Wen, P.; Bohé, L.; Crich, D. The experimental evidence in support of glycosylation mechanisms at the SN1–SN2 interface. *Chem. Rev.* **2018**, *118*, 8242–8284.
- [3] Dimakos, V.; Taylor, M. S. Site-selective functionalization of hydroxyl groups in carbohydrate derivatives. *Chem. Rev.* **2018**, *118*, 11457–11517.
- [4] Janssens, J.; Risseeuw, M. D. P.; Van der Eycken, J.; Van Calenbergh, S. Regioselective ring opening of 1,3-dioxane-type acetals in carbohydrates. *Eur. J. Org. Chem.* **2018**, 6405–6431.
- [5] Ohlin, M.; Johnsson, R.; Ellervik, U. Regioselective reductive openings of 4,6-benzylidene acetals: synthetic and mechanistic aspects. *Carbohydr. Res.* **2011**, *346*, 1358–1370.
- [6] Doukas, H. M.; Fontaine, T. D. Cleavage of sapogenin terminal rings with lithium aluminium hydride. *J. Am. Chem. Soc.* **1951**, *73*, 5917–5918.
- [7] Eliel, E. L.; Rerick, M. Reduction of acetals to ethers by means of lithium aluminum hydride-aluminum chloride. *J. Org. Chem.* **1958**, *23*, 1088.
- [8] Eliel, E. L.; Badding, V. G.; Rerick, M. N. Reduction with metal hydrides. XII Reduction of acetals and ketals with lithium aluminum hydride-aluminum chloride. *J. Am. Chem. Soc.* **1962**, *84*, 2371–2377.
- [9] Leggetter, B. E.; Brown, R. K. The influence of substituents on the ease and direction of ring opening in the LiAlH₄ reductive cleavage of substituted 1,3-dioxolanes. *Can. J. Chem.* **1964**, *42*, 990–1004.
- [10] Leggetter, B. E.; Diner, U. E.; Brown, R. K. The relative ease of reductive cleavage of 1,3-dioxolanes and 1,3-dioxanes in ether solution by LiAlH₄-AlCl₃. *Can. J. Chem.* **1964**, *42*, 2113–2117.
- [11] Bhattacharjee, S. S.; Gorin, P. A. J. Hydrogenolysis of carbohydrate acetals, ketals and cyclic orthoesters with lithium aluminum hydride - aluminum trichloride. *Can. J. Chem.* **1969**, *47*, 1195–1206.
- [12] Lipták, A.; Jodál, I.; Nánási, P. Stereoselective ring-cleavage of 3-O-benzyl- and 2,3-di-O-benzyl-4,6-O-benzylidenehexopyranoside derivatives with the LiAlH₄-AlCl₃ reagent. *Carbohydr. Res.* **1975**, *44*, 1–11.
- [13] Horne, D. A.; Jordan, A. An efficient reduction of acetals and ketals to methyl ethers. *Tetrahedron Lett.* **1978**, *14*, 1357–1358.
- [14] Garegg, P. J.; Hultberg, H. A novel, reductive ring-opening of carbohydrate benzylidene acetals, with unusual regioselectivity. *Carbohydr. Res.* **1981**, *93*, C10–C11.
- [15] Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. Reductive ring openings of carbohydrate benzylidene acetals using borane-tyrimethylamine and aluminum chloride. Regioselectivity and solvent dependence. *J. Carbohydr. Chem.* **1983**, *2*, 305–311.
- [16] Mikami, T.; Asano, H.; Mitsunobu, O. Acetal-bond cleavage of 4,6-O-alkylidenehexopyranosides by diisobutylaluminum hydride and by lithium triethylborohydride-TiCl₄. *Chem. Lett.* **1987**, *16*, 2033–2036.
- [17] Jiang, L.; Chang, T-H. Borane/Bu₂BOTf: a mild reagent for the regioselective reductive ring opening of benzylidene acetals in carbohydrates. *Tetrahedron Lett.* **1998**, *39*, 355–358.
- [18] Bartels, B.; Hunter, R. A selectivity study of activated ketal reduction with borane dimethyl sulfide. *J. Org. Chem.* **1993**, *58*, 6756–6765.
- [19] Johnsson, R.; Cukalevski, R.; Dragén, F.; Ivanisevic, D.; Johansson, I.; Petersson, L.; Wettergren, E. E.; Bo Yam, K.; Yang, B.; Ellervik, U. Reductive openings of benzylidene acetals. Kinetic studies of borane and alane activation by Lewis acids. *Carbohydr. Res.* **2008**, *343*, 2997–3000.
- [20] Johnsson, R.; Olsson, D.; Ellervik, U. Reductive openings of acetals: explanation of regioselectivity in borane reductions by mechanistic studies. *J. Org. Chem.* **2008**, *73*, 5226–5232.
- [21] Johnsson, R.; Ohlin, M.; Ellervik, U. Reductive openings of benzylidene acetals revisited: a mechanistic scheme for regio- and stereoselectivity. *J. Org. Chem.* **2010**, *75*, 8003–8011.
- [22] Lee, I-C.; Zulueta, M. M. L.; Shie, C.-R.; Arcob, S. D.; Hung, S.-C. Deuterium-isotope study on the reductive ring opening of benzylidene acetals. *Org. Biomol. Chem.* **2011**, *9*, 7655–7658.
- [23] DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. A Method for the selective reduction of carbohydrate 4,6-O-benzylidene acetals. *Tetrahedron Lett.* **1995**, *36*, 669–672.
- [24] Sakagami, M.; Hamana, H. A selective ring opening reaction of 4,6-O-benzylidene acetals in carbohydrates using trialkylsilane derivatives. *Tetrahedron Lett.* **2000**, *41*, 5547–5551.
- [25] Debenham, S. D.; Toone, E. J. Regioselective reduction of 4,6-O-benzylidenes using triethylsilane and BF₃·Et₂O. *Tetrahedron: Asymmetry* **2000**, *11*, 385–387.
- [26] Shie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S.-C. Cu(OTf)₂ as an efficient and dual-purpose catalyst in the regioselective reductive ring opening of benzylidene acetals. *Angew. Chem. Int. Ed.* **2005**, *44*, 1665–1668.
- [27] Panchadhayee, R.; Misra, A. K. Regioselective reductive ring opening of benzylidene acetals using triethylsilane and iodine. *Synlett* **2010**, 1193.
- [28] Sun, B.; Srinivasan, B.; Huang, X. Pre-activation-based one-pot synthesis of an alpha-(2,3)-sialylated core-fucosylated complex type Bi-antennary N-glycan dodecasaccharide. *Chem. Eur. J.* **2008**, *14*, 7072–7081.

- [29] Zhu, C.-J.; Yi, H.; Chen, G.-R.; Xie, J. Synthesis of novel photolabile glycosides from methyl 4,6-O-(*o*-nitro)benzylidene- α -D-glycopyranosides. *Tetrahedron* **2008**, *64*, 10687-10693.
- [30] Kojima, M.; Nakamura, Y.; Ito, Y.; Takeuchi, S. Ring cleavage reactions of methyl α -D-allopyranoside derivatives with phenylboron dichloride and triethylsilane. *Molecules* **2011**, *16*, 10303-10313.
- [31] Wright, J. A.; Yu, J.; Spencer, J. B. Sequential removal of the benzyl-type protecting groups PMB and NAP by oxidative cleavage using CAN and DDQ. *Tetrahedron Lett.* **2001**, *42*, 4033-4036.
- [32] Xue, J.; Han, Z.; Li, G.; Emmanuel, K. A.; McManus, C. L.; Sui, Q.; Ge, D.; Gao, Q.; Cai, L. Synthesis of monophosphorylated lipid A precursors using 2-naphthylmethyl ether as a protecting group. *Beilstein J. Org. Chem.* **2020**, *16*, 1955-1962.
- [33] Saito, T.; Fujiwara, K.; Sano, Y.; Sato, T.; Kondo, Y.; Akiba, U.; Ishigaki, Y.; Katoono, R.; Suzuki, T. An improved synthesis of the C42-C52 segment of ciguatoxin 3C. *Tetrahedron Lett.* **2018**, *59*, 1372-1376.
- [34] Asano, S.; Tanaka, H.-N.; Imamura, A.; Ishida, H.; Ando, H. *p*-*tert*-Butyl groups improve the utility of aromatic protecting groups in carbohydrate synthesis. *Org. Lett.* **2019**, *21*, 4197-4200.
- [35] Kojima, M.; Nakamura, Y.; Takeuchi, S. A practical fluororous benzylidene acetal protecting group for a quick synthesis of disaccharides. *Tetrahedron Lett.* **2007**, *48*, 4431-4436.
- [36] Madalinski, M.; Stoll, M.; Dietrich, U.; Kunz, H. A selectively deprotectable 2,6-diaminogalactose scaffold for the solid-phase synthesis of potential RNA ligands. *Synthesis* **2008**, *7*, 1106-1120.
- [37] Bera, S.; Linhardt, R. J. Design and synthesis of unnatural heparosan and chondroitin building blocks. *J. Org. Chem.* **2011**, *76*, 3181-3193.
- [38] Nagano, T.; Pospíšil, J.; Chollet, G.; Schulthoff, S.; Hickmann, V.; Moulin, E.; Herrmann, J.; Müller, R.; Fürstner, A. Total synthesis and biological evaluation of the cytotoxic resin glycosides Ipomoeassin A-F and analogues. *Chem. Eur. J.* **2009**, *15*, 9697-9706.
- [39] Miyachi, A.; Miyazaki, A.; Shingu, Y.; Matsuda, K.; Dohi, H.; Nishida, Y. Synthesis and absolute structures of *Mycoplasma pneumoniae* beta-glyceroglycolipid antigens. *Carbohydr. Res.* **2009**, *344*, 36-43.
- [40] Hagiwara, M.; Dohi, M.; Nakahara, Y.; Komatsu, K.; Asahina, Y.; Ueki, A.; Hojo, H.; Nakahara, Y.; Ito, Y. Synthesis of biantennary complex-type nonasaccharyl Asn building blocks for solid-phase glycopeptide synthesis. *J. Org. Chem.* **2011**, *76*, 5229-5239.
- [41] Hojo, H.; Tanaka, H.; Hagiwara, M.; Asahina, Y.; Ueki, A.; Katayama, H.; Nakahara, Y.; Yoneshige, A.; Matsuda, J.; Ito, Y.; Nakahara, Y. Chemoenzymatic synthesis of hydrophobic glycoprotein: synthesis of saposin C carrying complex-type carbohydrate. *J. Org. Chem.* **2012**, *77*, 9437-9446.
- [42] Gavard, O.; Alais, J.; Bascou, A.; Hersant, Y.; Duverger, V.; Dilhas, A.; Bonnaffé, D. Efficient preparation of three building blocks for the synthesis of heparan sulfate fragments: Towards the combinatorial synthesis of oligosaccharides from hypervariable regions. *Eur. J. Org. Chem.* **2003**, 3603-3620.
- [43] Dilhas, A.; Bonnaffé, D. PhBCl_2 promoted reductive opening of 2',4'-O-*p*-methoxybenzylidene: new regioselective differentiation of position 2' and 4' of α -L-iduronyl moieties in disaccharide building blocks. *Tetrahedron Lett.* **2004**, *45*, 3643-3645.
- [44] Bonnaffé, D. Bioactive synthetic Heparan Sulfate and Heparin derivatives: from long fragments mimetics to chimeras' C. *R. Chimie* **2011**, *14*, 29-73.
- [45] Debarnot, C.; Monneau, Y. R.; Roig-Zamboni, V.; Delaunay, V.; Le Narvor, C.; Richard, E.; Hénault, J.; Goulet, A.; Fadel, F.; Vivès, R. R.; Priem, B.; Bonnaffé, D.; Lortat-Jacob, H.; Bourne, Y. Substrate binding mode and catalytic mechanism of human heparan sulfate D-glucuronyl C5 epimerase. *Proc. Natl. Acad. Sci. USA* **2019**, *116* (14), 6760-6765.
- [46] Ekholm, F. S.; Ardá, A. Eklund, P.; André, S.; Gabius, H.-J.; Jiménez-Barbero, J.; Leino, R. Studies related to Norway spruce galactoglucomannans: chemical synthesis, conformation analysis, NMR spectroscopic characterization, and molecular recognition of model compounds. *Chem. Eur. J.* **2012**, *18*, 14392-14405.
- [47] Collot, M.; Wilson, I. B. H.; Bublin, M.; Hoffmann-Sommergruber, K.; Mallet, J.-M. Synthesis of cross-reactive carbohydrate determinants fragments as tools for in vitro allergy diagnosis. *Bioorg. Med. Chem.* **2011**, *19*, 1306-1320.
- [48] Tani, S.; Sawadi, S.; Kojima, M.; Akai, S.; Sato, K.-I. A novel method for regioselective ring-opening reduction of 4,6-O-benzylidene hexopyranoside derivatives using CoCl_2 and $\text{BH}_3\cdot\text{THF}$. *Tetrahedron Lett.* **2007**, *48*, 3103-3104.
- [49] Zamyatina, A.; Sekljic, H.; Brade, H.; Kosma, P. Synthesis and purity assessment of tetra- and pentaacyl lipid A of *Chlamydia* containing (*R*)-3-hydroxyicosanoic acid. *Tetrahedron* **2004**, *60*, 12113-12137.
- [50] Cohen, J. L.; Chamberlin, A. R. Synthesis of the dysiherbaine tetrahydropyran core employing a tethered aminohydroxylation reaction. *Tetrahedron Lett.* **2007**, *48*, 2533-2536.
- [51] Vesely, J.; Rydner, L.; Oscarson, S. Variant synthetic pathway to glucuronic acid-containing di- and trisaccharide thioglycoside building blocks for continued synthesis of *Cryptococcus neoformans* capsular polysaccharide structures. *Carbohydr. Res.* **2008**, *343*, 2200-2208.
- [52] Komori, T.; Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. Study on systematizing the synthesis of the a-series ganglioside glycans GT1a, GD1a, and GM1 using the newly developed N-Troc-protected GM3 and GalN intermediates. *Carbohydr. Res.* **2009**, *344*, 1453-1463 Special Issue: SI.
- [53] Koizumi, A.; Yamano, K.; Schweizer, F.; Takeda, T.; Kiuchi, F.; Hada, N. Synthesis of the carbohydrate moiety from the parasite *Echinococcus multilocularis* and their antigenicity against human sera. *Eur. J. Med. Chem.* **2011**, *46*, 1768-1778.
- [54] Muñoz-García, J. C.; López-Prados, J.; Angulo, J.; Díaz-Contreras, I.; Reichardt, H.; de Paz, J.-L.; Martín-Lomas, M.; Nieto, P. M. Effect of the substituents of the neighboring ring in the conformational equilibrium of iduronate in heparin-like trisaccharides. *Chem. Eur. J.* **2012**, *18*, 16319-16331.
- [55] Lemetais, A.; Bourdreux, Y.; Lesot, P.; Farjon, J.; Beau, J.-M. Synthesis of a *Mycobacterium tuberculosis* tetra-acylated sulfolipid analogue and characterization of the chiral acyl chains using anisotropic NAD 2D-NMR spectroscopy. *J. Org. Chem.* **2013**, *78*, 7648-7657.

- [56] Wakao, M.; Obata, R.; Miyachi, K.; Kaitsubata, Y.; Kondo, T.; Sakami, C.; Suda, Y. Synthesis of a chondroitin sulfate disaccharide library and a GAG-binding protein interaction analysis. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1407-1411.
- [57] Li, T.; Huang, M.; Liu, L.; Wang, S.; Moremen, K. W.; Boons, G.-J. Divergent chemoenzymatic synthesis of asymmetrical-core-fucosylated and core-unmodified N-glycans. *Chem. Eur. J.* **2016**, *22*, 18742-18746.
- [58] Paramasivam, S.; Fairbanks, A. J. Rapid synthesis of N-glycan oxazolines from locust bean gum via the Lafont rearrangement. *Carbohydr. Res.* **2019**, *477*, 11-19.
- [59] Aboussafy, C. L.; Andersen Gersby, L. B.; Molinaro, A.; Newman, M.-A.; Lowary, T. L. A convergent route to enantiomers of the bicyclic monosaccharide bradyrhizose leads to insight into the bioactivity of an immunologically silent lipopolysaccharide. *J. Org. Chem.* **2019**, *84*, 14-41.
- [60] Poh, Z. W.; Gan, C. H.; Lee, E. J.; Guo, S.; Yip, G. W.; Lam, Y. Divergent synthesis of chondroitin sulfate disaccharides and identification of sulfate motifs that inhibit triple negative breast cancer. *Scientific Rep.* **2015**, *5*, Article Number: 14355.
- [61] Koizumi, A.; Hada, N.; Kaburaki, A.; Yamano, K.; Schweizer, F.; Tadahiho, T. Synthetic studies on the carbohydrate moiety of the antigen from the parasite *Echinococcus multilocularis*. *Carbohydr. Res.* **2009**, *344*, 856-868.
- [62] Fang, T.; Mo, K.-F.; Boons, G.-J. Stereoselective assembly of complex oligosaccharides using anomeric sulfonium ions as glycosyl donors. *J. Am. Chem. Soc.* **2012**, *134*, 7545-7552.
- [63] Yadav, R.; Ben-Arye, S. L.; Subramani, B.; Padler-Karavani, V.; Kikkeri, R. Screening of Neu5Ac- α -(2-6)-Gal isomer preferences of siglecs with a sialic acid microarray. *Org. Biomol. Chem.* **2016**, *14*, 10812-10815.
- [64] Hadi, T.; Pfeffer, J. M.; Clarke, A. J.; Tanner, M. E. Water-soluble substrates of the peptidoglycan-modifying enzyme O-acetylpeptidoglycan esterase (Ape1) from *Neisseria gonorrhoeae*. *J. Org. Chem.* **2011**, *76*, 1118-1125.
- [65] Zhang, Y.; Gaekwad, J.; Wolfert, M. A.; Boons, G.-J. Innate immune responses of synthetic lipid A derivatives of *Neisseria meningitidis*. *Chem. Eur. J.* **2008**, *14*, 558-569.
- [66] Yagami, N.; Vibhute, A. M.; Tanaka, H.-N.; Komura, N.; Imamura, A.; Ishida, H.; Ando, H. Stereoselective Synthesis of Diglycosyl Diacylglycerols with Glycosyl Donors Bearing a β -Stereodirecting 2,3-Naphthalenedimethyl Protecting Group. *J. Org. Chem.* **2020**, *85*, 16166-16181.
- [67] El Masri, R.; Seffouh, A.; Lortat-Jacob, H.; Vivès, R. R. The "in and out" of glucosamine 6-O-sulfation: the 6th sense of heparan sulfate. *Glycoconj. J.*, **2017**, *34*, 285-298.
- [68] Lee, H.-Y.; Yeh, B.-W.; Chan, T.-C.; Yang, K.-F.; Li, W.-M.; Huang, C.-N.; Ke, H.-L.; Li, C.-C.; Yeh, H.-C.; Liang, P.-I.; Shiue, Y.-L.; Wu, W.-J.; Li, C.-F. Sulfatase-1 overexpression indicates poor prognosis in urothelial carcinoma of the urinary bladder and upper tract. *Oncotarget*, **2017**, *8*, 47216-47229.
- [69] Soundararajan, R.; Matteson, D. S. Hydroboration with boron halides and trialkylsilanes. *J. Org. Chem.* **1990**, *55*, 2274-2275.
- [70] Soundararajan, R.; Matteson, D. S. Hydroboration with haloborane/trialkylsilane mixtures. *Organometallics* **1995**, *14*, 4157-4166.
- [71] Brown, H. C.; Midland, M. M.; Kabalka, G. W. The stoichiometrically controlled reaction of organoboranes with oxygen under very mild conditions to achieve essentially quantitative conversion into alcohols. *J. Am. Chem. Soc.* **1971**, *93*, 1024-2025.
- [72] Brown, H. C.; Midland, M. M.; Levy, A. B. Facile reaction of alkyl- and aryl-dichloroboranes with organic azides. A general stereospecific synthesis of secondary amines. *J. Am. Chem. Soc.* **1973**, *97*, 2394-2396.
- [73] Imperio, D.; Del Grosso, E.; Fallarini, S.; Lombardi, G.; Panza, L. Synthesis of sugar-boronic acid derivatives: a class of potential agents for boron neutron capture therapy. *Org. Lett.* **2017**, *19*, 1678-1681.
- [74] Chaudhari, S. R. Screening and assignment of phenylboronic acid and its anhydride formation by NMR spectroscopy. *Chem. Phys. Lett.* **2015**, *634*, 95-97.
- [75] Brown, H. C.; Ravindran, N. Reaction of representative olefins with dichloroborane ethyl etherate induced by boron trichloride. An exceptionally simple, general synthesis of alkyl-dichloroboranes and alkylboronic acid derivatives via hydroboration. *J. Am. Chem. Soc.* **1973**, *95*, 2396-2397.
- [76] Roche, M. J.; Madren, S. M.; Tallent, C. R.; Carroll, F. I.; Seltzman, H. H. Mild acetal cleavage using B-chlorocatecholborane in the synthesis of rearrangement-sensitive 2-arachidonoylglycerol. *Tetrahedron Lett.* **2012**, *53*, 3825-3827.
- [77] Kaufmann, D. Borylierung von Arylsilanen, I Ein allgemeiner, einfacher und selektiver Zugang zu Phenyl-dihalogenboranen. *Chem. Ber.* **1987**, *120*, 853-854.
- [78] H. C. Brown, H. C.; Salunkhe, A. M.; Argade, A. B. Organoboranes. 55. Improved procedure for the conversion of representative achiral and chiral alkyl-, (E)-1-alkenyl-, (Z)-1-alkenyl-, and arylboronates into the corresponding organyl-dichloroboranes. *Organometallics* **1992**, *11*, 3094-3097.
- [79] Rembold, H.; Schmidt, R. R. Synthesis of Kdo- α -glycosides of lipid A derivatives. *Carbohydr. Res.* **1993**, *246*, 137-159.