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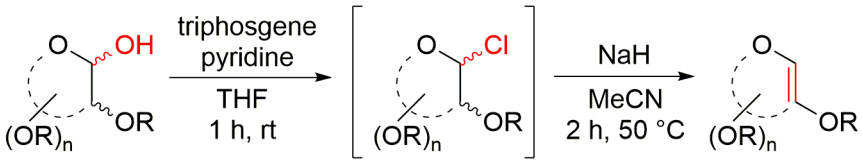

- up to 85% yield over two steps
- R = benzyl, benzylidene, isopropylidene
- interglycosidic linkage tolerated
- both 1,2-*cis* and 1,2-*trans* glycosyl chlorides

Straightforward synthesis of protected 2-hydroxyglycals by chlorination-dehydrochlorination of carbohydrate hemiacetals

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Abstract:

A straightforward and scalable method for the synthesis of protected 2-hydroxyglycals is described. The approach is based on the chlorination of carbohydrate-derived hemiacetals, followed by an elimination reaction to establish the glycal moiety. 1,2-dehydrochlorination reactions were studied on a range of glycosyl chlorides to provide suitable reaction conditions for this transformation. Benzyl ether, isopropylidene and benzylidene protecting groups, as well as interglycosidic linkage, were found to be compatible with this protocol. The described method is operationally simple and allows for the quick preparation of 2-hydroxyglycals with other than ester protecting groups, providing a feasible alternative to existing methods.

Keywords:

Glycals

2-Hydroxyglycals

Dehydrochlorination

Glycosyl chlorides

Carbohydrates

1. Introduction

Glycals are 1,2-unsaturated cyclic enol ether derivatives of carbohydrates. These compounds, formally classified as derivatives of 1,4- or 1,5-anhydro alditols, are an important class of intermediates in natural product synthesis, mainly due to the presence of the enol ether double bond and the broad possibilities of its derivatization. [1,2]

Among glycals, compounds containing an oxygen atom at C-2 (derivatives of 2-hydroxyglycals) have gained considerable attention owing to their closer resemblance to the native carbohydrate scaffold. Acetyl-protected 2-hydroxyglycals have been studied extensively for their Ferrier rearrangement [3,4], which is widely used in

carbohydrate chemistry. However, other common protecting groups such as ether or acetal groups have been introduced, providing higher stability towards a wider range of reaction conditions. On 2-hydroxyglycals protected with other than acyl protecting groups, multiple types of transformations have been described. These include the addition of sulfur [5] and carbon [6–8] radicals, cyclopropanation [9] (in some cases followed by ring expansion to septanosides) [10–12], epoxidation [13], ring-opening arylation with arylboronic acids [14], as well as an attempt at C-1 lithiation [15].

The preparation of 2-hydroxyglycals bearing ester protecting groups can most conveniently be carried out by an anomeric bromination of peracetylated carbohydrates with HBr followed by dehydrobromination by a base. [16,17] This method is well established and generally straightforward, but it requires the presence of an anomeric acyl group and is furthermore limited to substrates with acid-stable protecting groups.

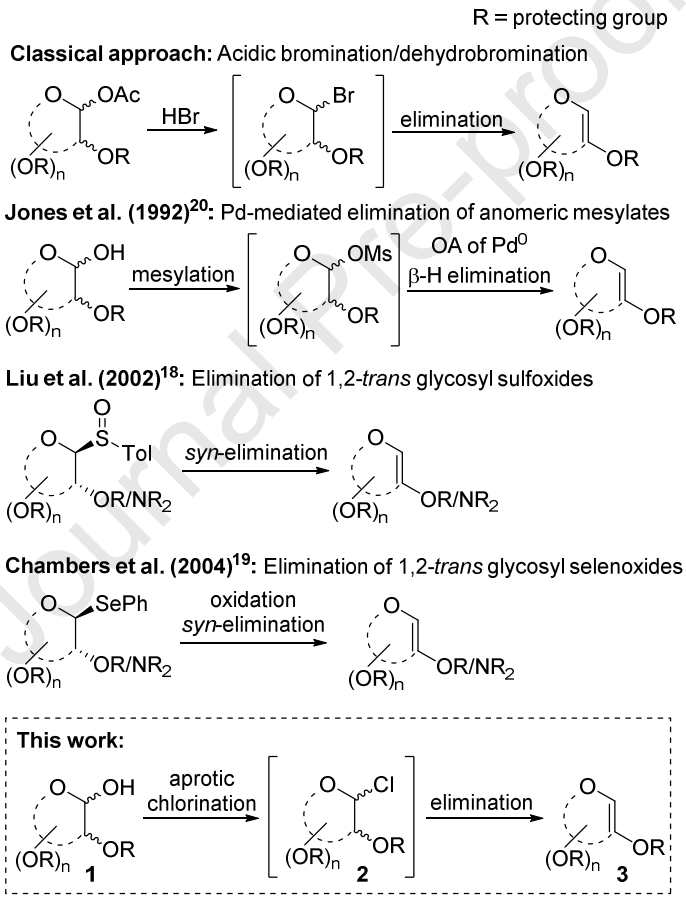


Figure 1. General methods for the synthesis of protected 2-hydroxyglycals.

Therefore, alternative methods are needed to account for these limitations and to provide a synthetic approach to 2-hydroxyglycals with acid-sensitive protection. In the past, several such methods emerged, as outlined in Figure 1. The more general approaches include *syn*-elimination reactions of glycosyl sulfoxides [18] and selenoxides [19]. Although these methods work well, the starting thio- and selenoglycosides are not always readily available. Moreover, these approaches are limited by the inherent *syn*-periplanar stereochemical

requirements which narrow the range of utilizable substrates to 1,2-*trans* derivatives only. Another published method [20] uses an oxidative addition of Pd(0) species to *in situ* generated glycosyl mesylates followed by spontaneous β-hydride elimination of the anomeric palladium intermediate. Besides that, the synthesis of 2-benzyloxyglucal **3a** has been reported via bromolysis of a corresponding pentenyl glycoside [9] or halogenation of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose [21,22]. However, none of these reports demonstrated the compatibility with acid-labile protection.

Herein, we provide a simple way of converting reducing carbohydrates to variously protected 2-hydroxyglycals by a two-stage chlorination-dehydrochlorination protocol. The described method is applicable to both 1,2-*cis* and 1,2-*trans* glycosyl chlorides and is carried out under aprotic conditions, allowing for the use of acid-sensitive protecting groups and thus providing an approach to previously undescribed products. Additionally, improved synthetic pathways to several partially protected carbohydrate-derived hemiacetals are described.

2. Results and discussion

2.1. Preparation of substrates

In order to develop the proposed methodology, a variety of hemiacetal substrates have been synthesized. 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1a** [23], 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose **1b** [24] and 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose **1c** [25] have been synthesized following literature procedures.

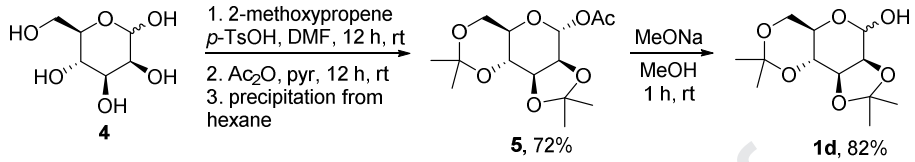
Regarding the synthesis of 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose **1d**, some conflicting evidence can be found in the literature. A thermodynamic product of acetonation of D-mannose is the diisopropylidene D-mannofuranose **1k** [26]; however several reports describe direct kinetic acetonation to the pyranose **1d**. In our experience, these methods result in an inseparable mixture of pyranose and furanose diacetonides **1d** and **1k**, and isolation via the recrystallization of the anomeric acetate **5** is needed to obtain the pure pyranose **1d**, as described in the original report by Gelas and Horton [27]. (Scheme 1)

The 2,3:4,6-di-*O*-isopropylidene-D-glucopyranose **1e** and -galactopyranose **1f** are currently only available through the hydrogenolysis of their benzyl glycosides [28,29]. Nevertheless, this reaction is complicated by over-reduction to the corresponding 2,3:4,6-di-*O*-isopropylidene alditols. Herein, we used an aprotic deallylation of the known allyl glucoside **7** [30] and galactoside **9** [31] by allylic rearrangement and ozonolysis. (Scheme 2)

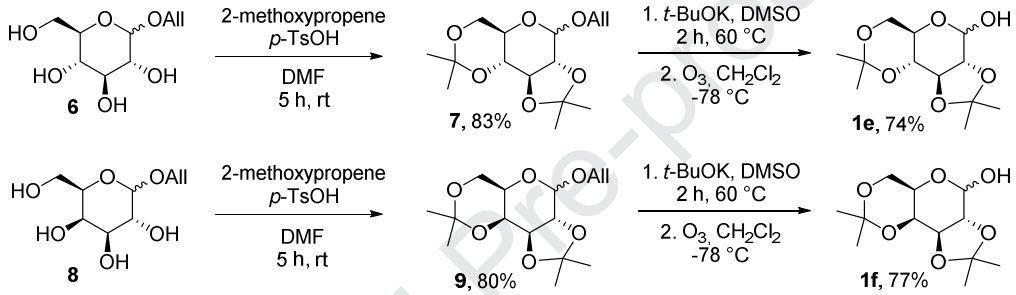
To test the compatibility of the presented method with an interglycosidic linkage, the hepta-*O*-benzyl lactose **1g** was synthesized**.** Existing synthetic approaches to this compound involve peracetylated lactosyl bromide [32–36], lactose peracetate [37,38], lactosucrose [39] or octa-*O*-benzyl lactose [40] as key intermediates. We

developed an alternative approach based on the use of piperidine as a temporary anomeric protecting group of lactose, as revealed in Scheme 3.

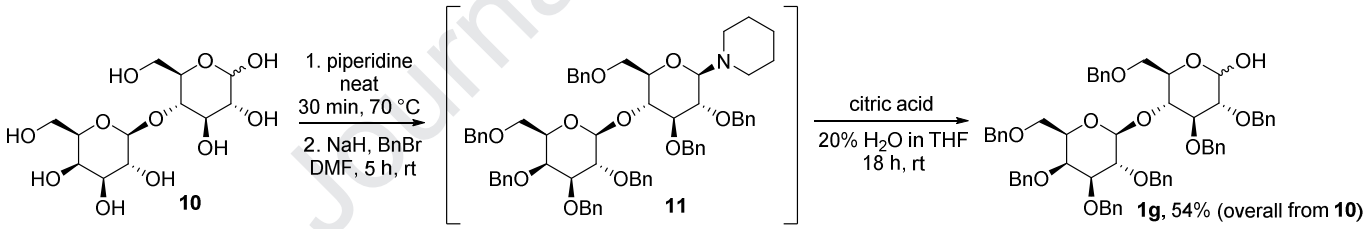
Next, 2,3,5-tri-*O*-benzyl aldopentofuranoses with D-*ribo* (**1h** [41]), D-*arabino* (**1i** [42]) and D-*xylo* (**1j** [43]) configuration have been prepared by the hydrolysis of their methyl glycosides. Additionally, at the time of the writing of this manuscript compounds **1a**, **1b**, **1h**, **1i** and **1k** are also available from commercial suppliers.



Scheme 1. Synthesis of 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose **1d**. [27]



Scheme 2. Synthesis of diisopropylidene derivatives **1e** and **1f**.



Scheme 3. Synthesis of hepta-*O*-benzyl lactose **1g** via its *N*-piperidine derivative **11**.

2.2. Chlorination-Dehydrochlorination

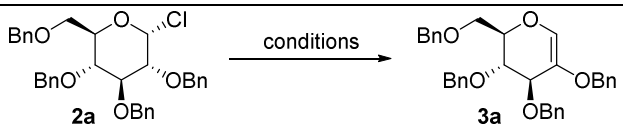
Having the partially protected hemiacetals in hand, we considered the possibilities of converting the anomeric hydroxyl to a suitable leaving group. This type of transformation is well documented in carbohydrate chemistry, with sulfonate esters or halogens being a common choice. We decided to use anomeric chlorides, as they can be obtained from hemiacetals by several known methods under aprotic or mildly protic conditions. Notably, chlorination with Vilsmeier reagent [44,45], diphenyl chlorophosphate [46], 2-chloro-1,3-dimethylimidazolinium chloride (DMC) [47], a mixture of pyridine and triphosgene [48], as well as the Appel reaction [49–51] were described.

Base-promoted 1,2-dehydrochlorination reactions of glycosyl chlorides were previously described on perbenzylated lactosyl and maltosyl chlorides [12] and also reported a number of times as an unwanted side reaction in minor amounts [52–58]. Other than that, this important transformation was to this date not systematically studied with respect to reaction conditions, substrate configuration and protecting group compatibility.

To address this problem, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride **2a** was prepared by chlorination with Vilsmeier reagent and purified by column chromatography. The chloride **2a** was then used for a screening of multiple bases and solvents as summarized in Table 1. Three of the evaluated bases were found to be effective in promoting the dehydrochlorination of **2a** and gave the glycal **3a** in excellent yields. The use of NaH in DMF at room temperature provided glycal **3a** in 91% yield in the reaction mixture, as determined by ^{1}H NMR with an internal standard (Table 1, entry 3). Switching to acetonitrile led to a yield of 85% after 16 h of reaction at room temperature (Table 1, entry 2); however, raising the temperature to 50 °C increased the yield to 99% with a shortened reaction time of 2 h (Table 1, entry 1). NaH also provided excellent results in THF (96%, Table 1, entry 4), but reflux temperature and increased amounts of NaH (10 equivalents instead of 5) were required. We also found that elimination by *t*-BuOK in THF at room temperature resulted in 98% yield of **3a** (Table 1, entry 5), making it a promising candidate for this transformation.

Finally, several tertiary amine bases were evaluated under several conditions (Table 1, entries 6 - 14) with DBU being the only efficient of them. DBU provided a good result in acetonitrile (90%, Table 1, entry 6) but was less effective in other solvents (Table 1, entries 7 - 9). Experiments with weaker amine bases such as DABCO, DIPEA or DMAP led to low or no conversions of the chloride **2a** and did not provide the elimination product in any measurable amount.

Table 1. Screening of elimination conditions.[a]



Entry	Base (eq.)	Solvent	T [°C][b]	Time [h]	NMR conversion [%][c]	NMR yield [%][c]
1	**NaH (5)**	**MeCN**	**50**	**2**	**100**	**99**
2	NaH (5)	MeCN	rt	16	100	85
3	NaH (5)	DMF	rt	2	100	91
4	NaH (10)	THF	80	16	100	96
5	***t*-BuOK (2.5)**	**THF**	**rt**	**2**	**100**	**98**
6	DBU (4)	MeCN	rt	16	100	90

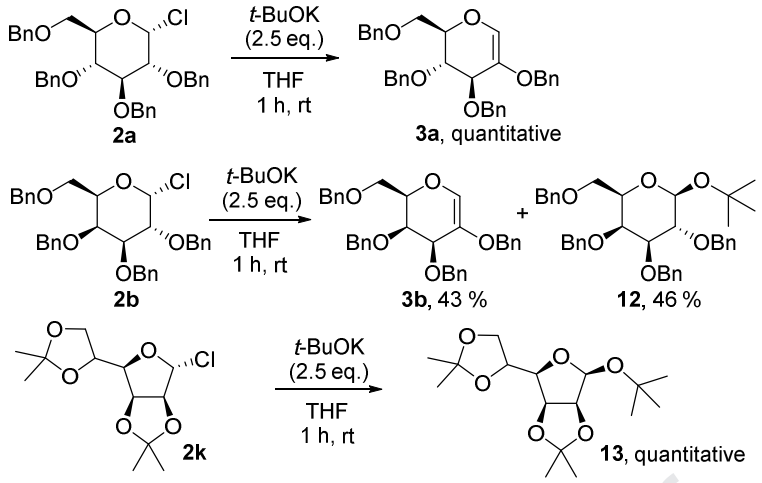
7	DBU (4)	CH_2Cl_2/MeCN (1:1)	rt	16	100	73
8	DBU (4)	CH_2Cl_2	50	24	100	62
9	DBU (4)	DMF	rt	16	85	57
10	DABCO (4)	CH_2Cl_2	50	24	23	0
11	DIPEA (4)	DMF	rt	24	7	0
12	DIPEA (4)	CH_2Cl_2	50	24	5	0
13	DMAP (4)	DMF	rt	24	0	0
14	DMAP (4)	CH_2Cl_2	50	24	0	0

[a] All reactions carried out with 100 mg (179 µmol) of **2a**. [b] Oil bath temperature, except for rt. [c] Corresponds to a calculated mass determined by ^{1}H NMR of the reaction mixture after work-up using 1,3,5-trimethoxybenzene as an internal standard.

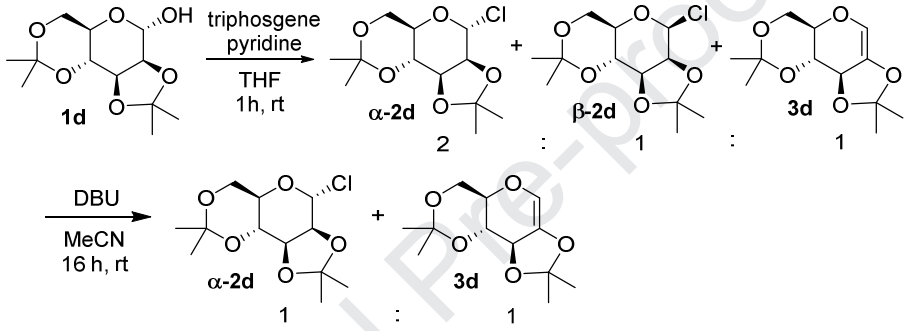
With several promising conditions for the β-elimination of glycosyl chlorides identified, the versatility of these conditions was tested on a wider range of substrates. In some cases, *t*-BuOK was found to provide significant amounts of byproducts arising from S_N2 processes, as pictured in Scheme 4. Notably, the reaction of benzyl protected α-D-galactopyranosyl chloride **2b** led to the formation of the desired elimination product **3b** in 43% yield together with 46% of *tert*-butyl β-glycoside **12**. The reaction of α-D-mannofuranosyl chloride **2k** provided the S_N2 product **13** in a very clean fashion in quantitative yield. These results suggest that with *t*-BuOK, the relative rates of elimination and nucleophilic substitution can vary significantly across different glycosyl chlorides and the outcome of the reaction is strongly substrate-dependent.

We have also discovered that DBU, albeit successful in the elimination of chloride **2a**, was not effective in promoting dehydrochlorination on other substrates and was found to be more sensitive to the configuration on C-1 relative to C-2. This effect can be seen on the D-mannopyranose diacetonide **1d** (Scheme 5). The chlorination of this substrate with a triphosgene/pyridine mixture leads to the 2:1:1 ratio of the α-chloride **α-2d**, β-chloride **β-2d** and the glycal product **3d**, which is formed spontaneously during the chlorination. This mixture of chlorination products, upon treatment with DBU in acetonitrile, converts to an equimolar mixture of **α-2d** and **3d** and the reaction does not proceed further even with longer reaction time or higher temperature. This shows that only the intermediate chloride with β-configuration **β-2d** underwent elimination under the given conditions.

Overall, NaH was found to be the most potent base for this transformation; however, other factors such as the reaction solvent and temperature were identified to be important as well. The most consistent results and best yields were obtained using acetonitrile as a solvent at 50 °C.



Scheme 4. Competition between S_N2 and β-elimination pathways on selected glycosyl chlorides.



Scheme 5. Chlorination/elimination of **1d** with DBU.

2.3. Substrate scope

To test the generality of the aforementioned process, the partially protected sugar hemiacetals **1a-k** were subjected to a two-stage protocol consisting of chlorination and subsequent elimination under the conditions established earlier. The results of this endeavor are summarized in Table 2.

Several known chlorination methods were tested first to obtain the best results. Initially, the Vilsmeier reagent[44] was used for chlorinations, but it was found to give inferior results in this protocol, as seen in Table 2, entries 1 and 2. Moreover, this chlorination method was problematic on 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose **1d**, as the treatment of this substrate with the Vilsmeier reagent provided a mixture of the expected 2,3:4,6-di-*O*-isopropylidene-D-mannopyranosyl chloride **2d** with the 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl chloride **2k** in the 1:20 ratio. This rearrangement to a five-membered ring is likely catalyzed by a hydrogen chloride, which is generated in the solution during the chlorination. A similar result was reported on the same substrate under Appel conditions [59]. Thus, our investigations turned to the use a combination of pyridine and triphosgene in the 3:1 ratio as described originally by Mobashery [60] and later adapted by Norris [48]. With this system, no rearrangements were observed, and the reaction proceeded cleanly under aprotic conditions.

Nevertheless, the use of pyridine proved problematic on more reactive furanose substrates **1h**, **1i** and **1j**, where significant amounts of anomeric pyridinium salts were recovered from the reaction mixture after chlorination. These pyridinium products arise from the displacement of the anomeric chlorine atom with pyridine and were observed on substrates that show high electrophilicity on the anomeric center. In these cases, the problem was overcome by the use of less nucleophilic 2,6-lutidine, which facilitated the chlorination of these substrates effectively. On the other hand, 2,6-lutidine showed little or no reactivity on the less reactive substrates, indicating that the use of pyridine or lutidine should be considered complementary.

The scope of this method was then explored with the emphasis on acid-sensitive substrates, as these are not easily accessible by current methods. The 2-benzyloxy glycals **3a** and **3b** derived from D-glucose and D-galactose were obtained in 85% and 71%, respectively, providing two-step one-chromatography approach to these important substrates from commercially available materials.

Benzylidene protecting group was found to be compatible as well, even though a lower yield of 54% and a somewhat more sluggish reaction was observed in the case of glucal **3c**. Another acetal group, isopropylidene, was generally well tolerated, although some differences in reaction yields were observed between differently configured hemiacetals. The 2,3:4,6-di-*O*-isopropylidene-D-glucal **3d** was obtained in 74% yield upon using diisopropylidene D-mannose **1d** and the elimination protocol employing NaH in acetonitrile, as seen in Table 2, entry 4. The same glycal was obtained from diisopropylidene D-glucopyranose **1e**, although elimination with *t*-BuOK provided better yield than NaH in this case (78%, Table 2, entry 5). All things considered, our results provide a relatively straightforward approach from D-mannose or D-glucose to glucal **3d**, which is currently only available in acceptable yield via the selenoxide method [19]. 2,3:4,6-di-*O*-isopropylidene-D-galactal **3f** can be accessed by this protocol as well, albeit in a moderate yield of 37% after elimination with NaH (Table 2, entry 6). Despite lower yield, this synthetic approach to galactal **3f** is valuable, as no other approach to this compound was described to this day, and according to our experience, the galactal **3f** is not accessible by the selenoxide elimination (see Supplementary material, S2.3.). Importantly, interglycosidic linkage is tolerated in this protocol, as demonstrated on the transformation of hemiacetal **1g** to 2-benzyloxy lactal **3g** in 68% yield (Table 2, entry 7). This transformation was already reported earlier under very similar conditions. [12]

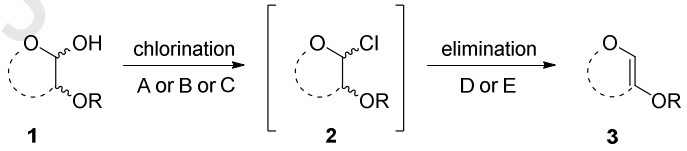
The effort to extend this chlorination-dehydrochlorination methodology to furanose hemiacetals has only met with limited success. The chlorination of pentofuranoses **1h**, **1i** and **1j** required the use of 2,6-lutidine instead of pyridine for the reasons mentioned above. Although the furanosyl chlorides **2h**, **2i** and **2j** could be obtained using this approach, their elimination was successful only in the case of ribosyl chloride **2h**, giving 2-benzyloxy-D-ribal **3h** in 75% yield after elimination with *t*-BuOK. The same product was also obtained from protected D-arabinose **1i**, but only in negligible yields of 4 - 8% (Table 2, entry 9) due to a major degradation under the elimination conditions. Similarly, the elimination of D-xylofuranosyl chloride **2j** resulted in complete decomposition to an unidentified mixture of products. Furthermore, the chlorination of

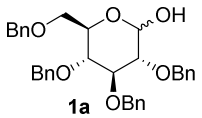
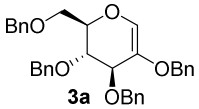
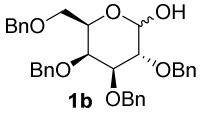
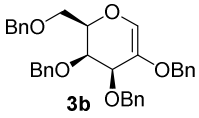
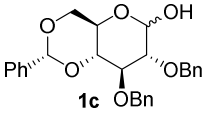
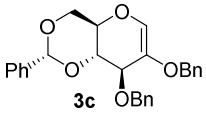
diisopropylidene D-mannofuranose **1k** proceeded smoothly with triphosgene/pyridine to give the corresponding α-chloride **2k**, as reported earlier. This chloride, however, proved to be particularly resilient to 1,2-dehydrochlorination reactions. The treatment with NaH in acetonitrile led to double aldol condensation with acetonitrile yielding an unstable *N*-glycoside product **14**.[61] The reaction with *t*-BuOK resulted in a clean S_N2 reaction to give *tert*-butyl-β-D-mannofuranoside **13** (Scheme 4). Further attempts to use other elimination conditions from Table 1 or more forcing conditions did not provide the desired glycal either.

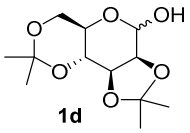
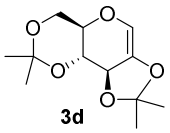
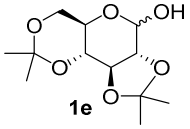
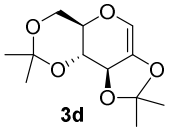
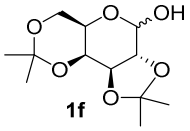
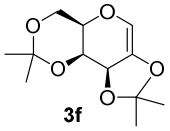
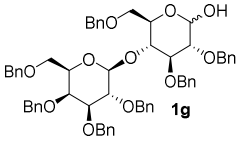
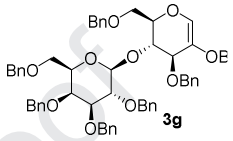
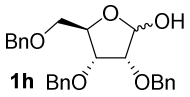
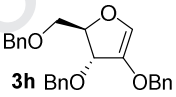
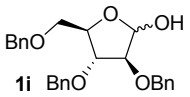
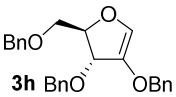
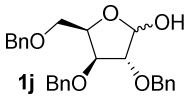
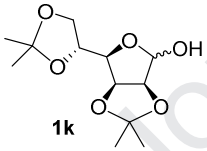
To put our observations into the stereochemical context, the chlorination reactions resulted in most cases in the formation of glycosyl chlorides with α-configuration. However, in the case of chlorides **2f**, **2h** and **2j**, major amounts of the β-isomer were observed. It is worth noting that the observed anomeric ratio for chlorides **2d** and **2f** is influenced by a partial elimination which takes place under the chlorination conditions (Table 2, entries 4 and 6). For this reason, the true stereochemical preference of the reaction could not be determined in these cases.

The anomeric configuration of the glycosyl chlorides did not seem to have a major influence on the success of the elimination reactions, as seen in Table 2, entries 4 and 8. In these cases, the intermediate chlorides **2d** and **2h** have mainly 1,2-*trans* configuration, which would be generally considered less favorable for elimination. Yet, the elimination proceeded in favorable overall yields of 74% and 75%. This observation suggests that 1,2-dehydrochlorination reactions of glycosyl chlorides with NaH or *t*-BuOK do not necessarily rely on a bimolecular mechanism and unlike with DBU, the relative configuration on C-1 and C-2 is not critical. Other factors, such as the stability of the chloride or susceptibility to substitution reactions or other unwanted processes, seem to be more important.

Table 2. Scope of the chlorination-dehydrochlorination of partially protected hemiacetals.[a]



Entry	Substrate	Chlorination method	Chloride α/β ratio	Elimination method	Product	Isolated yield over 2 steps [%]
1	 **1a**	A	**2a** α only	D	 **3a**	85
		C		D		64
2	 **1b**	A	**2b** α only	D	 **3b**	71
		C		D		61
3	 **1c**	A	**2c** α only	D	 **3c**	54

4	 **1d**	A	**2d** α/β/**3d** 2:1:1	D	 **3d**	74
5	 **1e**	A A	**2e** α only	D E	 **3d**	36 78
6	 **1f**	A A	**2f** α/β/**3f** 1:1.5:1	E[d]	 **3f**	36
7	 **1g**	A	**2g** α only	D	 **3g**	68
8	 **1h**	B B	**2h** α/β 1:7	D E	 **3h**	24 75
9	 **1i**	B B	**2i** α/β 1:0.2	D E	 **3h**	8 4
10	 **1j**	B B	**2j** α/β 1:1.3	D E	-	ND[b] ND[b]
11	 **1k**	A A	**2k** α only	D E	-	ND[78] ND[c]

[a] All reactions were carried out with 2 mmol of a substrate **1a**-**k**. Isolated yields over 2 steps after column chromatography are given. Conditions: **A**: triphosgene/pyridine, THF, rt, 1 h; **B**: triphosgene/2,6-lutidine, THF, rt, 1 h; **C**: Vilsmeier reagent, CH_2Cl_2, 0 ˚C, 30 min [44] ; **D**: 60% NaH, MeCN, 50 ˚C, 2 h; **E**: *t*-BuOK, THF, rt, 2 h. [b] Decomposition. [c] S_N2 reaction was observed (see Scheme 4). [d] Elimination was carried out for 30 min at 0 ˚C and then for 30 min at rt; ND = not determined

3. Conclusion

In this paper, base-promoted dehydrochlorination reactions of glycosyl chlorides have been explored and suitable conditions for the preparation of a variety of protected 2-hydroxyglycals have been identified. The presented synthetic approach is particularly advantageous in the cases where the partially protected hemiacetal substrates with a free anomeric hydroxyl group are readily available. For this reason, improved synthetic access to several known hemiacetal substrates from unprotected sugars has been developed.

This method is carried out as a two-step one-chromatography protocol and it relies on chlorination of the anomeric position of carbohydrates and subsequent 1,2-dehydrochlorination to establish the glycal double

bond. The aprotic conditions of this protocol enable the use of acid-sensitive substrates and protecting groups. Moreover, it provides a concise approach to several important 2-benzyloxy glycals.

Under the identified elimination conditions (method D or E), both 1,2-*cis* and 1,2-*trans* glycosyl chlorides have been found to undergo 1,2-dehydrochlorination. However, differences in yields (4 - 85%) were observed through differently configured substrates and some substrates even proved entirely resilient or unstable under the reaction conditions.

4. Experimental section

General considerations, experimental procedures for the preparation of substrates, other experimental details, and copies of ^{1}H and ^{13}C NMR spectra are included in the Supplementary material.

Method A (triphosgene/pyridine) [48]**:**

Triphosgene (1 mmol, 0.5 eq.) was added to a solution of substrate **1** (2 mmol, 1 eq.) in anhydrous THF (10 mL) under Ar atmosphere. The solution was cooled to 0 °C and pyridine (3.2 mmol, 1.6 eq.) was added dropwise. The formation of a white precipitate (pyridinium chloride) was observed immediately during the addition. The reaction was stirred at room temperature for 1 h and then filtered. The filtrate was concentrated under reduced pressure, dissolved in EtOAc (100 mL) and washed with H_2O (2 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was kept under high vacuum for 1 h.

Method B (triphosgene/2,6-lutidine)

The same as Method A, except that 2,6-lutidine (3.2 mmol, 1.6 eq.) was used instead of pyridine.

Method C (Vilsmeier reagent) [44]**:**

Oxalyl chloride (3 mmol, 1.5 eq.) was added dropwise to the solution of the substrate **1** (2 mmol, 1 eq.) and DMF (3.4 mmol, 1.7 eq.) in CH_2Cl_2 (15 mL) under Ar atmosphere at 0 °C. An exothermic reaction with gas evolution was observed. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Then, the mixture was poured into ice water and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with chilled H_2O (150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was kept under high vacuum for 1 h.

Method D (NaH in MeCN):

The crude glycosyl chloride **2** obtained with chlorination Method A, B or C was dissolved in anhydrous MeCN (15 mL) and NaH (10 mmol, 5 eq. relative to substrate **1**, 60% in mineral oil) was added. The heterogeneous mixture was stirred at 50 °C for 2 h. After the elimination was finished, MeOH (5 mL) was

added slowly at 0 °C and the solvents were evaporated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with H_2O (100 mL). The aqueous phase was separated and washed with EtOAc (100 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Method E (*t*-BuOK in THF):

The crude glycosyl chloride **2** obtained with chlorination Method A, B or C was dissolved in anhydrous THF (20 mL) and *t*-BuOK (5 mmol, 2.5 eq. relative to substrate **1**) was added. The reaction mixture was stirred for 2 h at room temperature and then quenched with H_2O (5 mL). The reaction mixture was extracted between EtOAc (100 mL) and H_2O (100 mL). The aqueous phase was then washed with EtOAc (2 × 100 mL), the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Practical considerations:

1. In general, when running chlorination reactions of sugar hemiacetals to form glycosyl chlorides, TLC is not an entirely reliable method to track the conversion of the reaction. Frequently, the starting material would display on the TLC plate, when in fact the reaction is fully completed. This is likely due to a reverse hydrolytic reaction happening on the silica gel plate. For reliable determination of the reaction conversion, ^{1}H NMR is more suitable.
2. In the Mobashery chlorination protocol involving triphosgene/pyridine mixture, it is recommended to add pyridine relatively slowly, dropwise, to avoid creating local excess of pyridine. If pyridine is added rapidly, there is a higher risk of secondary nucleophilic substitution and formation of anomeric pyridinium salts on some substrates.

*4.1. 1,5-Anhydro-2,3,4,6-tetra-O-benzyl-D-arabino-hex-1-enitol (**3a**):*

Methods A and D: Following Method A, substrate **1a** (1.1 g, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following Method D, the crude chloride **2a** was reacted with NaH (400.0 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 891 mg (85%).

Methods C and D: Following Method C, substrate **1a** (1.1 g, 2 mmol) was reacted with oxalyl chloride (257 µL, 3 mmol) and *N*,*N*-dimethylformamide (263 µL, 3.4 mmol). Then, following Method D, the crude chloride **2a** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 665 mg (64%).

Isolation: The product **3a** was purified by column chromatography on silica gel (Hexane/EtOAc 10:1) and obtained in the form of a colorless oil which solidified upon standing. The characterization data were consistent with the literature. [9,19]

R_f = 0.52 (Hexane/EtOAc 5:1); **m.p.** 64 - 66 °C (acetone); **$[\alpha]^{20}_D$** = - 4.6 (*c* = 0.3 in $CHCl_3$); **^{1}H NMR** (401 MHz, Chloroform-*d*): δ = 7.41 – 7.19 (m, 20H; Ar-H), 6.32 (s, 1H; H-1), 4.77 – 4.69 (m, 4H; C*H*Ph), 4.62 (d, J_{gem} = 11.5 Hz, 1H; C*H*Ph), 4.60 (d, J_{gem} = 11.7 Hz, 1H; C*H*Ph), 4.56 – 4.54 (m, 2H; C*H*Ph), 4.27 (d, $J_{3,4}$ = 4.7 Hz, 1H; H-3), 4.13 – 4.07 (m, 1H; H-5), 3.91 (dd, $J_{4,5}$ = 6.7 Hz, $J_{4,3}$ = 4.7 Hz, 1H; H-4), 3.78 (dd, J_{gem} = 10.6 Hz, $J_{6a,5}$ = 6.0 Hz, 1H; H-6a), 3.69 (dd, J_{gem} = 10.6 Hz, $J_{6b,5}$ = 3.5 Hz, 1H; H-6b); **^{13}C NMR** (101 MHz, Chloroform-*d*): δ = 139.0 (C-2), 138.5 (Ar-C_{ipso}), 138.2 (Ar-C_{ipso}), 138.1 (Ar-C_{ipso}), 137.3 (Ar-C_{ipso}), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 127.98, 127.96 (Ar-C), 127.91 (C-1), 127.85, 127.77, 127.74, 127.70 (Ar-C), 76.4 (C-5), 75.7 (C-3), 74.4 (C-4), 73.6 (*C*H_2Ph), 73.0 (*C*H_2Ph), 72.4 (*C*H_2Ph), 71.2 (*C*H_2Ph), 68.4 (C-6); **IR** ($CHCl_3$): $\tilde{\nu}$ = 3090, 3067, 3032, 2910, 2869, 1670, 1605, 1587, 1497, 1454, 1159, 1100, 1071, 1028, 911, 698, 467 cm^{-1}; **MS** (ESI): *m*/*z* = 545.2 [*M*+Na]$^+$; **HRMS** (ESI): *m*/*z* calcd for $C_{34}H_{34}O_5Na$: 545.2299 [*M*+Na]$^+$; found 545.2294.

*4.2. 1,5-Anhydro-2,3,4,6-tetra-O-benzyl-D-lyxo-hex-1-enitol (**3b**):*

Methods A and D: Following Method A, substrate **1b** (1.1 g, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following Method D, the crude chloride **2b** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 743 mg (71%).

Methods C and D: Following Method C, substrate **1b** (1.1 g, 2 mmol) was reacted with oxalyl chloride (257 µL, 3 mmol) and *N*,*N*-dimethylformamide (263 µL, 3.4 mmol). Then, following Method D, the crude chloride **2b** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 638 mg (61%).

Isolation: The product **3b** was purified by column chromatography on silica gel (Hexane/EtOAc 10:1) and obtained in the form of a colorless oil which solidified upon standing. The characterization data were consistent with the literature. [8]

R_f = 0.37 (Hexane/EtOAc 8:1); **$[\alpha]^{20}_D$** = - 44.7 (*c* = 0.3 in $CHCl_3$); **^{1}H NMR** (401 MHz, Chloroform-*d*): δ = 7.37 – 7.27 (m, 20H; Ar-H), 6.19 (d, $J_{1,3}$ = 1.0 Hz, 1H; H-1), 4.84 (d, J_{gem} = 12.0 Hz, 1H; C*H*Ph), 4.79 (d, J_{gem} = 12.0 Hz, 1H; C*H*Ph), 4.78 (d, J_{gem} = 12.0 Hz, 1H; C*H*Ph), 4.73 (d, J_{gem} = 11.3 Hz, 1H; C*H*Ph), 4.63 (d, J_{gem} = 11.3 Hz, 1H; C*H*Ph), 4.62 (d, J_{gem} = 12.0 Hz, 1H; C*H*Ph), 4.55 (d, J_{gem} = 12.0 Hz, 1H; C*H*Ph), 4.45 (d, J_{gem} = 12.0 Hz, 1H; C*H*Ph), 4.25 (dd, $J_{3,4}$ = 4.2 Hz, $J_{3,1}$ = 1.0 Hz, 1H; H-3), 4.24 – 4.20 (m, 1H; H-5), 3.96 – 3.89 (m, 2H; H-4, H-6a), 3.71 (dd, J_{gem} = 10.9 Hz, $J_{6b,5}$ = 3.4 Hz, 1H; H-6b); **^{13}C NMR** (101 MHz, Chloroform-*d*): δ = 138.92 (Ar-C_{ipso}), 138.85 (C-2), 138.4 (Ar-C_{ipso}), 138.2 (Ar-C_{ipso}), 137.4 (Ar-C_{ipso}), 128.53, 128.48, 128.4, 128.09, 128.01, 127.95, 127.94, 127.85, 127.73, 127.70, 127.6 (Ar-C), 127.0 (C-1), 75.3 (C-5), 73.7 (*C*H_2Ph), 73.5 (*C*H_2Ph), 73.3 (C-4), 72.7 (*C*H_2Ph), 71.9 (C-3), 71.5 (*C*H_2Ph), 67.8 (C-6); **IR** ($CHCl_3$): $\tilde{\nu}$ = 3090, 3067, 2923, 2871, 1604, 1588, 1497, 1454, 1149, 1101, 1028, 913, 698, 459; **MS** (ESI): *m*/*z* = 545.2 [*M*+Na]$^+$; **HRMS** (ESI): *m*/*z* calcd for $C_{34}H_{34}O_5Na$: 545.2299 [*M*+Na]$^+$; found 545.2296.

*4.3. 1,5-Anhydro-2,3-di-O-benzyl-4,6-O-benzylidene-D-arabino-hex-1-enitol (**3c**):*

Methods A and D: Following Method A, substrate **1c** (897 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following Method D, the crude chloride **2c** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 467 mg (54%).

Isolation: The product **3c** was purified by column chromatography on silica gel (Hexane/EtOAc 10:1) and obtained in the form of a white solid. The characterization data were consistent with the literature. [19] $\mathbf{R_f}$ = 0.32 (Hexane/EtOAc 10:1); **m.p.** not determined (decomposition at 220 °C); $\mathbf{[\alpha]^{20}_D}$ = - 34.1 (*c* = 0.2 in $CHCl_3$); **^{1}H NMR** (401 MHz, Chloroform-*d*): δ = 7.54 (dd, *J* = 7.7, 2.1 Hz, 2H; Ar-H), 7.46 – 7.25 (m, 13H; Ar-H), 6.32 (d, $J_{1,3}$ = 1.0 Hz, 1H; H-1), 5.61 (s, 1H; C*H*Ph), 4.92 (d, J_{gem} = 12.0 Hz, 1H; CH_aCH_bPh), 4.88 (d, J_{gem} = 12.0 Hz, 1H; CH$_a$CH_bPh), 4.76 (d, J_{gem} = 11.4 Hz, 1H; CH_aCH$_b$Ph), 4.73 (d, J_{gem} = 11.4 Hz, 1H; CH$_a$CH_bPh), 4.53 (dd, $J_{3,4}$ = 7.4 Hz, $J_{3,1}$ = 1.0 Hz, 1H; H-3), 4.38 (dd, J_{gem} = 9.6 Hz, $J_{6a,5}$ = 4.3 Hz, 1H; H-6a), 4.11 (dd, $J_{4,5}$ = 9.9 Hz, $J_{4,3}$ = 7.4 Hz, 1H; H-4), 3.89 – 3.74 (m, 2H; H-6b, H-5); **^{13}C NMR** (101 MHz, Chloroform-*d*): δ = 139.7 (C-2), 138.6 (Ar-C_{ipso}), 137.3 (Ar-C_{ipso}), 137.1 (Ar-C_{ipso}), 129.4 (C-1), 129.1 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.7 (Ar-C), 127.7 (Ar-C), 126.2 (Ar-C), 101.1 (*C*HPh), 80.0 (C-4), 74.9 (C-3), 73.5 (*C*H_2Ph), 71.5 (*C*H_2Ph), 69.2 (C-5), 68.5 (C-6); **IR** ($CHCl_3$): $\tilde{\nu}$ = 3091, 3068, 2933, 2871, 1659, 1606, 1586, 1497, 1466, 1454, 1375, 1342, 1165, 1149, 1095, 1075, 1066, 1028, 995, 915, 698, 467 cm^{-1}; **MS** (ESI): *m*/*z* = 453.2 [*M*+Na]$^+$; **HRMS** (ESI): *m*/*z* calcd for $C_{27}H_{26}O_5Na$: 453.1671 [*M*+Na]$^+$; found 453.1673.

*4.4. 1,5-Anhydro-2,3:4,6-di-O-isopropylidene-D-arabino-hex-1-enitol (**3d**):*

From 1d:

Methods A and D: Following Method A, substrate **1d** (521 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following Method D, the crude chloride **2d** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 359 mg (74%).

From 1e:

Methods A and D: Following Method A, substrate **1e** (521 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following Method D, the crude chloride **2e** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 175 mg (36%).

Methods A and E: Following Method A, substrate **1e** (521 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following Method E, the crude chloride **2e** was reacted with *t*-BuOK (561 mg, 5 mmol). Isolated yield 379 mg (78%).

Isolation: The product **3d** was purified by column chromatography on silica gel (Hexane/EtOAc 15:1) and obtained in the form of a colorless oil. The characterization data were consistent with the literature. [19] $\mathbf{R_f}$ = 0.59 (Hexane/EtOAc 5:1); $\mathbf{[\alpha]^{20}_D}$ = + 62.0 (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (401 MHz, Chloroform-*d*): δ = 6.22

(d, $J_{1,3}$ = 1.8 Hz, 1H; H-1), 4.59 (dd, $J_{3,4}$ = 7.4 Hz, $J_{3,1}$ = 1.8 Hz, 1H; H-3), 4.00 (dd, J_{gem} = 11.0 Hz, $J_{6a,5}$ = 5.6 Hz, 1H; H-6a), 3.90 (dd, $J_{4,5}$ = 10.5 Hz, $J_{4,3}$ = 7.4 Hz, 1H; H-4), 3.85 (dd, J_{gem} = 11.0 Hz, $J_{6b,5}$ = 10.5 Hz, 1H; H-6b), 3.59 (td, $J_{5,4}$ = $J_{5,6b}$ = 10.5 Hz, $J_{5,6a}$ = 5.6 Hz, 1H; H-5), 1.55 (s, 3H; C(CH_3)$_2$), 1.49 (s, 3H; C(CH_3)$_2$), 1.46 (s, 3H; C(CH_3)$_2$), 1.45 (s, 3H; C(CH_3)$_2$); **^{13}C NMR** (101 MHz, Chloroform-*d*): δ = 134.3 (C-2), 122.3 (C-1), 113.4 (*C*(CH$_3$)$_2$),99.8 (*C*(CH$_3$)$_2$), 73.8 (C-3), 71.3 (C-4), 67.4 (C-5), 62.1 (C-6), 29.0 (C(*C*H$_3$)$_2$), 26.9 (C(*C*H$_3$)$_2$), 25.5 (C(*C*H$_3$)$_2$), 19.2 (C(*C*H$_3$)$_2$); **IR** (CHCl$_3$): $\tilde{\nu}$ = 2992, 2940, 2901, 1802, 1736, 1706, 1460, 1383, 1375, 1347, 1318, 1267, 1232, 1217, 1201, 1165, 1123, 1104, 1083, 1053, 1007, 967, 936, 914, 851, 796, 762, 752, 680, 663, 601, 560, 524, 506, 483, 468 cm^{-1}; **MS** (APCI): *m*/*z* = 243.1 [*M*+H]$^+$; **HRMS** (ESI): *m*/*z* calcd for $C_{12}H_{18}O_5Na$: 265.1046 [*M*+Na]$^+$; found 265.1047.

*4.5. 1,5-Anhydro-2,3:4,6-di-O-isopropylidene-D-lyxo-hex-1-enitol (**3f**):*

Methods A and E: Following Method A, substrate **1f** (521 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following modified Method E, the crude chloride **2f** was reacted with *t*-BuOK (561 mg, 5 mmol) for 30 min at 0 ˚C and then for 30 min at room temperature. Isolated yield 176 mg (36%).

Isolation: The product **3f** was purified by column chromatography on silica gel Hexane/EtOAc 15:1 + 1% Et$_3$N) and obtained in the form of a colorless oil. **R$_f$** = 0.47 (Hexane/EtOAc 2:1); **[α]$^{20}_D$** = + 65.4 (*c* = 0.3 in acetone); **^{1}H NMR** (401 MHz, Acetone-d_6): δ = 6.23 (d, $J_{1,3}$ = 2.3 Hz, 1H; H-1), 4.67 (ddd, $J_{3,4}$ = 4.3 Hz, $J_{3,1}$ = 2.3 Hz, $J_{3,5}$ = 0.8 Hz, 1H; H-3), 4.49 (dd, $J_{4,3}$ = 4.3 Hz, $J_{4,5}$ = 1.6 Hz, 1H; H-4), 4.15 (dd, J_{gem} = 12.6 Hz, $J_{6a,5}$ = 1.7 Hz, 1H; H-6a), 3.83 (dd, J_{gem} = 12.6 Hz, $J_{6b,5}$ = 2.0 Hz, 1H; H-6b), 3.64 (dddd, $J_{5,6b}$ = 2.0 Hz, $J_{5,6a}$ = 1.7 Hz, $J_{5,4}$ = 1.6 Hz, $J_{5,3}$ = 0.8 Hz, 1H; H-5), 1.48 (s, 3H; C(CH_3)$_2$), 1.43 (s, 3H; C(CH_3)$_2$), 1.37 (s, 3H; C(CH_3)$_2$), 1.30 (s, 3H; C(CH_3)$_2$); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 133.69 (C-2), 122.30 (C-1), 112.52 (*C*(CH$_3$)$_2$), 98.88 (*C*(CH$_3$)$_2$), 71.70 (C-3), 66.30 (C-5), 64.03 (C-4), 63.52 (C-6), 29.58 (C(*C*H$_3$)$_2$), 26.40 (C(*C*H$_3$)$_2$), 26.20 (C(*C*H$_3$)$_2$), 18.99 (C(*C*H$_3$)$_2$); **IR** (CHCl$_3$): $\tilde{\nu}$ = 2990, 2939, 2905, 2867, 1614, 1458, 1382, 1374, 1333, 1233, 1146, 1086, 1041, 1028, 854, 516 cm^{-1}; **MS** (ESI): *m*/*z* = 265.1 [*M*+Na]$^+$; **HRMS** (ESI): *m*/*z* calcd for $C_{12}H_{18}O_5Na$: 265.1043 [*M*+Na]$^+$; found 265.1046.

*4.6. 1,5-Anhydro-2,3,6-tri-O-benzyl-4-O-(2',3',4',6'-tetra-O-benzyl-β-D-galactopyranosyl)-D-arabino-hex-1-enitol (**3g**):*

Methods A and D: Following Method A, substrate **1g** (1.95 g, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and pyridine (258 µL, 3.2 mmol). Then, following Method D, the crude chloride **2g** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 1.3 g (68%).

Isolation: The product **3g** was purified by column chromatography on silica gel Hexane/EtOAc 5:1) and obtained in the form of a colorless oil. The characterization data were consistent with the literature. [12,62] **R$_f$** = 0.23 (Hexane/EtOAc 10:1); **[α]$^{20}_D$** = - 8.2 (*c* = 0.2 in CHCl$_3$); **^{1}H NMR** (401 MHz, Chloroform-*d*): δ = 7.36

– 7.21 (m, 35H; Ar-H), 6.28 (d, $J_{1,3}$ = 1.3 Hz, 1H; H-1), 4.95 (d, J_{gem} = 11.6 Hz, 1H; CH_2Ph), 4.85 (d, J_{gem} = 10.7 Hz, 1H; CH_2Ph), 4.76 (d, J_{gem} = 11.9 Hz, 1H; CH_2Ph), 4.74 – 4.63 (m, 6H; CH_2Ph), 4.61 (d, J_{gem} = 11.6 Hz, 1H; CH_2Ph), 4.51 (d, J_{gem} = 12.1 Hz, 1H; CH_2Ph); 4.49 (d, $J_{1',2'}$ = 7.7 Hz, 1H; H-1'), 4.45 (d, J_{gem} = 12.1 Hz, 1H; CH_2Ph), 4.39 (d, J_{gem} = 11.7 Hz, 1H; CH_2Ph), 4.34 (d, J_{gem} = 11.7 Hz, 1H; CH_2Ph), 4.34 – 4.29 (m, 1H; H-5), 4.28 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3,1}$ = 1.3 Hz, 1H; H-3), 4.19 (dd, $J_{4,3}$ = 3.2 Hz, $J_{4,5}$ = 3.5 Hz, 1H; H-4), 3.88 (d, J = 2.9 Hz, 1H; H-4'), 3.83 (dd, $J_{6a,6b}$ = 10.6 Hz, $J_{6a,5}$ = 7.1 Hz, 1H; H-6a), 3.79 (dd, $J_{2',3'}$ = 9.8 Hz, $J_{2',1'}$ = 7.7 Hz, 1H; H-2'), 3.62 (dd, $J_{6b,6a}$ = 10.6 Hz, $J_{6b,5}$ = 4.2 Hz, 1H; H-6b), 3.57 – 3.43 (m, 4H; H-3', H-5', H-6'a, H-6'b); **^{13}C NMR** (101 MHz, Chloroform-*d*): δ = 138.8, 138.7, 138.3, 137.9 (Ar-C_{ipso}), 137.8 (C-2), 137.5 (Ar-C_{ipso}), 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1 (Ar-C), 128.0 (C-1), 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.5 (Ar-C), 103.2 (C-1'), 82.3 (C-3'), 79.3 (C-2'), 75.3 (*C*HPh), 75.0 (C-5), 74.8 (*C*HPh), 73.9 (C-3), 73.7 (C-4), 73.7 (C*H*Ph), 73.6 (C-4'), 73.5 (C-5'), 73.3 (*C*HPh), 73.2 (*C*HPh), 70.0 (*C*HPh), 71.2 (*C*HPh), 68.8 (C-6'), 67.9 (C-6); **IR** ($CHCl_3$): $\tilde{\nu}$ = 3090, 3067, 3033, 1605, 1586, 1497, 1454, 1158, 1093, 1076, 1076, 1028, 983, 912, 699, 461 cm^{-1}; **MS** (ESI): *m*/*z* = 977.4 [*M*+Na]$^+$; **HRMS** (ESI): *m*/*z* calcd for $C_{61}H_{62}O_{10}Na$: 977.4235 [*M*+Na]$^+$; found 977.4237.

*4.7. 1,4-Anhydro-2,3,5-tri-O-benzyl-D-erythro-pent-1-enitol (**3h**):*

From 1h:

Methods B and D: Following Method B, substrate **1h** (841 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and 2,6-lutidine (371 µL, 3.2 mmol). Then, following Method D, the crude chloride **2h** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 192 mg (24%).

Methods B and E: Following Method B, substrate **1h** (841 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and 2,6-lutidine (371 µL, 3.2 mmol). Then, following Method E, the crude chloride **2h** was reacted with *t*-BuOK (561 mg, 5 mmol). Isolated yield 602 mg (75%).

From 1i:

Methods B and D: Following Method B, substrate **1h** (841 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and 2,6-lutidine (371 µL, 3.2 mmol). Then, following Method D, the crude chloride **2h** was reacted with NaH (400 mg, 10 mmol, 60% suspension in mineral oil). Isolated yield 66 mg (8%).

Methods B and E: Following Method B, substrate **1h** (841 mg, 2 mmol) was reacted with triphosgene (297 mg, 1 mmol) and 2,6-lutidine (371 µL, 3.2 mmol). Then, following Method E, the crude chloride **2h** was reacted with *t*-BuOK (561 mg, 5 mmol). Isolated yield 32 mg (4%).

Isolation: The product **3h** was purified by column chromatography on silica gel (Hexane/EtOAc 15:1 + 1% Et_3N) and obtained in the form of a colorless oil. The characterization data were consistent with the literature. [20] $\mathbf{R_f}$ = 0.43 (Hexane/EtOAc 6:1); $\mathbf{[\alpha]^{20}_D}$ = + 59.3 (*c* = 0.2 in $CHCl_3$); **^{1}H NMR** (401 MHz, Chloroform-*d*): δ = 7.39 – 7.27 (m, 15H; Ar-H), 6.19 (d, $J_{1,3}$ = 0.8 Hz, 1H; H-1), 4.79 (d, J_{gem} = 11.4 Hz, 1H; CH_2Ph), 4.73 (d,

J_{gem} = 11.4 Hz, 1H; CH_2Ph), 4.71 (d, J_{gem} = 12.0 Hz, 1H; CH_2Ph), 4.67 (dd, $J_{3,4}$ = 3.3 Hz, $J_{3,1}$ = 0.8 Hz, 1H; H-3), 4.58 (d, J_{gem} = 12.1 Hz, 1H; CH_2Ph), 4.54 (d, J_{gem} = 12.2 Hz, 1H; CH_2Ph), 4.52 (ddd, $J_{4,5a}$ = 6.2 Hz, $J_{4,5b}$ = 5.8 Hz, $J_{4,3}$ = 3.3 Hz, 1H; H-4), 3.56 (dd, J_{gem} = 10.2 Hz, $J_{5a,4}$ = 6.2 Hz, 1H; H-5a), 3.42 (dd, J_{gem} = 10.2 Hz, $J_{5b,4}$ = 5.8 Hz, 1H; H-5b); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 140.84 (C-2), 138.38 (Ar-C_{ipso}), 138.13 (Ar-C_{ipso}), 136.85 (Ar-C_{ipso}), 128.38, 128.29, 128.22, 127.91, 127.67, 127.62, 127.57, 127.54, 127.44 (Ar-C), 127.28 (C-1), 82.62 (C-4), 80.74 (C-3), 72.32 (*C*H_2Ph), 71.74 (*C*H_2Ph), 69.64 (C-5), 69.38 (*C*H_2Ph); **IR** ($CHCl_3$): $\tilde{\nu}$ = 3113, 3090, 3067, 3033, 2931, 2867, 1667, 1606, 1587, 1497, 1454, 1364, 1310, 1289, 1157, 1099, 1073, 1028, 912, 853, 699 cm^{-1}; **MS** (ESI): *m*/*z* = 425.2 [*M*+Na]$^+$; **HRMS** (ESI): *m*/*z* calcd for $C_{26}H_{26}O_4Na$: 425.1722 [*M*+Na]$^+$; found 425.1723.

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Dedication

Dedicated to the memory of Prof. Jitka Moravcová.

Supplementary Material

Supplementary Material containing additional experimental data can be found at the online version of this article.

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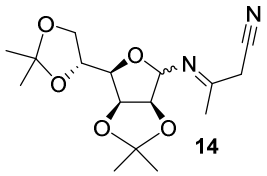

14

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Highlights

- 2-Hydroxyglycals were synthesized *via* chlorination-dehydrochlorination of carbohydrate hemiacetals.
- Simple synthetic protocol, gram-scale amounts.
- Aprotic conditions were utilized, allowing for the use of acid-sensitive substrates.
- Both 1,2-*cis* and 1,2-*trans* glycosyl chlorides provide 2-hydroxyglycals after elimination.
- Piperidine was used as a temporary anomeric protecting group of lactose.

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: