SnCl₄ Promoted Efficient Cleavage of Acetal/Ketal Groups with the Assistance of Water in CH₂Cl₂

Tao Luo, Tian-Tian Xu, Yang-Fan Guo and Hai Dong *

Key Laboratory of Material Chemistry for Energy Conversion and Storage, Ministry of Education, Hubei Key Laboratory of Material Chemistry and Service Failure, School of Chemistry & Chemical Engineering, Huazhong University of Science & Technology, Luoyu Road 1037, Wuhan 430074, China
*
Correspondence: hdong@mail.hust.edu.cn

Abstract: Acetalization and deacetalation are a pair of routine manipulations to protect and deprotect the 4- and 6-hydroxyl groups of glycosides in the synthesis of glycosyl building blocks. In this study, we found that treatment of SnCl₄ with various carbohydrates containing acetal/ketal groups with the assistance of water in CH₂Cl₂ led to deacetalization/deketalization products in almost quantitative yields. In addition, for substrates containing both acetal/ketal and p-methoxylbenzyl groups, we also found that the p-methoxylbenzyl group was selectively cleaved by the use of a catalytic amount of SnCl₄, while the acetal/ketal groups remained. Furthermore, based on this, 4,6-benzylidene glycosides can be conveniently converted to 4,6-OAc or 4-OH, 6-OAc glycosides.

Keywords: glycosides; SnCl₄; 4,6-arylidene; deacetalization; selectivity

1. Introduction

Orthogonally protected glycosyl building blocks play key roles in the synthesis of oligosaccharides, whose preparation usually requires multiple steps of selective protection and deprotection [1–7]. Acetalation is a routine manipulation for protecting the 4- and 6-hydroxyl groups of glycosides in the synthesis of glycosyl building blocks [8–17], and thus methods for removing 4,6-arylidene acetals were extensively reported [18–33]. Acidic hydrolysis of the 4,6-arylidene group is the most commonly used method, including the use of AcOH [18,19], CF₃COOH [18,19], VO(OTf)₂ [20], Er(OTf)₃ [21], SnCl₂ [22], NaHSO₄ [23], I₂ [24] and so on (Entries 1–7 in Table 1). Improved methods included the combined use of Lewis acids and dithiols (Entries 8–9) [25,26], and the use of silica gel supported acids (Entries 10–15) [27–32]. In addition, an improved method for deprotection of the 4,6-arylidene group under hydrogenation conditions was to use Et₃SiH instead of H₂ (Entry 16) [33]. These methods each have their own advantages and disadvantages, and the disadvantages usually include relatively harsh conditions, long reaction times, incompatibility with many functional groups and the formation of unwanted byproducts.

SnCl₄, as a Lewis acid, was used in the selective removal of benzyl groups in carbohydrate synthesis, but exhibited relatively low reactivity [34]. Considering the difference in the stability of benzyl and benzylidene under acidic conditions, we then attempted to use SnCl₄ to achieve rapidly and highly selective removal of acetal and ketal groups. In this study, we found that treatment of carbohydrates containing acetal/ketal groups with SnCl₄ with the assistance of water in CH₂Cl₂ (DCM) led to deacetalization/deketalization products in almost quantitative yields. For substrates containing both acetal/ketal and PMB groups, we also found that the PMB group was selectively cleaved by the use of a catalytic amount of SnCl₄ in DCM, while the acetal/ketal groups remained (Scheme 1a). Furthermore, based on SnCl₄-promoted deacetalization, 4,6-benzylidene glycosides can be conveniently converted to 4,6-OAc glycosides (Scheme 1b) or 4-OH, 6-OAc glycosides (Scheme 1c).
leads to the cleavage of the benzylidene group, and the formation of the intermediate 1a.

**Table 1.** Comparison of methods for removing 4,6-arylidene acetics.

| Entry | Reaction Conditions | Lit. |
|-------|---------------------|------|
| 1     | AcOH/H$_2$O, 100 °C, 0.5–1 h | [18,19] |
| 2     | TFA/H$_2$O, CH$_2$Cl$_2$, rt, 0.5–1 h | [18,19] |
| 3     | VO(OTf)$_2$, MeOH/CH$_2$Cl$_2$, 55 °C, 16–18 h | [20] |
| 4     | Er(OTf)$_3$, CH$_3$CN, rt, 2–24 h | [21] |
| 5     | SnCl$_2$, CH$_2$Cl$_2$, rt, 12 h | [22] |
| 6     | NaHSO$_4$, MeOH/CH$_2$Cl$_2$, rt, 1–24 h | [23] |
| 7     | I$_2$, CH$_3$OH, rt/reflux, 24/2.5 h | [24] |
| 8     | VO(OTf)$_2$/HS(CH$_2$)$_2$SH, CH$_3$CN/CH$_2$Cl$_2$, rt, 1 h | [25] |
| 9     | CSA/DTT, CH$_2$Cl$_2$, rt, 2 h | [26] |
| 10    | FeCl$_3$-SiO$_2$, CHCl$_3$, rt, 10 h | [27] |
| 11    | NaHSO$_4$-SiO$_2$, MeOH/CH$_2$Cl$_2$, rt, 10–20 h | [28] |
| 12    | HClO$_2$-SiO$_2$, CH$_3$CN, rt, 0.5 h | [29] |
| 13    | H$_2$SO$_4$-SiO$_2$, CH$_2$Cl$_2$, rt, 0.5 h | [30] |
| 14    | PMA-SiO$_2$, CH$_2$Cl$_2$, 0.5–5 h | [31] |
| 15    | AcOH/H$_2$O-SiO$_2$, microwave, 10 min | [32] |
| 16    | Et$_3$SiH, Pd/C, CH$_3$OH, rt, 0.5–2 h | [33] |

**Scheme 1.** Application of SnCl$_4$-promoted cleavage of acetal/PMB in this study.

**2. Results**

We first evaluated the potential of SnCl$_4$ to remove the 4,6-O-benzylidene group of glycosides using methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside 1a as a model compound. Thus, 1a was allowed to react with SnCl$_4$ in DCM at rt (Table 2). Interestingly, as the used amount of SnCl$_4$ was gradually increased from 0.2 equiv to 2.5 equiv, the yield of the deacetalation product 2 increased from 19% to a nearly quantitative yield (Entries 1–3). These results seem to support an equilibrium reaction. The reaction mechanism is proposed in Figure 1a, where the coordination of SnCl$_4$ to the 4,6-oxygen atoms of 1a leads to the cleavage of the benzylidene group, and the formation of the intermediate M and dichlorotoluene. However, we failed when we tried to capture dichlorotoluene by an NMR experiment to support this mechanism (Figure S1 in SI). The fact that benzaldehyde
was captured instead of dichlorotoluene supports the mechanism shown in Figure 1b, where trace amounts of water play an indispensable role in the cleavage of the benzylidene group. The mechanism also explained why it is not feasible to use a catalytic amount of SnCl₄ in the reaction. When the solvent used in the reaction was changed from DCM to the more polar methanol and acetonitrile, the yields of 2 were greatly reduced (Entry 4). The reason must be due to the competitive coordination of SnCl₄ with polar solvents.

Table 2. Various conditions for deacetalation of 1.

| Entry | Additives (equiv) | Reaction Conditions | Yield of 2 (%) |
|-------|-------------------|---------------------|---------------|
| 1     | SnCl₄ (0.2\(0.5\)) | DCM, rt. 0.5 h      | 19\(47\)     |
| 2     | SnCl₄ (1.0\(1.5\)) | DCM, rt. 0.5 h      | 69\(79\)     |
| 3     | SnCl₄ (2.0\(2.5\)) | DCM, rt. 0.5 h      | 93\(95\)     |
| 4     | SnCl₄ (2.5)        | MeOH\(\text{MeCN}\), rt. 0.5 h | 20\(40\)     |
| 5      | SnCl₄ (1.2), H₂O (0.5\(1.0\)) | DCM, rt. 0.5 h | 85\(92\)     |
| 6     | SnCl₄ (1.2), H₂O (0.5\(1.0\)) | DCM, rt. 0.5 h | 80\(91\)     |
| 7     | SnCl₄ (0.5\(1.0\)), H₂O (1.0) | DCM, rt. 0.5 h | 47\(75\)     |
| 8     | SnCl₄ (1.2\(1.5\)), H₂O (1.5\(1.0\)) | DCM, rt. 10 min | 93\(95\)     |
| 9     | SnCl₄ (1.5), MeOH (2.0\(3.0\)) | DCM, rt. 0.5 h | 37\(41\)     |
| 10    | HCl (36%, 0.3)    | DCM, rt. 0.5 h      | 32            |
| 11    | SnCl₂\(\text{FeCl}_3\) (1.2), H₂O (1.0) | DCM, rt. 0.5 h | 63\(71\)     |
| 12    | CuCl₂\(\text{Cu(OTf)}_2\) (1.2), H₂O (1.0) | DCM, rt. 0.5 h | 0\(10\)      |
| 13    | SnCl₄ (1.2), AcCl (1.2\(2.2\)) | DCM, rt. 0.5 h | -            |
| 14    | SnCl₄ (1.2), Ac₂O (1.2\(2.2\)) | DCM, rt. 0.5 h | 2a: 30\(78\) |

\(^a\) Reaction conditions: substrate 1 (50 mg), DCM (1 mL). \(^b\) Water was added after stirring for 10 min after the addition of SnCl₄.

As can be seen from the NMR spectrum (Figure S1 in SI), the reaction was terminated when the trace amounts of water in the \(\delta\)-chloroform was consumed. We then tried using water to assist this reaction (Entries 5–8). As can be seen, optimal conditions were to use 1.2–1.5 equiv of SnCl₄ and 1.0–1.5 equiv of water; reaction at rt for 10 min under these conditions led to 2 in a nearly quantitative yield (Entry 8). Similar results for Entries 5 and 6 indicate that the simultaneous addition of SnCl₄ and water had no adverse effect on the yield of 2. However, methanol used as a hydrogen source instead of water in the reaction proved to be ineffective (Entry 9). The use of HCl, SnCl₂, FeCl₃, CuCl₂ and Cu(OTf)₂ instead
of SnCl₄ in the reaction resulted in varying degrees of reduced yields of 2 (Entries 10–12). We also envisaged that the reaction of AcCl/Ac₂O with M might produce selectively acetylated products. Therefore, AcCl/Ac₂O instead of water was added to the reaction. However, the addition of AcCl led to the formation of a complex mixture (Entry 13), and the addition of Ac₂O led to the formation of 4,6-OAc product 2a as the main product (Entry 14), indicating poor selective acetylations.

With the optimized conditions in hand, 4,6-O-arylidene glycosides 1b, 1c, 3, 5, 7, 11, 13, 15, 17 and 19 were further evaluated in the reaction (Entries 1–6 in Table 3). It can be seen that deacetalized products 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 were obtained in 89–98% yields after treating the substrates with 1.5 equiv of SnCl₄ in the presence of 1.0 equiv of water in DCM for 10 min at rt. The results indicate that this method was compatible with various configurations of glycosides and functional groups. In particular, unlike the reported effect of SnCl₄ on 1-STol/SBn glycosides [35], SnCl₄ did not cause cleavage or configurational isomerization of the 1-STol/SBn group for 1-STol/SBn glycoside substrates (Entry 4). Encouraged by these results, we further tested removal of the isopropylidene ketal protecting group under these conditions. Similarly, the deketalized products 22, 24 and 26 were obtained in 94–97% yields from 21, 23 and 25 after only 10 min of reaction at rt (Entries 7 and 8). Especially, for the 1,2,5,6-diisopropylidene ketal-protected furanose substrates 23 and 25, the 5,6-isopropylidene ketal were preferentially removed to obtain the 1,2-isopropylidene ketal-protected furanose products 24 and 26 in excellent yields by this method (Entry 8).

We also noticed that the 4-methoxybenzyl (PMB) protecting group could be deprotected in the presence of catalytic amounts of SnCl₄ [36]. The catalytic mechanism involved the formation of the desired alcohol, the release of a PMB cation, and the subsequent formation of a lipophilic side product through the Friedel–Crafts alkylation of the PMB cation with another PMB ether [37,38]. Indeed, after treatment of methyl 2,4,6-tri-O-acetyl-3-O-PMB-galactoside/mannoside 27/29 with 0.2 equiv of SnCl₄ in DCM at rt for 10 min, the PMB-removed products 28/30 were obtained in 92/98% yield (Entries 9 and 10). Since the reactivity for removing PMB is much higher than that for removing acetal/ketal by SnCl₄, we guessed that PMB should be preferentially removed from substrates containing both PMB and acetal/ketal in the presence of catalytic amounts of SnCl₄. Therefore, four substrates 31, 33, 35 and 37 containing both PMB and acetal/ketal were treated with 0.2–0.5 equiv of SnCl₄ in DCM at rt for 5 min, leading to the selective PMB-removed products 32, 34, 36 and 38 in 80–85% yields (Scheme 2).

In the control experiment shown for Entry 14 in Table 2, the 4,6-benzylidene acetal was conveniently converted to 4,6-OAc for 1a when acetic anhydride was used instead of H₂O during the SnCl₄-promoted deacetalation; in addition, a 78% yield of 2a was obtained when acetic anhydride was directly added dropwise to the reaction mixture. Further experiments indicate that the yield of 2a increased to 91% when a solution of acetic anhydride in dry acetonitrile was added dropwise to the reaction mixture (Scheme 3). Using this method, 4,6-OAc glycosides 41 (82%), 42 (85%) and 43 (88%) were obtained in high yields from 4,6-benzylidene glycosides 15, 39 and 40 (Scheme 3). As seen in Table 2, the SnCl₄-mediated deacetalation method led to deprotected diol products in almost quantitative yields. We thus envisioned a directly selective acetylation of 6-OH after deprotection of 4,6-benzylidene glycosides without purification of the 4,6-OH glycoside products. After the SnCl₄-promoted deacetalation of 4,6-O-benzylidene glycosides 1a, 15, 39 and 40 was completed, the reaction mixture was dissolved in dichloromethane and extracted using a saturated sodium bicarbonate solution and a saturated sodium potassium tartrate solution. The concentrated crude products were then dissolved in dry acetonitrile, followed by the addition of 1.1 equiv of Ac₂O and 0.2 equiv of DIPEA [39]. The reaction proceeded at 40 °C for 12 h, resulting in 6-OAc products 44, 45, 46 and 47 in 70%, 64%, 69% and 65% yields, respectively (Scheme 3).
We also noticed that the 4-methoxylbenzyl (PMB) protecting group could be removed by reaction with SnCl₄:  

(1): SnCl₄ (1.5 equiv), H₂O (1 equiv), DCM, rt, 10 min;  
(2): DIPEA (0.2 equiv), Ac₂O (1.1 equiv), MeCN, 40 °C, 12 h.

Table 3. Deprotection of Acetal, Ketal and PMB groups with SnCl₄/H₂O.

| Entry | Substrate | Product | Yield |
|-------|-----------|---------|-------|
| 1     |           |         |       |
| 1b: R = 4-OMe-Ph | 2 | 92% from 1b |
| 1c: R = 4-Bn-Ph | 2 | 90% from 1c |
| 2     |           |         |       |
| 3: R = Me, 5: R = Ac | 4 | 6: 98% |
| 7: R = Ph | 8 | 8: 97% |
| 3     |           |         |       |
| 11: R = Sb | 12 | 12: 90% |
| 13: R = STol | 14 | 14: 94% |
| 4     |           |         |       |
| 15: R₆ = H, R₇ = OMe | 16 | 16: 89% |
| 17: R₆ = H, R₇ = OMe | 18 | 18: 90% |
| 5     |           |         |       |
| 19: R₆ = OMe | 20 | 97% |
| 21: OMe | 22 | 97% |
| 6     |           |         |       |
| 23: R = Bz, 25: R = Bn | 24 | 25: 94% |
| 26: R = Bz, 26: R = Bn | 27 | 27: 95% |
| 7     |           |         |       |
| 28: OMe | 29 | 92% |
| 10 b  |           |         |       |
| 27: OMe | 30 | 98% |

Reagents and conditions: a SnCl₄ (1.5 equiv), water (1.0 equiv), DCM, rt, 10 min. b SnCl₄ (0.2 equiv), DCM, rt, 10 min.

Scheme 2. Selective cleavage of PMB group in the presence of SnCl₄. Reagents and conditions:  
(a) SnCl₄ (0.2 equiv), DCM, rt, 5 min; (b) SnCl₄ (0.5 equiv), DCM, rt, 5 min.
was added to a solution of a carbohydrate substrate containing PMB in DCM (1 mL). The residue was purified by silica gel flash chromatography.

The mixture was stirred at room temperature for 5 min and then poured onto a cold saturated NaHCO₃ solution (15 mL), dried with anhydrous MgSO₄, and concentrated in vacuo. The residue was purified by silica gel flash chromatography.

3. Conclusions

In this study, it was found that acetal and ketal protective groups could be efficiently removed in the presence of SnCl₄ for orthogonally protected carbohydrate substrates. The reaction can be completed in DCM within 10 min at room temperature, and a small amount of water has an obvious promoting effect on the reaction. It was also found that the PMB could be preferentially removed from the substrates containing both acetal/ketal and PMB by a catalytic amount of SnCl₄. Based on SnCl₄-promoted deacetalation, 4,6-benzylidene glycosides can be conveniently converted to 4,6-OAc glycosides and 4-OH, 6-OAc glycosides. These methods provide efficient approaches to synthesizing orthogonally protected carbohydrate building blocks.

4. Materials and Methods

General Methods. All chemicals were purchased as reagent grade and used without further purification. The solvents were purified before use and CH₃CN was distilled from CaH₂. Chemical reactions were monitored by thin-layer chromatography using precoated silica gel 60 (0.25 mm thickness) plates. Flash column chromatography was performed on silica gel 60 (SDS 0.040–0.063 mm). Spots were visualized by UV light (254 nm) then by charring with a solution of H₂SO₄ (5%) in ethanol. ¹H NMR spectra were recorded by 400 MHz or 600 MHz (¹H) and 100 MHz (¹³C) at 298 K in CDCl₃ using the residual signals from CDCl₃ (¹H: δ = 7.26 ppm; ¹³C: δ = 77.16 ppm) or CD₂OD (¹H: δ = 3.31 ppm) as the internal standard. ¹H peak assignments were made by first order analysis of the spectra, supported by standard ¹H–¹H correlation spectroscopy (COSY). High-resolution mass spectra (HRMS) were obtained by TOF detection. Optical rotations were measured on an SGW-1 automatic polarimeter with [α]D values reported in degrees; concentration (c) is in g/100 mL.

General procedure A for SnCl₄-mediated deacetalization. SnCl₄ (1.5 equiv) and H₂O (1.0 equiv) were added to a solution of a carbohydrate substrate containing acetal/ketal in DCM (1 mL). The mixture was stirred at room temperature for 10 min and then poured onto a cold saturated NaHCO₃ solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with saturated sodium potassium tartrate solution (1 × 15 mL), dried with anhydrous MgSO₄, and concentrated in vacuo. The residue was purified by silica gel flash chromatography.

General procedure B for SnCl₄-mediated removal of PMB. SnCl₄ (0.2–0.5 equiv) was added to a solution of a carbohydrate substrate containing PMB in DCM (1 mL). The mixture was stirred at room temperature for 5 min and then poured onto a cold saturated NaHCO₃ solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with the saturated NaHCO₃ solution (1 × 15 mL), dried with anhydrous MgSO₄, and concentrated in vacuo. The residue was purified by silica gel flash chromatography.
**General procedure C** for converting of 4,6-benzylidene to 4,6-OAc for glycosides. SnCl₄ (1.5 equiv) and a solution of acetic anhydride (2.0 equiv), added dropwise in dry acetonitrile (0.5 mL), were added to a solution of a 4,6-benzylidene glycoside in DCM (1 mL). The mixture was stirred at rt for 10 min and then poured onto a cold saturated NaHCO₃ solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with the saturated NaHCO₃ solution (1 × 15 mL), dried with anhydrous MgSO₄, and concentrated in vacuo. The residue was purified by silica gel flash chromatography.

**General procedure D** for converting of 4,6-benzylidene to 4-OH, 6-OAc for glycosides. SnCl₄ (1.5 equiv) and H₂O (1.0 equiv) were added to a solution of a carbohydrate substrate containing acetal/ketal in DCM (1 mL). The mixture was stirred at rt for 10 min and then poured onto cold saturated a NaHCO₃ solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with saturated sodium potassium tartrate solution (1 × 15 mL), dried with anhydrous MgSO₄ and concentrated in vacuo. The residue was allowed to react with acetic anhydride (1.1 equiv) in the presence of DIPEA (0.2 equiv) in dry acetonitrile (1 mL) at 40 °C for 12 h. After cooling and evaporation of the solvent, the reaction mixture was directly purified by flash column chromatography.

Methyl 2,3-di-O-benzyl-α-D-glucopyranoside (2) [26]. Following general process A, starting from 1a (100 mg, 0.22 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 2 as a white solid (77 mg, 95%). ¹H NMR (600 MHz, CDCl₃) δ 7.40–7.28 (m, 10H), 5.03 (d, J = 11.5 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 3.5 Hz, 1H), 3.83–3.76 (m, 2H), 3.74 (dd, J = 11.5, 4.6 Hz, 1H), 3.62 (dt, J = 8.4, 4.1 Hz, 1H), 3.55–3.47 (m, 2H), 3.38 (s, 3H).

Methyl 2,3-di-O-methyl-α-D-glucopyranoside (4) [40]. Following general process A, starting from 3 (72 mg, 0.23 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 4 as a white solid (46.7 mg, 91%). ¹H NMR (400 MHz, CDCl₃) δ 4.85 (d, J = 3.5 Hz, 1H), 3.92–3.74 (m, 2H), 3.64 (s, 4H), 3.53–3.46 (m, 5H), 3.44 (s, 3H), 3.28–3.18 (m, 1H).

Methyl 2,3-di-O-acetyl-α-D-glucopyranoside (6) [26]. Following general process A, starting from 5 (41 mg, 0.11 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 6 as a colorless oil (30.5 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ 5.34–5.25 (m, 1H), 4.91 (d, J = 11.5 Hz, 1H), 4.83 (dd, J = 10.1, 3.6 Hz, 1H), 3.95–3.82 (m, 2H), 3.76–3.65 (m, 2H), 3.40 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H).

Methyl 2,3-di-O-pivaloyl-α-D-glucopyranoside (8) [41]. Following general process A, starting from 7 (28.2 mg, 0.063 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 8 as a colorless oil (22 mg, 97%). ¹H NMR (400 MHz, CD$_2$OD) δ 5.46–5.30 (m, 1H), 4.73 (dd, J = 10.1, 3.6 Hz, 1H), 3.85 (dd, J = 11.9, 2.2 Hz, 1H), 3.74 (dd, J = 11.9, 5.1 Hz, 1H), 3.66 (ddd, J = 10.1, 5.1, 2.2 Hz, 1H), 3.58 (t, J = 9.5 Hz, 1H), 3.42 (s, 3H), 3.36–3.30 (m, 1H), 1.21 (s, 9H), 1.18 (s, 9H).

Methyl 2,3-di-O-benzoyl-β-D-glucopyranoside (10) [26]. Following general process A, starting from 9 (64 mg, 0.13 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 10 as a colorless oil (49.8 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 8.02–7.89 (m, 4H), 7.51 (t, J = 7.8 Hz, 2H), 7.37 (td, J = 7.8, 3.6 Hz, 4H), 5.49–5.28 (m, 2H), 4.74–4.54 (m, 1H), 4.04–3.90 (m, 3H), 3.60 (dt, J = 9.2, 4.0 Hz, 1H), 3.53 (s, 3H).

**Benzyl 2,3-di-O-acetyl-1-thio-β-D-glucopyranoside** (12). Following general process A, starting from 11 (25 mg, 0.055 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 12 as a colorless oil (18.8 mg, 93%). [α]$_D^{12}$ = −88 (c 0.2, CH$_2$Cl$_2$), ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.23 (m, 5H), 5.07–4.91 (m, 2H), 4.39 (d, J = 8.0 Hz 1H), 3.95–3.87 (m, 3H), 3.80–3.64 (m, 2H), 3.39–3.17 (m, 2H), 2.34–2.18 (b, 1H), 2.08 (s, 3H), 2.03 (s, 3H). ¹C NMR (100 MHz, CDCl₃) δ 171.58, 169.68, 163.45, 128.95, 128.61, 128.56, 127.38, 82.63, 79.65, 69.69, 69.28, 62.12, 34.40, 20.86, 20.74. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for [C$_{11}$H$_{22}$O$_7$SNa]$^+$: 393.0984; found: 393.0964.
4-Methylphenyl 2,3-di-O-acetyl-1-thio-D-glucopyranoside (14) [25]. Following general process A, starting from 13 (26 mg, 0.06 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 14 as a colorless oil (19.4 mg, 94%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.41-7.35\) (m, 2H), \(7.15\) (d, \(J = 7.9\) Hz, 2H), \(5.05\) (t, \(J = 9.3\) Hz, 1H), 4.92 (t, \(J = 9.6\) Hz, 1H), 4.69 (d, \(J = 10.0\) Hz, 1H), 4.02–3.89 (m, 1H), 3.83 (d, \(J = 12.2\) Hz, 1H), 3.73 (t, \(J = 9.6\) Hz, 1H), 3.53–3.42 (m, 1H), 2.36 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H).

Methyl 2,3-di-O-benzyl-\(\alpha\)-D-galactopyranoside (16) [20]. Following general process A, starting from 15 (53 mg, 0.11 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 16 as a colorless oil (38 mg, 89%). \(^1\)H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta 7.42-7.26\) (m, 10H), 4.81 (d, \(J = 11.8\) Hz, 2H), 4.70 (dd, \(J = 7.4, 4.2\) Hz, 2H), 4.67 (d, \(J = 12.1\) Hz, 1H), 4.05 (dd, \(J = 2.9, 1.4\) Hz, 1H), 3.93–3.83 (m, 3H), 3.79–3.73 (m, 2H), 3.38 (s, 3H).

Methyl 2,3-di-O-benzyl-\(\beta\)-D-galactopyranoside (18) [42]. Following general process A, starting from 17 (48 mg, 0.1 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 18 as a white solid (38.8 mg, 90%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.42-7.27\) (m, 10H), 4.90 (d, \(J = 11.0\) Hz, 1H), 4.77–4.68 (m, 3H), 4.30 (d, \(J = 7.7\) Hz, 1H), 4.04–3.93 (m, 2H), 3.83 (dd, \(J = 11.7, 4.5\) Hz, 1H), 3.67–3.61 (m, 1H), 3.58 (s, 3H), 3.53–3.46 (m, 2H), 2.66 (s, 1H), 2.21 (t, \(J = 7.6\) Hz, 1H).

Methyl 2,3-di-O-acetyl-\(\alpha\)-mannopyranoside (20) [43]. Following general process A, starting from 19 (27 mg, 0.15 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 20 as a white solid (19.5 mg, 95%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 5.22\) (dd, \(J = 3.5, 1.7\) Hz, 1H), 5.17 (dd, \(J = 9.9, 3.4\) Hz, 1H), 4.67 (d, \(J = 1.7\) Hz, 1H), 3.98 (t, \(J = 9.8\) Hz, 1H), 3.89 (dd, \(J = 4.0, 2.1\) Hz, 2H), 3.70 (dt, \(J = 9.8, 3.9\) Hz, 1H), 3.39 (s, 3H), 2.69 (s, 1H), 2.12 (s, 3H), 2.07 (s, 3H), 1.79 (s, 1H).

Methyl 2,6-di-O-benzyl-\(\alpha\)-D-galactopyranoside (22) [44]. Following general process A, starting from 21 (64 mg, 0.15 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 22 as a colorless oil (56 mg, 97%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.43-7.22\) (m, 10H), 4.70 (d, \(J = 3.7\) Hz, 1H), 4.70–4.61 (m, 2H), 4.57 (d, \(J = 1.9\) Hz, 2H), 4.04 (d, \(J = 3.4\) Hz, 1H), 3.96 (dd, \(J = 9.8, 3.4\) Hz, 1H), 3.94–3.86 (m, 1H), 3.76–3.68 (m, 3H), 3.35 (s, 3H).

3-O-benzoyl-1,2-O-isopropylidene-\(\alpha\)-D-glucofuranose (24) [45]. Following general process A, starting from 23 (78.7 mg, 0.22 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 24 as a colorless oil (66.1 mg, 94%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 8.14-7.98\) (m, 2H), 7.67–7.57 (m, 1H), 7.47 (t, \(J = 7.7\) Hz, 2H), 6.01 (d, \(J = 3.7\) Hz, 1H), 5.53 (d, \(J = 2.6\) Hz, 1H), 4.73 (d, \(J = 3.7\) Hz, 1H), 4.30 (dd, \(J = 8.6, 2.6\) Hz, 1H), 3.87 (d, \(J = 8.1\) Hz, 1H), 3.75 (d, \(J = 8.3\) Hz, 2H), 3.19 (s, 1H), 2.29–2.13 (m, 1H), 1.56 (s, 3H), 1.34 (s, 3H).

3-O-Benzyl-1,2-O-isopropylidene-\(\alpha\)-D-glucofuranose (26) [26]. Following general process A, starting from 25 (139 mg, 0.4 mmol), purification by column chromatography (petroleum ether/ethyl acetate 1/1.5) afforded 26 as a colorless oil (112 mg, 91%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 7.44-7.29\) (m, 5H), 5.96 (d, \(J = 3.8\) Hz, 1H), 4.75 (d, \(J = 11.8\) Hz, 1H), 4.65 (d, \(J = 3.8\) Hz, 1H), 4.58 (d, \(J = 11.7\) Hz, 1H), 4.14–4.09 (m, 2H), 4.05–4.00 (m, 1H), 3.82 (dd, \(J = 11.5, 3.4\) Hz, 1H), 3.71 (dd, \(J = 11.5, 5.4\) Hz, 1H), 2.70 (s, 1H), 1.91 (s, 1H), 1.50 (s, 3H), 1.34 (s, 3H).

Methyl 2,4,6-tri-O-acetyl-\(\alpha\)-D-galactopyranoside (28) [46]. Following general process B, starting from 27 (45 mg, 0.1 mmol), purification by column chromatography (petroleum ether/ethyl acetate 2/1) afforded 28 as a white solid (30 mg, 92%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 5.35\) (dd, \(J = 3.7, 1.2\) Hz, 1H), 4.98 (dd, \(J = 10.1, 8.0\) Hz, 1H), 4.38 (d, \(J = 7.9\) Hz, 1H), 4.22–4.17 (m, 2H), 3.91–3.84 (m, 1H), 3.54 (s, 3H), 2.58 (d, \(J = 6.3\) Hz, 1H), 2.20 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H).

Methyl 2,4,6-tri-O-acetyl-\(\alpha\)-D-mannopyranoside (30) [43]. Following general process B, starting from 29 (88 mg, 0.2 mmol), purification by column chromatography (petroleum ether/ethyl acetate 2/1) afforded 30 as a colorless oil (53 mg, 98%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta 5.15–5.00\) (m, 2H), 4.77 (d, \(J = 1.6\) Hz, 1H), 4.31 (dd, \(J = 12.2, 5.4\) Hz, 1H), 4.14 (dd,
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1H, 4.81 (d, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H).

43 (petroleum ether/ethyl acetate 3/1) afforded

38 as a colorless oil (37.1 mg, 84%). 1H NMR (400 MHz, CDCl3) δ 5.57 (d, J = 5.0 Hz, 1H), 4.62 (dd, J = 8.0, 2.4 Hz, 1H), 4.34 (dd, J = 5.1, 2.4 Hz, 1H), 4.32–4.23 (m, 1H), 3.87 (d, J = 9.4 Hz, 2H), 3.82–3.68 (m, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 1.34 (s, 6H).

Methyl 2,3-di-O-benzyl-4,6-di-O-acetyl-a-D-galactopyranoside (2a) [29]. Following general process C, starting from 1a (100 mg, 0.22 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 2a as a white solid (90 mg, 91%). 1H NMR (400 MHz, CDCl3) δ 7.42–7.28 (m, 10H), 4.99 (dd, J = 10.3, 9.3 Hz, 1H), 4.89 (d, J = 11.6 Hz, 1H), 4.81 (d, J = 12.1 Hz, 1H), 4.65 (d, J = 12.1 Hz, 2H), 4.59 (d, J = 3.6 Hz, 1H), 4.21 (dd, J = 12.1, 4.9 Hz, 1H), 4.00 (dd, J = 12.1, 2.3 Hz, 1H), 3.92 (t, J = 9.4 Hz, 1H), 3.88–3.82 (m, 1H), 3.59 (dd, J = 9.6, 3.5 Hz, 1H), 3.39 (s, 3H), 2.06 (s, 3H), 1.91 (s, 3H).

Methyl 2,3-di-O-benzyl-4,6-di-O-acetyl-a-D-galactopyranoside (41) [29]. Following general process C, starting from 15 (80 mg, 0.17 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 41 as a colorless oil (65 mg, 82%). 1H NMR (400 MHz, CDCl3) δ 7.43–7.22 (m, 10H), 5.54 (d, J = 3.4 Hz, 1H), 4.85 (d, J = 12.1 Hz, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.69 (d, J = 3.6 Hz, 1H), 4.65 (d, J = 12.1 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 4.14–4.05 (m, 3H), 3.97 (dd, J = 10.0, 3.5 Hz, 1H), 3.78 (dd, J = 10.0, 3.7 Hz, 1H), 3.39 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H).

Methyl 2,3-di-O-benzyl-4,6-di-O-acetyl-a-D-mannopyranoside (42) [50]. Following general process C, starting from 19 (180 mg, 0.4 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 42 as a colorless oil (151 mg, 85%). 1H NMR (400 MHz, CDCl3) δ 7.38–7.27 (m, 11H), 5.41 (dd, J = 10.0, 9.1 Hz, 1H), 4.81–4.74 (m, 2H), 4.69 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 4.23 (dd, J = 12.1, 5.6 Hz, 1H), 4.13 (dd, J = 12.1, 2.5 Hz, 1H), 3.85–3.75 (m, 3H), 3.33 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 170.91, 169.75, 138.17, 138.12, 128.36, 128.32, 127.86, 127.65, 127.63, 127.41, 99.44, 73.96, 72.86, 71.86, 68.97, 68.08, 63.06, 55.00, 29.71, 20.92, 20.84.

Methyl 2,3-di-O-benzyl-4,6-di-O-acetyl-b-D-glucopyranoside (43) [50]. Following general process C, starting from 40 (90 mg, 0.19 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 43 as a colorless oil (78 mg, 88%). 1H NMR (400 MHz, CDCl3) δ 7.43–7.14 (m, 10H), 5.04 (dd, J = 10.0, 9.3 Hz, 1H), 4.91 (d, J = 10.9 Hz, 1H), 4.83 (d, J = 11.5 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.34 (d,
$J = 7.7$ Hz, 1H), 4.25 (dd, $J = 12.2, 5.0$ Hz, 1H), 4.08 (dd, $J = 12.2, 2.4$ Hz, 1H), 3.64–3.52 (m, 5H), 3.49 (dd, $J = 9.2, 7.7$ Hz, 1H), 2.08 (s, 3H), 1.92 (s, 3H).

$^13$C NMR (100 MHz, CDCl$_3$) δ 170.85, 169.58, 138.25, 138.23, 128.40, 128.38, 128.15, 127.83, 127.78, 127.74, 104.72, 81.96, 81.52, 75.15, 74.91, 71.81, 69.72, 62.40, 57.29, 20.80.

**Methyl 2,3-di-O-benzyl-6-acetyl-$\alpha$-D-glucopyranoside** (44) [39]. Following general process D, starting from 1a (100 mg, 0.22 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 44 as a colorless oil (63.5 mg, 70%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.40–7.27 (m, 10H), 5.00 (d, $J = 11.3$ Hz, 1H), 4.82–4.72 (m, 2H), 4.66 (d, $J = 12.1$ Hz, 1H), 4.62 (d, $J = 3.5$ Hz, 1H), 4.42 (dd, $J = 12.1, 4.7$ Hz, 1H), 4.21 (dd, $J = 12.1, 2.2$ Hz, 1H), 3.79 (t, $J = 9.2$ Hz, 1H), 3.74 (ddd, $J = 10.0, 4.7, 2.2$ Hz, 1H), 3.51 (s, 3H), 2.08 (s, 3H).

**Methyl 2,3-di-O-benzyl-6-acetyl-$\alpha$-D-galactopyranoside** (45) [51]. Following general process D, starting from 15 (155 mg, 0.33 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 45 as a colorless oil (89 mg, 64%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.41–7.22 (m, 10H), 4.81 (dd, $J = 11.8, 2.2$ Hz, 2H), 4.74–4.62 (m, 3H), 4.34–4.19 (m, 2H), 3.97 (t, $J = 2.8$ Hz, 1H), 3.96–3.82 (m, 3H), 3.37 (s, 3H), 2.55 (t, $J = 1.5$ Hz, 1H), 2.07 (s, 3H).

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.43–7.11 (m, 10H), 4.98 (d, $J = 5.0$ Hz, 1H), 4.79 (d, $J = 3.6$ Hz, 1H), 4.73–4.55 (m, 4H), 4.20–4.06 (m, 2H), 4.06–4.00 (m, 1H), 3.77–3.74 (m, 2H), 3.67 (dd, $J = 10.1, 3.1$ Hz, 1H), 3.26 (s, 3H), 2.05 (s, 3H).

**Methyl 2,3-di-O-benzyl-6-acetyl-$\alpha$-D-mannopyranoside** (46) [39]. Following general process D, starting from 39 (116 mg, 0.25 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 46 as a colorless oil (72 mg, 69%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.42–7.23 (m, 10H), 4.78 (d, $J = 1.7$ Hz, 1H), 4.66 (q, $J = 12.3$ Hz, 2H), 4.52 (dd, $J = 11.7, 36$ Hz, 2H), 4.38 (qd, $J = 12.0, 3.8$ Hz, 2H), 3.95 (td, $J = 9.7, 2.2$ Hz, 1H), 3.79 (dd, $J = 3.1, 1.8$ Hz, 1H), 3.76–3.65 (m, 2H), 3.34 (s, 3H), 2.65 (d, $J = 2.2$ Hz, 1H), 2.09 (s, 3H).

**Methyl 2,3-di-O-benzyl-6-acetyl-$\beta$-D-glucopyranoside** (47) [51]. Following general process D, starting from 40 (190 mg, 0.41 mmol), purification by column chromatography (petroleum ether/ethyl acetate 3/1) afforded 47 as a white solid (111 mg, 65%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.52–7.13 (m, 10H), 4.93 (dd, $J = 11.2, 6.6$ Hz, 2H), 4.72 (dd, $J = 11.2, 5.8$ Hz, 2H), 4.41 (dd, $J = 12.1, 4.4$ Hz, 1H), 4.36–4.25 (m, 2H), 3.57 (s, 3H), 3.49–3.34 (m, 4H), 2.65 (d, $J = 2.2$ Hz, 1H), 2.09 (s, 3H).

**Supplementary Materials:** The following supporting information can be downloaded at: [https://www.mdpi.com/article/10.3390/molecules27238258/s1](https://www.mdpi.com/article/10.3390/molecules27238258/s1), Synthesis of substrates [26,49,52–63].

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