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A high-yielding synthesis of allylglycosides from peracetylated glycosyl donors

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Abstract

β -Configured peracetylated sugars are often used as easily accessible glycosyl donors that are typically activated with common Lewis acids such as boron trifluoride or trimethylsilyltrifluoromethane sulfonate. Often these glycosylations occur with unsatisfactory yields due to incomplete reactions or extensive byproduct formation, primarily as a result of loss of an additional acetyl group generating partially unprotected glycosides. Here we report a simple glycosylation-reacetylation protocol for the generation of peracetylated β -allylglycoside, -galactoside, -lactoside, and -maltoside with substantially improved reaction yields.

Keywords

Glycosylation; Allylglycosides; Reacetylation; Acetylated Glycosyl Donors

Allylglycosides are often used as intermediate products in the synthesis of oligosaccharides, in which the allyl group may serve as an orthogonal protecting group for the anomeric center. For example, it can be cleaved by isomerization to the propenyl glycoside with potassium *tert*-butoxide in dimethylsulfoxide followed by hydrolysis in the presence of mercury-II-chloride/mercury oxide,^[1] or by allyl transfer with palladium(II)chloride/sodium acetate in aqueous acetic acid, generating a hemiacetal.^[2] The double bond of allyl glycosides has also been utilized as a handle to functionalize carbohydrates for generating glycoconjugates. For example, ozonolysis of a trisaccharide allylglycoside followed by reductive amination with 7-amino-4-methylcoumarin gives a fluorescent trisaccharide conjugate.^[3] Furthermore, the allylic double bond can be modified by radical addition of thiols such as 2-aminoethanethiol or mercaptoethanol, which allows for further functionalization and derivatization at the amino or hydroxyl group.^[4] Radical addition of thioacetic acid affords a thioacetate,^[5] which can then be saponified. The resulting thiol undergoes nucleophilic substitution with iodoacetyl moieties, which can be used for immobilization by reaction with iodoacetyl-derivatized matrices, or for conjugation with maleimide-modified proteins.^[6]

While allyl- -glucosides and galactosides can be easily synthesized by Fischer glycosylation, the -configured derivatives are best synthesized from glycosyl donors with neighboring

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group participation via the cationic species **2** (Scheme 1). Easily accessible glycosyl donors suitable for this purpose are the peracetylated -configured glucose and galactose derivatives (**7** and **8**), which can be activated with inexpensive Lewis acids such as boron trifluoride etherate or trimethylsilyltrifluoromethane sulfonate (TMSOTf), but other Lewis acid promoters, e.g., zinc chloride, tin tetrachloride and tin tetrachloride/silver acetate mixtures have also been used.^[7] Depending on the reaction conditions certain Lewis acids can also produce predominantly -glycosides via acid catalyzed anomerization.^[7c,d] While there are reports of high glycosylation yields and good stereocontrol achievable with peracetylated donors, in particular for the synthesis of O-aryl glycosides,^[7d] often reaction efficiencies are disappointingly low.^[7b] Therefore, despite the fact that classical peracetylated donors can be easily prepared and stored, their use has been largely replaced with more modern glycosyl donors such as trichloroacetimidates and thioglycosides. We felt that if the low glycosylation efficiencies of peracetylated donors could be overcome, they would be more attractive donors for the preparation of -allylglycosides.

Here we report a simple two-step procedure that affords fully acetylated, predominantly -configured allylglycosides of glucose, galactose, lactose, and maltose in high yield. When monitoring the BF₃·Et₂O or TMSOTf promoted glycosylation of allyl alcohol with peracetylated -configured sugars (**1**) under standard conditions (1–4 equiv. AlOH, 2 equiv. BF₃·Et₂O or TMSOTf, CH₂Cl₂, 0°C → rt), the silica thin layer chromatograms (TLC) of the crude mixtures typically show the presence of several byproducts of higher polarity when compared to the peracetylated allylglycoside product (**3**). A well-known prominent byproduct of this glycosylation reaction is the glycoside **5** that has suffered loss of its 2-O-acetyl group, most likely via nucleophilic attack of allyl alcohol at an intermediate orthoester **4** (Scheme 1).^[7b,8] Other polar byproducts could result from acetyl migration to give allyl glycosides of the general structure **6**.

We envisioned that if most of the byproducts formed are partially deacetylated glycosides, but as long as the -allyl glycosidic linkage formed successfully, high yields of the peracetylated allyl glycosides **3** should be salvagable by reacetylation after the glycosylation reaction. An improvement of reaction yields by reacetylation had been reported for the synthesis of the -methyl and -ethyl-2,3,4,6-tetra-O-acetyl glycosides of glucose and galactose, for which loss of the 2-OAc group had been observed.^[7c] To further investigate the idea of improving yields by a subsequent reacetylation step, peracetylated -configured glucose, galactose, lactose, and maltose (**7–10**) were chosen as model glycosyl donors to be converted into their predominantly -configured allylglycosides (**11–14**), Scheme 2. Indeed, after aqueous workup and treatment of the crude glycosylation mixtures with acetic anhydride in pyridine, much cleaner TLCs were obtained, i.e., each glycosylation reaction showed a very prominent spot of the desired peracetylated -allylglycoside (**3**), a small amount of peracetylated starting material (**1**), and the absence of polar byproducts.^[9] This reacetylation procedure not only increases the reaction yields of product, but also simplifies its purification by column chromatography.

Liu et al. reported that the formation of allylglycoside **5** is favored when allyl alcohol is used in excess, and that the formation of allylglycoside **3** is favored when only 1 equiv. of allyl alcohol is used.^[8a] Therefore, we included varying quantities of allyl alcohol in this study. A total of 12 glycosylation reactions were performed, monitored by TLC, and analyzed by ¹H NMR spectroscopy. Table 1 summarizes the glycosylation results with varying quantities of allyl alcohol, and compares product yields with and without reacetylation. All experiments showed evidence not only of the formation of the desired peracetylated allylglycoside **3**, but also of multiple byproducts, even when only 1.1 equiv. of allyl alcohol was used. In contrast to Liu's findings, in our hands the glycosylation reactions with -acetates **7**, **8**, **9** and **10**, which were performed with only 1.1 equiv. of allyl alcohol, showed low yields of the

peracetylated allylglycoside **3** (20 – 39%) due to incomplete conversion, regardless of whether a reacetylation was performed (entries 1, 4, and 7) or not (entry 10). An increase in the amount of allyl alcohol to four equivalents resulted in substantial byproduct formation, but the starting materials were nearly consumed. When no reacetylation was performed after the glycosylation, the reaction yields of the desired peracetylated allylglycosides were only 18–24% (entries 2, 5, 8, and 11). These reaction yields could be drastically increased to 61–76% when a reacetylation was performed (entries 3, 6, 9, and 12).

In summary, we have demonstrated that α -configured peracetylated sugars give the peracetylated allylglycosides in high yield when the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or TMSOTf promoted glycosylation is followed by a simple reacetylation step. The observation that several polar byproducts converge to the peracetylated allylglycoside upon reacetylation lends support to the fact that nearly all of the byproducts of an individual reaction consisted of partially deacetylated allylglycosides. The applied reacetylation protocol resulted in a substantial increase in yields of the peracetylated, predominantly 1,2-trans configured allylglycosides by a factor of approximately three. This procedure may have implications for the improvement of yields for glycosylations involving other acetylated glycosyl donors and acceptors as well as other glycosylation methods.

1. Experimental

General methods

Thin layer chromatography was performed with silica gel 60 F254, 5–20 m, on aluminum sheets, EMD. Flash chromatography was performed with silica gel, grade A, 32–63 m, Dynamic Adsorbents. ^1H NMR spectra were recorded on a Bruker 300 MHz or a JEOL 600 MHz NMR spectrometer using tetramethylsilane as an internal standard in CDCl_3 as a solvent. ^{13}C NMR spectra were recorded on the same JEOL NMR spectrometer at 150 MHz. Mass spectra were recorded on a JEOL Accu TOF mass spectrometer using electrospray ionization. Dichloromethane and pyridine were refluxed over calcium hydride and then distilled. Allyl alcohol was dried with $3\text{\AA}$ molecular sieves.

Typical glycosylation and reacetylation procedure

A solution of peracetyl- α -lactose **9** (0.2 g, 0.29 mmol) and allyl alcohol (0.08 mL, 1.18 mmol) in anhydrous dichloromethane (2.3 mL) was placed in a 25 mL round bottom flask under argon, and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.15 mL, 0.59 mmol) was added at 0°C . The reaction was stirred at room temperature for 16 hours. Triethylamine (0.08 mL, 0.58 mmol) was then added for neutralization. The reaction mixture was diluted with ethyl acetate (50 mL) and extracted with water (25 mL 3 times) and brine solution (25 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness. To the solution of the crude mixture in pyridine (5 mL), acetic anhydride (5 mL) was added at room temperature under argon and the mixture was stirred for 12 hours. Toluene (25 mL) was then added to the reaction mixture and the solvents were coevaporated under reduced pressure. The residue was diluted with ethyl acetate (50 mL) and washed with water (25 mL, three times) and with cold saturated sodium bicarbonate solution (25 mL). After drying over anhydrous magnesium sulfate and evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexanes/ EtOAc 1:1) to give 76% of the anomeric mixture in an α/β ratio 1:2. R_f of α -allyllactoside **13**: 0.66 (ethyl acetate/hexanes 7:3).

Allyl 2,3,4,6-tetra-O-acetyl- α -D-glucopyranoside (**11**): Glucoside **11** was prepared by the typical glycosylation and reacetylation procedure, except that a small amount of molecular sieves ($3\text{\AA}$) was used in the glycosylation reaction. ^1H NMR (600MHz, CDCl_3 , 300K): δ 5.82 (m, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.16–5.24 (m, 3H, H-3, $\text{CH}_2\text{CH}=\text{CH}_2$, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.06

(dd, 1H, $^3J_{H3/H4}=10.3$ Hz, $^3J_{H4/H5}=10.3$ Hz, H-4); 4.99 (dd, 1H, $^3J_{H2/H3}=9.6$ Hz, H-2); 4.52 (d, 1H, $^3J_{H-1/H-2}=8.3$ Hz, H-1); 4.3 (m, 1H, $OCH_2CH=CH_2$); 4.22 (dd, 1H, $^3J_{H5/H6}=12.4$ Hz, $^2J_{H6/H6'}=4.81$ Hz, H-6); 4.06–4.11 (m, 2H, $OCH_2CH=CH_2$, H6'); 3.65 (m, 1H, H-5), 2.03; 1.99; 1.96; 1.95 (4s, 12H, 4 Ac) ppm. ^{13}C NMR (150MHz, $CDCl_3$, 300K): δ 170.7; 170.3; 169.4; 169.3; 133.3; 117.7; 99.6; 72.9; 71.8; 71.3; 70.1; 68.5; 62.0; 20.7 ppm

Allyl 2,3,4,6-tetra-O-acetyl- β -D-galactopyranoside (**12**): Galactoside **12** was prepared by the typical glycosylation and reacylation procedure, except that a small amount of molecular sieves (3Å) was used in the glycosylation reaction. 1H NMR (600MHz, $CDCl_3$, 300K): δ 5.83 (m, 1H, $CH_2CH=CH_2$); 5.37 (dd, 1H, $^3J_{H4/H5}=1.5$ Hz, H-4); 5.18–5.26 (m, 3H, H-2, $CH_2CH=CH_2$, $CH_2CH=CH_2'$); 5.0 (dd, 1H, $^3J_{H2/H3}=11.0$ Hz, $^3J_{H3/H4}=3.4$ Hz, H-3); 4.5 (d, 1H, $^3J_{H-1/H-2}=7.5$ Hz, H-1); 4.33 (m, 1H, $OCH_2CH=CH_2$); 4.09–4.17 (m, 3H, $OCH_2CH=CH_2$, H-6, H-6'), 3.87 (m, 1H, H-5); 2.13; 2.04; 2.03; 1.96 (4s, 12H, 4 Ac) ppm. ^{13}C NMR (150MHz, $CDCl_3$, 300K): δ 170.2; 170.1; 169.9; 169.3; 177.6; 133.3; 99.6; 70.8; 70.5; 69.8; 68.8; 67.1; 61.3; 20.5 ppm.

Allyl 2,3,4,6-tetra-O-acetyl- β -D-galactopyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-O-acetyl- β -D-glucopyranoside (**13**): The 1H -NMR spectrum of the purified allyl -lactoside **13** in $CDCl_3$ was identical with that reported in the literature.^[10] ^{13}C NMR (150MHz, $CDCl_3$, 300K): δ : 170.5; 170.4; 170.2; 170.2; 169.9; 169.7; 169.2; 133.4; 117.7; 101.2; 99.4; 76.4; 72.9; 72.7; 71.7; 71.1; 70.7; 70.1; 69.2; 66.7; 62.1; 60.9; 21.0; 20.9; 20.8; 20.7; 20.6 ppm. ESI-TOF MS: calcd. for $C_{29}H_{40}NaO_{18}$ $[M+Na]^+$ 699.2112, found 699.2149.

Allyl 2,3,4,6-tetra-O-acetyl- β -D-galactopyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-O-acetyl- β -D-glucopyranoside (**14**): The 1H and ^{13}C NMR spectra of the purified allyl -maltoside **14** in $CDCl_3$ were identical with those reported in the literature.^[11]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Lewis acid (LA) promoted glycosylation with peracetylated glycosyl donors (**1**): Allyl alcohol may attack the cationic species **2** at two different positions leading to the allylglycoside **3** or to the ortho-ester **4**, which can rearrange to produce allylglycoside **3**, or react with allyl alcohol to the partially deprotected allylglycosides **5** and possibly **6**, which may be reprotected to **3**.

Scheme 2.

Conversion of peracetyl- -glycosyl donors into their predominantly -configured allylglycosides: a) AlOH , CH_2Cl_2 , $\text{BF}_3\cdot\text{Et}_2\text{O}$ or TMSOTf , rt; b) aqueous workup with refrigerated solvents ($\sim 5^\circ\text{C}$); c) Ac_2O , pyr, rt.

Table 1
Comparison of reaction yields of allyl glycoside formation using varying procedures or conditions

Entry	Glycosyl Donor (conc.: 0.128M in CH ₂ Cl ₂)	Lewis Acid (2 equiv.)	Allyl Alcohol [equiv.]	Reacetylation	Peracetylated allyl glycoside ^a	Yield (isolated)
1	7	BF ₃ ·Et ₂ O	1.1	yes	11 (: = 1:12)	20%
2	7	TMSOTf	4	no	11 (: = 1:6)	20%
3	7	TMSOTf	4	yes	11 (: = 1:13)	68%
4	8	BF ₃ ·Et ₂ O	1.1	yes	12 (: = 1:12)	36%
5	8	BF ₃ ·Et ₂ O	4	no	12 (: = 1:10)	22%
6	8	BF ₃ ·Et ₂ O	4	yes	12 (: = 1:12)	61%
7	9	BF ₃ ·Et ₂ O	1.1	yes	13 (: = 1:25)	39%
8	9	BF ₃ ·Et ₂ O	4	no	13 (only)	24%
9	9	BF ₃ ·Et ₂ O	4	yes	13 (: = 1:2)	76%
10	10	BF ₃ ·Et ₂ O	1.1	no	14 (: = 1:3)	22%
11	10	BF ₃ ·Et ₂ O	4	no	14 (only)	18%
12	10	BF ₃ ·Et ₂ O	4	yes	14 (: = 1:3)	70%

^aThe ratio of and anomers was determined by ¹H NMR spectroscopy.