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Graphical abstract

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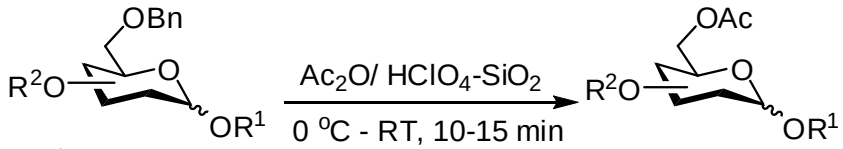

R^1 = alkyl, aryl

R^2 = protecting group

Selective acetolysis of primary benzyl groups in carbohydrate derivatives under the mild reaction condition

Monalisa Kundu and Anup Kumar Misra*

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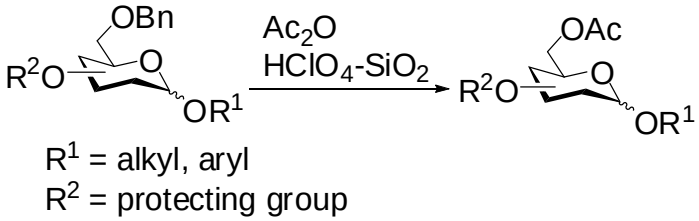
Abstract: Selective acetolysis of the primary benzyloxy groups in a wide variety of carbohydrate derivatives was achieved in excellent yield using acetic anhydride and perchloric acid supported over silica ($HClO_4$-SiO_2) as a solid acid catalyst in a fast reaction condition without using any organic solvent. The reaction condition is significantly rapid and can be scaled up for its use in the multi-step oligosaccharide synthesis.

Keywords: Carbohydrates; acetylation; acetolysis; benzyl; protecting groups; $HClO_4$-SiO_2.

1. Introduction

Due to their biological significance, synthesis of complex oligosaccharides is an important area of research,[1,2] which requires a wide range of monosaccharide intermediates having persistent and temporary protecting groups.[3,4] Judicious selection of functional groups for derivatization of monosaccharides plays decisive roles in the stereoselective glycosylations.[5,6] Among several protecting groups used in the functionalization of carbohydrates, benzyl ether is widely used because of the ease of its installation and removal. Although, benzyl ether protecting group is considered as a stable protecting group, sometimes it is required to convert it into other functional groups. Acetolysis[7,8] is one of the age-old techniques for the hydrolysis of glycosidic bonds as well as selective transformation of benzyl ethers into acetoxy groups providing late stage functionalization of monosaccharides. Because of its application in the synthesis of oligosaccharides, a number of reports appeared in the literature on the development of suitable reaction conditions for the selective acetolysis of benzyloxy groups. The commonly used reaction conditions require the treatment of benzylated monosaccharide derivatives with an excess amount of strong protic or Lewis acids such as H_2SO_4,[9] TFA,[10] *p*-TsOH,[11] $FeCl_3$,[12] $ZnCl_2$,[13] ZnI_2,[14] $BF_3{\cdot}OEt_2$,[15] TMSOTf[16] together with acetic anhydride. Besides using the acidic catalysts few other reaction conditions have also been reported using iodine,[17] a combination of Et_3SiH/I_2[18] and Selectfluor.[19] Despite their

wide applications most of the earlier reported reaction conditions suffer from several shortcomings such as, use of harsh reaction condition, requirement of excess reagents, use of corrosive and moisture sensitive reagents, longer reaction time, formation of by-products, low yields etc. Since all the earlier reported reaction conditions are homogeneous nature, rigorous workup of the reaction mixture is required for quenching the reaction. In this context, the application of an efficient insoluble solid acid catalyst for the regioselective acetolysis of benzyl ethers would be highly beneficial avoiding the use of stoichiometric quantity of catalysts and workup procedures. In an ongoing program, treatment 6-*O*-benzylated monosaccharide derivatives with H_2SO_4 or *p*-TsOH together with acetic anhydride did not furnish selective 6-*O*-acetylated product instead a mixture products were obtained as a result of non-selective acetolysis. In order to overcome this situation, it was envisioned that catalytic amount of perchloric acid supported over silica ($HClO_4$-SiO_2) could act as a solid acid catalyst in the presence of acetic anhydride for the selective acetolysis of 6-*O*-benzylated monosaccharide derivatives. Chakraborti and co-workers [20-22] reported the preparation of $HClO_4$-SiO_2 and demonstrated its catalytic potential in several organic transformations. Later, many researchers have applied $HClO_4$-SiO_2 as an efficient solid acid catalyst[23-28] alternative to the commonly used protic or Lewis acid catalysts. Inspired by the catalytic potential of $HClO_4$-SiO_2 it was decided to carry out selective acetolysis of 6-*O*-benzylated monosaccharide intermediates under a mild reaction condition and reported herein. It is worth mentioning that this method will be useful as alternative to the use of bulky protecting groups such as TBDPS, TBDMS, trityl etc. at the primary position for selective removal and thus support the atom economy in protecting group manipulations.



Scheme 1: Selective acetolysis of primary benzyloxy group of carbohydrate derivatives using acetic anhydride in the presence of $HClO_4$-SiO_2.

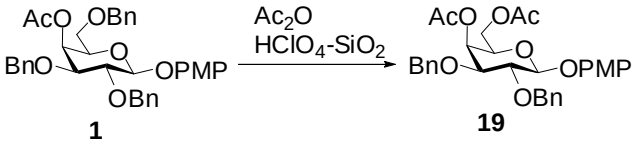
2. Results and discussion

In a set of initial experiments, *p*-methoxyphenyl 4-*O*-acetyl-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**1**) was treated with a varied quantity of acetic anhydride (1.0-2.0 equiv.) and $HClO_4$-SiO_2 in different temperatures without using any solvent. It was observed that use

of 1.5 equiv. of acetic anhydride and $HClO_4$-SiO_2 (10 mg/100 mg of substrate) at 0 °C under solvent-free condition furnished 85% yield of compound **19** in 10 min. without formation of any by products. Increasing the quantity of the reagent and catalyst did not give significantly improved yield of the product. Carrying out the reaction at room temperature proceeded with the formation of by products (Table 1). After completion of the reaction it was filtered and concentrated under reduced pressure without the requirement of any special workup. A variety of 6-*O*-benzylated carbohydrate derivatives were transformed into 6-*O*-acetylated products in excellent yields under the optimized reaction condition of the regioselective acetolysis of the primary benzyloxy groups (Table 2). In some cases the reaction was carried out at room temperature due to the extra stability of the 6-*O*-benzyl group. However, per-*O*-benzylated methyl D-mannoside (**7**) was found very reactive at 0 °C and produced significant quantity of anomeric acetolysis product, which was controlled by carrying out the reaction at −15 °C. The reaction condition is applicable in disaccharide derivative also to give satisfactory yield (75%) without affecting the inter-glycosidic linkage and isopropylidene ketal as observed in the case of compound **18**. Several commonly used functional groups such as acetyl, benzoyl, allyl, *p*-methoxyphenyl (PMP), azido, octyl, 2-trimethylsilylethyl (TMSET), *N*-benzyloxycarbonyl (Cbz) and secondary benzyloxy groups as well as isopropylidene group were found unaffected under the reaction conditions. As expected, the other acid sensitive protecting group such as *p*-methoxybenzyl (PMB) group present in compound **13** was also transformed into acetate under the reaction condition. Isomerization of the anomeric protecting groups was not observed under the reaction condition, which was witnessed in many acid catalyzed reactions. The reaction is significantly fast to furnish the required products in very short interval of time in comparison to the other reported methods. It is noteworthy that the reaction condition does not require any organic solvent and very less quantity of catalyst was required for the completion of the reaction in contrast to the requirement of stoichiometric quantity of acidic catalyst reported earlier, which may be due to the increased surface area of the $HClO_4$ due to the impregnation over SiO_2. It is also worthy to mention that allowance of the reaction for a longer reaction time led to the formation of by-products, which might be due to the acetolysis of secondary benzyl or other protecting groups present in the substrate resulting a decrease in over all yield of the expected product. The catalyst was prepared following exactly the reaction condition reported by Chakraborti and co-workers [20-22] and used without measuring the exact acid strength of the catalyst. The reaction condition can be scaled up without loss of the yield. The analytical

samples were prepared by passing through a short pad of SiO_2 and characterized by their NMR and mass spectral analysis.

Table 1: Optimization of selective acetolysis of primary benzyl group in compound **1**.

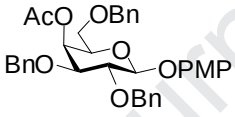
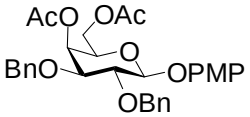
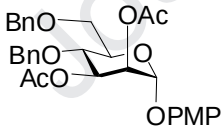
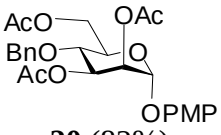
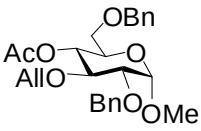
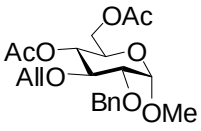
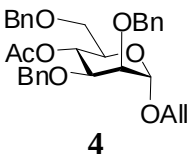
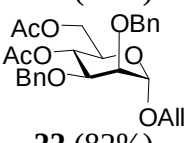
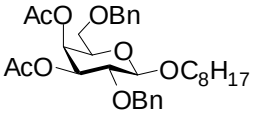
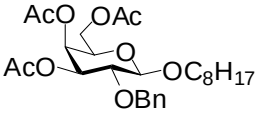


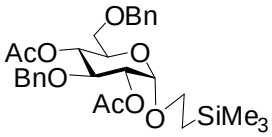
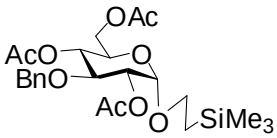
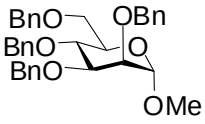
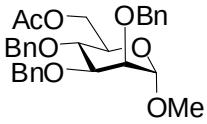
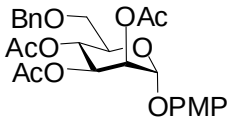
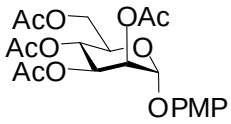
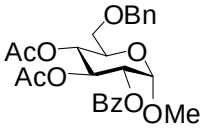
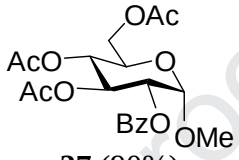
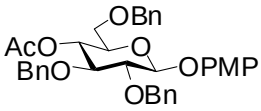
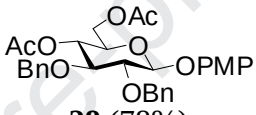
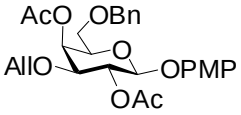
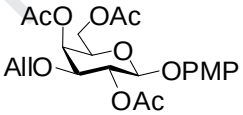
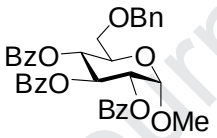
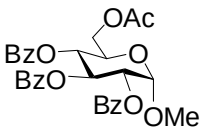
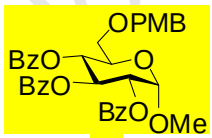
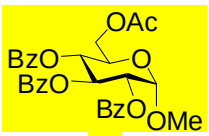
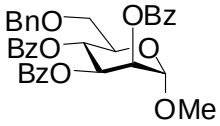
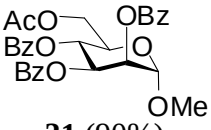
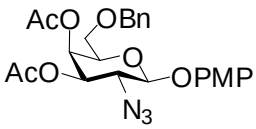
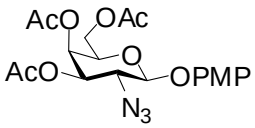
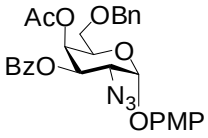
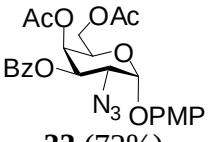
1 **19**

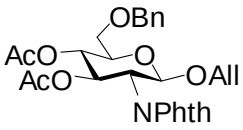
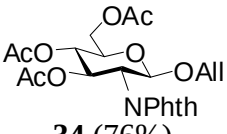
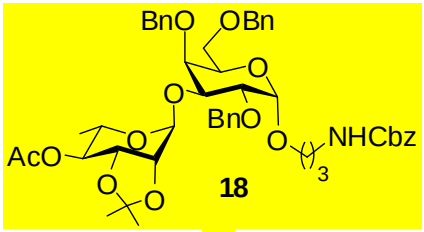
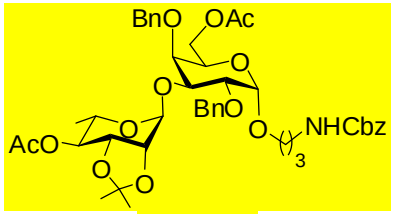
Sl. No.	Ac_2O Equiv.	$HClO_4$-SiO_2 mg/100 mg	Temp. (°C)	Time (min)	Yield (%)
1	1.5	25	0 °C	10	85
2	2.0	25	0 °C	10	85
3	1.2	25	0 °C	10	78
4	1.5	10	0 °C	10	85
5	1.5	10	–10 °C	30	70
6	1.5	10	RT	5	60[a]

[a]: Together with some by products.

Table 2: Selective acetolysis of primary benzyloxy groups of differentially protected monosaccharide derivatives using acetic anhydride (1.5 equiv.) and $HClO_4$-SiO_2 (10 mg/100 mg of substrate) as solid acid catalyst.

Sl. No.	Starting material	Acetolysis product (Yield in %)	Temp. (°C)	Time (min)
1	 **1**	 **19** (85%; 82%[a])	0 °C	10
2	 **2**	 **20** (82%)	0 °C	10
3	 **3**	 **21** (80%)	0 °C	10
4	 **4**	 **22** (82%)	0 °C	10
5	 **5**	 **23** (78%)	0 °C	10

6	 **6**	 **24** (74%)	0 °C	10
7	 **7**	 **25** (80%)	–15 °C	30
8	 **8**	 **26** (86%)	RT	15
9	 **9**	 **27** (90%)	RT	15
10	 **10**	 **28** (78%)	RT	15
11	 **11**	 **29** (80%)	RT	15
12	 **12**	 **30** (85%)	RT	20
13	 **13**	 **30** (90%)	RT	10
14	 **14**	 **31** (90%)	RT	15
15	 **15**	 **32** (76%)	RT	15
16	 **16**	 **33** (72%)	RT	15

17	 **17**	 **34** (76%)	RT	20
18	 **18**	 **35** (75%)	0 °C	5

[a]: in a scale 10 g of the substrate **1**.

3. Conclusion

In conclusion, a significantly fast, mild and convenient reaction condition has been developed for the preparation of the selectively acetolysis products of the primary benzyloxy groups in carbohydrate derivatives using acetic anhydride in the presence of a catalytic quantity of $HClO_4$-SiO_2 under solvent-free conditions. This method will be considered as alternative for the temporary protection of primary hydroxyl group with benzyl ether avoiding the conventional bulky protecting groups such as TBDPS, TBDMS, trityl etc. A large number of functional groups used for protecting group manipulation of carbohydrates remained unaffected under the reaction condition. This operationally simple reaction protocol will certainly be considered as better alternative to the reported methods and find applications in oligosaccharide syntheses.

4. Experimental

4.1. General methods: All reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulphate (2% $Ce(SO_4)_2$ in 2N H_2SO_4) sprayed plates in hot plate. Silica gel 230-400 mesh was used for column chromatography. NMR spectra were recorded on Bruker Avance 500 MHz using $CDCl_3$ as solvent and TMS as internal reference unless stated otherwise. Chemical shift value is expressed in δ ppm. The complete assignment of proton and carbon spectra was carried out by using a standard set of NMR experiments, e.g. ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT 135 etc. HRMS were recorded on a Bruker mass spectrometer. $HClO_4$-SiO_2 was prepared following the reported method.[20-22]

4.2. Preparation of $HClO_4$-SiO_2 catalyst[20]: $HClO_4$ (1.8 g, 12.5 mmol, as a 70% aq. solution) was added to a suspension of SiO_2 (230-400 mesh, 23.7 g) in Et_2O (70.0 mL). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to furnish $HClO_4$-SiO_2 (0.5 mmol/g) as a free flowing powder. (50 mg = approx. 0.025 mmol of $HClO_4$).

4.3. Typical reaction condition for the acetolysis of 6-benzyloxy group in carbohydrate derivative: A mixture of compound **1** (100 mg, 0.17 mmol) in acetic anhydride (25 μL, 1.5 mmol) was cooled to 0 °C. To the cooled reaction mixture was added $HClO_4$-SiO_2 (10 mg) and the reaction mixture was stirred at same temperature for appropriate time mentioned in Table 2. The reaction mixture was filtered and washed with EtOAc (15 mL) and concentrated under reduced pressure to give the product, which was passed through a short pad of SiO_2 to give analytically pure compound **19** (80 mg, 85%). Following the similar reaction condition, a set of 6-*O*-acetylated products were prepared from their corresponding 6-benzyloxy derivatives.

4.4. Spectral data of synthesized 6-*O*-acetylated products:

***p*-Methoxyphenyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (19)**: Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.24 (m, 10 H, Ar-H), 6.99 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.78 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.49 (d, *J* = 3.0 Hz, 1 H, Ar-H), 4.96 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.82 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.80 (d, $J_{1,2}$ = 9.5 Hz, 1 H, H-1), 4.74 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.53 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.17-4.15 (m, 2 H, H-6_{ab}), 3.90-3.79 (m, 2 H, H-2, H-5), 3.77 (s, 3 H, OCH_3), 3.59 (dd, $J_{2,3;3,4}$ = 9.5, 3.5 Hz, 1 H, H-3), 2.17 (s, 3 H, COCH_3), 2.07 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1 (*C*OCH_3), 170.0 (*C*OCH_3), 155.5-114.5 (Ar-C), 103.1 (C-1), 79.0 (C-3), 78.5 (C-4), 75.5 (Ph*C*H_2), 72.2 (Ph*C*H_2), 70.9 (C-5), 66.2 (C-2), 61.9 (C-6), 55.5 (O*C*H_3), 20.8 (CO*C*H_3), 20.7 (CO*C*H_3); HRMS $[M+Na]^+$: 573.2101 (calcd.); found: 573.2092 (found).

***p*-Methoxyphenyl 2,3,6-tri-*O*-acetyl-4-*O*-benzyl-α-D-mannopyranoside (20):** Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.20 (m, 5 H, Ar-H), 6.98 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.78 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.53 (dd, $J_{2,3;3,4}$ = 3.0, 9.5 Hz, 1 H, H-3), 5.34-5.32 (m, 1 H, H-2), 5.28 (br s, 1 H, H-1), 4.70 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.60 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.30-4.28 (m, 2 H, H-6_{ab}), 4.07-4.04 (m, 1 H, H-5), 3.83 (t, $J_{3,4;4,5}$ = 9.5 Hz each, 1 H, H-4), 3.75 (s, 3 H, OCH_3), 2.16 (s, 3 H, COCH_3), 2.03 (s, 3 H, COCH_3), 1.99 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1 (*C*OCH_3), 169.5 (*C*OCH_3), 169.3 (*C*OCH_3),

155.3-114.5 (Ar-C), 96.6 (C-1), 74.8 (Ph*C*H_2), 73.0 (C-5), 71.6 (C-3), 70.1 (C-2), 69.9 (C-4), 62.8 (C-6), 55.4 (O*C*H_3), 20.9 (O*C*H_3), 20.8 (CO*C*H_3), 20.7 (CO*C*H_3); HRMS $[M+Na]^+$: 525.1737 (calcd.); 525.1747 (found).

Methyl 4,6-di-*O*-acetyl-3-*O*-allyl-2-*O*-benzyl-α-D-glucopyranoside (21): Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.26 (m, 5 H, Ar-H), 5.90-5.81 (m, 1 H, C*H*=CH_2), 5.25-5.11 (m, 2 H, CH=C*H*$_2$), 4.91 (t, $J_{3,4;4,5}$ = 10.0 Hz each, 1 H, H-4), 4.79 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.62 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.54 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.34-4.30 (m, 1 H, OC*H*), 4.19 (dd, $J_{6a,6b;6a,5}$ = 12.0, 5.0 Hz, 1 H, H-6_a), 4.13-4.08 (m, 1 H, OC*H*), 3.99 (dd, $J_{6a,6b;6b,5}$ = 12.0, 2.0 Hz, 1 H, H-6_b), 3.81-3.78 (m, 1 H, H-5), 3.75 (t, $J_{2,3;3,4}$ = 9.5 Hz each, 1 H, H-3), 3.49 (dd, $J_{1,2;2,3}$ = 3.0, 9.5 Hz, 1 H, H-2), 3.36 (s, 3 H, OC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (*C*OCH_3), 169.2 (*C*OCH_3), 137.9-116.6 (Ar-C), 98.3 (C-1), 79.3 (C-3), 78.7 (C-4), 74.1 (Ph*C*H_2), 73.5 (O*C*H_2), 69.8 (C-5), 67.6 (C-2), 62. 2 (C-6), 55.3 (O*C*H_3), 20.9 (CO*C*H_3), 20.8 (CO*C*H_3); HRMS $[M+Na]^+$: 431.1682 (calcd.); 431.1673 (found).

Allyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (22): Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.20 (m, 10 H, Ar-H), 5.86-5.80 (m, 1 H, C*H*=CH_2), 5.39 (t, $J_{3,4;4,5}$ = 10.0 Hz each, H-4), 5.23-5.16 (m, 2 H, CH=C*H*$_2$), 4.85 (d, $J_{1,2}$ = 10.0 Hz, 1 H, H-1), 4.74 (d, *J* = 12.0 Hz, 1 H, PhC*H*), 4.67 (d, *J* = 12.0 Hz, 1 H, PhC*H*), 4.56 (d, *J* = 12.0 Hz, 1 H, PhC*H*), 4.47 (d, *J* = 12.0 Hz, 1 H, PhC*H*), 4.19 (dd, $J_{6a,6b;6a,5}$ = 12.0, 5.0 Hz, 1 H, H-6_a), 4.14-4.08 (m, 2 H, OC*H*$_2$), 3.95 (dd, $J_{6a,6b;6b,5}$ = 12.0, 2.5 Hz, 1 H, H-6_b), 3.82-3.80 (m, 2 H, H-3, H-5), 3.78 (br s, 1 H, H-2), 2.07 (s, 3 H, COC*H*$_3$), 1.99 (s, 3 H, COC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (*C*OCH_3), 169.3 (*C*OCH_3), 138.1-127.3 (Ar-C), 117.6 (*C*H=CH_2), 97.5 (C-1), 77.2 (C-5), 74.1 (C-3), 72.8 (Ph*C*H_2), 71.9 (Ph*C*H_2), 69.3 (C-4), 68.1 (O*C*H_2), 68.0 (C-2), 62.9 (C-6), 20.8 (CO*C*H_3), 20.7 (CO*C*H_3); HRMS $[M+Na]^+$: 507.1995 (calcd.); 507.2004 (found).

Octyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-β-D-galactopyranoside (23): Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.23 (m, 5 H, Ar-h), 5.30 (d, $J_{3,4;4,5}$ = 3.0 Hz each, 1 H, H-4), 4.93 (dd, $J_{2,3;3,4}$ = 9.5, 3.0 Hz, 1 H, H-3), 4.87 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.60 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.43 (d, $J_{1,2}$ = 8.0 Hz, 1 H, H-1), 4.13-4.07 (m, 2 H, H-6_{ab}), 3.96-3.90 (m, 1 H, OC*H*), 3.84-3.80 (m, 1 H, H-5), 3.59-3.50 (m, 2 H, H-2, OC*H*), 2.09 (s, 3 H, COC*H*$_3$), 2.03 (COC*H*$_3$), 1.93 (s, 3 H, COC*H*$_3$), 1.68-1.60 (m, 2 H, C*H*$_2$), 1.40-1.20 (m, 10 H, C*H*$_2$), 0.87 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9 (*C*OCH_3), 169.8 (*C*OCH_3),

169.6 (*C*OCH$_3$), 138.3-127.5 (Ar-C), 103.8 (C-1), 76.3 (C-3), 74.6 (Ph*C*H$_2$), 72.1 (C-4), 70.4 (O*C*H$_2$), 70.3 (C-5), 67.3 (C-2), 61.2 (C-6), 31.8 (*C*H$_2$), 29.7 (*C*H$_2$), 29.4 (*C*H$_2$), 29.1 (*C*H$_2$), 25.8 (*C*H$_2$), 22.6 (*C*H$_2$), 20.7 (CO*C*H$_3$), 20.6 (2 C, 2 CO*C*H$_3$), 14.4 (*C*H$_3$); HRMS [M+Na]$^+$: 531.2570 (calcd.); 531.2561 (found).

2-Trimethylsilylethyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranoside (24): Colorless syrup; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28-7.15 (m, 5 H, Ar-H), 5.00 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.98 (t, $J_{3,4;4,5}$ = 9.5 Hz each, 1 H, H-4), 4.76 (dd, $J_{1,2;2,3}$ = 3.0, 9.5 Hz, 1 H, H-2), 4.63 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.52 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.09 (dd, $J_{6a,6b;6a,5}$ = 12.5, 5.0 Hz, 1 H, H-6$_a$), 3.97 (dd, $J_{6a,6b;6b,5}$ = 12.5, 2.5 Hz, 1 H, H-6$_b$), 3.88 (t, $J_{2,3;3,4}$ = 9.5 Hz each, 1 H, H-3), 3.83-3.79 (m, 1 H, H-5), 3.76-3.71 (m, 1 H, OC*H*), 3.48-3.40 (m, 1 H, OC*H*), 2.02 (s, 3 H, COC*H*$_3$), 1.98 (s, 3 H, COC*H*$_3$), 1.88 (s, 3 H, COC*H*$_3$), 0.87-0.77 (m, 2 H, C*H*$_2$), 0.00 (s, 9 H, Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.3 (*C*OCH$_3$), 170.1 (*C*OCH$_3$), 169.8 (*C*OCH$_3$), 137.1-126.0 (Ar-C), 96.0 (C-1), 75.0 (C-5), 73.6 (Ph*C*H$_2$), 68.4 (C-3), 67.5 (C-4), 64.0 (2 C, C-2, O*C*H$_2$), 61.9 (C-6), 25.6 (*C*H$_2$), 20.9 (2 C, 2 CO*C*H$_3$), 20.8 (CO*C*H$_3$); HRMS [M+Na]$^+$: 519.2027 (calcd.); 519.2016 (found).

Methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (25): Colorless syrup; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.33-7.16 (m, 15 H, Ar-H), 4.91 (d, *J* = 11.0 Hz, 1 H, PhC*H*), 4.71-4.68 (m, 2 H, 2 PhC*H*), 4.59-4.55 (m, 3 H, H-1, 2 PhC*H*), 4.32-4.22 (m, 2 H, H-4, PhC*H*), 3.89-3.88 (m, 1 H, H-5), 3.87-3.81 (m, 2 H, H-6$_{ab}$), 3.74-3.72 (m, 2 H, H-2, H-3), 3.30 (s, 3 H, OC*H*$_3$), 2.04 (s, 3 H, COC*H*$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.5 (*C*OCH$_3$), 138.3-127.6 (Ar-C), 98.9 (C-1), 80.2 (C-5), 75.3 (Ph*C*H$_2$), 74.5 (2 C, C-3, C-4), 72.6 (Ph*C*H$_2$), 72.1 (Ph*C*H$_2$), 70.0 (C-2), 63.1 (C-6), 54.7 (O*C*H$_3$), 20.8 (CO*C*H$_3$); HRMS [M+Na]$^+$: 529.2203 (calcd.); 529.2212 (found).

***p*-Methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (26):** Colorless syrup; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.18 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.80 (d, *J* = 9.0 hz, 2 H, Ar-H), 5.51 (dd, $J_{2,3;3,4}$ = 3.0, 9.5 Hz, 1 H, H-3), 5.39 (br s, 1 H, H-2), 5.37 (br s, 1 H, H-1), 5.29 (t, $J_{3,4;4,5}$ = 9.5 Hz each, 1 H, H-4), 4.26 (dd, $J_{6a,6b;6a,5}$ = 12.0, 4.0 Hz, 1 H, H-6$_a$), 4.12-4.09 (m, 1 H, H-5), 4.05 (dd, $J_{6a,6b;6b,5}$ = 12.0, 2.0 Hz, 1 H, H-6$_b$), 3.76 (s, 3 H, OC*H*$_3$), 2.19 (s, 3 H, COC*H*$_3$), 2.05 (s, 3 H, COC*H*$_3$), 2.04 (s, 3 H, COC*H*$_3$), 2.02 (s, 3 H, COC*H*$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.1 (*C*OCH$_3$), 169.6 (*C*OCH$_3$), 169.5 (*C*OCH$_3$), 169.4 (*C*OCH$_3$), 155.4-114.6 (Ar-C), 96.6 (C-1), 69.5 (C-5), 69.0 (C-3), 68.9 (C-4), 66.0 (C-2), 62.1 (C-6), 55.4

(O*C*H$_3$), 20.8 (CO*C*H$_3$), 20.7 (2 C, 2 CO*C*H$_3$), 20.6 (CO*C*H$_3$); HRMS [M+Na]$^+$: 477.1373 (calcd.); 477.1380 (found).

Methyl 3,4,6-tri-*O*-acetyl-2-*O*-benzoyl-α-D-glucopyranoside (27): Colorless syrup; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.60-7.27 (m, 5 H, Ar-H), 5.69 (t, $J_{2,3;3,4}$ = 10.0 Hz each, 1 H, H-3), 5.15 (t, $J_{3,4;4,5}$ = 9.5 Hz each, 1 H, H-4), 5.13 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 5.07 (dd, $J_{1,2;2,3}$ = 3.5, 9.5 Hz, 1 H, H-2), 4.31 (dd, $J_{6a,6b;6a,5}$ = 12.0, 5.0 Hz, 1 H, H-6$_a$), 4.13 (dd, $J_{6a,6b;6b,5}$ = 12.0, 2.5 Hz, 1 H, H-6$_b$), 4.08-4.03 (m, 1 H, H-5), 3.40 (s, 3 H, OC*H*$_3$), 2.12 (s, 3 H, COC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$), 1.95 (s, 3 H, COC*H*$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.7 (*C*OCH$_3$), 170.2 (*C*OCH$_3$), 169.6 (*C*OCH$_3$), 165.7 (*C*OPh), 133.5-128.6 (Ar-C), 96.9 (C-1), 71.6 (C-5), 70.0 (C-4), 68.4 (C-3), 67.2 (C-2), 61.9 (C-6), 55.5 (O*C*H$_3$), 20.7 (CO*C*H$_3$), 20.6 (CO*C*H$_3$), 20.5 (CO*C*H$_3$); HRMS [M+Na]$^+$: 447.1267 (calcd.); 447.1276 (found).

***p*-Methoxyphenyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-β-D-glucopyranoside (28):** Colorless syrup; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.33-7.17 (m, 10 H, Ar-H), 7.17 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.80 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.07-5.00 (m, 2 H, H-4, PhC*H*), 4.85-4.78 (m, 2 H, H-1, PhC*H*), 4.62-4.60 (m, 2 H, 2 PhC*H*), 4.25-4.18 (m, 1 H, H-6$_a$), 4.10-4.07 (m, 1 H, H-6$_b$), 3.77 (s, 3 H, OC*H*$_3$), 3.71 (t, $J_{2,3;3,4}$ = 9.5 Hz each, 1 H, H-3), 3.65-3.58 (m, 2 H, H-2, H-5), 2.11 (s, 3 H, COC*H*$_3$), 1.91 (s, 3 H, COC*H*$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.3 (*C*OCH$_3$), 168.1 (*C*OCH$_3$), 154.5-113.4 (Ar-C), 101.8 (C-1), 80.6 (C-5), 80.4 (C-4), 74.1 (2 C, 2 Ph*C*H$_2$), 70.9 (C-3), 67.9 (C-2), 61.2 (C-6), 54.5 (O*C*H$_3$), 20.0 (CO*C*H$_3$), 19.9 (CO*C*H$_3$); HRMS [M+Na]$^+$: 573.2101 (calcd.); 573.2092 (found).

***p*-Methoxyphenyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-β-D-galactopyranoside (29):** Colorless syrup; ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.96 (d, *J* = 9.0 hz, 2 H, Ar-H), 6.80 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.82-5.74 (m, 1 H, C*H*=CH$_2$), 5.43 (dd, $J_{3,4;4,5}$ = 2.5 Hz each, 1 H, H-4), 5.27 (t, $J_{1,2;2,3}$ = 9.5 Hz each, 1 H, H-2), 5.23-5.16 (m, 2 H, CH=C*H*$_2$), 4.82 (d, $J_{1,2}$ = 9.5 Hz, 1 H, H-1), 4.18-4.12 (m, 3 H, H-6$_a$, OC*H*$_2$), 3.93-3.87 (m, 2 H, H-5, H-6$_b$), 3.76 (s, 3 H, OC*H*$_3$), 3.55 (dd, $J_{2,3;3,4}$ = 9.5, 3.0 Hz, 1 H, H-3), 2.17 (s, 3 H, COC*H*$_3$), 2.09 (s, 3 H, COC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.1 (*C*OCH$_3$), 170.0 (*C*OCH$_3$), 168.9 (*C*OCH$_3$), 155.6-114.4(Ar-C), 100.8 (C-1), 76.3 (C-3), 71.1 (C-4), 70.5 (O*C*H$_2$), 70.3 (C-5), 65.7 (C-2), 61.8 (C-6), 55.5 (O*C*H$_3$), 20.8 (CO*C*H$_3$), 20.7 (CO*C*H$_3$), 20.6 (CO*C*H$_3$); HRMS [M+Na]$^+$: 475.1580 (calcd.); 475.1590 (found).

Methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (30): Colorless syrup; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.90-7.27 (m, 15 H, Ar-H), 6.10 (t, $J_{2,3;3,4}$ = 9.5 Hz, 1 H, H-3),

5.57 (t, $J_{3,4;4,5}$ = 9.5 Hz each, 1 H, H-4), 5.25 (dd, $J_{1,2;2,3}$ = 3.5, 9.5 Hz, 1 H, H-2), 5.22 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.31-4.20 (m, 3 H, H-5, H-6_{ab}), 3.48 (s, 3 H, OCH_3), 2.07 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2 (*C*OCH$_3$), 165.6 (2 C, 2 *C*OPh), 165.1 (*C*OPh), 133.3-128.2 (Ar-C), 97.1 (C-1), 71.9 (C-5), 70.3 (C-3), 69.2 (C-4), 67.5 (C-2), 62.4 (C-6), 55.6 (O*C*H$_3$), 20.7 (CO*C*H$_3$); HRMS $[M+Na]^+$: 571.1580 (calcd.); 571.1589 (found).

Methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (31): Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15-7.23 (m, 15 H, Ar-H), 5.88 (t, $J_{3,4;4,5}$ = 9.5 Hz each, 1 H, H-4), 5.84 (dd, $J_{2,3;3,4}$ = 3.0, 9.5 Hz, 1 H, H-3), 5.63-5.62 (m, 1 H, H-2), 4.96 (br s, 1 H, H-1), 4.34-4.24 (m, 3 H, H-5, H-6_{ab}), 3.54 (s, 3 H, OCH_3), 2.01 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2 (*C*OCH$_3$), 165.3 (*C*OPh), 165.2 (*C*OPh), 165.1 (*C*OPh), 133.4-128.2 (Ar-C), 98.6 (C-1), 70.3 (C-5), 69.8 (C-3), 68.5 (C-2), 67.0 (C-4), 62.8 (C-6), 55.5 (O*C*H$_3$), 20.6 (CO*C*H$_3$); HRMS $[M+Na]^+$: 571.1580 (calcd.); 571.1589 (found).

***p*-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-galactopyranoside (32):** Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (d, *J* = 9.0 Hz, 2 H, Ar-H), 6.72 (d, *J* = 9.0 Hz, Ar-H), 5.83 (dd, $J_{2,3;3,4}$ = 9.5, 3.0 Hz, 1 H, H-3), 5.78 (d, $J_{1,2}$ = 10.0 Hz, 1 H, H-1), 5.49 (dd, $J_{3,4;4,5}$ = 2.5 Hz each, 1 H, H-4), 4.74 (dd, $J_{1,2;2,3}$ = 9.5 Hz each, 1 H, H-2), 4.25-4.09 (m, 3 H, H-5, H-6_{ab}), 3.72 (s, 3 H, OCH_3), 2.24 (s, 3 H, COCH_3), 2.06 (s, 3 H, COCH_3), 1.88 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (*C*OCH$_3$), 169.9 (2 C, 2 *C*OCH$_3$), 155.3-114.4 (Ar-C), 97.9 (C-1), 71.0 (C-3), 68.0 (C-4), 66.5 (C-5), 61.2 (C-6), 55.4 (O*C*H$_3$), 51.3 (C-2), 20.7 (CO*C*H$_3$), 20.6 (CO*C*H$_3$), 20.5 (CO*C*H$_3$); HRMS $[M+Na]^+$: 460.1332 (calcd.); 460.1343 (found).

***p*-Methoxyphenyl 4,6-di-*O*-acetyl-2-azido-3-*O*-benzoyl-2-deoxy-α-D-galactopyranoside (33):** Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.0-6.82 (m, 9 H, Ar-H), 5.79 (dd, $J_{2,3;3,4}$ = 9.5, 3.0 Hz, 1 H, H-3), 5.69 (dd, $J_{3,4;4,5}$ = 2.5 Hz each, 1 H, H-4), 5.55 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 4.50-4.47 (m, 1 H, H-5), 4.18-4.07 (m, 2 H, H-6_{ab}), 3.90 (dd, $J_{1,2;2,3}$ = 9.5, 3.5 Hz, 1 H, H-2), 3.78 (s, 3 H, OCH_3), 2.12 (s, 3 H, COCH_3), 1.99 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9 (*C*OCH$_3$), 169.4 (*C*OCH$_3$), 165.1 (*C*OPh), 155.7-114.6 (Ar-C), 98.2 (C-1), 68.7 (C-3), 67.6 (C-4), 67.5 (C-2), 61.4 (C-6), 57.8 (C-5), 55.5 (O*C*H$_3$), 20.6 (CO*C*H$_3$), 20.5 (CO*C*H$_3$); HRMS $[M+Na]^+$: 522.1489 (calcd.); 522.1480 (found).

Allyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (34): Colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.70 (m, 4 H, Ar-H), 5.75 (t, *J* = 9.5 Hz, 1 H, H-3), 5.73-5.68 (m, 1 H, C*H*=CH$_2$), 5.39 (d, *J* = 8.5 Hz, 1 H, H-1), 5.15 (t, *J* = 9.0 Hz, 1 H, H-

2), 5.14-5.06 (m, 2 H, CH=CH_2), 4.33-4.25 (m, 3 H, H-4, H-6_a, OC*H*), 4.16-4.13 (m, 1 H, OC*H*), 4.05 (dd, *J* = 12.0, 2.5 Hz, 1 H, H-6_b), 3.85-3.82 (m, 1 H, H-5), 2.11 (s, 3 H, COCH_3), 2.02 (s, 3 H, COCH_3), 1.86 (s, 3 H, COCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (*C*OCH_3), 169.9 (*C*OCH_3), 169.1 (*C*OCH_3), 134.1-117.9 (Ar-C), 97.1 (C-1), 71.9 (C-5), 70.8 (C-3), 70.0 (C-4), 68.9 (O*C*H_2), 61.9 (C-6), 54.5 (C-2), 20.7 (CO*C*H_3), 20.6 (CO*C*H_3), 20.4 (CO*C*H_3); HRMS $[M+Na]^+$: 498.1376 (calcd.); 498.1385 (found).

3-(*N*-Benzyloxycarbonyl)aminopropyl (4-*O*-acetyl-2,3-*O*-isopropylidene-α-L-rhamno-pyranosyl)-(1→3)-6-*O*-acetyl-2,4-di-*O*-benzyl-*α*-D-galactopyranoside (35): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.28 (m, 15 H, Ar-H), 5.38 (br s, 1 H, H-1_B), 5.25-5.14 (m, 2 H, PhCH_2Cbz), 4.84-4.76 (m, 3 H, H-1_A, H-4_B, N*H*), 4.64-4.58 (m, 3 H, 3 PhC*H*), 4.16-4.09 (m, 4 H, H-3_A, H-3_B, H-6_{aA}, PhC*H*), 4.07-4.01 (m, 2 H, H-6_{bA}, OC*H*), 3.97 (dd, *J* = 9.5 Hz, 3.5 Hz, 1 H, H-2_A), 3.92 (m, 1 H, H-5_A), 3.83-3.79 (m, 2 H, H-2_B, H-5_B), 3.78-3.73 (m, 1 H, OC*H*), 3.71 (br s, 1 H, H-4_A), 3.64-3.58 (m, 1 H, NC*H*), 3.42-3.35 (m, 1 H, NC*H*), 2.09 (s, 3 H, COCH_3), 1.98 (s, 3 H, COCH_3), 1.88-1.76 (m, 2 H, CH_2), 1.53 (s, 3 H, CCH_3), 1.34 (s, 3 H, CCH_3), 1.15 (d, *J* = 6.0 Hz, 3 H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4 (*C*OO-), 170.0 (*C*OCH_3), 169.5 (*C*OCH_3), 138.2-127.8 (Ar-C), 109.6 (*C*$(CH_3)_2$), 98.8 (C-1_A), 97.0 (C-1_B), 77.3, 76.8, 76.0, 75.8, 75.6 (Ph*C*H_2), 74.8, 74.4, 72.5 (Ph*C*H_2), 68.7, 68.4 (Ph*C*H_2), 66.1 (C-6_A), 64.8, 63.4 (O*C*H_2), 41.6 (N*C*H_2), 28.8 (*C*H_2), 27.7 (C*C*H_3), 26.7 (C*C*H_3), 20.9 (CO*C*H_3), 20.6 (CO*C*H_3), 16.7 (C*C*H_3); HRMS $[M+Na]^+$: 844.3521 (calcd.); 844.3530 (found).

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Research Highlights

- A convenient methodology for the selective acetolysis of primary benzyloxy groups.
- The reaction condition is significantly fast, mild and highly selective.
- A catalytic quantity of $HClO_4$-SiO_2 is required avoiding organic solvents.
- $HClO_4$-SiO_2 has been used as a solid acid catalyst.
- Most of the functional groups used in carbohydrates remained unaffected.

Conflicts of Interest

There are no conflicts to declare.