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Mild and efficient method for the cleavage of benzylidene acetals using $HClO_4$–SiO_2 and direct conversion of acetals to acetates ☆

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Abstract—$HClO_4$–SiO_2 has been used successfully for the deprotection of benzylidene acetals and the direct conversion of benzylidene acetals to the corresponding di-*O*-acetates. The reactions are very fast and yields are excellent.

Selective protection and deprotection of polyhydroxylated substrates is often of decisive importance for the successful outcome of a chemical synthesis. Numerous methods and reagents are available for this purpose, particularly for carbohydrate and natural product synthesis.[1] Conversion of the assembled carbohydrates into functional derivatives is a necessary prerequisite for the synthesis of complex oligosaccharides.

A benzylidene acetal, a widely used functional group for the protection of 1,2- and 1,3-diols, has an advantage that it can be used to protect two hydroxyl groups simultaneously and can be removed by hydrogenation or hydrolysis under acidic conditions.[1,2] Furthermore, one of the two C–O bonds of the benzylidene acetal can be regioselectively opened for application in oligosaccharide synthesis.[2,3] Besides the selective opening of benzylidene acetals, there are a plethora of methods available for the complete removal of benzylidene acetals, which include strong acidic media[1] (H_2SO_4, AcOH, $Zn(OTf)_2$, $FeCl_3$, BCl_3, $SnCl_2$, camphorsulfonic acid) or other demanding conditions[4] (H_2/Pd–C, hydrazine, EtSH, I_2, Na/NH_3, $Er(OTf)_3$, etc.). However, in spite of their potential utility, many of these methods suffer from drawbacks such as relatively low yields, formation of by-products, use of expensive reagents, incompatibility with other functional groups and relatively harsh reaction conditions. Therefore, the development of mild, efficient and metal-free reaction conditions would extend the scope of this conversion. Use of a catalytic quantity of cheap solid supported acid, which could be removed from the reaction mixture by simple filtration avoiding expensive and toxic reagents, could be useful for this purpose.

Recently, we have devoted considerable effort towards the development of a more environmentally benign catalyst for several important organic transformations.[5] During our study on the acetylation of carbohydrate derivatives containing acid-labile functionalities, (such as benzylidene acetals) using perchloric acid supported on silica[5b] ($HClO_4$–SiO_2), a non-toxic cheaper alternative of triflate salts and solid acids and acetic anhydride, we observed that a clean deprotection of benzylidene acetals was taking place with exclusive formation of the corresponding acetylated products. Prompted by this observation, we set out to explore the use of $HClO_4$–SiO_2 for the removal of benzylidene acetals in carbohydrate derivatives and for the direct conversion of benzylidene acetals to the corresponding acetates. Although $HClO_4$–SiO_2[6] is not commercially available, it can be easily prepared in the laboratory and the free flowing powder obtained can be stored for years without any loss of catalytic activity. We herein disclose a convenient methodology for the rapid deprotection of benzylidene acetals and direct conversion of benzylidene acetals to the acetylated carbohydrate derivatives using $HClO_4$–SiO_2 (Schemes 1 and 2).

Keywords: Carbohydrate; Debenzylidenation; Acetylation; Acetates; $HClO_4$–SiO_2; 1,3-diol.
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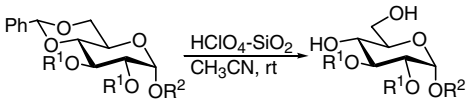
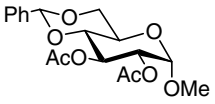
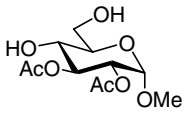
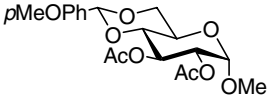
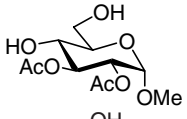
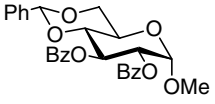
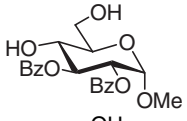
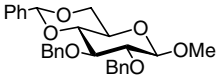
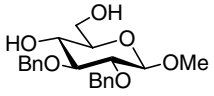
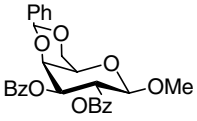
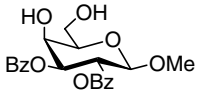
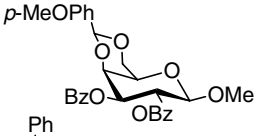
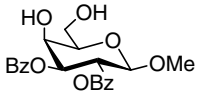
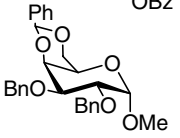
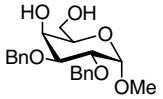
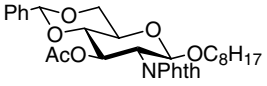
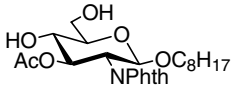
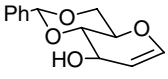
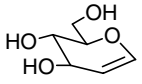
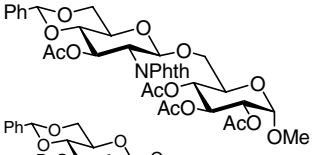
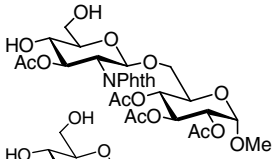
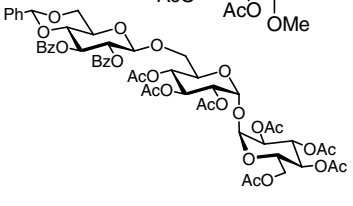
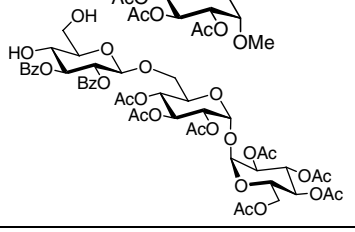


Scheme 1.

As a model, methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside was treated with $HClO_4$–SiO_2 in a variety of solvents and reaction conditions. After a series of experiments, it was observed that the use of 50 mg of $HClO_4$–SiO_2 (0.025 mmol of $HClO_4$) per millimole of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside in commercial CH_3CN at room temperature gave clean deprotection of the benzylidene acetal in a few minutes. In order to test the reaction protocol, a series of protected mono-, di- and trisaccharide derivatives containing benzylidene acetals were treated with $HClO_4$–SiO_2 in CH_3CN and the results are presented in Table 1. Following similar reaction conditions, 4-methoxybenzylidene acetals were also deprotected successfully. A series of anomeric protecting groups and interglycosidic linkages remained intact under the reaction conditions. Pure products were obtained by removal of the catalyst by simple filtration and evaporation of the solvent. CH_3CN was found to be

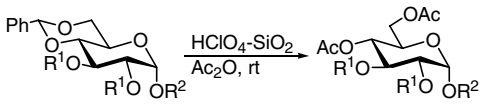
Table 1. Cleavage of benzylidene acetals using $HClO_4$–SiO_2 in CH_3CN at room temperature

Entry	Substrate	Product	Time (min)	Yield (%)	Ref.
1			20	95	7
2			20	96	7
3			20	95	—
4			20	92	8
5			20	96	9
6			20	95	9
7			20	95	9
8			30	96	—
9			15	90	10
10			30	95	—
11			30	92	—

the best solvent in comparison to other commonly used apolar solvents (e.g. CH_2Cl_2, $CHCl_3$, THF) in which lower yields were obtained (Table 2).

Table 2. Deprotection of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside at room temperature in different solvents

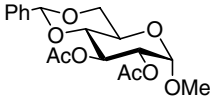
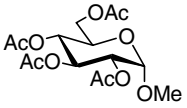
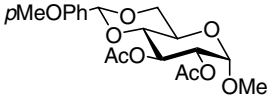
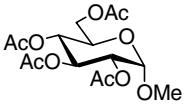
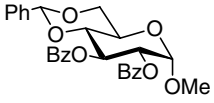
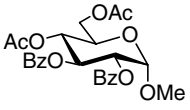
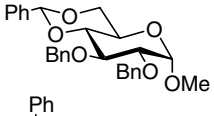
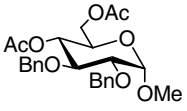
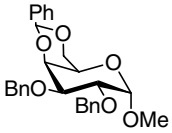
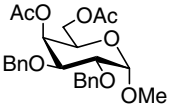
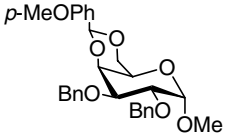
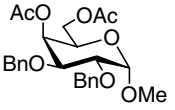
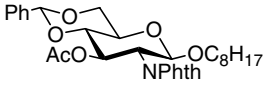
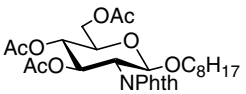
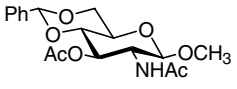
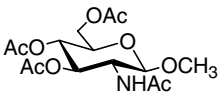
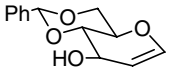
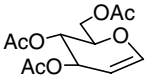
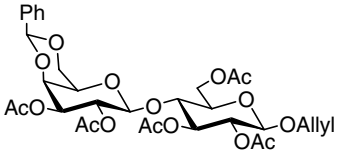
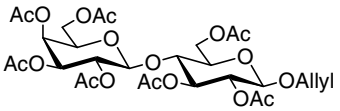
Entry	Solvent	Time (min)	Yield (%)
1	CH_3CN	20	95
2	CH_2Cl_2	60	40
3	$CHCl_3$	60	45
4	THF	60	75
5	Toluene	120	30



Scheme 2.

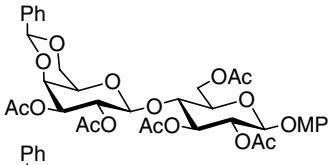
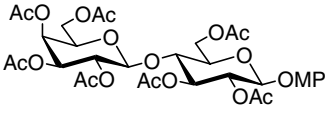
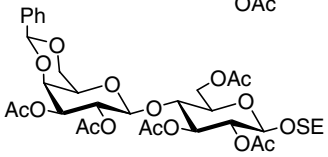
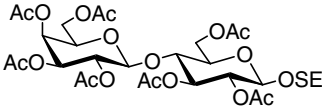
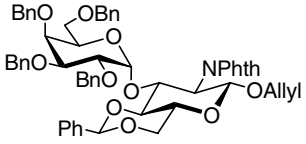
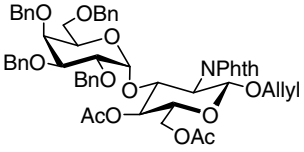
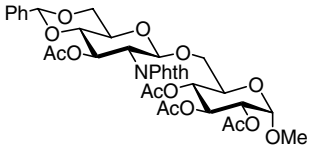
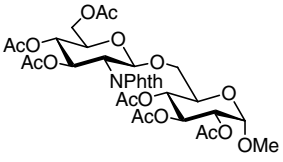
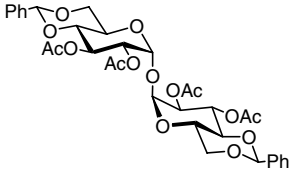
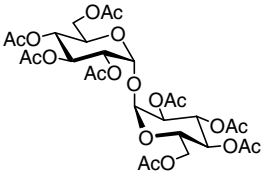
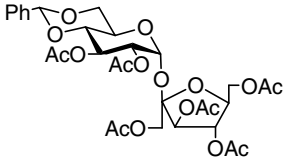
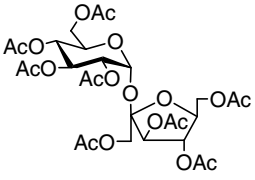
After achieving satisfactory yields in the deprotection of benzylidene acetals, we turned our attention to the applicability of the catalyst for a sequential deprotection of benzylidene acetal and acetylation of the diol generated in situ following a one-pot protocol. Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside was treated with acetic anhydride (5.0 equiv) in the presence of $HClO_4$–SiO_2 (50 mg of $HClO_4$–SiO_2 per millimole) at room temperature (Scheme 2). The exothermic reaction started immediately and quantitative formation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside was achieved in 15 min. The protocol was successfully applied to a series of mono-, di- and trisaccharide derivatives containing benzylidene or 4-methoxybenzylidene acetals and excellent yields were achieved in every case as presented in Table 3. A variety of anomeric protecting groups and interglycosidic linkages remained unaffected under the reaction conditions. Pure products were isolated by removal of the catalyst and evaporation under reduced pressure.

Table 3. One-pot cleavage-acetylation of benzylidene acetals using $HClO_4$–SiO_2 in Ac_2O at room temperature

Entry	Substrate	Product	Time (min)	Yield (%)	Ref.
1			15	98	11
2			15	96	11
3			15	95	—
4			15	92	—
5			15	95	—
6			15	96	—
8			15	95	12
9			20	95	13
10			20	90	10
11			20	96	14

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	Product	Time (min)	Yield (%)	Ref.
12			20	92	15
13			20	96	16
14			20	95	17
15			20	95	—
16			20	98	5b
17			20		18

MP: *p*-Methoxyphenyl; SE: trimethylsilyl ethyl; Phth: phthalimido.

Furthermore, the catalyst can be reused several times without significant loss of activity. After filtering the catalyst from the reaction mixture, it could be recycled after drying under vacuum. The recovered catalyst was used three times in the direct deprotection and acetylation of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside and the yields were higher than 90% in each case.

A typical experimental protocol for the deprotection of benzylidene acetal is as follows: to a solution of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (366 mg, 1.0 mmol) in commercial grade CH_3CN (5 mL) was added $HClO_4$–SiO_2 (50 mg) and the reaction mixture was stirred at room temperature for 20 min. After completion (TLC), the reaction mixture was filtered with ethyl acetate through a Celite bed and concentrated to dryness to give methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside (265 mg, 95%). Although the product was pure enough, analytical samples were prepared by passing the crude reaction product through a short column of SiO_2 using toluene–EtOAc (1:1) as eluant. Following similar reaction conditions, a series of di-hydroxylated carbohydrate derivatives were prepared (Table 1). All the products are known compounds and gave acceptable NMR spectra[19] that matched data reported in the literature.

A typical experimental protocol for the direct conversion of benzylidene acetals to the corresponding di-O-acetates is as follows: to a solution of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (366 mg, 1.0 mmol) in acetic anhydride (0.5 mL) was added $HClO_4$–SiO_2 (50 mg) and the reaction mixture was stirred at room temperature for 15 min. After completion (TLC), the reaction mixture was filtered with ethyl acetate through a Celite bed and concentrated to dryness to give methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (355 mg, 98%). Although the product was pure enough, analytical samples were prepared by passing the crude reaction product through a short column of SiO_2 using hexane–EtOAc (1:1) as eluant. Following similar reaction conditions, a series of acetylated carbohydrate derivatives were prepared directly from carbohydrate benzylidene acetals (Table 1). All the products are known compounds and gave acceptable NMR spectra[19] that

matched data reported in the literature. *Caution*: Although no explosions occured under these conditions, extreme care has to be applied for large-scale reactions. The generation of the catalyst should be performed with special care and in a safe environment.

In summary, we have introduced a new method for the rapid deprotection of benzylidene acetals and direct conversion of acid labile benzylidene acetals to the base-labile acetate derivatives in a one-pot reaction using $HClO_4$–SiO_2 with almost quantitative yields avoiding the formation of by-products. $HClO_4$–SiO_2 is a non-toxic catalyst system, which can be reused after easy recovery from the reaction mixture. As the reaction does not require any toxic reagents and chromatographic purification, this environmentally benign reaction protocol should find application in synthetic organic chemistry.

Acknowledgements

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6. *Preparation of $HClO_4$–SiO_2*: $HClO_4$ (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.
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19. Spectral data of selected compounds:
Methyl 2,3-di-O-benzoyl-α-D-glucopyranoside (Table 1, entry 3): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97–7.25 (m, 10H, aromatic protons), 5.70 (t, $J = 9.0$ Hz, 1H), 5.19 (t, $J = 8.8$ Hz, 1H), 5.08 (d, $J = 3.6$ Hz, 1H), 3.91–3.70 (m, 4H), 3.43 (s, 3H); ESI-MS: m/z 425 [M+Na]; Anal. calcd for $C_{21}H_{22}O_8$ (402): C, 62.68; H, 5.51; found: C, 62.84; H, 5.80.
Octyl 3-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (Table 1, entry 8): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88–7.71 (m, 4H, aromatic protons), 5.62 (t, $J = 8.0$ Hz, 1H), 5.40 (d, $J = 8.4$ Hz, 1H), 4.16 (dd, $J = 8.5$ Hz, 8.5 Hz, 1H), 4.0–3.55 (m, 5H), 3.52–3.40 (m, 1H), 1.93 (s, 3H), 1.39–1.20 (m, 2H), 1.25–1.10 (m, 10H), 0.81 (t, $J = 6.8$ Hz, 3H); ESI-MS: m/z 486 [M+Na]; Anal. calcd for $C_{24}H_{33}NO_8$ (463): C, 62.19; H, 7.18; found: C, 62.40; H, 7.40.
Methyl (3-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-O-acetyl-α-D-glucopyranoside (Table 1, entry 10): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84–7.71 (m, 4H, aromatic protons), 5.62 (t, $J = 9.0$ Hz, 1H), 5.42 (d, $J = 8.4$ Hz, 1H), 5.31 (t, $J = 9.6$ Hz, 1H), 4.80 (t, $J = 9.6$ Hz, 1H), 4.67 (dd, $J = 10.2$ and 3.3 Hz, 1H), 4.53 (d, $J = 3.3$ Hz, 1H), 4.20 (t, $J = 8.7$ Hz, 1H), 4.0–3.85 (m, 3H), 3.81–3.75 (m, 2H), 3.64–3.60 (m, 1H), 3.54–3.47 (m, 1H), 3.05 (s, 3H), 1.99 (s, 3H), 1.90 (s, 6H), 1.87 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5, 170.4 (2C), 170.0, 168.3 (2C), 134.5–123.7 (aromatic carbons), 98.8, 96.7, 76.3, 73.9, 71.2, 70.4, 70.1, 69.5, 69.1, 68.0, 62.3, 55.3, 54.9, 21.0, 20.9 (2C), 20.8; ESI-MS: m/z 676 [M+Na]; Anal. calcd for $C_{29}H_{35}NO_{16}$ (653): C, 53.29; H, 5.40; found: C, 53.10; H, 5.58.
(2,3-Di-O-benzoyl-β-D-glucopyranosyl)-(1 → 6)-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-(1 → 1)-2,3,4-tri-O-acetyl-α-D-glucopyranose (Table 1, entry 11): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96–7.32 (m, 10H, aromatic protons), 5.43–5.36 (m, 3H), 5.01–4.87 (m, 5H), 4.74–4.65 (m, 4H), 4.17–4.01 (m, 2H), 3.97–3.89 (m, 5H), 3.59–3.52 (m, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.04 (s, 6H), 1.99 (s, 6H), 1.93 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.6, 170.9, 170.6, 170.4, 170.2, 170.0, 169.9, 167.2, 165.5, 133.7–128.7 (aromatic carbons), 101.1, 92.5, 92.3, 76.6 (2C), 71.6, 70.6, 70.3, 70.2 (2C), 69.7, 69.4, 68.9, 68.6, 68.4, 62.2, 62.0, 60.8, 21.3, 21.1 (2C), 21.0 (2C), 20.9, 20.7; ESI-MS: m/z 1029 [M+Na]; Anal. calcd for $C_{46}H_{54}O_{25}$ (1006): C, 54.87; H, 5.41; found: C, 54.70; H, 5.60.
Methyl 4,6-di-O-acetyl-2,3-di-O-benzoyl-α-D-glucopyranoside (Table 3, entry 3): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97–7.32 (m, 10H, aromatic protons), 5.90 (br s, 2H), 5.31 (t, $J = 8.8$ Hz, 1H), 5.17 (br s, 1H), 4.30 (dd, $J = 11.0$ and

4.5 Hz, 1H), 4.16–4.09 (m, 2H), 3.45 (s, 3H), 2.13, 1.94 (2s, 6H); ESI-MS: *m/z* 509 [M+Na]; Anal. calcd for $C_{25}H_{26}O_{10}$ (486): C, 61.72; H, 5.39; found: C, 61.50; H, 5.60.

Methyl 4,6-di-O-acetyl-2,3-di-O-benzyl-α-D-glucopyranoside (Table 3, entry 4): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27–7.13 (m, 10H, aromatic protons), 4.87 (t, $J = 10.0$ Hz, 1H), 4.76–4.52 (2 ABq, 4H), 4.48 (d, $J = 3.5$ Hz, 1H), 4.09 (dd, $J = 9.9$ and 3.5 Hz, 1H), 3.91 (dd, $J = 12.8$ and 2.2 Hz, 1H), 3.84 (t, $J = 9.3$ Hz, 1H), 3.75–3.70 (m, 1H), 3.51 (dd, $J = 12.8$ and 3.5 Hz, 1H), 3.31 (s, 3H), 1.98, 1.81 (2s, 6H); ESI-MS: *m/z* 481 [M+Na]; Anal. calcd for $C_{25}H_{30}O_8$ (458): C, 65.49; H, 6.60; found: C, 65.32; H, 6.80.

Methyl 4,6-Di-O-acetyl-2,3-di-O-benzyl-α-D-galacto-pyranoside (Table 3, entries 5 and 6): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.14 (m, 10H, aromatic protons), 5.44 (br s, 1H), 4.84 (d, $J = 11.0$ Hz, 1H), 4.68 (dd, 11.0 and 3.8 Hz, 2H), 4.50 (d, $J = 11.3$ Hz, 1H), 4.24 (m, 1H), 4.14–4.10 (m, 2H), 3.74–3.70 (m, 1H), 3.56 (s, 3H), 3.53–3.50 (m, 2H), 2.14, 2.06 (2s, 6H); ESI-MS: *m/z* 481 [M+Na]; Anal. calcd for $C_{25}H_{30}O_8$ (458): C, 65.49; H, 6.60; found: C, 65.31; H, 6.78.

Methyl (3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-O-acetyl-α-D-glucopyranoside (Table 3, entry 15): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86–7.65 (m, 4H, aromatic protons), 5.75 (t, $J = 10.2$ Hz, 1H), 5.38 (t, $J = 8.3$ Hz, 1H), 5.30 (br s, 1H), 5.17 (t, $J = 9.4$ Hz, 1H), 4.79–4.65 (m, 2H), 4.45 (br s, 1H), 4.38–4.19 (m, 3H), 3.90–3.80 (m, 3H), 3.54–3.45 (m, 1H), 3.01 (s, 3H), 2.12, 2.03, 2.0, 1.92, 1.90, 1.86 (6s, 18H); ESI-MS: *m/z* 760 [M+Na]; Anal. calcd for $C_{33}H_{39}NO_{18}$ (737): C, 53.73; H, 5.33; found: C, 53.55; H, 5.52.