Carbohydrate Research 346 (2011) 2965–2969

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

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# Photochemical conversion of the *o*-nitrobenzyl-C-glucoside to a sugar lactone

Michinari Kohri *, Takuma Kimura, Yoshihiro Shinoda, Tatsuo Taniguchi, Takayuki Nakahira

*Division of Applied Chemistry and Biotechnology, Graduate School of Engineering, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan*

ARTICLE INFO

*Article history:*
Received 29 August 2011
Received in revised form 14 October 2011
Accepted 15 October 2011
Available online 20 October 2011

*Keywords:*
Photochemical conversion
*o*-Nitrobenzyl group
Sugar lactone

ABSTRACT

A new family of activated glycosidic compounds has been designed and synthesized: (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-nitrophenylmethane (**1**). It is stable in conditions commonly used for synthesis, and it can be converted to a sugar lactone derivative merely by photoirradiation ($\lambda$ = 365 nm): 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone (**2**). A mechanism for the reaction is proposed. The photochemical conversion of **1** in the presence of methanol has also been demonstrated, giving rise to methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate (**3**).

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Sugar lactones have found broad application as building blocks for the synthesis of important bioactive compounds[1–6] and precursors of various sugar derivatives, such as aza sugars,[7] *exo*-glycals,[8,9] and C-glycoside derivatives.[10] They are typically synthesized by selective anomeric oxidation of unprotected sugars with bromine[11] or by their dehydrogenation using a transition metal complex in the presence of a hydrogen acceptor.[12–14] Protected sugars with a free anomeric hydroxyl group can be converted into the corresponding lactone derivatives by chromium(VI) reagents[15] or DMSO.[16,17] Although widely various reactions leading to sugar lactones have been reported, no reagent-free reaction has been achieved.

Photoreactive protecting groups have found wide applications in synthetic chemistry and bioorganic chemistry. Their deprotection requires only light irradiation: no reagent is needed. The *o*-nitrobenzyl group is a widely used photoreactive protecting group.[18–22] In carbohydrate chemistry, while photoreactive groups have been used as linkers for solid phase synthesis of oligosaccharides[23] or as a protecting group for oligosaccharide syntheses,[24–26] no example exists in the literature of photoreactive groups used for activation of the anomeric position of sugars.

For this study, we synthesized a novel activated glycosidic compound, that is, (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-nitrophenylmethane (**1**), and conducted photochemical conversion of **1** to 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone (**2**). To our knowledge, this report is the first to describe the use of a photoreactive group for the activation of anomeric position in carbohydrate. The proposed method is expected to be an effective method for sugar lactone synthesis using a reagent-free reaction, with possible advantages, for example, synthetic applications in solid phase synthesis and bioorganic chemistry. The use of photo-energy to promote the reaction of **1** in situ with a primary alcohol through a lactone derivative **2** as an intermediate has been demonstrated, giving rise to the glycoconjugate, methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **3**, with ester linkage (Scheme 1a). The methodology demonstrated here may also allow a reagent-free conversion of a sugar lactone, and the subsequent reaction of lactone moiety with alcohols or amines in biomolecules under mild reaction conditions: solely UV irradiation (Scheme 1b).

*O*-Nitrobenzyl-C-glucoside **1** was prepared from commercially available glycosyl bromide **1a** in two steps (Scheme 2). Compound **1a** reacted with benzylmagnesium chloride in THF to give benzyl *C*-glucosyl compound **1b** in a 13% yield. Then, **1b** was reacted with copper(II) nitrate and acetic anhydride and was purified using silica gel chromatography, giving rise to an isomeric mixture of nitrobenzyl C-glucoside **1** and **1c** (1/1). In this reaction, *p*-nitrobenzyl-C-glycoside **1c** was formed as a by-product, which can be removed by recrystallization. Finally, the mixture was purified using high-performance chromatography to give **1** (13% yield). The $^1$H NMR spectrum of **1** showed a double double doublet peak at 2.15 ppm derived from the anomeric proton with the coupling constant of 9.35 Hz ($J_{1,2}$), indicating that the anomeric configuration of the product is β-type.

First, photoinduced hydrolysis experiments of **1** were performed in chloroform at room temperature to ascertain whether an *o*-nitrobenzyl glycosidic moiety can be photosensitized. The residual value of **1** versus time curves obtained by HPLC is presented in Figure 1. Almost no glycosidic bond cleavage was observed, indicating that compound **1** is stable in chloroform (open circle in Fig. 1). After UV irradiation (100 W, $\lambda$ = 365 nm), compound **1** was degraded smoothly (closed circle in Fig. 1). As the

* Corresponding author. Tel./fax: +81 43 290 3393.
*E-mail address:* kohri@faculty.chiba-u.jp (M. Kohri).

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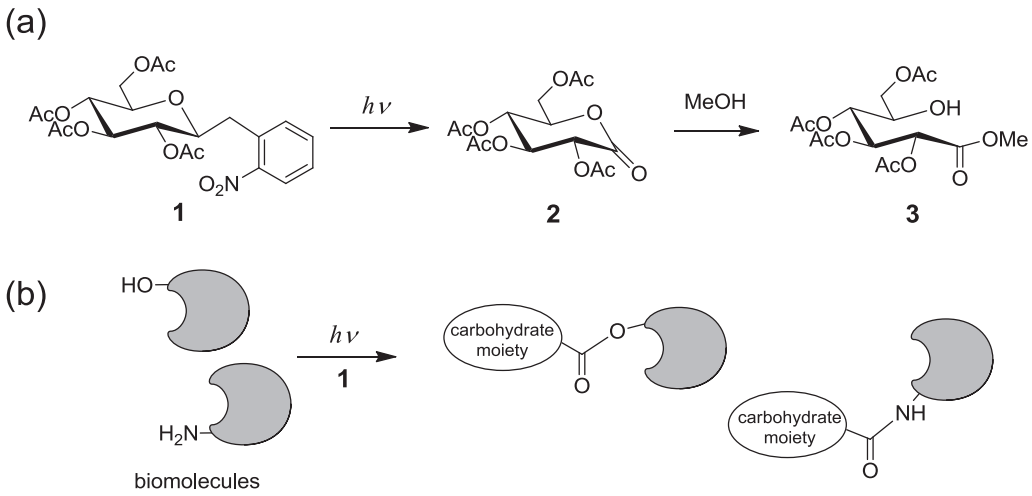
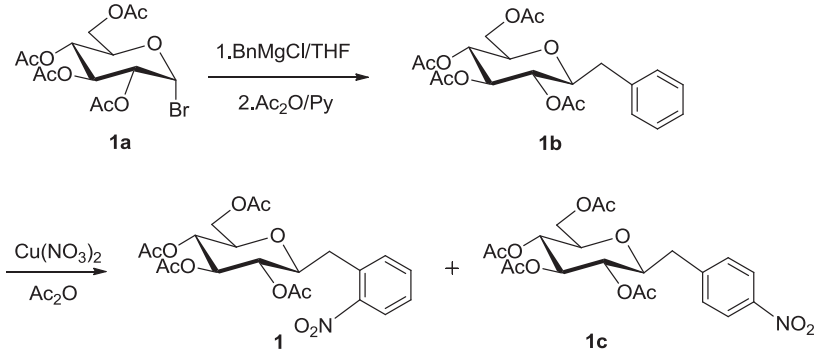
doi:10.1016/j.carres.2011.10.027




**Scheme 1.** (a) Photochemical conversion of **1**, and alcohol addition to a sugar lactone derivative **2**. (b) Schematic illustration of the reaction of **1** with alcohols or amines in biomolecules.




**Scheme 2.** Synthesis of **1**.

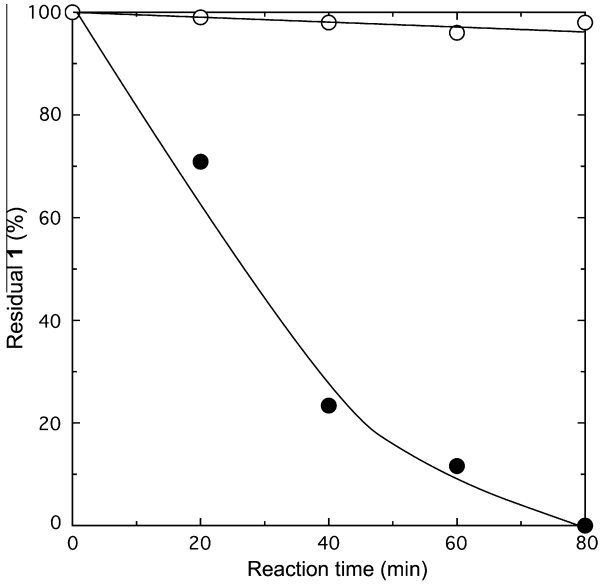



**Figure 1.** Time-course of consumption of **1**. Open circle, in dark; closed circle, irradiated with 365 nm (100 W).

irradiation time increased, the degradation yield increased, suggesting that **1** was released with UV irradiation. On the other hand, *p*-nitrobenzyl-C-glucoside **1c** was stable under UV irradiation.

A dilute solution of **1** in chloroform-*d* was exposed to UV light (400 W, $\lambda$ = 365 nm), and the photoinduced hydrolysis reaction was followed by $^1$H NMR spectroscopy (Fig. 2). The reaction proceeded, with most of the nitrobenzyl group cleaved after 20 min of exposure. The obtained photolysis product was identified as 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone (**2**) by comparison of spectroscopic data with an authentic sample.[27] The NMR spectrum of the reaction mixture recorded after 5 min irradiation revealed the presence of unreacted compound **1**, although this was consumed almost completely after 20 min: however, the yield of **2** was ca. 60%. Although the reason is not yet fully understood, we believed that this phenomenon is probably due to the partial degradation of samples by UV irradiation. The observed ESI-MS data of the reaction mixture were also consistent with the calculated value, clearly indicating the lactone derivative formation solely by UV irradiation. However, virtually no signals due to the aglycon (aromatic ring moiety) were observed. (The peaks at 8.0 and 9.1 ppm were not yet identified.)

Scheme 3a shows the general photoreactivity of the *o*-nitrobenzyl compounds. A number of photochemical rearrangements of *o*-nitrobenzyl compounds have been rationalized by postulating an intramolecular hydrogen abstraction by the n$\pi^*$-excited states from benzylic hydrogen.[28–30] Following hydrogen transfer step, the cyclic intermediate was proceeded, and ring chain tautomerism yields the familiar nitroso aldehyde compound. A possible mechanism for the photolysis of **1** is indicated in Scheme 3b. The mechanism for a lactone derivative formation is probably due to the intramolecular reaction between an anomeric carbon substituted

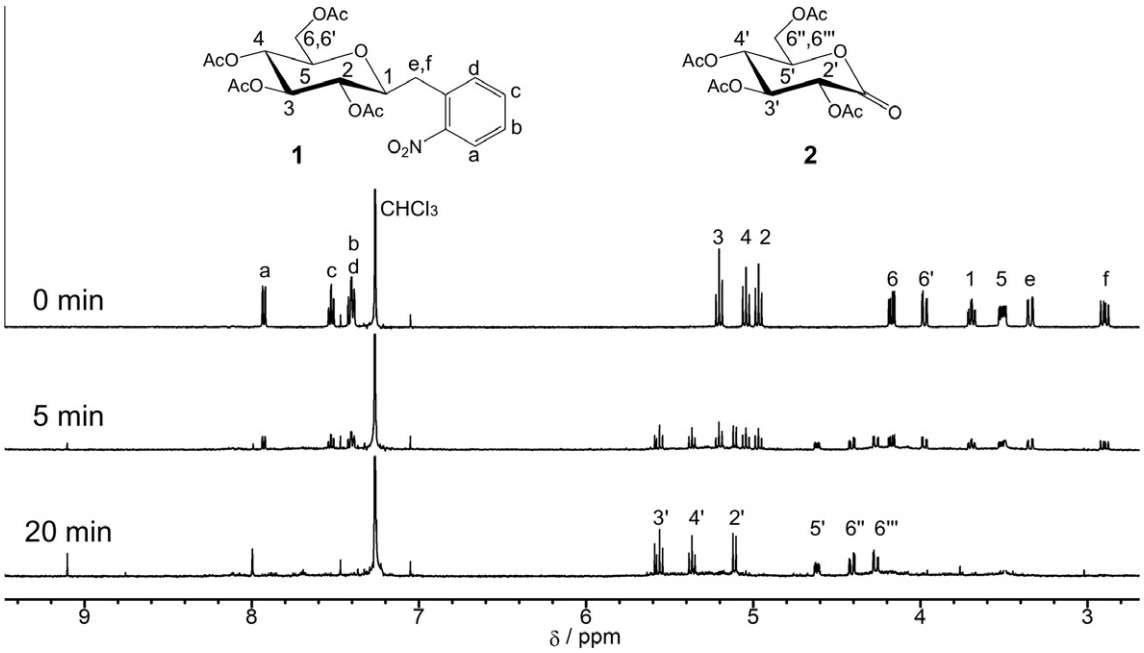
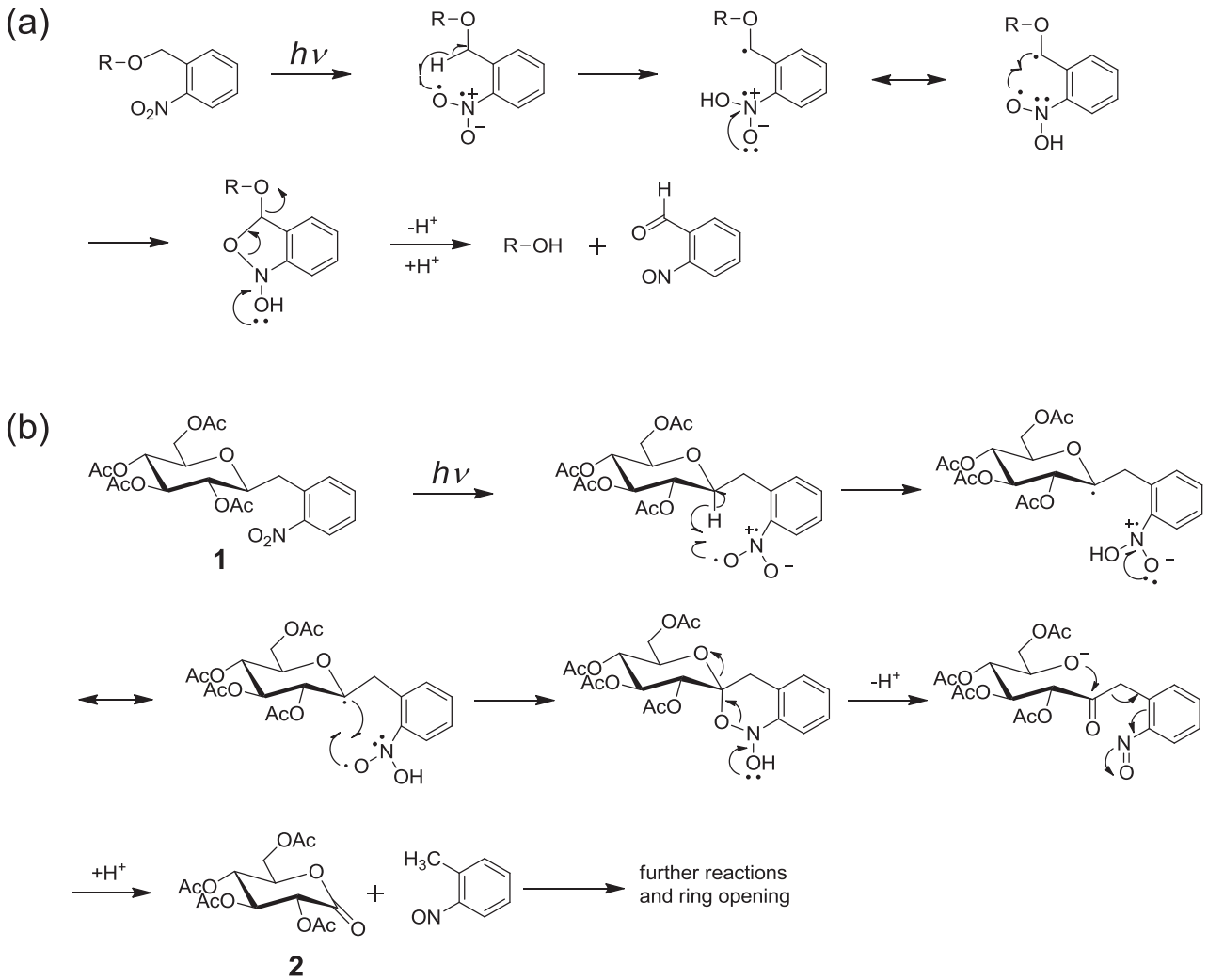



**Figure 2.** $^{1}$H NMR spectra of the reaction mixture irradiated with 365 nm (400 W) in $CDCl_3$ monitored at different times.




**Scheme 3.** (a) General photoreactivity of the *o*-nitrobenzyl compounds. (b) Proposed mechanism for the photolysis of **1**.

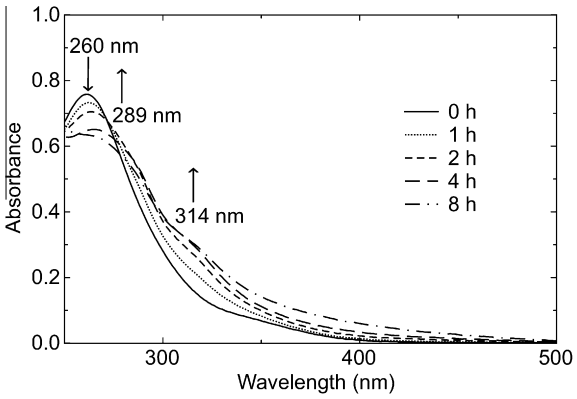



**Figure 3.** UV–vis absorption spectra of **1** irradiated with 365 nm (15 W) in $CHCl_3$ ([M] = $1.7 \times 10^{-4}$ M). Spectra recorded at 0, 1, 2, 4, and 8 h.

with a leaving group and an *o*-nitro group. Then, an intramolecular attack to the carbonyl group occurred, affording a sugar lactone derivative **2** and a nitroso derivative. However, we did not detect a nitroso derivative by $^1$H NMR measurements (vide supra). Therefore, we performed UV–vis measurement of the reaction mixture, as shown in Figure 3. Irradiation of **1** in chloroform at 365 nm (15 W) induced the decrease of absorption band at 260 nm due to nitrobenzoic moieties, and the new absorption bands at 289 and 314 nm appeared, supporting the assumption of the formation of nitroso compounds.[30,31] (For these experiments, weak UV lamp (15 W) was used to improve the assay sensitivity.) Although formation of a nitroso derivative was suggested by UV–vis measurements, we did not detect them by $^1$H NMR measurements, indicating further reactions including oxidation and ring opening: the degradation of a nitroso derivative, in accord with a report by Pelizzetti et al.,[32] who showed that the photocatalytic degradation of nitrosobenzene. However, it is early to draw conclusions with the results presented here, and more experiments are needed to clarify detailed mechanisms of a sugar lactone formation. In contrast to the *o*-nitrobenzyl compounds case, the reaction path to the product is assumed to be an intramolecular hydrogen abstraction from anomeric hydrogen, indicating that the difference was probably due to the steric effect of **1**. Additionally, *p*-nitrobenzyl-C-glycoside **1c** was not hydrolyzed by UV irradiation, indicating no initiation of an intramolecular hydrogen abstraction from *p*-nitro group.

Encouraged by these new findings, we examined in situ alcohol addition to lactone derivative **2** obtained by photochemical conversion of **1**. The reaction in the presence of methanol as a glycosyl acceptor (**1**/acceptor ratio = 1/1) was monitored using $^1$H NMR spectroscopy. When these solutions were allowed to stand overnight at rt, neither decomposition of **1** nor formation of **2** could not be detected. On the other hand, after UV irradiation (400 W, $\lambda$ = 365 nm, 30 min), the spectrum of **1** became smaller and that of **2** appeared as shown above. New peaks identified as methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate (**3**)[27] appeared, indicating construction of the glycoconjugate with ester linkage solely by UV irradiation. When the reaction was conducted under the condition of **1**/acceptor ratio 1/10, the overall yields of **3** based on **1** increased to ca. 48% was achieved. The low conversion was due to the conversion of **1** to **2**: compound **1** was converted by UV irradiation to give **2** in ca. 60% yield (vide supra), and the yield of **3** based on **2** was ca. 80%. When methanol (**1**/methanol ratio 1/10) was added to a chloroform solution of **1** after UV irradiation (400 W, $\lambda$ = 365 nm, 30 min) and allowed to stand 30 min at rt, methyl gluconate derivative **3** was not detected by $^1$H NMR measurements. Furthermore, when a purified lactone derivative **2** was dissolved in chloroform in the presence of methanol and allowed to stand 30 min at rt (**2**/methanol ratio 1/10), **3** was not observed: most of **2** remained. When the sample was allowed to react for another one day, only a small amount of **3** was obtained (ca. 5%). In contrast, UV irradiation (400 W, $\lambda$ = 365 nm, 30 min) of solutions of purified **2** and methanol in chloroform resulted in complete formation of **3**. These control experiments suggest that the formation of **3** by an addition reaction of methanol was also promoted under the photoirradiation. This will be discussed in a separate paper.

In summary, a novel glycosyl compound, that is, *o*-nitrobenzyl-C-glycoside, was prepared and converted by UV irradiation to give a sugar lactone derivative, which reacts in situ with primary alcohol to give the glycoconjugate with ester linkage. This new methodology is expected to be an efficient and practical tool for the construction of glycoconjugates by photoirradiation. However, some unclear points about mechanism of a sugar lactone formation still remain. Further studies include understanding the detailed mechanism of lactone formation and developing applications of this methodology using other carbohydrates are in progress. Results of those investigations will be reported in a future publication.

## 1. Experimental

### 1.1. General methods

NMR spectra were recorded using a Fourier transform NMR spectrometer (JNM-ECA500 JEOL). Assignments of $^1$H and $^{13}$C NMR spectra were performed by H–H COSY and HMQC experiments. The ESI-MS spectra were measured using a mass spectrometer (Exactive; Thermo Scientific). High-performance chromatography, using an Inertsil Ph-3 column (GL Sciences Inc.) with methanol/$H_2O$ (3/1) as a mobile phase at a flow rate of 0.4 mL/min at 30 °C, was used for the purification and detection of **1**. A high-pressure mercury lamp (HL100G (100 W), HB400P (400 W); SEN Lights Corp.) and handy UV lamp (SLUV 6 (15 W); AS ONE) supplied the UV light. UV–vis spectra were obtained using a spectrophotometer (U-3010; Hitachi Ltd).

### 1.2. (2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-nitrophenylmethane (1)

A solution of benzylmagnesium chloride (1 mol/L THF soln, 36.6 mL, 36.6 mmol) in THF (10 mL) was added to a stirred solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1a** (1.0 g, 2.44 mmol) in THF at 0 °C; then the mixture was stirred for 12 h at room temperature under argon. The resulting sample was reacetylated using the standard method and purified with silica gel chromatography, giving rise to (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-phenylmethane **1b** (0.13 g, 0.31 mmol) in a 13% yield. Then, the resulting **1b** (56 mg, 0.13 mmol) was reacted with copper(II) nitrate (0.32 g, 1.3 mmol) and acetic anhydride (7 mL) for 3 h at 105 °C. The sample was then purified using silica gel chromatography and HPLC, giving rise to **1** (8.0 mg, 0.017 mmol) in a 13% yield. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.91 (d, 1H, Ar), 7.51 (m, 1H, Ar), 7.3 (m, 2H, Ar), 5.19 (m, 1H, H3), 5.04 (m, 1H, H4), 4.96 (m, 1H, H2), 4.15 (m, 1H, H6), 4.39 (m, 1H, H6'), 3.67 (ddd, 1H, H1, $J_{1,2}$ = 9.35 Hz), 3.51 (m, 1H, H5), 3.31 (m, 1H, $-CH_2-$) 2.89 (m, 1H, $-CH_2-$), 2.00 (12H, $4 \times COCH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 170.6, 170.3, 170.1 (C=O acetate), 150.0, 134.0, 132.6, 132.0, 128.0, 124.7, (Ar), 77.0 (C1), 75.4 (C5), 74.1 (C3), 71.9 (C2), 68.6 (C4), 62.2 (C6), 34.9 ($-CH_2-$), 20.8, 20.7, 20.6 ($4 \times COCH_3$); ESI calcd for $C_{21}H_{25}O_{11}NNa$ ([M+$Na^+$]) 490.1320, found 490.1319.

### 1.3. (2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-nitrophenylmethane (1c)

Compound 1c was synthesized similarly as **1** in a 9% yield. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.15 (d, 2H, Ar), 7.38 (2H, d, Ar), 5.19

(m, 1H, H3), 5.04 (m, 1H, H4), 4.94 (m, 1H, H2), 4.20 (m, 1H, H6), 4.06 (m, 1H, H6'), 3.65 (ddd, 1H, H1), 3.57 (m, 1H, H5), 2.91 (m, 2H, $-CH_2-$), 2.03 (12H, $4 \times COCH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 170.5, 170.4, 169.7, 169.5 (C=O acetate), 147.0, 144.7, $130.5 \times 2$, $123.4 \times 2$, (Ar), 77.6 (C1), 75.7 (C5), 74.2 (C3), 71.8 (C2), 68.5 (C4), 62.1 (C6), 37.5 ($-CH_2-$), 20.7 20.6 ($4 \times COCH_3$); ESI calcd for $C_{21}H_{25}O_{11}NNa$ ([M+Na$^+$]) 490.1320, found 490.1314.

### 1.4. 2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone (2)

A solution of **1** (2.0 mg, 4.28 μmol) in $CHCl_3$ (0.5 mL) was irradiated with 365 nm (400 W) for 20 min. The sample was concentrated in vacuo, giving rise to **2** in a 60% yield. (A yield was determined by $^1H$ NMR using an internal standard (styrene).) $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.57 (m, 1H, H3), 5.37 (m, 1H, H4), 5.11 (d, 1H, H2), 4.61 (m, 1H, H5), 4.41 (m, 1H, H6), 4.27 (m, 1H, H6'), 2.28–2.09 (12H, $4 \times COCH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 170.2 (C=O ester), 169.9, 169.5, 169.1, 164.5 (C=O acetate), 75.8 (C5), 70.4 (C3), 70.3 (C2), 66.5 (C4), 61.3 (C6), $20.6 \times 2$, 20.5, 20.4 ($4 \times COCH_3$); ESI calcd for $C_{14}H_{18}O_{10}Na$ ([M+Na$^+$]) 369.0792, found 369.0789.

### 1.5. Methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate (3)

A solution of **1** (2.0 mg, 4.28 μmol) and methanol (1.37 mg, 42.8 μmol) in $CHCl_3$ (0.5 mL) was irradiated with 365 nm (400 W) for 30 min. The sample was concentrated in vacuo to give **3** in a 48% yield. (A yield was determined by $^1H$ NMR using an internal standard (styrene).) $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.72 (t, 1H, H3), 5.31 (d, 1H, H2), 5.20 (dd, 1H, H4), 4.13 (m, 2H, H6), 3.85 (d, 1H, H5), 3.74 (s, 3H, OMe), 2.17, 2.16, 2.14, 2.10 (12H, $4 \times COCH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 171.1 (C=O ester), 170.4, 169.7, 167.3 (C=O acetate), 71.6 (C2), 70.7, 69.4 (C3/4), 68.3 (C5), 64.6 (C6), 52.8 ($OCH_3$-methoxy), 20.7, $2 \times 20.5$, 20.4 ($4 \times COCH_3$); ESI calcd for $C_{15}H_{22}O_{11}Na$ ([M+Na$^+$]) 401.1054, found 401.1059.

## Acknowledgments

We thank Dr. Masato Noguchi and Dr. Masaki Ishihara of Tohoku University for their discussions and valuable comments on the manuscript.

## Supplementary data

Supplementary data ($^1H$ and $^{13}C$ NMR spectra for **1** and **1c)** associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.10.027.

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