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Note

# Transformation of the (2-nitrophenyl)acetyl protecting group in the presence of trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]-undec-7-ene

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ABSTRACT

When treated with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5,4,0]-undec-7-ene, the (2-nitrophenyl)acetyl protecting group (NPAc) was partially transformed into mono-(NPClAc) and dichlorinated ($NPCl_2Ac$) species, but no chlorination occurred in the presence of solid potassium carbonate. The monochlorinated NPClAc group, which is suitable for use in glycosylation reaction, can be selectively removed by treatment with thiourea.



The concept of orthogonal protection,[1] in which any of a set of various protecting groups can be introduced and removed selectively without affecting the other present on a molecule is highly suitable, especially in carbohydrate chemistry. Although numerous protecting groups have been reported,[2] only a few sets fulfil these requirements. In the course of a programme dealing with the stereocontrolled synthesis of oligosaccharide derivatives from the carbohydrate–protein linkage region of proteoglycans,[3] we were looking for a robust, stable and orthogonal temporary protection at O-4 of the D-glucuronic acid (D-GlcA) moiety allowing further extension at these non-reducing position. The recently reported use of the (2-nitrophenyl)acetyl group[4] caught our attention. It is easily introduced, showed apparent stability under common carbohydrate transformations, and is selectively removed by assisted cleavage through reduction of the nitro group. We would like to report here the results of our observations regarding its behaviour during the preparation of Schmidt's trichloroacetimidates.[5]

Treatment of the known[6] methyl(4-methoxyphenyl 2,3-di-*O*-benzoyl-β-D-glucopyranosyl)uronate **1** with (2-nitrophenyl)acetic acid, 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane afforded readily the ester **2** in 90% yield (Scheme 1). Oxidative removal of the 4-methoxyphenyl group with Cerium(IV) diammonium hexanitrate (CAN) gave the hemiacetal **3** in 87% yield. This later was then treated with trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) in dichloromethane, conditions that are known to give nearly exclusively the corresponding α-imidate. However, the reaction proceeded sluggishly, and sequential additions of reagents were necessary to complete the reaction. The expected α-imidate **4** was isolated after chromatography and crystallization in modest yield (58%). Careful examination of the mother liquor from crystallization (**5**, not distinguishable from **4** in t.l.c.) by $^1$H NMR showed unexpectedly the presence of three compounds. Two major telling signals characteristic of a –*CH*Cl– motif (R and S isomers) were identified at $\delta$ 6.11 and 5.97 ppm, and no signal was found for the methylene group. HRESIMS of this mixture showed two peaks: one (major) corresponding to a derivative of **4** containing one additional chlorine atom (NPClAc), and one (minor) containing two additional chlorine atoms ($NPCl_2Ac$). The monochloro/dichloro derivative ratio was ~9:1 (integrated $^1$H NMR). It was obvious that under these conditions mono- and/or di-chlorination occurred at the methylene moiety of the NPAc group. To assess this hypothesis, fully protected compound **2** was treated under similar conditions with sequential addition of reagents. An inseparable mixture of compounds **6** was obtained, whose NMR and MS data matched those reported for **5**. Treatment of **6**, as described for the preparation of **4** and **5**, gave a mixture of imidates **5** in which the monochloro/dichloro derivative ratio was ~4:1. However, when hemiacetal **3** was treated with trichloroacetonitrile but in the presence of solid potassium carbonate,[7] imidates **4α** and **4β** were isolated separately in 86% overall yield, and only traces (<3%) of chlorinated species were observed in their $^1$H NMR spectra.

Although the mechanistic details of this reaction are not known, the reaction of trichloroacetonitrile with active methylene groups,[8] as well as its use as a source of positive chlorine ion[9] has been reported. In the homogeneous reaction with the amidine DBU, one or two protons of the methylene group in the NPAc should be

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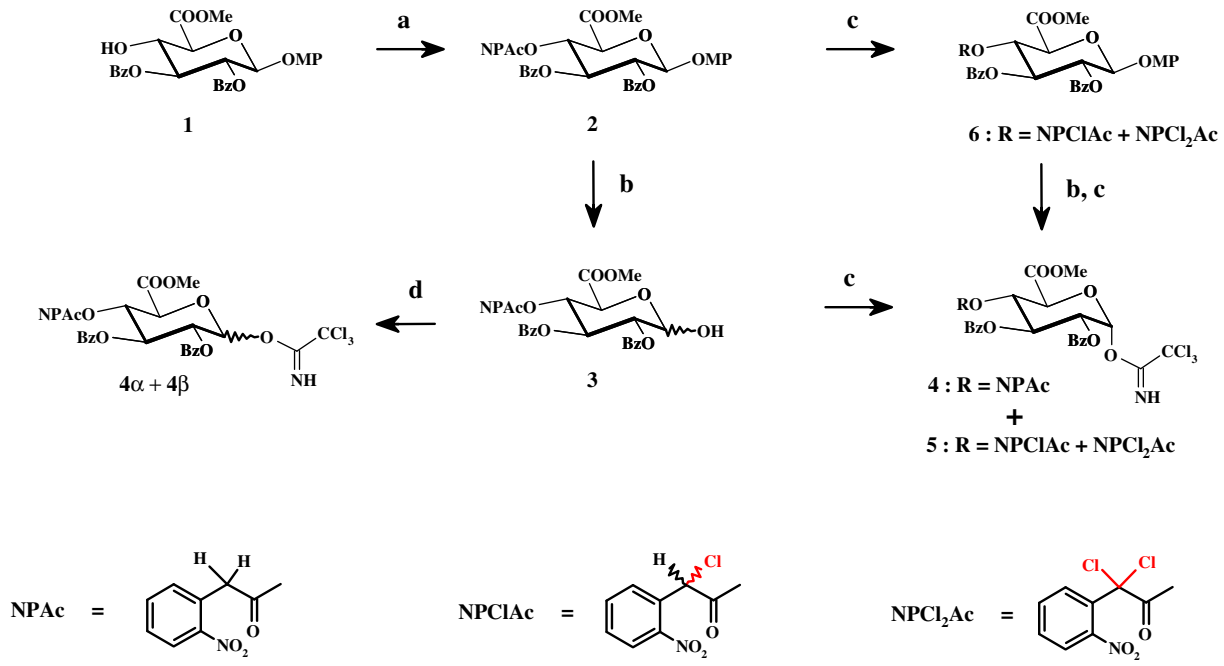


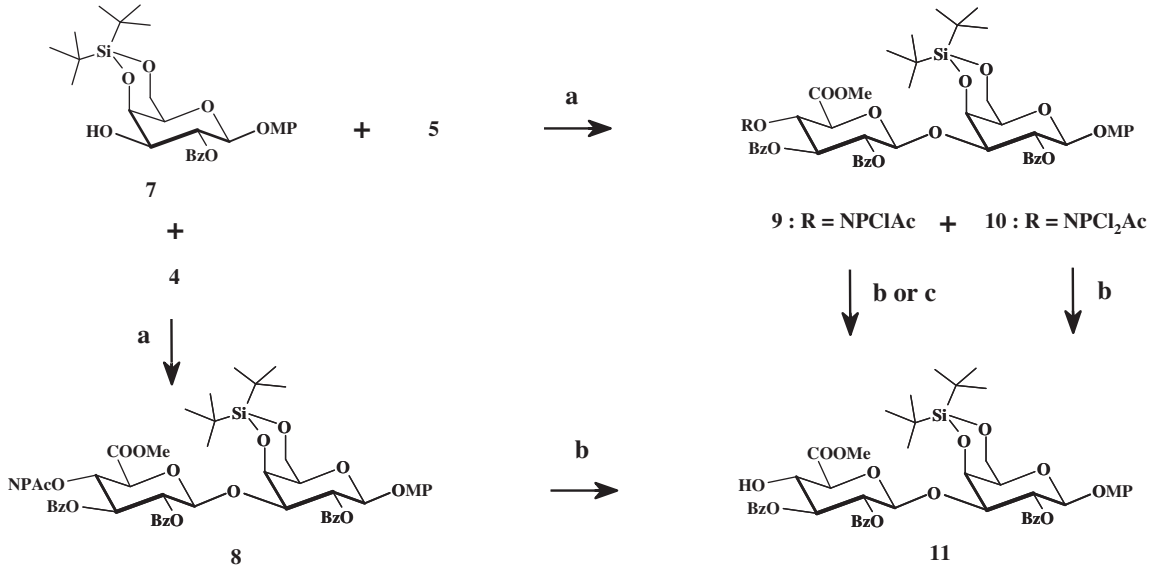

**Scheme 1.** Reagents and conditions: (a) (2-Nitrophenyl)acetic acid, DCC, DMAP, $CH_2Cl_2$, rt, 1 h; (b) CAN, toluene/MeCN/$H_2O$, rt, 15 min; (c) $Cl_3CCN$, DBU, $CH_2Cl_2$, rt, 1 h; (d) $Cl_3CCN$, $K_2CO_3$, $CH_2Cl_2$, rt, 1 h.

abstracted and replaced by chlorine atom(s). In the heterogeneous reaction with solid potassium carbonate, this side-reaction does not occur.

Next was examined the behaviour of imidates **4** and **5** under glycosylation conditions in the preparation of the D-GlcA-D-Gal building block **8** (Scheme 2). Coupling reaction of known[10] 4-methoxyphenyl 2-*O*-benzyl-4,6-*O*-di-*tert*-butylsilylene-β-D-galactopyranoside **7** with imidate **4** (α,β mixture) in the presence of trimethylsilyl triflate (TMSOTf) in dichloromethane gave **8** in 80% yield, the structure of which was easily deduced from its $^1$H NMR spectrum. Similar coupling of imidates **5** with **7** gave the disaccharide derivatives **9** (60%) and **10** (14%), respectively, that were easily separated by chromatography. The $^1$H NMR and MS spectra for **9** and **10** showed unambiguously that **9** was a monochlorinated derivative (mixture of isomers) and **10** a dichlorinated species.

Selective removal of these modified NPAc groups was then studied. When compounds **8**, **9** and **10** were treated with zinc dust and ammonium chloride in methanol/1,4-dioxane, as reported,[4] a single alcohol **11** was isolated in 88–90% yield. When the monochlorinated derivative **9** was treated with thiourea, usual conditions used to remove selectively a monochloroacetyl group, the same alcohol **11** was obtained in 87% yield.

In conclusion, care has to be taken when the NPAc group is present on a molecule that has to be transformed into a trichloroacetimidate using trichloroacetonitrile and DBU. Such unexpected




**Scheme 2.** Reagents and conditions: (a) TMSOTf, 4 Å mol. sieves, $CH_2Cl_2$, rt, 30 min; (b) Zn powder, $NH_4Cl$, MeOH/1,4-dioxane, rt, 1 h; (c) Thiourea, pyridine/EtOH, 80 °C, 3 h.

side-reaction was not encountered in the initial report since only thioglycosides were used as glycosyl donors. Interesting enough is the fact that the monochlorinated NPAc group (NPClAc) can be removed selectively under two different conditions.

## 1. Experimental

### 1.1. General methods

Solvents were dried by standard methods, and molecular sieves were activated prior to use by heating for 4 h at 500 °C. Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Perkin–Elmer 341 polarimeter. $^1$H and $^{13}$C NMR spectra were recorded at 25 °C with a Bruker Advance II 400 instrument, with $Me_4Si$ as internal standard, unless otherwise stated. Assignments were based on homo- and heteronuclear correlations using the supplier's software. Low-resolution mass spectra (ISMS) were obtained on a Perkin–Elmer SCIEX API 300 spectrometer operating in the ion-spray mode or on a Micromass Quattro Ultima spectrometer equipped with a Z-spray ionization source operating in the negative mode. High-resolution mass spectra (HRESIMS) were performed on a Bruker maXis mass spectrometer by the "Fédération de Recherche ICOA/CBM (FR 2708) platform. Flash-silica chromatography was performed on Silica gel 60 (0.040–0.063 mm, Merck, Darmstadt). The reactions were monitored by TLC on coated aluminium sheets (silica gel 60 $GF_{254}$, Merck), and spots were detected under UV light and by charring with a 95/5 mixture of ethanol and sulfuric acid. Elemental analyses were carried out at the Service Central d'Analyse du CNRS (Institut des Sciences Analytique, Solaize, France).

### 1.2. Methyl [4-methoxyphenyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)acetyl-β-D-glucopyranosid]uronate (2)

A mixture of methyl (4-methoxyphenyl 2,3-di-*O*-benzoyl-β-D-glucopyranosid)uronate **1**[6] (5.23 g, 10 mmol), 2-nitrophenylacetic acid (2.72 g, 15 mmol) and DMAP (0.3 g, 2.5 mmol) in anhyd $CH_2Cl_2$ (100 mL) was treated in portions with DCC (2.47 g, 12 mmol), and the mixture was stirred for 1 h at rt. The precipitated DCU was filtered off, washed with $CH_2Cl_2$, and the filtrate was washed with cold 0.1 M HCl, satd aq $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. The solid residue was recrystallized from hot EtOAc to give **2** (6.18 g, 90%) as a white cotton: mp 158–159 °C; $[\alpha]_D^{20}$ +58 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.0–6.80 (m, 18H, Ar-*H*), 5.72 (dd, 1H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 5.68 (dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 5.61 (dd, 1H, $J_{1,2}$ 7.0 Hz, H-2), 5.20 (d, 1H, H-1), 4.30 (d, 1H, H-5), 3.88 (ABq, 2H, C$H_2$CO), 3.77, 3.72 (2s, 6H, OC$H_3$, COOC$H_3$); ISMS: *m/z* 708.5 [M+Na]$^+$. Anal. Calcd for $C_{36}H_{31}NO_{13}$: C, 63.06; H, 4.56; N, 2.04. Found: C, 62.88; H, 4.41; N, 1.89.

### 1.3. Methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)acetyl-D-glucopyranuronate (3)

A mixture of **2** (1.09 g, 1.6 mmol) and CAN (4.39 g, 8 mmol) in 1:1.5:1 toluene/MeCN/$H_2O$ (42 mL) was stirred for 15 min at rt, then was poured into ice-cold water (300 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The organic layer was washed twice with brine, and water, dried ($MgSO_4$), and concentrated. Flash silica chromatography (19:1 $CH_2Cl_2$/acetone) gave hemiacetal **3** (0.80 g, 87%) as a yellow foam. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.0–7.05 (m, 14H, Ar-*H*), 5.98 (dd, 0.8H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3α), 5.76 (dd, 0.8H, $J_{1,2}$ 3.5, $J_{1,OH}$ 4.2 Hz, H-1α), 5.72 (dd, 0.2H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3β), 5.52 (dd, 0.2H, $J_{4,5}$ 9.5 Hz, H-4β), 5.47 (dd, 0.8H, $J_{4,5}$ 9.5 Hz, H-4α), 5.22 (ddd, 0.8 H, $J_{2,OH}$ 1.0 Hz, H-2α), 4.98 (dd, 0.2H, H-2β), 4.72 (d, 0.8H, H-5α), 4.26 (d, 0.2H, H-5β), 3.88 (ABq, 2H, C$H_2$CO), 3.76 (s, 3H, COOC$H_3$); ISMS: *m/z* 602.5 [M+Na]$^+$. Anal. Calcd for $C_{29}H_{25}NO_{12}$: C, 60.10; H, 4.35; N, 2.42. Found: C, 59.88; H, 4.41; N, 2.10.

### 1.4. Methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)acetyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranuronate (4α) and methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)chloroacetyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranuronate (5)

A mixture of the hemiacetal **3** (0.6 g, 1 mmol), $Cl_3CCN$ (1.0 mL, 10 mmol) and DBU (30 μL, 0.2 mmol) in anhyd $CH_2Cl_2$ (6 mL) was stirred for 30 min at rt. More $Cl_3CCN$ (1.0 mL, 10 mmol) and DBU (30 μL, 0.2 mmol) were added, and the mixture was stirred for 30 min, then was concentrated. Flash silica chromatography (8:1 toluene/EtOAc, containing 0.1% of $Et_3N$) and crystallization of the residue from ethyl ether gave the α-imidate **4α** (420 mg, 58%): mp 151–152 °C; $[\alpha]_D^{20}$ +124 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.64 (s, 1H, C=N*H*), 8.0–7.05 (m, 14H, Ar-*H*), 6.82 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 6.07 (dd, 1H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 5.57 (dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 5.50 (dd, 1H, H-2), 4.65 (d, 1H, H-5), 3.90 (ABq, 2H, C$H_2$CO), 3.78 (s, 3H, COOC$H_3$). Anal. Calcd for $C_{31}H_{25}Cl_3N_2O_{12}$: C, 51.43; H, 3.48; N, 3.87. Found: C, 51.27; H, 3.51; N, 3.61.

Flash silica chromatography (5:2 petroleum ether/EtOAc, containing 0.1% of $Et_3N$) of the mother liquors gave the chlorinated derivatives **5** (152 mg, 20%) as a white foam; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.64, 8.63, 8.62 (3s, 1H, C=N*H*), 8.0–7.25 (m, 14H, Ar-*H*), 6.83, 6.82 (2d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 6.13, 6.07 (2dd, 0.9H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 6.11, 5.97 (2s, 0.9H, C*H*ClCO), 5.65, 5.63, 5.62 (3dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 5.49, 5.47, 5.45 (3dd, 1H, H-2), 4.59, 4.55 (2d, 0.9H, H-5), 4.50 (d, 0.1H, H-5), 4.85 (s, 0.3H, COOC$H_3$), 4.79, 4.76 (2s, 2.7H, COOC$H_3$); HRESIMS: Calcd for $C_{31}H_{24}Cl_4N_2NaO_{12}$ [M+Na]$^+$ (major): *m/z* 778.99755. Found: 778.99556; Calcd for $C_{31}H_{23}Cl_5N_2NaO_{12}$ [M+Na]$^+$ (minor): *m/z* 813.96640. Found: 813.96556.

### 1.5. Methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)chloroacetyl-D-glucopyranuronate (6)

A mixture of **2** (686 mg, 1 mmol), $Cl_3CCN$ (1.0 mL, 10 mmol) and DBU (30 μL, 0.2 mmol) in anhyd $CH_2Cl_2$ (6 mL) was stirred for 30 min at rt. More $Cl_3CCN$ (1.0 mL, 10 mmol) and DBU (30 μL, 0.2 mmol) were added after 30 min, 60 min and 90 min, and the mixture was concentrated. Flash silica chromatography (8:1 toluene/EtOAc, containing 0.1% of $Et_3N$) gave the chlorinated derivatives **6** (562 mg, 78%) as a white foam: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.10-6.70 (m, 18H, Ar-*H*), 6.07, 5.95 (2s, 0.8H, C*H*ClCO), 5.75–5.68 (m, 1H, H-3), 5.64–554 (m, 2H, H-2,4), 5.22, 5.19 (2d, 0.8H, $J_{1,2}$ 7.0 Hz, H-1), 5.18 (d, 0.2H, $J_{1,2}$ 7.0 Hz, H-1), 4.34, 4.27 (2d, 0.8H, $J_{4,5}$ 9.5 Hz, H-5), 4.29 (d, 0.2H, $J_{4,5}$ 9.5 Hz, H-5), 3.78, 3.76, 3.70 (3s, 3H, COOC$H_3$).); HRESIMS: Calcd for $C_{36}H_{30}ClNNaO_{13}$ [M+Na]$^+$ (major): *m/z* 742.12986 Found: 742.12970; Calcd for $C_{36}H_{29}Cl_2NNaO_{13}$ [M+Na]$^+$ (minor): *m/z* 777.09780. Found: 777.09720.

### 1.6. Methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)chloroacetyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranuronate (5)

Compound **6** (360 mg, 0.5 mmol) was treated as described for the preparation of **3**. Flash silica chromatography (1:1 EtOAc/petroleum ether) gave the corresponding hemiacetal (277 mg, 90%) as a yellow foam. A mixture of the hemiacetal (277 mg, 0.45 mmol), $Cl_3CCN$ (0.45 mL, 4.5 mmol) and DBU (14 μL, 0.1 mmol) in anhyd $CH_2Cl_2$ (6 mL) was stirred for 30 min at rt, then was concentrated. Flash silica chromatography (2:1 petroleum ether/EtOAc, containing 0.1% of $Et_3N$) gave the mixture of chlori-

nated derivatives **5** (266 mg, 70% from **6**) as a white foam; $^1$H NMR and HRESIMS data matched those reported above for **5** prepared from **3**. The ratio monochloro/dichloro was ~4:1.

### 1.7. Methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)acetyl-1-*O*-trichloroacetimidoyl-α,β-D-glucopyranuronate (4α,β)

A mixture of hemiacetal **3** (530 mg, 0.92 mmol), anhyd $K_2CO_3$ (500 mg) and $Cl_3CCN$ (1 mL, 10 mmol) in anhyd $CH_2Cl_2$ (8 mL) was stirred for 1 h at rt, then was filtered through a pad of Celite and concentrated. Flash silica chromatography (3:2 petroleum ether/EtOAc, containing 0.1% of $Et_3N$) gave first the crystalline α-imidate **4α** (334 mg, 50%) whose physical data matched those reported above. Next eluted was the β-imidate **4β** (240 mg, 36%): mp 130–131 °C (from EtOAc/petroleum ether); $[\alpha]_D^{20}$ +91 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.68 (s, 1H, C=N*H*), 8.0–7.0 (m, 14H, Ar-*H*), 6.16 (d, 1H, $J_{1,2}$ 7.0 Hz, H-1), 5.75–5.65 (m, 2H, H-3,4), 5.62 (dd, 1H, $J_{2,3}$ 9.0 Hz, H-2), 4.65 (d, 1H, $J_{4,5}$ 9.5 Hz, H-5), 3.88 (ABq, 2H, C$H_2$CO), 3.78 (s, 3H, COOC$H_3$). Anal. Calcd for $C_{31}H_{25}Cl_3N_2O_{12}$: C, 51.43; H, 3.48; N, 3.87. Found: C, 51.21; H, 3.33; N, 3.58.

### 1.8. 4-Methoxyphenyl *O*-(methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)acetyl-β-D-glucopyranosyluronate)-(1→3)-2-*O*-benzoyl-4,6-*O*-di-*tert*-butylsilylene-β-D-galactopyranoside (8)

A mixture of imidate **4α,β** (655 mg, 0.90 mmol), alcohol **7**[10] (610 mg, 1.15 mmol) and powdered 4 Å molecular sieves (0.5 g) in anhyd $CH_2Cl_2$ (10 mL) was stirred for 45 min at rt under dry Ar. A solution of $Me_3SiOTf$ in anhyd toluene (1 M, 0.14 mL) was added, and the mixture was stirred for 30 min at rt. Triethylamine (0.14 mL) was added, and the mixture was filtered, and concentrated. Flash silica chromatography (1:1 EtOAc/petroleum ether, containing 0.1% of $Et_3N$) gave **8** (787 mg, 80%): mp 194–195 °C (from EtOAc/petroleum ether); $[\alpha]_D^{20}$ +79 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.0–6.60 (m, 23H, Ar-*H*), 5.72 (dd, 1H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.0 Hz, Gal H-2), 5.52–5.45 (m, 2H, GlcA H-3,4), 5.42 (dd, 1H, $J_{1,2}$ 7.5, $J_{2,3}$ 9.0 Hz, GlcA H-2), 5.04 (d, 1H, GlcA H-1), 4.84 (d, 1H, Gal H-1), 4.68 (dd, 1H, $J_{3,4}$ 3.0, $J_{4,5}$ <1 Hz, Gal H-4), 4.29–4.19 (m, 2H, Gal H-6a,6b), 4.13 (d, 1H, $J_{4,5}$ 10.0 Hz, GlcA H-5), 3.92 (dd, 1H, Gal H-3), 3.84 (ABq, 2H, C$H_2$CO), 3.75 (s, 3H, COOC$H_3$), 3.67 (s, 3H, OC$H_3$), 3.48 (br s, 1H, Gal H-5), 1.04 (s, 18H, (C$H_3$)$_3$C); HRESIMS: Calcd for $C_{57}H_{61}KNO_{19}Si$ $[M+K]^+$: *m/z* 1130.32386. Found: 1130.32335. Anal. Calcd for $C_{57}H_{61}NO_{19}$ Si: C, 62.68; H, 5.63; N, 1.28 Found: C, 62.49; H, 5.41; N, 1.12.

### 1.9. 4-Methoxyphenyl *O*-(methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)chloroacetyl-β-D-glucopyranosyluronate)-(1→3)-2-*O*-benzoyl-4,6-*O*-di-*tert*-butylsilylene-β-D-galactopyranoside (9) and 4-methoxyphenyl *O*-(methyl 2,3-di-*O*-benzoyl-4-*O*-(2-nitrophenyl)dichlorochloroacetyl-β-D-glucopyranosyluronate)-(1→3)-2-*O*-benzoyl-4,6-*O*-di-*tert*-butylsilylene-β-D-galactopyranoside (10)

A mixture of imidates **5** (758 mg, 1 mmol) and alcohol **7** (664 mg, 1.25 mmol) was treated as described for the preparation of **8**. Flash silica chromatography (3:2 petroleum ether/EtOAc, containing 0.1% of $Et_3N$) gave first the monochloroacetyl derivative **9** (676 mg, 60%) as a white foam: $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.0–6.60 (m, 23H, Ar-*H*), 6.05, 5.93 (2s, 1H, C*H*ClCO), 5.74, 5.73 (2dd, 1H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.0 Hz, Gal H-2), 5.60–5.50 (m, 2H, GlcA H-3,4), 5.39, 5.38 (2dd, 1H, $J_{1,2}$ 7.5, $J_{2,3}$ 9.0 Hz, GlcA H-2), 5.10, 5.07 (2d, 1H, GlcA H-1), 4.86 (d, 1H, Gal H-1), 4.71, 4.70 (2dd, 1H, $J_{3,4}$ 3.0, $J_{4,5}$ <1 Hz, Gal H-4), 4.32–4.22 (m, 2H, Gal H-6a,b), 4.21, 4.14 (2d, 1H, $J_{4,5}$ 10.0 Hz, GlcA H-5), 3.95 (dd, 1H, Gal H-3), 3.77, 3.73 (2s, 3H, COOC$H_3$), 3.69 (s, 3H, OC$H_3$), 3.52 (br s, 1H, Gal H-5), 1.05, 1.04 (2s, 18H, (C$H_3$)$_3$C); $^{13}$C NMR ($C_6D_6$, 100 MHz): δ 166.81–152.02 (3 C=O, GlcA C-6), 147.25, 147.15 (1C, CHCl*C*=O), 133.51–114.57 (30C, Ar-*C*), 102.23, 102.05 (2C, GlcA C-1, Gal C-1), 80.41, 80.35 (1C, Gal C-3), 73.25–70.98 (7C, GlcA C-2,3,4,5, Gal C-2,4,5), 66.89 (1C, Gal C-6), 55.46, 55.32 (1C, *C*HCl), 54.89 (1C, O*C*$H_3$), 52.76, 52.64 (1C, COO*C*$H_3$), 27.70, 27.58 (6C, (*C*$H_3$)$_3$C), 23.51, 20.87 (2C, (CH$_3$)$_3$*C*). HRESIMS: Calcd for $C_{57}H_{60}ClKNO_{19}Si$ $[M+K]^+$: *m/z* 1164.28489. Found: 1164.28409. Anal. Calcd for $C_{57}H_{60}ClNO_{19}$ Si: C, 60.77; H, 5.37; N, 1.24. Found: C, 60.49; H, 5.11; N, 1.09.

Next eluted was the dichloroacetyl derivative **10** (163 mg, 14%): mp 152–153 °C (from 2-propanol); $[\alpha]_D^{20}$ +38 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.06–6.60 (m, 23H, Ar-*H*), 5.71 (dd, 1H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.0 Hz, Gal H-2), 5.65 (dd, 1H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.5 Hz, GlcA H-4), 5.58 (dd, 1H, $J_{2,3}$ 9.0 Hz, GlcA H-3), 5.37 (dd, 1H, $J_{1,2}$ 7.0 Hz, GlcA H-2), 5.08 (d, 1H, GlcA H-1), 4.85 (d, 1H, Gal H-1), 4.68 (dd, 1H, $J_{3,4}$ 3.0, $J_{4,5}$ <1 Hz, Gal H-4), 4.32–4.23 (m, 2H, Gal H-6a,b), 4.16 (d, 1H, GlcA H-5), 3.92 (dd, 1H, Gal H-3), 3.82 (s, 3H, COOC$H_3$), 3.69 (s, 3H, OC$H_3$), 3.51 (br s, 1H, Gal H-5), 1.05 (s, 18H, (C$H_3$)$_3$C); $^{13}$C NMR ($C_6D_6$, 100 MHz): δ 166.31–145.91 (4 C=O, GlcA C-6), 132.92–114.35 (30C, Ar-*C*), 102.06, 101.79 (2C, GlcA C-1, Gal C-1), 82.25 (1C, *C*Cl$_2$CO), 80.54 (1C, Gal C-3), 73.60–70.68 (7C, GlcA C-2,3,4,5, Gal C-2,4,5), 66.66 (1C, Gal C-6), 54.68 (1C, O*C*$H_3$), 52.73 (1C, COO*C*$H_3$), 27.48, 27.37 (6C, (*C*$H_3$)$_3$C), 23.32, 20.65 (2C, (CH$_3$)$_3$*C*). HRESIMS: Calcd for $C_{57}H_{63}Cl_2N_2O_{19}Si$ $[M+NH_4]^+$: *m/z* 1177.31658. Found: 1177.31684. Anal. Calcd for $C_{57}H_{59}ClNO_{19}$ Si: C, 58.96; H, 5.12; N, 1.21. Found: C, 58.80; H, 5.02; N, 1.14.

### 1.10. 4-Methoxyphenyl *O*-(methyl 2,3-di-*O*-benzoyl-β-D-glucopyranosyluronate)-(1→3)-2-*O*-benzoyl-4,6-*O*-di-*tert*-butylsilylene-β-D-galactopyranoside (11)

From **8**, **9** or **10**: To a solution of esters **8**, **9** or **10** (0.1 mmol) in 1,4-dioxan (1 mL) and MeOH (1.5 mL) were added Zn powder (33 mg, 0.5 mmol) and $NH_4Cl$ (16 mg, 0.3 mmol), and the mixture was stirred for 1 h at rt, then was filtered through a pad of Celite. The solids were washed with MeOH, and the filtrate was concentrated. Flash silica chromatography (3:1 toluene/EtOAc) afforded the alcohol **11** (47–48 mg, 88–90%) as a white foam: $[\alpha]_D^{20}$ +75 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.95–6.60 (m, 19H, Ar-*H*), 5.73 (dd, 1H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.0 Hz, Gal H-2), 5.40 (dd, 1H, $J_{1,2}$ 7.0, $J_{2,3}$ 9.0 Hz, GlcA H-2), 5.30 (dd, 1H, $J_{3,4}$ 9.0 Hz, GlcA H-3), 5.02 (d, 1H, GlcA H-1), 4.85 (d, 1H, Gal H-1), 4.72 (dd, 1H, $J_{3,4}$ 3.5, $J_{4,5}$ <1 Hz, Gal H-4), 4.30–4.22 (m, 2H, Gal H-6a,b), 4.19 (ddd, 1H, $J_{4,5}$ 9.5, $J_{4,OH}$ 3.2 Hz, GlcA H-4), 3.80 (s, 3H, COOC$H_3$), 3.68 (s, 3H, OC$H_3$), 3.52 (br s, 1H, Gal H-5), 3.32 (d, 1H, GlcA 4-OH), 1.04 (s, 18H, (C$H_3$)$_3$C). HRESIMS: Calcd for $C_{49}H_{60}O_{16}Si$ $[M+NH_4]^+$: *m/z* 946.36759. Found: 946.36827. Anal. Calcd for $C_{49}H_{56}O_{16}$ Si: C, 63.65; H, 6.08. Found: C, 63.11; H, 5.95.

From **9**: A mixture of **9** (338 mg, 0.3 mmol) and thiourea (76 mg, 1 mmol) in pyridine (3 mL) and EtOH (2 mL) was stirred for 3 h at 80 °C, then was cooled and concentrated. A solution of the residue in $CH_2Cl_2$ (30 mL) was washed with satd aq $NaHCO_3$, brine and water, dried ($MgSO_4$) and concentrated. Flash silica chromatography (3:1 toluene/EtOAc) afforded the alcohol **11** (243 mg, 87%), whose physical data matched those reported above.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.11.003.

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