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Note

Preparation and characterisation of solid state forms of paracetamol-*O*-glucuronide

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ABSTRACT

The synthesis and crystallisation of the pharmaceutically important metabolite, paracetamol-*O*-glucuronide, is described. Hydrated and anhydrous forms of the target molecule have been characterised by PXRD, DSC and TGA. In addition, a methanol solvate has been analysed, including single crystal analysis, which represents the first structure solution for this system.

Glucuronides are a group of biologically active molecules formed in vivo as a result of phase II metabolism.[1] This metabolic pathway is primarily concerned with the bioconjugation of non-polar xenobiotics to glucuronic acid resulting in more water soluble forms of the parent compound which then can be readily excreted. For example, paracetamol, one of the world's most widely used analgesic and antipyretics, is metabolised extensively in the body, mainly in the liver. The main metabolites from this pathway are paracetamol-*O*-sulfate, *N*-acetyl-*p*-benzoquinone imine and paracetamol-*O*-glucuronide **5**. Formation of paracetamol-*O*-glucuronide accounts for up to two thirds of this metabolic pathway.[2]

Glucuronides are highly polar molecules which have traditionally been synthesised on milligram scales for the purposes of pharmacological testing, testing for drug substances of abuse and investigation of possible metabolites of new APIs during clinical trials.[3] Many synthetic methods exist for the synthesis of O-linked glucuronides and their various derivatives. Acyl protected intermediates such as methyl tetra-*O*-acetyl-β-D-glucopyranuronate **1** seem to be the most prevalent intermediates for the synthesis of the glucuronide series, although higher priority alkyl and aryl protecting groups such as the iso-butyryl,[4] pivaloyl[5] and benzyl[6] groups have also been employed.

Based on Etter's rules,[7] the ratio of hydrogen bond donors: acceptors for a typical glucuronide suggests that it is possible to incorporate one or more hydrate or solvate molecule within the hydrogen bonding framework in the solid state.[8,9] This guideline for the formation of hydrates and solvates is based on the concept of multi-point recognition.[9] Hydrate forms of both the parent acid and sodium salt of paracetamol-*O*-glucuronide **5** have been reported[10,11] as well as an anhydrous form.[12] To date no solid state forms of this biologically important molecule have been fully elucidated. Herein we report the preparation, crystallisation and crystal forms of 4-acetomidophenyl-β-D-glucopyranosiduronic acid **5** (Scheme 1) and for the first time the crystal structure of a methanol solvate of the target compound. The only reported crystal structure of a glucuronide is that of estrone glucuronide[13] (CSD[14] ref. code RESKAB).

A number of syntheses of compound **5** have been reported.[10,12,15] Brown et al.[15] used a tri-*O*-isobutyryl protected trichloroacetimidate as glucuronidating agent. However, we found that use of the tri-*O*-acetyltrichloroacetimidate **3**[16] provided the most practical route to useful quantities of compound **5** (Scheme 1). Treatment of methyl tetra-*O*-acetyl-β-D-glucopyranuronate **1** with tributyltin methoxide in dichloromethane[17] yielded the hemiacetal **2** as a mixture of diastereoisomers (approximately 75:25 α/β) in 87% yield. Coupling **2** to trichloroacetonitrile with DBU resulted in the exclusive formation of the α-imidate **3**. Methyl (4-acetamidophenyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate **4** was obtained using the glucuronide donor **3**, paracetamol and $BF_3{\cdot}OEt_2$ in dichloromethane. Base hydrolysis of **4** was achieved using 2 equiv of K_2CO_3 in 5:5:1 MeOH/THF/H_2O.[18] Following neutralisation with a strongly acidic ion-exchange resin and column chromatography, 4-acetomidophenyl-β-D-glucopyranosiduronic acid **5** was isolated in 47% yield. A coupling constant of 7.5 Hz for the 1H doublet was assigned to the hydrogen on C-1 of the glucopyranose, indicative of β stereochemistry, which was also confirmed by single crystal analysis (see below).

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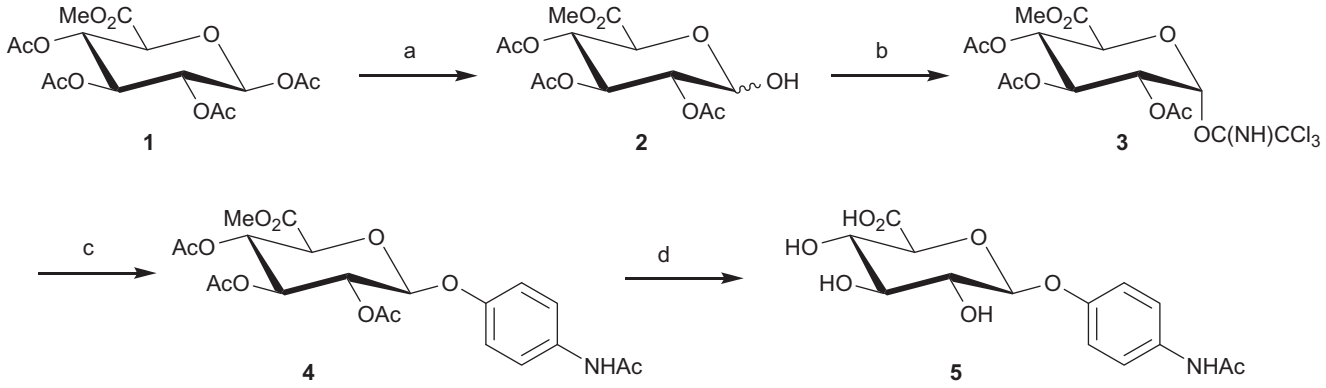

Scheme 1. Reagents and conditions: (a) Bu_3SnOMe, CH_2Cl_2, 87%; (b) CCl_3CN, DBU, CH_2Cl_2, 65%; (c) paracetamol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 76%; (d) 2 equiv K_2CO_3 in 5:5:1 MeOH–THF–H_2O, followed by Amberlyst® 15 H^+ ion-exchange resin, 47% (for sodium salt, Amberlyst® 15 H^+ resin, then aq $NaHCO_3$ soln, MeOH, 85%).

In our hands, complete evaporation to dryness of solutions of **5** gave amorphous material, displaying typical amorphous halos in their powder X-ray diffraction (PXRD) patterns. Attempts to crystallise these batches from solvents also gave amorphous material. Crystalline material could be obtained by clarifying the product solution with charcoal, reducing to approximately half volume and cooling to between 0 and 5 °C. This resulted in the formation of two distinct crystalline forms of target compound **5**, an anhydrous form and a hydrated form. The anhydrous form of **5** was characterised by PXRD (Supplementary data) and shows no significant weight loss in the corresponding TGA traces (Supplementary data). The other crystalline form of **5** was isolated as a monohydrate with a needle-like habit (Supplementary data). The TGA traces (Fig. 1) revealed two events, the first in the region of 20–60 °C which is due to residual solvent tightly held on the crystal surfaces, the second in the region of 100–120 °C, being due to the hydrate. On no occasion were both of these forms observed together. Concomitant polymorphism, in which two or more crystal forms are observed to be present simultaneously, is well reported.[19] Formation of either one particular form or another, but not both simultaneously, as observed in this case, is more unusual but still would not be a particularly surprising crystallisation phenomenon. It is likely that subcritical nuclei of both forms are present in solution but that once one form nucleates, growth of that form is exclusive at least on the occasions these crystallisation have been carried out by us. There was no obvious difference in how these crystallisations were carried out which would lend a bias towards one form or the other.

The crystalline sodium salt of **5** was achieved by reaction of the free acid with aqueous sodium bicarbonate in ethanol. However, recrystallisation of the sodium salt from aqueous ethanol yields microcrystalline **5** sodium salt as an agglomerated solid which was not suitable for structural analysis.

The only form observed in our studies suitable for single crystal analysis was a methanol solvate of **5** which was crystallised from methanol–dichloromethane. This form was found to be orthorhombic, crystallising in the $P2_12_12_1$ space group (see Table 1). Comparison of the PXRD pattern of the bulk material with the theoretically generated pattern based on the crystal structure we have

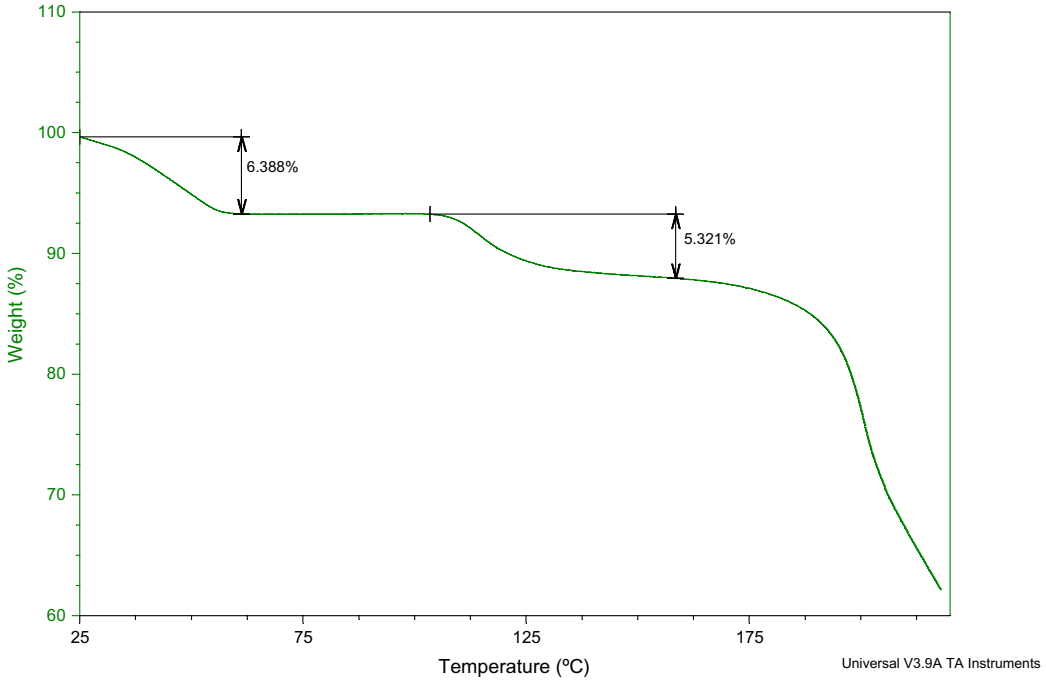

Figure 1. TGA trace **5**·H_2O.

Table 1
Crystal data for **5**·MeOH

Chemical formula	$C_{15}H_{21}NO_9$
Formula mass	359.33
Crystal system	Orthorhombic
a (Å)	8.3590(4)
b (Å)	8.4792(4)
c (Å)	22.8663(10)
Unit cell volume (Å^3)	1620.71(13)
Temperature (K)	296(2)
Space group	$P2_12_12_1$
No. of formula units per unit cell, *Z*	4
Radiation type	Cu K_α (1.5418 Å)
Absorption coefficient, μ (mm^{-1})	1.054
No. of reflections measured	12,824
No. of independent reflections	2699
R_{int}	0.032
Final R_1 values ($I > 2\sigma(I)$)	0.033
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.085
Final R_1 values (all data)	0.038
Final $wR(F^2)$ values (all data)	0.088
Goodness of fit on F^2	1.03
Flack parameter	0.3(2)

Figure 2. Lattice orientation of **5**·MeOH showing preferential growth along the crystallographic *b* axis.

obtained shows that the structure is representative of the bulk material (Supplementary data).

Face indexing experiments of the needle-like crystals observed for the methanol solvate indicate that the preferred growth direction is along the *b* axis of the unit cell (Fig. 2).

This can be rationalised by inspection of the single crystal data which show C(5) chains[7] along the crystallographic *b* axis (Fig. 3). These C(5) chains are made by the diol functionality on C-2 and C-3 of the glucopyranose ring, and are related by a 2_1 screw axis as represented in Figure 3. Unitary graph set analysis[7] along this crystallographic axis shows a discrete (capping) H···O–Me hydrogen bond between the OH group on C-4 of the glucopyranose ring and the interstitial MeOH molecule is also observed (Fig. 3).

1. Experimental

1.1. General

All commercial reagents were purchased from Sigma-Aldrich and were used without further purification. All solvents were either of a HPLC grade or distilled prior to use. Methyl tetra-*O*-acetyl-β-D-glucopryranuronate **1** was prepared as described by Bollenback et al.[20] Thin layer chromatography (TLC) was conducted on coated silica plates (Merck Silica Gel 60, F24). Column chromatography was conducted using Merck Silica Gel 60, typically with a 30:1 ratio of silica to sample. TLC plates were visualised either under ultraviolet (UV) light or an anisaldehyde stain. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Bruker AVANCE 300 or 400 MHz spectrometers. Spectra were recorded using either deuterated chloroform ($CDCl_3$), deuterated dimethyl sulfoxide (DMSO-d_6) or deuterated water (D_2O) using tetramethylsilane as the internal standard. Chemical shift values (δ_H and δ_C) are expressed as parts per million (ppm). Elemental analyses were performed by the Microanalysis Laboratory, University College Cork, using a Perkin-Elmer 240 and an Exeter Analytical CE440 elemental analyser.

1.2. Synthesis

1.2.1. Methyl 2,3,4-triacetyl-α,β-glucopyranuronate (2)

Methyl tetra-*O*-acetyl-β-D-glucopryranuronate (**1**) (15.0 g, 39 mmol) was dissolved in dry CH_2Cl_2 (120 mL) and tributyltin methoxide (12.6 mL, 43.8 mmol) was added. The solution was refluxed for 4 h until TLC indicated consumption of the starting material. The solution was cooled to room temperature and then washed with 10% aq HCl (2 × 20 mL), water (20 mL), dried and concentrated in vacuo. The resulting syrup was triturated with hexane (3 × 40 mL) to yield a solid which was recrystallised from EtOAc–hexane to give a white crystalline solid (11.6 g, 87%) ratio of α to β anomers (by ^{1}H NMR) = 75:25 (α:β) mp 89–90 °C, lit.[21] 91–92 °C; IR (KBr) *ν* 3469 (O–H), 2958 (C–H), 1752 (C=O) cm^{-1}; *m*/*z* (ESI): 357 (M^++Na, 15%). ^{1}H NMR ($CDCl_3$) (α anomer) *δ* 5.57 (t, 1H, *J* 9.5 Hz, H-3), 5.54 (d, 1H, d, *J* 3.6 Hz, H-1), 5.17 (t, 1H, *J* 9.5 Hz, H-4), 4.90 (dd, 1H, *J* 3.6, 9.5 Hz, H-2), 4.59 (d, 1H, *J* 9.5 Hz, H-5), 4.24 (br d, 1H, *J* 3.6 Hz, O**H**) 3.75 (s, 1H, CO_2**Me**), 2.09 (s, 3H, O**Ac**), 2.04 (s, 3H, O**Ac**), 2.03(s, 3H, O**Ac**). ^{13}C NMR ($CDCl_3$) (α anomer) *δ* 170.2 (C=O), 170.1 (C=O), 168.5 (C=O), 166.7 (C=O), 90.2 (**C**-1), 70.78 (**C**–H), 69.6 (**C**–H), 69.2 (**C**–H), 67.99 (**C**–H), 52.90 (CO_2**C**H$_3$), 20.6 (3 × OAc). ^{1}H NMR ($CDCl_3$) (β anomer) *δ* 5.29 (t, 1H, *J* 9.5 Hz), 5.21 (t, 1H, *J* 9.5 Hz), 4.95 (d, 1H, *J* 7.8 Hz, H-1), 4.82 (t, 1H, *J* 9.3 Hz), 4.36 (br d, 1H, *J* 7.8 Hz, O**H**), 4.12 (d, 1H, *J* 9.6 Hz, H-5), 3.76 (s, 3H, CO_2**Me**), 2.09 (s, 3H, O**Ac**), 2.04 (s, 3H, O**Ac**), 2.03 (s, 3H, O**Ac**). ^{13}C NMR (β anomer) *δ* 170.52 (C=O), 170.10 (C=O), 169.59 (C=O), 167.61 (C=O), 95.45 (**C**-1), 72.85 (**C**–H), 72.53 (**C**–H), 71.6 (**C**–H), 69.43 (**C**–H), 53.10 (CO_2**C**H$_3$), 20.51 (3 × OAc). Anal. Calcd for $C_{13}H_{18}O_{10}$: C, 46.71; H, 5.43. Found: C, 46.36; H, 5.70.

1.2.2. Methyl 2,3,4-triacetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate (3)

Methyl 2,3,4-triacetyl-α,β-glucopyranuronate (**2**) (12.0 g, 36 mmol) and trichloroacetonitrile (18 mL, 180 mmol) was stirred in dry CH_2Cl_2 at 0 °C for 30 min. DBU (1.5 mL, 10 mmol) was added dropwise and the solution was allowed warm to room temperature and stirred overnight. The solvent was removed in vacuo and the residue was subjected to flash chromatography (40:59:1 EtOAc–hexane–Et_3N). Appropriate fractions were pooled and the solvent removed under reduced pressure to yield a syrup which was triturated with diethyl ether. Following recrystallisation with EtOAc–hexane (50:50) to yield 8.5 g (65%) of an off white solid. mp 108–109 °C, lit.[22] 109–110 °C; IR (KBr) *ν* 3320 (N–H), 2958 (C–H), 1755 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 8.73 (s, 1H, N**H**), 6.64 (d, 1H, *J* 3.6 Hz, H-1), 5.63 (t, 1H, *J* 10 Hz, H-3), 5.27 (t, 1H, *J* 10 Hz, H-4), 5.16 (dd, 1H, *J* 3.6 Hz, 10 Hz, H-2), 4.49 (d, 1H, *J* 10 Hz, H-5), 3.75 (s, 3H, CO_2**Me**), 2.05 (s, 3H, O**Ac**), 2.04 (s, 3H, O**Ac**), 2.02 (s, 3H, O**Ac**). ^{13}C NMR ($CDCl_3$) *δ* 169.78 (**C**=O), 169.72 (**C**=O), 169.47 (**C**=O), 167.14 (**C**=O), 160.58 (**C**=N), 92.64 (**C**–H), 70.49 (**C**–H), 69.47 (**C**–H), 69.10 (**C**–H), 68.96 (**C**–H), 53.04 (CO_2**Me**), 21.04, 20.66, 20.48, 20.39 (3 × O**Ac** and 1 × **C**Cl_3).

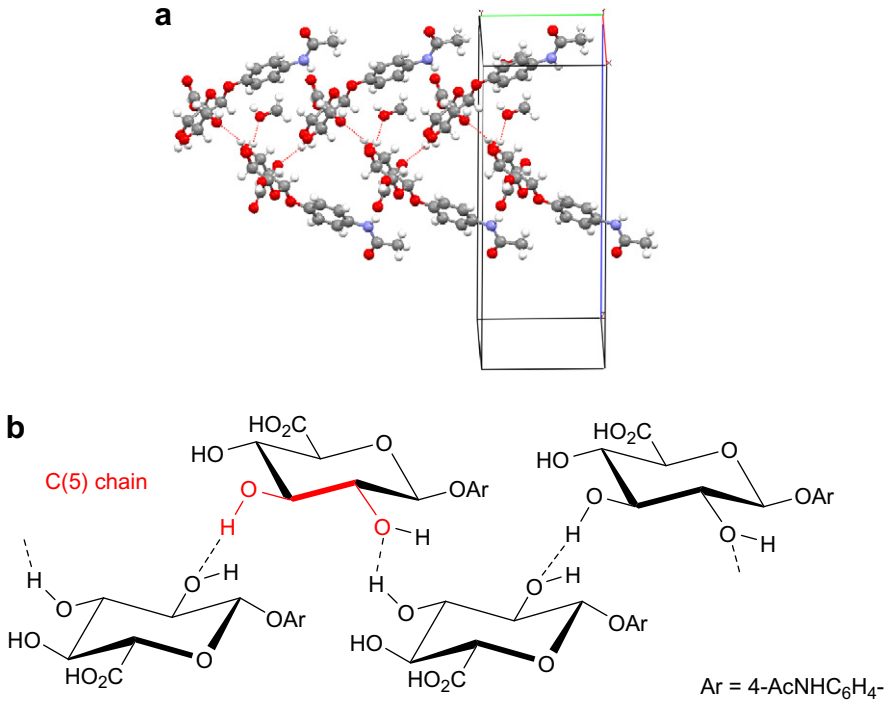

Figure 3. (a) Unit cell of **5**·MeOH along the crystallographic *b* axis, showing C(5) chains and interstitial MeOH molecules, along the preferential growth axis (some molecules have been removed for clarity). (b) Graphical representation of the C(5) chains along the *b* axis of the unit cell.

1.2.3. Methyl (4-acetamidophenyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (4)

Methyl 2,3,4-triacetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate (**3**) (10.0 g, 21.0 mmol), paracetamol (3.5 g, 23 mmol) and 4 Å molecular sieves were stirred in dry CH_2Cl_2 for 30 min. $BF_3{\cdot}Et_2O$ (4 mL, 23 mmol) was added dropwise at 0 °C and the solution was allowed to stir overnight. The solvent volume was reduced, washed with satd aq Na_2CO_3 (2 × 30 ml), water (2 × 30 ml) dried with $MgSO_4$ and concentrated in vacuo to yield a pale white solid. Column chromatography (40:1 $CHCl_3$–MeOH) followed by recrystallisation from IPA gave a white crystalline solid (7.5 g, 76%). mp 214–216 °C, lit.[23] 213.5–214.5 °C; IR (KBr) *ν* 3300 (N–H), 3146–2969 (C–H), 1758 (C=O), 1509 (Ar-H) cm^{-1}. *m*/*z* (ESI): 468 (M^+, 100%) ^1H NMR ($CDCl_3$) *δ* 7.42 (d, 2H, *J* 9 Hz, Ar-**H**), 7.2 (br s, 1H, N**H**), 6.96 (d, 2H, *J* 9 Hz, Ar-**H**), 5.35–5.23 (m, 3H, H-2, 3, 4), 5.07 (d, 1H, *J* 7.2 Hz, H-1), 4.14 (d, 1H, *J* 9.6 Hz, H-5), 3.74 (s, 3H, CO_2**Me**), 2.16 (s, 3H, N**Ac**), 2.06 (s, 3H, O**Ac**), 2.05 (s, 3H, O**Ac**), 2.04 (s, 3H, O**Ac**). ^{13}C NMR ($CDCl_3$) *δ* 170.08 (**C**=O), 169.35 (**C**=O), 169.25 (**C**=O), 168.29 (**C**=O), 166.91 (**C**=O), 153.28 (**C**q, *Ar*) 133.28 (**C**q, *Ar*), 121.66 (**C**–H, *Ar*), 117.82 (**C**–H, *Ar*), 99.64 (**C**^{1}–H), 72.62 (**C**–H), 71.91 (**C**–H), 71.1 (**C**–H), 69.16 (**C**–H), 52.97 (CO_2**Me**), 24.37 (NH**Ac**), 20.75, 20.6, 20.49 (3 × O**Ac**).

1.2.4. Acetamidophenyl-β-D-glucopyranosiduronic acid (5)

Methyl (4-acetamidophenyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**4**) (1.00 g, 2.15 mmol) was dissolved in a solution of MeOH–THF–H_2O (5:5:1, 40–50 mL) and allowed to stir under a nitrogen atmosphere at 0 °C. K_2CO_3 (0.6 g, 4.3 mmol) was added and the reaction mixture was heated to 40 °C for 5 h. The reaction mixture was cooled to room temperature and neutralised with strongly acidic ion-exchange resin (Amberlyst® 15 H^+ Form). The exchange resin was removed and the solution clarified with charcoal. The solvent volume was removed in vacuo and the residue subjected to column chromatography using EtOAc–MeOH–H_2O (60:30:10). Appropriate fractions were pooled and the solvent removed in vacuo. Recrystallisation of the residue yielded 0.34 g (47%) of crystalline material. Mp 135 °C (MeOH–CH_2Cl_2), lit.[15] 134–137 °C; IR (KBr) *ν* 3347 (O–H), 2925 (C–H), 1728 (C=O), 1663 (C=C), 1510 (C=C) cm^{-1}. *m*/*z* (ESI): 328 (M^+, 10%), 326 (M^-, 20%). ^1H NMR (DMSO-d_6) *δ* 9.89 (s, 1H, N**H**), 7.52 (d, 2H, *J* 8.8 Hz, Ar-**H**), 7.02 (d, 2H, *J* 8.8 Hz, Ar-**H**), 5.41 (br s, 1H, O**H**) 5.22 (br s, 1H, O**H**), 4.92 (d, 1H, *J* 7.5 Hz, H-1), 4.42 (br s, 1H, O**H**), 4.17(br s, 1H, O**H**), 2.06 (s, 3H, N**Ac**). δ_H (D_2O shake) 7.25 (d, 2H, *J* 9 Hz, Ar-**H**), 7.03 (d, 2H, *J* 9 Hz, Ar-**H**), 5.06 (d, 1H, *J* 7.5 Hz, H-1), 4.06 (d, 1H, *J* 9 Hz, H-5), 3.64–3.53 (m, 3H, H-2, 3, 4), 2.04 (s, 3H, N**Ac**). ^{13}C NMR (D_2O) *δ* 172.7 (**C**=O), 171.9 (**C**=O), 153.8 (**C***q*), 132.18 (**C***q*), 123.7, 117.2, 100.4 (**C**–H), 75.0 (**C**–H), 74.5 (**C**–H), 72.5 (**C**–H), 71.1 (**C**–H), 23.7 (NHCO**C**H_3).

1.2.5. 4-Acetomidophenyl-β-D-glucopyranosiduronic acid (5) sodium salt

Methyl (4-acetamidophenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**4**) (1.00 g, 2.15 mmol) was dissolved in a solution of MeOH–THF–H_2O (5:5:1, 40–50 mL) and the solution stirred under an N_2 atmosphere at 0 °C. K_2CO_3 (0.6 g, 4.3 mmol) was added and the reaction mixture was heated to 40 °C for 5 h. The reaction mixture was cooled to room temperature and neutralised with strongly acidic ion-exchange resin (Amberlyst® 15 H^+ Form). The exchange resin was removed and the solution was clarified with charcoal. After removal of the charcoal on a bed of Celite® the solvent was removed and the residue was dissolved in MeOH (50 mL). aq $NaHCO_3$ solution (20 ml) was added and the solution heated to boiling. After heating for 10 min the solution was allowed to cool to room temperature and left to stir for 1 h. The resulting solid was isolated and recrystallised from aq EtOH to give the product as a white crystalline solid 0.63 g (85% yield). Mp 220–230 °C, (decomp.). IR (KBr) *ν* 3298 (O–H), 2935 (C–H), 1578 (C=O), 1510 (C=C), 1414 (C=C), 1043 (C–O) cm^{-1}; ^1H NMR (D_2O) *δ* 7.36 (d, 2H, *J* 9.2 Hz, Ar-**H**), 7.14 (d, 2H, *J* 9.2 Hz, Ar-**H**), 5.10 (d, 1H, *J* 6.8 Hz, H-1), 3.89 (d, 1H, *J* 9.6 Hz, H-5), 3.64–3.55 (m, 3H, H-2, 3, 4), 2.16 (s, 3H, N**Ac**).

1.3. Crystal growth

1.3.1. Hydrated and anhydrous forms

Crystalline **5** was obtained as follows. Following neutralisation of the reaction mixture with acidic ion-exchange resin, removal of the resin and clarification of the solution with charcoal, the filtered solution was reduced to approximately half volume and cooled to between 0 and 5 °C. This procedure provided either the hydrate or the anhydrous form of compound **5** with no obvious bias towards either. Mixtures of the two forms were not observed on any occasion.

1.3.2. Amorphous form

Amorphous **5** was obtained by allowing a saturated solution of paracetamol-*O*-glucuronide, from a variety of solvents, including MeOH, EtOH and H_2O, to slowly evaporate at room temperature.

1.3.3. MeOH solvate

Compound **5** (100 mg) was suspended in a minimum of dichloromethane (approx 10 mL), a minimum of hot methanol (approx 5–6 mL) was added to affect dissolution, and following cooling and slow evaporation of the solvent crystalline **5** was isolated with a needle-like crystal habit.

1.3.4. Sodium salt

Compound **5** sodium salt (200 mg) was completely dissolved in a minimum of aqueous ethanol (approx 15 mL) and following cooling and slow evaporation of the solvent microcrystalline **5** sodium salt was isolated as an aggregated solid.

1.4. Solid state characterisation

DSC was performed using a TA Q1000 DSC with RSC 40 cooling system. The sample was placed into an aluminium DSC pan, and the weight accurately recorded. The pan was covered with a lid and then crimped. The sample cell was heated under a nitrogen purge at a rate of 5 °C min^{-1}, from 25 °C up to a final temperature of 160 °C. TGA analysis was performed using a TA Instruments Q500 thermogravimetric analyser. The sample was placed in an aluminium sample pan and inserted into the TG furnace. The furnace was heated under nitrogen at a rate of 5 °C min^{-1} from 25 °C up to a final temperature of 160 °C. Single-crystal X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Cu K_α radiation (1.5418 Å). All calculations were made using the APEX2 v2009. 3-0 software[24,25] and the diagrams prepared using Mercury.[26]

Acknowledgments

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Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC number 841974. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). PXRD data on the crystalline forms and TGA data on the anhydrous forms are also provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.12.018.

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