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Note

Synthesis of sugar-lactams from azides of glucuronic acid

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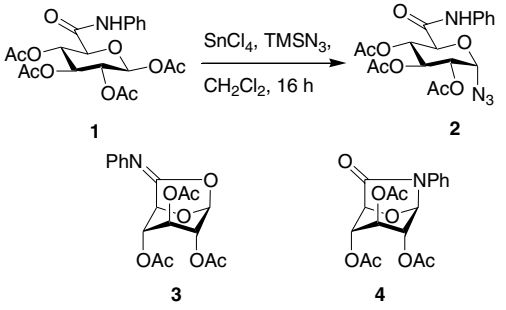
Abstract—Sugar-lactams have found application as glycosidase inhibitors, synthetic precursors of iminosugars and they are structural components of natural products. The synthesis of β-D-glucopyranosidurono-6,1-lactams from glucuronic acid derivatives are described. NMR data and X-ray crystal structures indicate that the sugar-lactams adopt distorted $^1C_4$ conformations in solution and in the solid state.

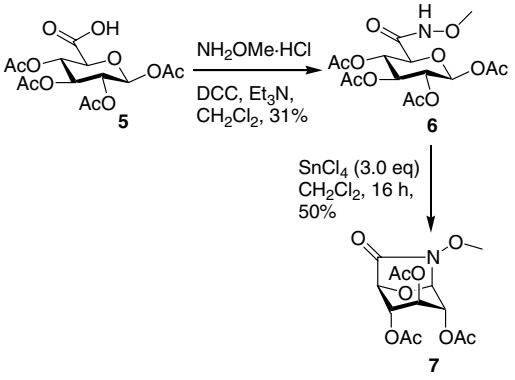
Keywords: Glucuronic acid; Amides, Glycosyl azides; Sugar-lactones; Sugar amino acids; Sugar-lactams

Sugar-lactams have been synthesised as analogues of transition states of reactions catalysed by glycosidases.[1] Mechanistic studies on bovine β-D-glucuronidase indicate that the critical transition state has appreciable oxocarbonium ion character that is primarily stabilised by the 6-carboxylate ion of the enzyme-bound substrate.[2] The electrostatic stabilisation of such a transition state would require the pyranose to adopt an inverted half chair or boat conformation and the formation of a covalent bond between carboxyl group and anomeric centre leading to a lactone structure also seems possible. Therefore 6,1-lactams derived from glucuronic acid could potentially inhibit glucuronidases. Sugar-lactams have been used for preparation of iminosugars[3] and they are structural components of natural products.[4] Sugar-lactam **4** is a putative intermediate in the formation of α-glycosyl azides **2** from **1** (Scheme 1). Synthetic routes to such compounds are therefore of interest and herein we describe approaches to the synthesis of 6,1-lactams from azides of glucuronic acid.[5]



Scheme 1.

The lactam derivative **7** was obtained from the $SnCl_4$-catalysed reaction of the methoxylamide derivative **6** (50%), which had been prepared by coupling of methoxylamine to the acid **5** (Scheme 2). The lactam **7** proved



Scheme 2.

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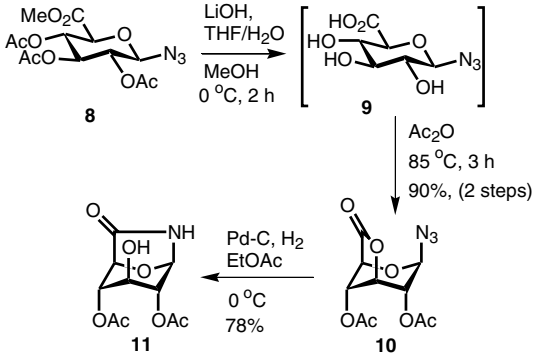
to be stable and could not be activated as a glycosyl donor in the presence of azidotrimethylsilane and $SnCl_4$. This contrasted with the behaviour of cyclic-imidates such as **3** (Scheme 1) which gave glycosyl azides under similar conditions.[6]

A route to lactams was next explored from the glycosyl azide **10**,[7] which was prepared in two steps from D-glucurono-6,3-lactone. Saponification of **8**[8] to give **9** and subsequent acetylation provided the 3,6-lactone **10** in 90% yield (2 steps), after chromatography (Scheme 3). It was possible to obtain multi-gram quantities of **10** by removal of excess acetic anhydride and pyridine under diminished pressure keeping the temperature below 40 °C, followed by evaporation of toluene from the residue under similar conditions and subsequent chromatographic purification of the residue. The 6,3-lactone **10** was prone to hydrolysis in the presence of trace quantities of water but crystallisation of the residue obtained after chromatography gave **10** as colourless prisms which were stable and which were suitable for the X-ray crystal structure determination (Fig. 1). The catalytic hydrogenation of **10** provided an amine that spontaneously cyclised to give the 6,1-lactam **11**, possessing a free hydroxyl group at C-3 (Scheme 3). The reductive-cyclisation reaction that gives **11** was carried out optimally (78%) on a 200–250 mg scale at atmospheric pressure in the presence of hydrogen and Pd–C at 0 °C. Alternatively, the hydrogenation could be carried out in similar yield using a H-Cube™ flow reaction system by passing a 0.05 M solution of the substrate in EtOAc through a 10% Pd–C CatCart™ cartridge column (size 30 × 4 mm); this approach worked best on a 250 mg scale and with an optimum flow rate of 0.5 mL/min. Hydrogenation reactions on larger scales (0.5–5 g) led to mixtures of unreacted 6,3-lactone **10** and 6,1-lactam **11**. Nevertheless, the lactam and lactone could be separated by chromatography. The structure of 6,1-lactam **11** was confirmed by determination of its X-ray crystal structure (Fig. 2).

Acetylation reactions of **11** were next investigated (Scheme 4). The reaction of **11** with acetic anhydride



Scheme 3. Synthesis of the lactam **11**.

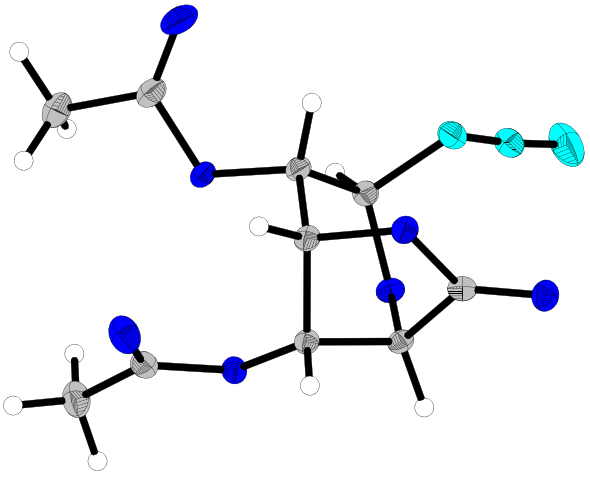


Figure 1. X-ray crystal structure of **10**. Thermal ellipsoids are drawn on the 50% probability level.

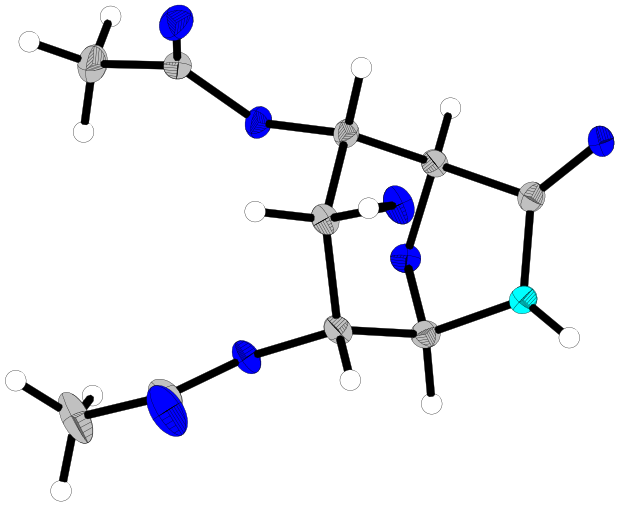
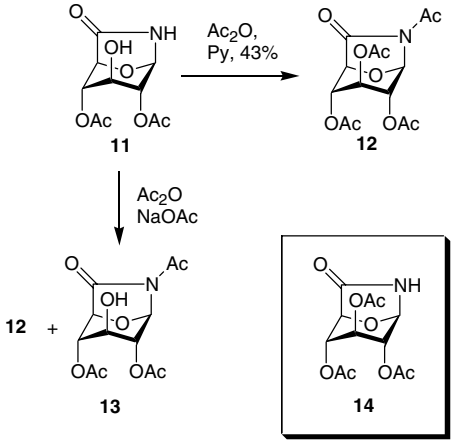


Figure 2. X-ray crystal structure of **11**. Thermal ellipsoids are drawn on the 50% probability level.



Scheme 4. Synthesis of 6,1-lactam.

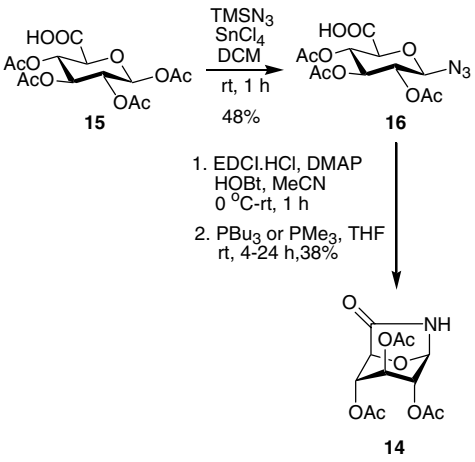
and pyridine gave only the N-acetylated product **12** after 4 h at rt; reaction of **7** with acetic anhydride and sodium acetate gave a 1:3 mixture of **12** and **13** (50%) after 3 h at rt. Analysis (TLC) of the latter reaction indicated that both products were formed simultaneously and that highly selective acylation is not possible under these conditions or at lower temperature (0 °C). The two products **12** and **13** were separable by chromatography and their structural assignments made on the basis of ^{1}H, ^{13}C NMR and MS analysis. The possibility that the O-acetylated compound **14** had formed was ruled out on the basis of HSQC, HMBC and NOESY experiments and this was later confirmed by the synthesis of **14** (Scheme 5).

The synthesis of **14** was achieved from the glycosyl azide **16** (Scheme 5). The azide **16** was first prepared by the reaction of acid **15** with $SnCl_4$ in presence of azidotrimethylsilane. This azidation reaction needs to be stopped after 1 h so that the β-anomer **16** is the major product isolated; longer reaction times led to anomerisation and mixtures where the α-anomer predominated.[9] Alternatively, the formation of the β-azide can be carried out using Et_2O as solvent at 40 °C where anomerisation is suppressed. Alternatively the acid **16** can be obtained by other routes.[10] The conversion of the β-azide **16** to the desired 6,1-lactam **14** was achieved by the reaction of the acid **16** with DCC and HOBt in acetonitrile followed by the addition of tributylphosphine which gave **14** in 40% yield. A similar yield (38%) but more straightforward purification of **14** was achieved by using EDCI and HOBt in acetonitrile and subsequent addition of tributylphosphine or trimethylphosphine in THF to effect the conversion to **14**.

The NMR (^{1}H, ^{13}C, ^{1}H–^{1}H-COSY, TOSCY, HSQC, HMBC) data obtained for 6,1-lactam **14** was consistent with the structure assigned, especially when the data was compared with those of the isomeric structure **13** and the other lactam derivatives described herein. For example, the ^{1}H NMR spectrum of **14** showed a signal for the anomeric proton H-1 at δ 5.36 ppm, whereas the signal for anomeric proton of **13** was observed at δ 5.93 ppm, which is consistent with the presence of the electron withdrawing acetyl group being bonded directly to the lactam nitrogen atom. Additionally, the signal for H-3 of **14** was observed at δ 4.99 ppm, consistent with an acyl group being bonded to O-3, whereas the H-3 of **13** was observed at δ 3.99 ppm, consistent with hydrogen being bonded to O-3. Finally, the signals for the *O*-acetyl groups of **14** were observed at δ 2.09–2.19 ppm, whereas for **13**, the *N*-acyl group was observed at δ 2.49 ppm. The confirmation of the structural assignment was provided by X-ray crystal structure determination of **14** (Fig. 3).

The sugar-6,1-lactams can be distinguished from cyclic-imidates by ^{13}C NMR spectroscopy. The chemical shifts for C-1 (δ ~101 ppm for imidate, δ 85–90 ppm for lactam) and C-6 (δ 150–152 ppm for imidate; δ 166–170 ppm for lactam) are the most useful. The lactams synthesised herein were inert to azidotrimethylsilane and $SnCl_4$ and also towards hydrolysis. By contrast the imidates were found to be more reactive[11] and give glycosyl azides in reactions with azidotrimethylsilane and $SnCl_4$ and are susceptible to hydrolysis. The analysis of ^{1}H NMR spectra suggest that the pyranose ring of the lactams (**7**, **11**–**14**) has a distorted $^{1}C_4$ conformation. In addition the X-ray crystal structures of the lactams **11** and **14** show that the pyranose ring has a distorted $^{1}C_4$ conformation in the solid state. In contrast lactams derived from hydrazine, synthesised by Takeda and Akimoto, adopt a $B_{0,3}$ conformation in solution[5a] and a distorted $^{1}C_4$ conformation in the solid state.[5b]

In summary, a series of sugar-lactams were prepared by novel strategies from glucuronic acid derivatives. These lactams were stable to $SnCl_4$ catalysed glycosidation reactions indicating that lactams are unlikely to be intermediates in glycosidation of amides derived from



Scheme 5. Synthesis of 6,1-lactam **14**.

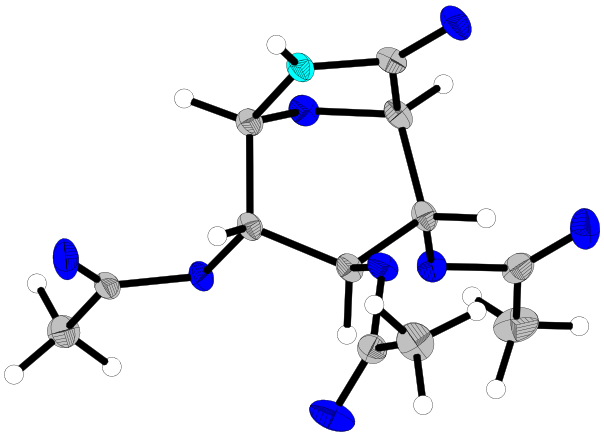


Figure 3. X-ray crystal structure of 6,1-lactam **14**. Thermal ellipsoids are drawn on the 50% probability level.

glucuronic acid that are promoted by $SnCl_4$. However, glycosyl amides have recently been shown to have glycosyl donor properties[12] and consequently the lactams could have potential in this regard. Other applications for sugar-lactams, such as their investigation as inhibitors of glucuronidases, could be envisaged.

1. Experimental

1.1. General

Optical rotations were determined with a Perkin–Elmer 241 model polarimeter at 23 °C. NMR spectra were recorded with Varian Inova spectrometers. Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ (δ 0.0) or HOD for D_2O (δ 4.79) for ^1H and (δ 77.16) for ^{13}C. ^1H NMR signals were assigned with the aid of COSY. ^{13}C NMR signals were assigned with the aid of DEPT-135 and/or HMBC and HSQC. IR spectra were recorded with a Mattson Galaxy Series IR 3000 or with a Varian 3100 FTIR. Electrospray mass spectra were recorded on a Micromass LCT KC420 or Micromass Quattro. Chemical ionisation mass spectra were obtained at the University of York. TLC was performed on aluminium sheets pre-coated with Silica Gel 60 (HF254, E. Merck) and spots visualised by UV and charring with 1:20 H_2SO_4–EtOH. Chromatography was carried out with Silica Gel 60 (0.040–0.630 mm, E. Merck) and employed a stepwise solvent polarity gradient correlated with the TLC mobility. Chromatography solvents used were EtOAc (Riedel-deHaen), cyclohexane and MeOH (Sigma–Aldrich). Dichloromethane (Riedel-deHaen) was freshly distilled from calcium hydride, MeOH was distilled from Mg.

1.2. 1,2,3,4-Tetra-*O*-acetyl-*N*-methoxy-β-D-glucopyranosiduronamide 6

Dicyclohexylcarbodiimide (2.76 mL of a 1.0 M solution in CH_2Cl_2, 2.76 mmol) was added to an ice-cold suspension of methoxyl amine hydrochloride (0.231 g, 2.77 mmol) and Et_3N (0.38 mL, 2.73 mmol) in dry CH_2Cl_2 (20 mL) under N_2, and stirred for 10 min and the acid **5** (1.0 g, 2.76 mmol) was then added. After 3 h the reaction mixture was filtered, and the filtrate was washed with satd aq $NaHCO_3$ (10 mL), 0.1 M HCl (10 mL) and dried ($MgSO_4$). Filtration, evaporation of solvent under diminished pressure and chromatography of the residue (EtOAc–petroleum ether, 1:4) gave **6** as a white solid (0.331 g, 31%); $R_f = 0.11$ (EtOAc–petroleum ether, 1:1); mp 163–165 °C; $[\alpha]_D$ +0.20 (*c* 0.5, $CHCl_3$); IR (KBr) cm^{-1}: 3270, 2943, 2483, 1763, 1701, 1353, 1207, 1031; ^1H NMR (300 MHz, $CDCl_3$): δ 8.81 (s, 1H, N*H*), 5.71 (d, 1H, $J_{1,2} = 8.0$, H-1), 5.30 (t, 1H, $J_{3,4} = J_{2,3} = 8.0$ Hz, H-3), 5.24 (t, $J_{3,4} = J_{4,5} = 8.0$ Hz, H-4), 5.11 (t, 1H, $J_{2,3} = J_{1,2} = 8.0$ Hz, H-2), 4.12 (d, 1H, $J_{4,5} = 8.0$ Hz, H-5), 3.76 (s, 3H, OCH_3), 2.14, 2.08, 2.05, 2.03 (each s, each 3H, each COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.8, 169.6, 169.2 (2s), 168.7 (s, *C*ONHOMe), 91.4 (d, C-1), 72.9, 71.7, 70.1, 68.8 (each d, C-2–5), 64.5 (q, CONHO*C*H_3), 20.7, 20.6, 20.6, 20.5 (each q, each CO*C*H_3); CI-HRMS *m*/*z*: $[M+NH_4]^+$ calcd for $C_{15}H_{25}N_2O_{11}$: 409.1458; found, 409.1459.

1.3. 2,3,4-Tri-*O*-acetyl-*N*-methoxy-β-D-glucopyranosidurono-6,1-lactam 7

Tin(IV) chloride (0.09 mL, 0.768 mmol) was added to a solution of **6** (0.1 g, 0.256 mmol) in dry CH_2Cl_2 (5 mL) under N_2. The reaction was stirred overnight, then diluted with CH_2Cl_2 and vigorously stirred for 30 min in presence of satd aq $NaHCO_3$ (5 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was removed under diminished pressure to afford **7** as a waxy solid (42 mg, 50%); IR (KBr) cm^{-1}: 2980, 2931, 2859, 1752, 1374, 1105, 1043, 804; ^1H NMR (500 MHz, $CDCl_3$): δ 5.37 (t, 1H, $J_{1,2} = J_{1,3} = 1.5$ Hz, H-1), 4.92 (t, 1H, $J_{2,3} = J_{3,5} = 1.5$ Hz, H-3), 4.89 (d, 1H, $J_{1,2}$1.5 Hz H-2), 4.82 (d, 1H, $J_{4,5}$1.5 Hz, H-4), 4.46 (t, 1H, $J_{3,5} = J_{4,5} = 1.5$ Hz, H-5), 3.92 (s, 3H, OCH_3), 2.19, 2.17, 2.09 (each s, each 3H, each COCH_3); ^{13}C NMR ($CDCl_3$): δ 169.6, 169.4, 168.8 (each s, each *C*OCH$_3$), 166.5 (s, *C*ONOCH$_3$), 84.5 (d, C-1), 73.8, 69.0, 65.9, 64.7 (each d, C-2–5), 64.4 (CONHO*C*H$_3$), 20.8 (2s), 20.6 (each q, each CO*C*H$_3$); CI-HRMS *m*/*z*: $[M+NH_4]^+$ calcd for $C_{13}H_{21}N_2O_9$: 349.1247; found, 349.1249.

1.4. 2,4-Di-*O*-acetyl-β-D-glucopyranosylurono-6,3-lactone azide 10

The azide **8** (5.0 g, 13.9 mmol) was suspended in a premixed solution of LiOH (0.3 M in water; 300 mL, 90 mmol) and MeOH–water–THF (5:4:1, 300 mL) at 0 °C. The reaction mixture was then stirred for 3 h and the pH adjusted to 2 using 2 M HCl. Filtration and evaporation of the solvents under diminished pressure, followed by freeze drying gave a residue containing **9**; ^1H NMR (300 MHz, D_2O): δ 4.67 (d, 1H, $J_{1,2} = 8.7$ Hz, H-1), 3.92 (d, 1H, $J_{4,5} = 9.2$ Hz, H-5), 3.37–3.47 (m, 2H, H-3, H-4), 3.15 (t, 1H, $J_{1,2} = J_{2,3} = 8.7$ Hz, H-2); ESI-LRMS *m*/*z*: $[M-H]^-$ found, 218.1. The residue was suspended in Ac_2O (200 mL) and heated at 85 °C for 2 h. The solvent was evaporated under diminished pressure at $T < 40$ °C, then toluene was added and further evaporation under diminished pressure was continued until a solid yellow residue remained. The residue was purified by chromatography (cyclohexane–EtOAc, 5:2) to give **10** as a white solid (3.56 g, 90%). Some of this product was recrystal-

lised from CH_2Cl_2 with dropwise addition of petroleum ether (bp 40–60 °C) to provide **9** as colourless prisms; $R_f = 0.48$ (cyclohexane–EtOAc, 1:1); $[\alpha]_D$ −23 (*c* 0.7, acetone); IR (KBr) cm^{-1}: 3031, 2967, 2119, 1816, 1754, 1395, 1371, 1265, 1231, 1067, 1047, 896, 743; ^1H NMR (400 MHz, $CDCl_3$): δ 5.39 (s, 1H, H-1), 5.01 (dd, $J_{3,4} = 5.2$ Hz, $J_{2,3} = 3.5$ Hz, 1H, H-3), 4.89 (dd, 1H, $J_{3,4} = 5.2$ Hz, $J_{4,5} = 3.5$ Hz, H-4), 4.86 (d, 1H, $J_{2,3} = 3.5$ Hz, H-2), 4.31 (d, 1H, $J_{4,5} = 5.2$ Hz, H-5), 2.14, 2.05 (each s, each 3H, each $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0 (s, CO_2), 167.9, 167.8 (each s, each $COCH_3$), 87.2 (d, C-1), 70.3, 67.7, 67.3, 66.3 (each d, C-2-C-5), 19.5, 19.4 (each q, each $COCH_3$); ESI-LRMS *m/z*: $[M+Na]^+$ found, 308.1, $[M-H]^-$ 284.0; CI-HRMS *m/z*: $[M+NH_4]^+$ calcd for $C_{10}H_{11}$- N_3O_7: 303.0941; found, 303.0941.

1.5. 2,4-Di-*O*-acetyl-β-D-glucopyranosidurono-6,1-lactam 11

The lactone **10** (0.2 g, 0.7 mmol) was dissolved in EtOAc (10 mL), previously dried over 4 Å molecular sieves, and the mixture was cooled to 0 °C, purged with nitrogen and degassed. Palladium (10%) on carbon (0.1 g) was quickly added and the mixture then placed under an atmosphere of hydrogen and the reaction mixture was stirred at 0 °C for 4 h. The catalyst was filtered through Celite and the filtrate concentrated under diminished pressure to give a yellow oil. Chromatography of this residue (cyclohexane–EtOAc, 2:3) gave **11** initially as a colourless oil (0.142 g, 78%), which crystallised on leaving to stand; $R_f = 0.20$ (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{20}$ −21 (*c* 0.3, $CHCl_3$); IR (KBr) cm^{-1}: 3440, 2964, 1817, 1751, 1375, 1261, 1099, 1041, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (br s, 1H, N*H*), 5.38 (s, 1H, H-1), 4.81 (s, 1H, H-4), 4.7 (br s, 1H, OH), 4.65 (s, 1H, H-2), 4.37 (s, 1H, H-5), 3.91 (s, 1H, H-3), 2.13 (2s, 6H, 2 $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8 (s, *C*ONH), 170.9, 170.6 (each s, each *C*OCH_3), 84.8 (d, C-1), 75.0, 69.8, 69.6, 69.5 (each d, C-2–5), 21.2, 21.2 (each q, each $COCH_3$); ESI-LRMS *m/z*: $[M-H]^-$ 258.0, $[M+Na]^+$ 282.0, $[2M-H]^-$ 517.3, $[2M+Na]^+$ 541.0, $[3M+Na]^+$ 800.0, $[4M+Na]^+$ 1059.0; ESI-HRMS: $[M+H]^+$ calcd for $C_{10}H_{14}NO_7$: 260.0770; found, 260.0769. Anal. Calcd for $C_{10}H_{13}NO_7$: C, 46.34; H, 5.06; N, 5.40. Found: C, 46.26; H, 5.05; N, 5.21.

1.6. 2,3,4-Tri-*O*-acetyl-*N*-acetyl-β-D-glucopyranosidurono-6,1-lactam 12

To **11** (0.1 g, 0.39 mmol) in anhydrous pyridine (1 mL) was added Ac_2O (0.04 mL, 0.42 mmol) and the reaction mixture was stirred at 0 °C for 2 h. Toluene was added and the volatile components were evaporated under diminished pressure. Chromatography of the residue (cyclohexane–EtOAc, 3:1) gave **12** as a colourless oil (57 mg, 43%); $R_f = 0.52$ (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{20}$ −42.2 (*c* 0.7, $CHCl_3$); IR (NaCl) cm^{-1}: 3026, 2963, 2925, 1752, 1373, 1218, 1046, 770; ^1H NMR (500 MHz, $CDCl_3$): δ 5.94 (s, 1H, H-1), 5.00 (s, 1H, H-3), 4.90 (s, 1H, H-2), 4.80 (s, 1H, H-4), 4.65 (s, 1H, H-5), 2.53 (s, 3H, $NCOCH_3$), 2.19, 2.18, 2.04 (each s, each 3H, each $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2 (s, *C*OCH_3), 169.1 (s, *C*OCH_3), 168.6 (s, N*C*OCH_3), 167.8 (s, *C*OCH_3), 167.7 (s, *C*$ONCOCH_3$), 86.0 (d, C-1), 76.8 (d, C-5), 68.7 (d, C-3), 65.9 (d, C-4), 64.9 (d, C-2), 23.9 (q, $NCOCH_3$), 20.8, 20.7 (each q, $COCH_3$ at C-2, C-4), 20.5 (q, $COCH_3$ at C-3); ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}NO_9$: 344.0982; found, 334.0997.

1.7. 2,4-Di-*O*-acetyl-*N*-acetyl-β-D-glucopyranosidurono-6,1-lactam 13

To a solution of lactam **11** (100 mg, 0.39 mmol) in Ac_2O (5 mL) was added sodium acetate (35 mg, 0.42 mmol) and the reaction mixture was stirred at 0 °C for 2 h. Most of the excess Ac_2O was removed under diminished pressure and chromatography of the residue (cyclohexane–EtOAc, 3:1) gave **12** (48 mg, 36%) and the title compound **13** (colourless oil, 16 mg, 14%) as well as recovered lactam **11** (30 mg, 30%). Analytical data for **13** $R_f = 0.40$ (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{20}$ −31.2 (*c* 0.5, $CHCl_3$); IR (NaCl) cm^{-1}: 3482, 3021, 2962, 2928, 1751, 1376, 1329, 1256, 1217, 1052, 756, 669; ^1H NMR (600 MHz, $CDCl_3$): δ 5.93 (s, 1H, H-1), 4.88 (s, 1H, H-2), 4.85 (s, 1H, H-4), 4.61 (s, 1H, H-5), 3.99 (s, 1H, H-3), 2.49 (s, 3H, $NCOCH_3$), 2.16 (2s, each 3H, each $COCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9, 169.8 (each s, *C*OCH_3), 169.1 (s, N*C*OCH_3), 167.8 (s, *C*$ONCOCH_3$), 86.2 (d, C-1), 76.9 (d, C-5), 68.8 (d, C-4), 68.7 (d, C-3), 67.0 (d, C-2), 23.9 (q, $NCOCH_3$), 20.9, 20.8 (each q, each $COCH_3$); ESI-LRMS *m/z*: $[M+Na]^+$ found, 324.0, $[M-H]^-$ 300.1; ESI-HRMS *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}NO_8$: 302.0876; found, 302.0869.

1.8. 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosidurono-6,1-lactam 14

A mixture of **16** (0.5 g, 1.45 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.278 g, 1.45 mmol) and DMAP (0.177 g, 1.45 mmol) in dry acetonitrile (25 mL) was stirred at 0 °C for 15 min under N_2. 1-Hydroxybenzotriazole (0.196 g, 1.45 mmol) was then added and the mixture was stirred for a further 45 min at room temperature. To the pale yellow solution was then added tri-*n*-butylphosphine (0.39 mL, 1.6 mmol) and the mixture turned gradually bright yellow and stirring was continued for 16 h. The solvent was removed under diminished pressure and

chromatography of the residue (Et_2O–CH_2Cl_2, 8:3) gave **14** as a colourless oil (0.165 g, 38%); $R_f = 0.44$ (cyclohexane–EtOAc, 1:1); $[\alpha]_D^{20}$ −39.0 (*c* 1.5, $CHCl_3$); IR (NaCl) cm^{-1}: 3348, 3021, 1748, 1372, 1218, 1047, 897, 755, 668; ^1H NMR (500 MHz, $CDCl_3$): δ 5.36 (s, 1H, H-1), 4.99 (s, 1H, H-3), 4.85 (s, 1H, H-4), 4.65 (s, 1H, H-2), 4.39 (s, 1H, H-5), 2.19, 2.18, 2.09 (each s, each 3H, each $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7 (s, *C*ONH), 170.1 (s, *C*OCH_3 at C-2), 169.5 (s, *C*OCH_3 at C-4), 168.8 (s, *C*OCH_3 at C-3), 84.0 (d, C-1), 74.7 (d, C-5), 70.2 (d, C-3), 68.2 (d, C-2), 67.2 (d, C-4), 20.9, 20.9 (each q, CO*C*H_3 at C-2, C-4), 20.8 (q, CO*C*H_3 at C-3); ESI-LRMS *m*/*z*: $[M-H]^-$ found, 300.1, $[M+Na]^+$ 324.0; ESI-HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{12}H_{15}NNaO_8$: 324.0695; found, 324.0688. Anal. Calcd for $C_{12}H_{15}NO_8$: C, 47.84; H, 5.02; N, 4.65. Found: C, 47.41; H, 4.96; N, 4.34.

1.9. 2,3,4-Tri-*O*-acetyl-β-D-glucopyranosyluronic acid azide 16

To a solution of acid **15** (5.0 g, 13.8 mmol) in dry CH_2Cl_2 (120 mL) were added, under an atmosphere of dry nitrogen with stirring, azidotrimethylsilane (4.5 mL, 34.5 mmol), followed by tin(IV) chloride (0.80 mL, 6.9 mmol). The reaction mixture was stirred for 1 h at 0 °C and then satd aq $NaHCO_3$ (75 mL) was added and stirring continued for 30 min, after which time the aqueous layer clearly separated from the organic phase. The mixture was filtered through Celite and washed with CH_2Cl_2 (4 × 25 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (2 × 25 mL) and the aqueous layer was washed with CH_2Cl_2 (2 × 25 mL). The combined organic layers were collected, dried ($MgSO_4$), filtered and the solvent evaporated off, to give a mixture of α- and β-anomers where the β-anomer **16** was the major component (white foam, 2.28 g, 48%). Analytical data for **16** was in good agreement with that described previously.[13]

1.10. Methods for X-ray crystal structure determination

Crystal data were collected using a Bruker SMART APEX CCD area detector diffractometer. A full sphere of the reciprocal space was scanned by phi-omega scans. Semi-empirical absorption correction based on redundant reflections was performed by the program SADABS.[14] The structures were solved by direct methods using SHELXS-97[15] and refined by full matrix least-squares on F^2 for all data using SHELXL-97.[16] Hydrogen atoms attached to oxygen or nitrogen were located in

Table 1. Crystal data and structure refinement for **10**

Empirical formula	$C_{10}H_{11}N_3O_7$
Formula weight	285.22
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (#19)
Unit cell dimensions	$a = 5.4460(7)$ Å $\alpha = 90°$ $b = 12.8588(17)$ Å $\beta = 90°$ $c = 17.357(2)$ Å $\gamma = 90°$
Volume (Å^3)	1215.5(3)
Z	4
Density (calculated) (Mg/m^3)	1.559
Absorption coefficient (mm^{-1})	0.134
F(000)	592
Crystal size (mm^3)	1.00 × 0.80 × 0.70
θ Range for data collection (°)	1.97–29.99
Index ranges	$-7 \leqslant h \leqslant 7$, $-18 \leqslant k \leqslant 18$, $-24 \leqslant l \leqslant 24$
Reflections collected	13033
Independent reflections	2064 ($R_{int} = 0.0369$)
Completeness to theta = 29.99°	100.0 %
Absorption correction	Semi-empirical from equivalents
Maximum and minimum transmission	0.9118 and 0.7287
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2064/0/183
Goodness-of-fit on F^2	1.037
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0350$, $wR_2 = 0.0852$
R indices (all data)	$R_1 = 0.0375$, $wR_2 = 0.0863$
Largest difference in peak and hole	0.304 and −0.308 e Å^{-3}

Table 2. Crystal data and structure refinement for **11**

Empirical formula	$C_{10}H_{13}NO_7$
Formula weight	259.21
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (#19)
Unit cell dimensions	$a = 7.8399(8)$ Å $\alpha = 90°$ $b = 10.7473(11)$ Å $\beta = 90°$ $c = 14.3177(14)$ Å $\gamma = 90°$
Volume (Å^3)	1206.4(2)
Z	4
Density (calculated) (Mg/m^3)	1.427
Absorption coefficient (mm^{-1})	0.123
F(000)	544
Crystal size (mm^3)	0.80 × 0.30 × 0.20
θ Range for data collection (°)	2.37–29.01
Index ranges	$-10 \leqslant h \leqslant 10$, $-14 \leqslant k \leqslant 14$, $-19 \leqslant l \leqslant 19$
Reflections collected	23,550
Independent reflections	1799 ($R_{int} = 0.0253$)
Completeness to theta = 29.01°	97.1%
Absorption correction	Semi-empirical from equivalents
Maximum and minimum transmission	0.9759 and 0.9215
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1799/0/173
Goodness-of-fit on F^2	1.028
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0404$, $wR_2 = 0.1063$
R indices (all data)	$R_1 = 0.0421$, $wR_2 = 0.1082$
Largest difference in peak and hole	0.298 and −0.199 e Å^{-3}

Table 3. Crystal data and structure refinement for **14**

Empirical formula	$C_{12}H_{15}NO_8$
Formula weight	301.25
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	Tetragonal
Space group	$P4_3$ (#78)
Unit cell dimensions	$a = 8.4835(6)$ Å $\alpha = 90°$ $b = 8.4835(6)$ Å $\beta = 90°$ $c = 19.298(3)$ Å $\gamma = 90°$
Volume (Å^3)	1388.9(2)
Z	4
Density (calculated) (Mg/m^3)	1.441
Absorption coefficient (mm^{-1})	0.123
$F(000)$	632
Crystal size (mm^3)	$0.60 \times 0.40 \times 0.20$
θ Range for data collection (°)	2.40–29.99
Index ranges	$-11 \leqslant h \leqslant 11$, $-11 \leqslant k \leqslant 10$, $-27 \leqslant l \leqslant 25$
Reflections collected	10,540
Independent reflections	2073 ($R_{int} = 0.0406$)
Completeness to theta = 29.99°	100.0%
Absorption correction	Semi-empirical from equivalents
Maximum and minimum transmission	0.9758 and 0.2432
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2073/1/197
Goodness-of-fit on F^2	1.020
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0433$, $wR_2 = 0.1006$
R indices (all data)	$R_1 = 0.0454$, $wR_2 = 0.1025$
Largest difference in peak and hole	0.403 and −0.238 e Å^{-3}

the difference fourier map and allowed to refine freely. All other hydrogen atoms were added at calculated positions and refined using a riding model. Their isotropic temperature factors were fixed to 1.2 times (1.5 times for methyl groups) the equivalent isotropic displacement parameters of the carbon atom the H-atom is attached to (Tables 1–3).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.04.003.

References

1. Hoos, R.; Naughton, A. B.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 1802–1807.
2. Parker, A.; Maw, B.; Fedor, L. *Biochem. Biophys. Res. Commun.* **1981**, *103*, 1390–1394.
3. Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215–4224.
4. Kinoshita, M.; Suzuki, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2375–2378.
5. For other lactams synthesised from glucuronic acid see: (a) Takeda, Y.; Akimoto, T.; Kyogoku, Y. *Carbohydr. Res.* **1982**, *106*, 175–192; (b) Akimoto, T.; Takeda, Y.; Nawata, Y.; Iitaka, Y. *Acta Crystallogr., Sect. C* **1988**, *44*, 760–762; (c) Revel'skaya, L. G.; Anikeeva, A. N.; Danilov, S. N. *Zh. Obsch. Khim.* **1973**, *43*, 1624–1630; (d) Timmers, C. M.; Turner, J. J.; Ward, C. M.; van der Marel, G. A.; Kouwijzer, M. L. C. E.; Grootenhuis, P. D. J.; van Boom, J. H. *Chem. Eur. J.* **1997**, *3*, 920–929.
6. Tosin, M.; O' Brien, C.; Fitzpatrick, G. M.; Müller-Bunz, H.; Glass, W. K.; Murphy, P. V. *J. Org. Chem.* **2005**, *70*, 4096–4106.
7. Tosin, M.; Murphy, P. V. *Org. Lett.* **2002**, *4*, 3675–3678.
8. (a) von Roedern, E. G.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156–10167; (b) Györgydeák, Z.; Thiem, J. *Carbohydr. Res.* **1995**, *268*, 85–92.
9. O'Brien, C.; Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Chem. Eur. J.* **2007**, *13*, 902–909.
10. See Ref. 5 and Ying, L.; Gervay-Hague, J. *Carbohydr. Res.* **2003**, *338*, 835–841.
11. Cronin, L.; Tosin, M.; Müller-Bunz, H.; Murphy, P. V. *Carbohydr. Res.* **2007**, *342*, 111–118.
12. (a) Pleuss, N.; Kunz, H. *Synthesis* **2005**, 122–130; (b) Pleuss, N.; Kunz, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3174–3176.
13. Malkinson, J. P.; Falconer, R. A.; Toth, I. *J. Org. Chem.* **2000**, *65*, 5249–5252.
14. Sheldrick, G. M. SADABS; Bruker AXS: Madison, WI, 2000.
15. Sheldrick, G.M. SHELXS-97: *Program for Crystal Structure Solution*; Göttingen, 1997.
16. Sheldrick, G.M. SHELXS-97: *Program for Crystal Structure Refinement*, *Release 2*; Göttingen, 1997.