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Note

The synthesis of cyclic imidates from amides of glucuronic acid and investigation of glycosidation reactions

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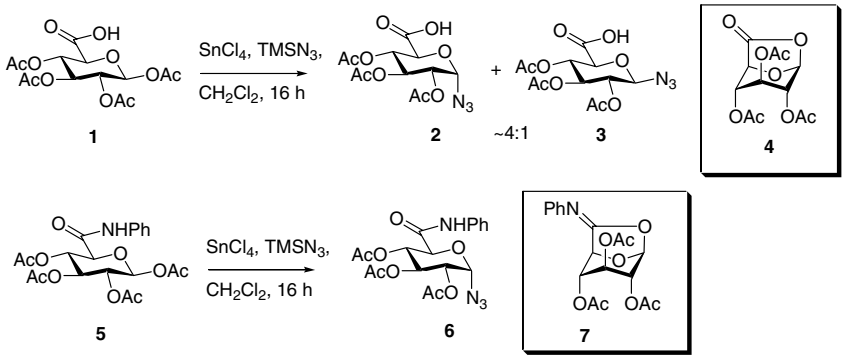
Abstract—The synthesis of novel cyclic glycosyl imidates and an investigation of their potential as donors in glycosidation reactions is described. The results show that 1,2-cis glycosides obtained from the reactions of glycosyl acetates or cyclic imidates, each derived from amides of glucuronic acid, result from the anomerisation of initially formed 1,2-trans glycosides.

Keywords: Imidates; Glycosidation; Anomerisation; Glucuronic acid; Amides; Lewis acid

Stereoselective glycoside synthesis has long been of interest because of the biological and medical relevance of oligosaccharides, glycoproteins, glycolipids[1] and other carbohydrate derivatives[2] and a range of strategies, including the application of imidate donors, have been investigated and developed.[3,4] Glycosyl azide **2** with α-configuration was the major product (after 16 h) from the $SnCl_4$ promoted reaction of acid **1** with azidotrimethylsilane (Scheme 1).[5] The 1,6-anhydro derivative **4**, formed during the reaction of **1** with $SnCl_4$, provided **2** and **3** in a similar yield and ratio to that observed from **1** when it is reacted with silylated acceptors in the presence of $SnCl_4$.[6] As the reaction of glucuronic acid anilide **5** proceeded to give 1,2-cis glycosides **6**,[5] there is also the possibility that cyclic imidate **7** is an intermediate in this glycosidation reaction; however, up to now **7** was not obtained in sufficiently high purity for confirmation of its structure and investigation of its $SnCl_4$ catalysed glycosidation reactions. Herein, we describe the synthesis of novel cyclic imidates and show



Scheme 1.

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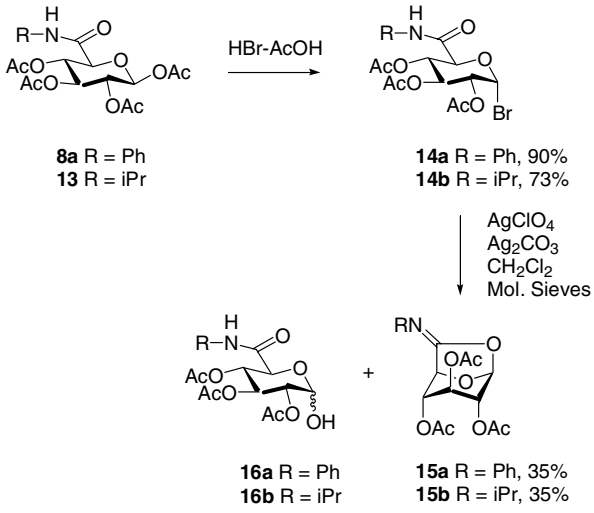
that they can be donors in glycosidation reactions catalysed by $SnCl_4$. The evidence presented supports the proposal that α-glycosides obtained from the reactions of glycosyl acetates **5** or cyclic imidates **7** are, as in the case of **1** and **4**, formed by anomerisation of the initially formed 1,2-trans glycosides.

The reaction of amide **8a** in dichloromethane catalysed by $SnCl_4$ in the presence of azidotrimethylsilane was re-examined and the experiments showed that the ratio of **9a:10a** (75–90%) present in the mixture varied depending on the reaction time (Scheme 2). Thus β-azide **10a** was the major component observed after 1.75 h (**9a:10a** = 1:2), whereas α-anomer **9a** predominated after 12 h (**9a:10a** >100:1). α-Acetate **11** and α-chloride **12** (**11**+**12** = 10–25%) were also detected by ^{1}H NMR during the course of this reaction. The reactions of tertiary amide **8b** also showed evidence that anomerisation was occurring; after 2 h only β-anomer **10b** was present, whereas after 12 h a 1:1 mixture of **9b** and **10b** was obtained.

The possibility that cyclic imidate **15a** could be an intermediate in the glycosidation reaction of **8a** was next explored. Efforts to synthesise **15a** directly from **8a** using $SnCl_4$ led only to recovery of the starting compound or to isolation of impure fractions containing **15a**. The glycosyl bromides **14a** and **14b** were prepared by the reaction of **8a** and **13**, respectively, with HBr–AcOH. The formation and isolation of **15a** (35%) and **15b** (35%) was achieved after activation of α-bromides **14a** and **14b**, respectively, using a mixture of silver carbonate and silver perchlorate in CH_2Cl_2 in the presence of molecular sieves (Scheme 3). Hemi-acetals **16a** and **16b** were the major side products obtained from both reactions, and presumably arise from a competing hydrolysis reaction of the bromide that occurs in the presence of water. The X-ray crystal structure of **15a** is shown (Fig. 1).

The glycosidation reactions of **15a** and **15b** catalysed by $SnCl_4$ were next investigated and the results are summarised in Table 1. The reaction of **15a** with azidotrimethylsilane and TMSOPh as nucleophiles promoted



Scheme 3. Synthesis of cyclic imidates.

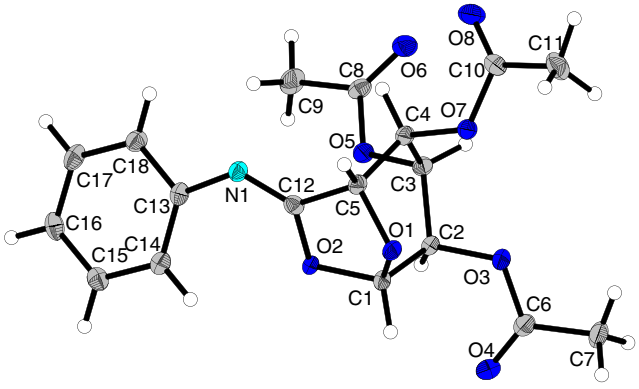
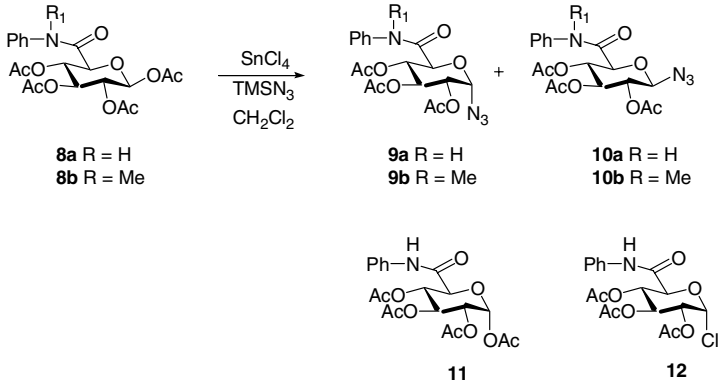


Figure 1. X-ray crystal structure of imidate **15a**. Thermal ellipsoids are drawn at the 50% probability level. The pyranose ring adopts a chair conformation in the solid state and the imine has the *Z*-configuration.

by TMSOTf gave, respectively, β-glycosides **10a** and **17** (Chart 1) as the major products of the reaction. Hemi-acetal **16a** was the main by-product from both reactions. When these reactions were carried out in the presence of molecular sieves, normally added to reac-



Scheme 2. Synthesis of glycosyl azides from amides of glucuronic acid.

Table 1. Reactions of cyclic imidates[a]

Entry	Nucleophile	Time (h)	Imidate	Temp (°C)	Promoter (equiv)	Product (isolated yield, %) ratio[b]
1	$TMSN_3$	1	**15a**	0	$SnCl_4$ (0.5)	**10a** (66), **16a** 5:1
2	TMSOPh	4	**15a**	20	$SnCl_4$ (0.5)	**16a**, **17** (22) 1:3
3	PhOH	24	**15a**	20	$SnCl_4$ (0.5)	**16a**, **17** 2:1[c]
4	PhOH	1	**15a**	20	TMSOTf (2.5), $SnCl_4$ (0.5)	**16a**, **17**, **18** 1:1.2:2[c]
5	PhOH	24	**15a**	20	TMSOTf (2.5), $SnCl_4$ (0.5)	**18** (63)
6	$TMSN_3$	24	**15b**	20	$SnCl_4$ (0.5)	**16b**, **19** (75) 1:14
7	TMSOPh	5	**15b**	20	$SnCl_4$ (0.5)	**21** (40)
8	TMSOCy	24	**15b**	20	$SnCl_4$ (0.5)	**22** (40)

[a] All reactions were carried out in CH_2Cl_2.
[b] Ratios were determined by ^1H NMR analysis of crude product mixtures.
[c] Yields were not obtained.

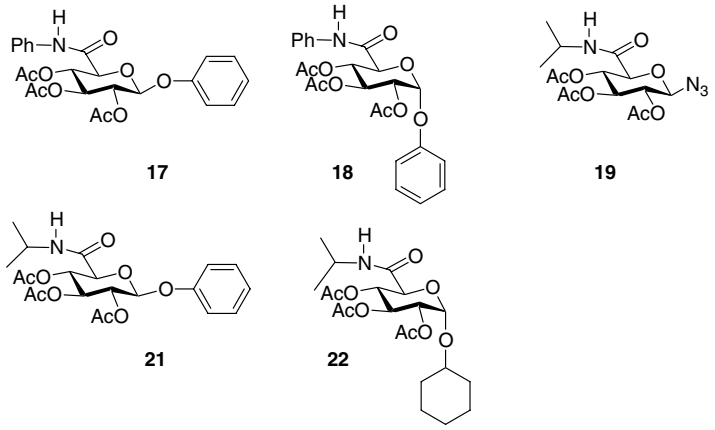
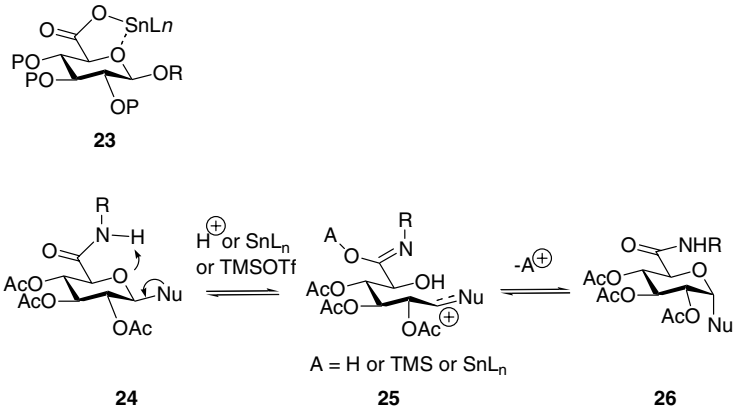


Chart 1. Structures of **17**–**22**.

tions as a drying reagent, only **16a** was obtained. The efficient in situ anomerisation of β-glycoside **10a**, formed from **15a**, could be promoted by the addition of TMSOTf (1 equiv) to the reaction mixture and gave **9a**. α-Glycoside **18** was obtained in high yield from the reactions of **15a** with phenol carried out in the presence of $SnCl_4$ and TMSOTf after 24 h. If this reaction was stopped after 2 h, a mixture of **16a**, **17** and **18** was obtained. Hemi-acetal **16a** most likely undergoes a Fischer type glycosidation to give initially **17** and subsequently **18** under these conditions. In the absence of TMSOTf, the reaction of **15a** with PhOH is less effective. Attempts to carry out glycosidation reactions of **15a** using $BF_3(OEt)_2$ or TMSOTf as promoters in the absence of $SnCl_4$ were unsuccessful. The structure of **17** was confirmed by its independent synthesis by reaction of aniline with the acid chloride prepared from phenyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid.[5] Removal of the protecting groups from **18** and characterisation of the unprotected compound confirmed the assignment of the α-configuration to **17**.

The reaction of imidate **15b** with $TMSN_3$ in the presence of $SnCl_4$ gave β-azide **19** (75%). This observation contrasts with the previous observation that the reaction of **13** under similar conditions and reaction time gave only the α-azide.[5] β-Glycoside **21** (40%) was isolated from the reaction of **15b** with PhOTMS. α-Glycoside **22** (40%) was isolated from the reaction of **15b** with CyOTMS.

A recent study from our group has shown that the tin(IV) chloride catalysed reaction of silylated nucleophiles with **4** can provide 1,2-trans glycosides or 1,2-cis glycosides, even when 2-acyl protecting groups are present.[7] When 1,2-cis glycoside formation occurs, this is due to the $SnCl_4$ catalysed anomerisation of the initially formed 1,2-trans glycosides. This anomerisation of β-glucopyranosiduronic acids was found to be faster than the anomerisation of related β-D-glucopyranosiduronic acid esters and β-glucopyranoside derivatives and the rates depend on the electron affinity of the aglycon, being faster for more electropositive aglycon groups (OCy faster than OPh).[7,8] The results observed herein indicate that anomerisation of the initially formed β-glycosides accounts for the formation of α-glycosides (e.g., formation of **9** from **10**, **18** from **17**), displaying a pattern of behaviour similar to that observed in the reactions of **1** and **4**.[7] A chelated intermediate **23** has been suggested to account for the anomerisation of intermediates generated from **4**. The anomerisation of β-glycoside intermediates generated from the reaction of cyclic imidates is slower than that from β-glycosides generated from glucuronic acid amides (comparing the reaction of



Scheme 4. Structure for **23**–**26** and a mechanistic proposal for anomerisation.

$TMSN_3$ with **13**[5] and **15b**). The reason for this is not clear to us. To explain the anomerisation of β-glucuronic acid amides a general acid catalysis[9] type mechanism, related to that proposed[7] for the anomerisation of β-D-glucopyranosiduronic acids, can be invoked and this involves coordination of the amide carbonyl group of **24** to $SnCl_4$ leading to increased acidity[10] of the amide proton, subsequent protonation of the pyranose oxygen and cleavage of the C-1–O-5 bond giving an open chair intermediate[11] **25** that ultimately gives **26** (Scheme 4). This would explain the observation that **10b** anomerises more slowly than **10a**.

In summary, 1,2-cis glycosides, when they are obtained from $SnCl_4$ catalysed 2-*O*-acyl-protected glucopyranosiduronic acid amides,[12] result from the anomerisation of initially formed 1,2-trans glycosides. Cyclic imidates may be intermediates but they also would predominantly give 1,2-trans glycosides initially.

1. Experimental

1.1. General

Optical rotations were determined with a Perkin–Elmer 241 model polarimeter at 23 °C. ^1H NMR spectra were recorded with a Varian Inova 300 or 500 MHz spectrometer; ^{13}C NMR spectra were recorded at 75 MHz. 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. ^{13}C signals were assigned with the aid of DEPT-135. ^1H NMR signals were assigned with the aid of COSY. IR spectra were recorded with a Mattson Galaxy Series IR 3000 using either thin film between NaCl plates or KBr discs, as specified. Mass spectra were recorded on a Micromass LCT KC420 or Micromass Quattro. TLC was performed on aluminium sheets precoated with Silica Gel 60 (HF254, E. Merck) and the spots were 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, which correlated with the TLC mobility. Chromatography solvents used were EtOAc (Riedel-deHaen), cyclohexane and MeOH (Sigma Aldrich). CH_2Cl_2 (Riedel-deHaen) was freshly distilled from calcium hydride, MeOH was distilled from Mg.

1.2. Preparation of glycosyl azides from glucuronic acid amides

To a soln of the amide in dry CH_2Cl_2 (0.1 g/mL) under N_2 atmosphere, $TMSN_3$ (2.5 equiv) and $SnCl_4$ (0.5 equiv) were added and the reaction mixture was stirred for the required time (see Scheme 2). Dilution with CH_2Cl_2 followed and the soln was vigorously stirred for further 30–40 min in the presence of an equal volume of satd aq $NaHCO_3$; a white emulsion formed and the organic and aq layers can be separated after filtration through a layer of Celite. The azide was obtained after purification by column chromatography (EtOAc–cyclohexane gradient).

1.3. 2,3,4-Tri-*O*-acetyl-1-azido-1-deoxy-α/β-D-glucopyranuronic acid, *N*-phenylamide 9a/10a

A 1:2 mixture of α-anomer **9a** and β-anomer **10a**[11] was obtained from **8a** after 2 h. α-Anomer **9a** (72%) was obtained from **8a**[13] after 12 h; R_f 0.21 (1:2 EtOAc–cyclohexane); $[\alpha]_D$ +81.1 (*c* 0.38, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, N*H*), 7.49 (dd, 2H, *J* 8.5, *J* 1.2, Ar H), 7.33 (t, 2H, *J* 7.5, Ar H), 7.14 (t, 1H, *J* 7.5, Ar H), 5.77 (d, 1H, $J_{1,2}$ 4.3, H-1), 5.49 (t, 1H, $J_{2,3} = J_{3,4}$ 9.5, H-3), 5.22 (t, 1H, $J_{4,5}$ 10.3, H-4), 4.96 (dd, 1H, $J_{1,2}$ 4.3, $J_{2,3}$ 9.5, H-2), 4.50 (d, 1H, $J_{5,4}$ 10.3, H-5), 2.13, 2.09, 2.04 (each s, each 3H, each

$COCH_3$); HRESIMS calcd for $C_{18}H_{19}O_8N_4$ 419.1203, found m/z 419.1213 $[M-H]^-$.

1.4. 2,3,4-Tri-*O*-acetyl-1-bromo-1-deoxy-α-D-gluco-pyranosiduronic acid, *N*-phenylamide 14a

To a soln of **8a**[11] (2.49 g, 5.7 mmol) in acetic acid (5 mL), 30% HBr in acetic acid (8 mL, 40 mmol) was added slowly and the mixture was stirred overnight. Ice and water (80 mL) were added and the mixture was allowed to stand until a creamy precipitate had formed, which was filtered off and washed with cold water. The solid obtained was dissolved in EtOAc (40 mL) and stirred with $NaHCO_3$ (60 mL) for 1 h. The organic layer was then washed with water, dried ($MgSO_4$), filtered and the solvent removed under diminished pressure. Recrystallisation (EtOAc–cyclohexane) gave **14a** as a white solid (2.35 g, 90%); R_f 0.4 (EtOAc–cyclohexane 2:3); mp 160–161 °C; $[\alpha]_D$ +159.5 (c 1.12, CH_2Cl_2); IR (KBr) cm^{-1} 3473, 3361, 1763, 1735, 1702, 1607, 1554, 1499, 1448, 1369, 1307, 1242, 1201, 1099, 1046, 885; ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (s, 1H, N*H*), 7.47 (d, 2H, J 8.0, Ar H), 7.34 (t, 2H, J 8.0, Ar H), 7.14 (t, 1H, J 8.0, Ar H), 6.71 (d, 1H, $J_{1,2}$ 4.2, H-1), 5.66 (t, 1H, $J_{3,2}$ 10.0, $J_{3,4}$ 9.6, H-3), 5.33 (t, 1H, $J_{4,3}$ 9.6, H-4), 4.85 (dd, 1H, $J_{2,1}$ 4.2, $J_{2,3}$10.0, H-2), 4.61 (d, 1H, $J_{5,4}$ 10.3, H-5), 2.12, 2.11, 2.06 (each s, each 3H, each $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 169.6, 169.5 (each s, each $COCH_3$), 163.5 (s, *C*ONH), 136.3 (s, Ar C), 129.0, 125.1, 120.5 (each d, Ar C), 84.3 (d, C-1), 72.2, 70.5, 69.3, 68.5 (each d, C-2–5), 20.6, 20.5 (overlapping signals, each q, each $COCH_3$); HRESIMS: calcd for $C_{15}H_{22}O_8N$ 458.0451, found m/z 458.0472 $[M+H]^+$.

1.5. 2,3,4-Tri-*O*-acetyl-1-bromo-1-deoxy-α-D-gluco-pyranosiduronic acid, *N*-isopropylamide 14b

To a soln of amide **13**[11] (2.32 g, 5.9 mmol) in acetic acid (6 mL), 30% HBr in acetic acid (7 mL, 41.3 mmol) was added slowly and the soln was stirred overnight. Ice and water (80 mL) were added and the mixture was allowed to stand until a creamy precipitate formed, which was filtered and washed with cold water. The solid, which was collected was dissolved in EtOAc (40 mL) and stirred with $NaHCO_3$ (60 mL) for 1 h. The organic layer was then washed with water, dried ($MgSO_4$), filtered and solvent removed. Recrystallisation (EtOAc–cyclohexane) gave **14b** as a white solid (1.83 g, 73%); ^1H NMR (300 MHz, $CDCl_3$): δ 6.64 (d, 1H, $J_{1,2}$ 4.06, H-1), 6.06 (d, 1H, J_{CH-NH} 7.65, N*H*), 5.61 (t, 1H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.6, H-3), 5.21 (t, 1H, $J_{4,3}$ 9.6, H-4), 4.81 (dd, 1H, $J_{2,1}$ 4.06, $J_{2,3}$ 10.0, H-2), 4.43 (d, 1H, $J_{5,4}$ 10.3, H-5), 4.04 (m, 1H, C*H*$(CH_3)_2$), 2.11, 2.09, 2.05 (each s, each 3H, each $COCH_3$), 1.16 and 1.14 (2 × d, 6H, J_{CH,CH_3} 6.6, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.6, 169.5 (each s, each *C*OCH_3), 164.7 (s, *C*ONH), 84.6 (d, C-1), 72.0, 70.4, 69.3, 68.5 (each d, C-2–5), 41.3 (d, *C*H$(CH_3)_2$), 22.4, 22.3 (each q, each CH(*C*H_3)$_2$), 20.6, 20.5, 20.5 (each q, each $COCH_3$); HRESIMS: calcd for $C_{15}H_{22}O_8NBrNa$ 446.1, found m/z 446.0 $[M+Na]^+$.

1.6. 2,3,4-Tri-*O*-acetyl-1,6-anhydro-6-*Z*-phenylimino-β-D-glucopyranose 15a

To a soln of bromide **14a** (2.28 g, 4.96 mmol) in dry CH_2Cl_2, activated 4 Å molecular sieves, silver carbonate (3 g, 10.9 mmol) and silver perchlorate (0.1 g, 0.48 mmol) were added and the soln was allowed to stir overnight. The soln was filtered through Celite, dried ($MgSO_4$), filtered and the solvent was removed. Chromatography (4:1 cyclohexane–EtOAc) of the residue gave **15a** as a white solid (0.64 g, 35%); R_f 0.28 (2:1 cyclohexane–EtOAc); mp 129–130 °C; $[\alpha]_D$ +113 (c 0.39, CH_2Cl_2); IR (KBr) cm^{-1} 1746, 1354, 1217, 1183, 1041, 957, 787, 721, 523, 433; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (t, 2H, J 7.3, Ar H), 7.26 (d, 2H, J 7.3, Ar H), 7.16 (t, 1H, J 7.3, Ar H), 5.90 (s, 1H, H-1), 4.97 (m, 2H, H-3, H-4), 4.90 (t, 1H, $J_{2,3}$ 1.9, H-2), 4.76 (d, 1H, $J_{4,5}$ 1.2, H-5), 2.21, 2.19, 1.99 (each s, each 3H, each $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 169.2, 168.5 (each s, each *C*OCH_3), 151.8 (s, *C*ONPh), 144.4 (s, Ar C), 128.7, 125.2, 123.1 (each d), 101.6 (d, C-1), 73.7, 69.2, 67.5, 66.3 (each d, C-2–5), 20.8, 20.6, 20.5 (q, $COCH_3$); HRESIMS: calcd for $C_{18}H_{20}O_8N$ 378.1189, found m/z 378.1204 $[M+H]^+$. Anal. Calcd for $C_{18}H_{19}O_8N$: C, 57.29; H, 5.08; N, 3.71. Found: C, 57.13; H, 5.09; N, 3.65. Chromatography also gave 2,3,4-tri-*O*-acetyl-D-glucopyranuronic acid, phenylamide **16a** (1.22 g, 65%); R_f 0.14 (3:2 cyclohexane–EtOAc), mp 116–117.5 °C; $[\alpha]_D$ +55.7 (c 0.24, CH_2Cl_2); IR (KBr) cm^{-1} 3490 (OH), 3359 (NH), 1698, 1627, 1581, 1467, 1395, 1209, 1019, 751, 685; ^1H NMR (500 MHz, CD_3OD, α-anomer): δ 7.42 (d, 2H, J 7.5, Ar H), 7.31 (t, 2H, J 7.5, Ar H), 7.13 (t, 1H, J 7.5, Ar H), 5.64 (t, 1H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.8, H-3), 5.55 (d, 1H, $J_{1,2}$ 3.5, H-1), 5.17 (t, 1H, $J_{4,3}$ 9.8, H-4), 4.87 (dd, 1H, $J_{2,1}$3.5, $J_{2,3}$10.0, H-2), 4.54 (d, 1H, $J_{5,4}$ 10.1, H-5), 2.08, 2.07, 2.07, (each s, each 3H, each $COCH_3$); ^{13}C NMR (125 MHz, CD_3OD): δ 172.5, 171.9, 169.3 (each s, each *C*OCH_3), 139.6 (s, *C*ONH), 130.7 (s, Ar C), 126.8, 122.9, 120.7 (each d, Ar C), 92.3 (d, C-1), 73.4, 72.6, 71.9, 71.4 (each d, C-2–5), 21.5, 21.4 (overlapping signals, each q, each $COCH_3$); HRESIMS: calcd for $C_{18}H_{20}O_9N$ 394.1165, found m/z 394.1153 $[M-H]^-$.

1.7. 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] All 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 to which the H-atom is attached.

1.8. Crystal data and structure refinement for 15a

Molecular formula, $C_{18}H_{19}NO_8$; $M = 377.34$. Temperature, 100(2) K. Wavelength, 0.71073 Å. Crystal system, triclinic. Space group, $P\bar{1}$ (#1). Unit cell dimensions, $a = 7.390(3)$ Å, $\alpha = 89.454(6)°$; $b = 8.596(3)$ Å, $\beta = 77.219(6)°$; $c = 14.777(6)$ Å, $\gamma = 78.456(6)°$. Volume, 896.4(6) Å^3. Z, 2. Density (calculated), 1.398 Mg/m^3. Absorption coefficient, 0.111 mm^{-1}. $F(000)$, 396. Crystal size, $0.80 \times 0.30 \times 0.20$ mm^3. Theta range for data collection, 2.42–28.37°. Index ranges, $-9 \leqslant h \leqslant 9$, $-11 \leqslant k \leqslant 11$, $-19 \leqslant l \leqslant 19$. Reflections collected, 15,186. Independent reflections, 8082 [R(int) = 0.0168]. Completeness to theta = 26.00°, 99.8%. Absorption correction, semi-empirical from equivalents. Max. and min. transmission, 0.9781 and 0.8513. Refinement method, full-matrix least-squares on F^2. Data/restraints/parameters, 8082/3/493. Goodness-of-fit on F^2, 1.022. Final R indices [$I > 2\sigma(I)$], $R1 = 0.0378$, $wR2 = 0.0936$. R indices (all data), $R1 = 0.0392$, $wR2 = 0.0947$. Absolute structure parameter, 0.0(5). Largest diff. peak and hole, 0.387 and −0.191 e Å^{-3}.

1.9. 2,3,4-Tri-*O*-acetyl-1,6-anhydro-6-isopropylimino-β-D-glucopyranose 15b

To a soln of bromide **14b** (0.27 g, 0.64 mmol) in dry CH_2Cl_2, activated 4 Å molecular sieves, silver carbonate (0.39 g, 1.4 mmol) and silver perchlorate (0.013 g, 0.063 mmol) were added and the mixture was stirred overnight. The soln was then filtered through a layer of Celite and dried ($MgSO_4$), filtered and the solvent removed under diminished pressure. Flash chromatography (8:1 CH_2Cl_2–EtOAc) of the residue gave **15b** as a white solid (75 mg, 35%); R_f 0.36 (8:1 CH_2Cl_2–EtOAc); $[\alpha]_D$ +89.7 (c 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (m, 1H, H-1), 4.90 (m, 1H, H-3), 4.84 (m, 1H, H-4), 4.69 (m, 1H, H-2), 4.64 (m, 1H, H-5), 3.90 (m, 1H, C*H*$(CH_3)_2$), 2.18, 2.17, 2.08 (each s, each 3H, each COC*H*$_3$), 1.17 and 1.15 (2 × d, 6H, J_{CH,CH_3} 6.4, CH(C*H*$_3)_2$); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.4, 169.1, 168.5 (each s, each *C*OCH$_3$), 150.5 (s, *C*ON), 100.5 (d, C-1), 72.9, 69.5, 67.8, 66.9 (each d, C-2–5), 48.4 (d, *C*H$(CH_3)_2$), 23.3, 23.2 (each q, each CH(*C*H$_3)_2$), 21.0 (q, CO*C*H$_3$), 20.8, 20.7 (each q, each CO*C*H$_3$); HRESIMS: calcd for $C_{15}H_{22}O_8N$ 344.1345, found m/z 344.1352 [M+H]$^+$.

1.10. Phenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosiduronic acid, *N*-phenylamide 17

Imidate **15a** (0.082 g, 0.22 mmol) was dissolved in anhyd CH_2Cl_2, and $SnCl_4$ (0.014 mL, 0.12 mmol) and TMSOPh (0.1 mL, 0.55 mmol) were added and the mixture was stirred at room temp for 1 h. CH_2Cl_2 was added and the mixture was then stirred in the presence of satd aq $NaHCO_3$ (20 mL) and then water (20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed. Chromatography (1:10 cyclohexane–EtOAc) of the residue gave the title compound as a colourless oil (25 mg, 22%); R_f 0.39 (3:2 cyclohexane–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, N*H*), 7.90–7.00 (m, 10H, Ar H), 5.50–5.10 (m, 4H, H-1–4), 4.28 (d, 1H, $J_{4,5}$ 9.4, H-5), 2.19, 2.18, 2.12 (each s, each 3H, each COC*H*$_3$); HRESIMS: calcd for $C_{24}H_{24}O_9N$ 470.1451, found m/z 470.1444 [M−H]$^-$. The title compound was dissolved in MeOH (5 mL), and a 1 M NaOMe soln in MeOH was then added dropwise. The soln was stirred with Amberlite IR-120, filtered and the solvent removed under diminished pressure to give phenyl β-D-glucopyranosiduronic acid, *N*-phenylamide; R_f 0.4 (30:1 EtOAc–MeOH); $[\alpha]_D$ −204 (c 0.24, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD): δ 7.59 (dd, 2H, J 1.2, J 8.8, Ar H), 7.30–6.99 (m, 8H, Ar H), 5.01 (d, 1H, $J_{1,2}$ 7.5, H-1), 4.02 (d, 1H, $J_{5,4}$ 9.5, H-5), 3.73 (t, 1H, $J_{4,3} = J_{4,5} = 9.5$, H-4), 3.61–3.5 (m, 2H, H-2, H-3); ^{13}C NMR (125 MHz, CD_3OD): δ 167.9 (s, *C*ONH), 157.6, 137.8 (each s, each Ar C), 129.2, 128.5, 124.4, 122.5, 120.3, 116.8 (each Ar C), 101.4 (d, C-1), 76.3, 76.2, 73.2, 71.7 (each d, C-2–5); HRESIMS: calcd for $C_{18}H_{18}O_6N$ 344.1134, found m/z 344.1141 [M−H]$^-$.

1.11. Phenyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranuronic acid, *N*-phenylamide 18

An analytical sample of **18** was prepared from phenyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid.[5] Thus, to an ice-cold soln of phenyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid (0.135 g, 0.34 mmol) in freshly distilled CH_2Cl_2 (5 mL), oxalyl chloride (0.03 mL, 0.34 mmol) and DMF (0.05 mL) were added. The soln was stirred for 30 min at 0 °C and for 1 h at room temp. In a separate flask, a suspension of aniline (0.031 mL, 0.34 mmol) and anhyd pyridine (0.028 mL, 0.34 mmol) in CH_2Cl_2 (1 mL) was stirred in the presence of 4 Å molecular sieves. The acid chloride soln was cooled to 0 °C again and the amine suspension was slowly poured into it. The mixture was stirred for 30 min at 0 °C and for a further 1.5 h at room temp, then it was transferred into a separatory funnel where it was washed with satd aq $NaHCO_3$ (7 mL). The

organic layer was washed with dilute HCl (0.1 M, 7 mL), dried (Na_2SO_4) and filtered. Removal of the solvent and chromatography (1:2 EtOAc–cyclohexane) of the residue gave **18** as a white solid (0.13 g, 86%); R_f 0.31 (0.5:12 EtOAc–CH_2Cl_2); mp 188–189 °C; $[\alpha]_D$ +65.5 (*c* 3.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (br s, 1H, N*H*), 7.46–7.03 (m, 10H, Ar H), 5.93 (d, 1H, $J_{1,2}$ 3.7, H-1), 5.83 (t, 1H, $J_{3,4}$ 9.5, $J_{3,2}$ 10.1, H-3), 5.31 (dd, 1H, $J_{4,5}$ 10.3, $J_{4,3}$ 9.5, H-4), 5.02 (dd, 1H, $J_{2,1}$ 3.7, $J_{2,3}$ 10.1, H-2), 4.47 (d, 1H, $J_{5,4}$ 10.3, H-5), 2.10, 2.08, 2.07 (each s, each 3H, each COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.8, 169.7 (each s, each *C*OCH3), 164.6 (s, *C*ONH), 155.7, 136.5 (each s, each Ar C), 129.8, 128.9, 124.9, 123.5, 120.3, 116.6 (overlapping signals, each s, each Ar C), 94.1 (d, C-1), 70.4, 69.6, 69.2, 69.1 (each d, C-2–5), 20.8, 20.7, 20.6 (each q, each CO*C*H$_3$); HRESIMS: calcd for $C_{24}H_{24}O_9N$ 470.1451, found *m*/*z* 470.1474 $[M-H]^-$. Anal. Calcd for $C_{24}H_{25}O_9N$: C, 61.1; H, 5.34; N, 2.97. Found: C, 60.84; H, 5.49; N, 2.82.

1.12. Phenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosiduronic acid, *N*-isopropylamide 21

Imidate **15b** (36 mg, 0.1 mmol) was dissolved in anhyd CH_2Cl_2, and $SnCl_4$ (6 μL, 0.05 mmol) and TMSOPh (0.048 mL, 0.25 mmol) were added and the mixture was stirred at room temp for 5 h. CH_2Cl_2 was added and the mixture then stirred in the presence of satd aq $NaHCO_3$ (20 mL) and then water (20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under diminished pressure and column chromatography (2.5:1 cyclohexane–EtOAc) of the residue gave the title compound as a colourless oil (20 mg, 40%); R_f 0.29 (1:1 cyclohexane–EtOAc); $[\alpha]_D$ −21.6 (*c* 0.185, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (t, 2H, *J* 7.5, Ar H), 7.05 (t, 1H, Ar H), 7.03 (d, 2H, Ar H), 6.17 (d, 1H, J_{CH-NH} 7.5, N*H*), 5.42 (t, 1H, $J_{3,2}$ 8.8, $J_{3,4}$ 9.1, H-3), 5.33 (t, 1H, $J_{1,2}$ 7.5, $J_{2,3}$ 8.8, H-2), 5.27 (t, 1H, $J_{4,3}$ 9.1, H-4), 5.23 (d, 1H, $J_{1,2}$ 7.5, H-1), 4.08 (d, 1H, $J_{5,4}$ 9.7, H-5), 4.04 (m, 1H, C*H*(CH$_3$)$_2$), 2.15, 2.13, 2.11 (each s, each 3H, each COC*H*$_3$), 1.17 (d, 6H, $J_{CH(CH_3)_2}$ 6.6, $J_{CH_3-CH_3}$ 4.0, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 169.7, 169.4 (each s, each *C*OCH$_3$), 165.4 (s, *C*ONH), 156.6 (s, Ar C), 129.8, 123.7, 116.8 (each s, each Ar C), 98.8 (d, C-1), 72.8, 71.8, 71.2, 69.4 (each d, C-2–5), 41.3 (d, *C*H(CH$_3$)$_2$), 22.4, 22.3 (each q, each CH(*C*H$_3$)$_2$), 20.7, 20.6, 20.5 (each q, each CO*C*H$_3$); HRESIMS: calcd for $C_{21}H_{28}O_9N$ 438.1764, found *m*/*z* 438.1780 $[M+H]^+$.

1.13. Cyclohexyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid, *N*-isopropylamide 22

Imidate **15b** (35 mg, 0.1 mmol) was dissolved in anhyd CH_2Cl_2, and $SnCl_4$ (5.9 μL, 0.05 mmol) and then TMSOCy (40 μL, 0.25 mmol) were added and the mixture was stirred at room temp for 25 h. CH_2Cl_2 was then added and the mixture stirred in the presence of satd aq $NaHCO_3$ (20 mL) and then water (20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed and chromatography (2:1 cyclohexane–EtOAc) of the residue gave the title compound as a colourless syrup (15 mg, 40%); R_f 0.2 (1:1 cyclohexane–EtOAc); $[\alpha]_D$ +56.8 (*c* 0.185, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (d, 1H, $J_{CH,NH}$ 8.2, N*H*), 5.57 (t, 1H, $J_{3,4}$ 9.8, H-3), 5.29 (d, 1H, $J_{1,2}$ 3.7, H-1), 5.04 (t, 1H, $J_{4,3}$ 9.8, H-4), 4.76 (dd, 1H, $J_{2,3}$ 10.0, $J_{2,1}$ 3.7, H-2), 4.24 (d, 1H, $J_{5,4}$ 10.0, H-5), 4.01 (m, 1H, C*H*(CH$_3$)$_2$), 3.98 (m, 1H, C_5H_{10}C*H*O, OCy), 2.08, 2.06, 2.02 (each s, each 3H, each COC*H*$_3$), 1.78 and 1.28 (each m, 10H, cyclohexyl protons), 1.16 and 1.14 (2 × d, 6H, $J_{CH,(CH_3)}$ 6.4, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.9, 169.8 (each s, each *C*OCH$_3$), 166.7 (s, *C*ONH), 93.7 (d, C-1), 76.8 (d, cyclohexyl *C*H), 71.2, 70.2, 69.4, 68.4 (each d, C-2–5), 41.1 (d, *C*H(CH$_3$)$_2$), 33.1, 31.2, 25.4 (each t, cyclohexyl CH$_2$), 22.5, 22.5 (each q, each CH(*C*H$_3$)$_2$), 20.8, 20.7, 20.6 (each q, each *C*H$_3$); HRESIMS: calcd for $C_{21}H_{34}O_9N$ 444.2234, found *m*/*z* 444.2234 $[M+H]^+$.

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Supplementary data

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