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Synthesis of the Key Saccharide Fragments of the Glucuronic Acid-Containing Repeat Unit of Pentosan Polysulfate, a Heparin Sulfate Mimetic

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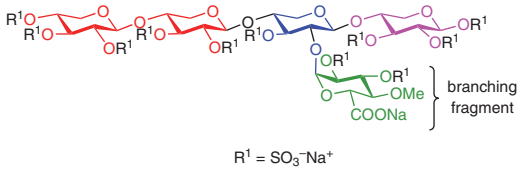

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Abstract Suitably protected mono- and di-saccharide residues associated with the glucuronic acid-containing repeat unit related to pentosan polysulfate have been prepared. The stereo-controlled coupling, using trichloroacetimidate chemistry, of certain of these is also described and the structure of a disaccharide so-formed has been confirmed by single-crystal X-ray analysis.

Key Words heparanase, mimetic, pentosan polysulfate (PPS), trichloroacetimidate, xylose

Heparan sulfates (HSs) are glycosaminoglycan polysaccharides and represent fundamental components of the extracellular matrix (ECM) and the cell surface glycocalyx. They play, as their conjugates with core proteins, pivotal roles in cell–cell interactions, cellular differentiation, cell proliferation and cell migration.[1] The endoglycosidase heparanase-1 (HSPE-1, EC 3.2.1.166)[2,3] acts on HSs so as to cleave them and thus facilitating the degradation and remodelling of the ECM. Since the overexpression of this enzyme is observed in tumours and is also associated with various other pathological conditions (notably inflammatory ones), inhibitors of it are of great interest. Mimetics of the natural substrates (viz. the HSs) are obvious starting points for the design and assembly of HPSE inhibitors (as well for creating probes for defining structure–activity relationships), but the structural complexities of the HSs means that such an approach presents significant synthetic challenges. These are being addressed, with some notable success, in a range of different ways, including by using both chemical and chemoenzymatic techniques.[4,5]

Pentosan polysulfate (PPS), also known as sodium pentosan polysulfate or NaPPS,[6] and marketed under the brand name ELMIRON®,[7] is a synthetically derived, heparin-like compound (or mimetic) that is deployed clinically for alleviating the pain associated with interstitial cystitis (bladder pain) as well as being used to treat osteoarthritis in dogs and horses. Furthermore, it has been shown to inhibit heparin-binding growth factors (HBGFs) released from tumour cells and so blocking the proliferation of these in animal models.[8]

The preparation of PPS starts with the isolation, from beech tree bark, of the hemi-cellulose-type polysaccharide xylan, which is largely comprised of xylose residues. Sulfation, oxidative deploymerization, salt-forming and membrane-based nano-filtration steps then follow and so delivering a heterogeneous product within the 3,000 to 10,000 amu range.[9] The associated backbones of the constituent xylo-oligosaccharides are of varying length and some, but not all, bear a branching glucuronic acid unit. To a first approximation, then, the smallest repeating unit associated with these constituents could be considered to be the pentasaccharide **1** (Figure 1), bearing eleven sodium sulfate residues with two of these being 'capping groups' attached to a hydroxyl group at each end of the tetraxylose backbone.[10]

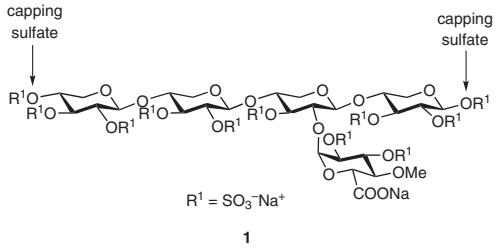


Figure 1 The structure, **1**, of the smallest repeat unit of PPS containing a glucuronic acid residue

Our ongoing interest[10,11] in developing chemical techniques for the preparation of HS mimetics and related species for probing the mechanisms of actions of HPSE, and so thereby developing new therapeutic agents for treating a range of disease states, prompted us to consider methods for the chemical synthesis of compound **1** and related systems. In so doing, we anticipated that this target could be attained by preparing (and then coupling) the suitably activated forms, **2**–**5** (Figure 2), of the component disaccharide, keystone, branching and capping fragments, respectively, of target **1**.[12]

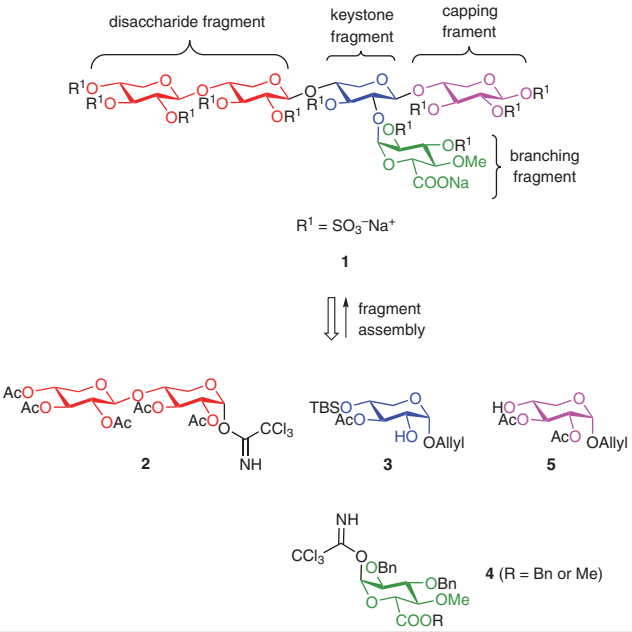
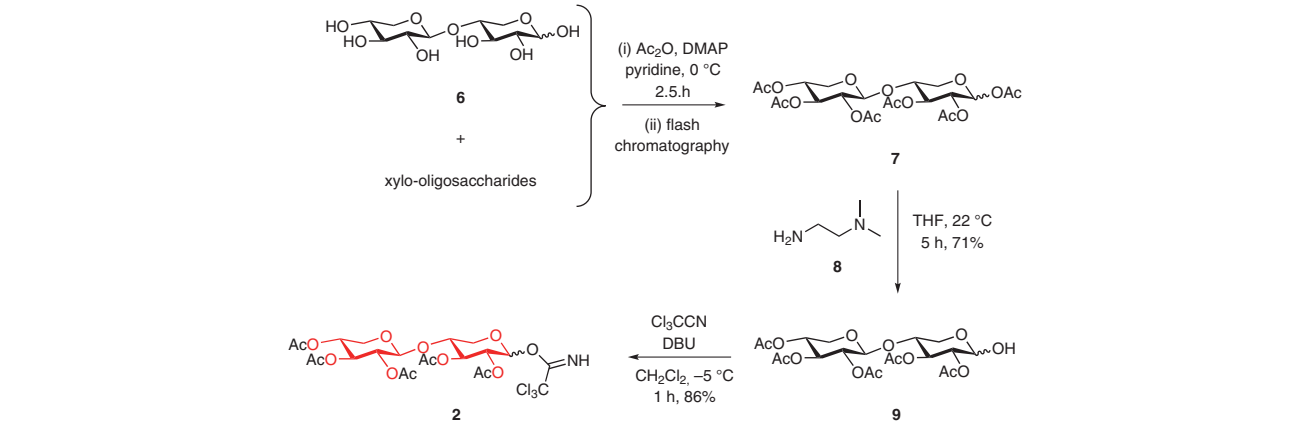


Figure 2 The carbohydrates **2**–**5** sought as possible precursors to the target pentasaccharide **1**

A key consideration in defining the activating functionalities associated with fragments **2**–**5** was the need to establish β-configured anomeric linkages between the backbone xylose residues and an α-configured one between the keystone xylose residue (**3**) and the appended/branching glucuronic acid residue (**4**). Amongst the various methods available for effecting glycosylations, the trichloroacetimidate method developed by Schmidt[13] appeared the most attractive in the present setting because of its mildness and the predictable stereochemical outcomes that can be realized depending upon the precise conditions used.

The initial focus of our efforts was on the preparation of fragment **2** by the route shown in Scheme 1. To that end a commercial sample of the xylo-oligosaccharide mixture derived from corn cobs was purchased and, on subjecting this to low-resolution electrospray ionization (positive mode) mass spectrometry, this material was confirmed to contain xylobiose (**6**) as an admixture with its tri- and tetra-meric counterparts. Accordingly, this mixture was subject to exhaustive acetylation under standard conditions and the desired per-acetylated product **7** was readily separated, by flash chromatography, from the corresponding and accompanying derivatives of the higher-order oligomers. By such means, compound **7**[10] was obtained as a near 1:1 mixture of α- and β-anomers and in 42% yield (on a w/w basis from the original xylo-oligosaccharide mixture). The anomeric acetyl group associated with compound **7** could be selectively cleaved on exposure of it to 3-(dimethylamino)-1-propylamine (**8**) in THF at 22 °C for 5 h and so affording compound **9**[10] in 71% yield as a ca. 3:1 mixture of α- and β-anomers. Finally, treatment of a dichloromethane solution of pentaacetate **9** with trichloroacetonitrile in the presence of 1,8-diazabicylo[5.4.0]undec-7-ene (DBU) at −5 °C afforded the targeted and previously reported[10] trichloroacetimidate **2** in 86% yield. As determined using standard NMR spectroscopic techniques, the α-anomeric form of compound **2** predominated.

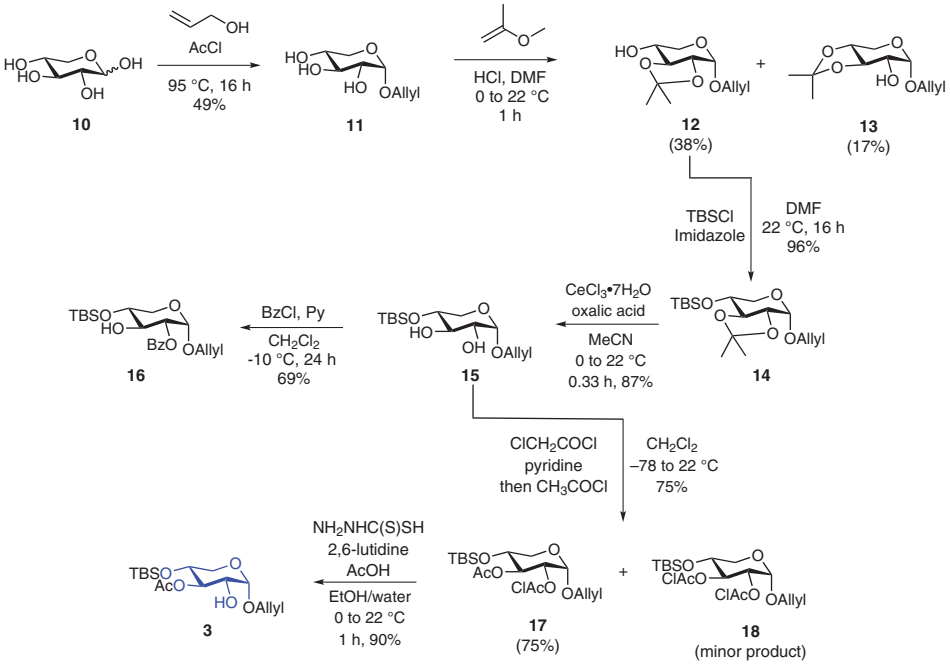


Scheme 1 Synthesis of the xylobiose-derived trichloroacetimidate **2**

The synthesis of the previously unreported keystone fragment **3** was achieved by the route shown in Scheme 2. So, in the opening step, and by following an established procedure,[14] D-xylose (**10**) was treated with allyl alcohol in the presence of acetyl chloride and so affording ether **11**[14] as a ca. 6:1 mixture of α- and β-anomers in 49% combined yield. Fractional recrystallization of this mixture from ethanol afforded a nearly pure sample of the α-anomer and so facilitating spectral analysis. On reacting a DMF solution of compound **11** with 2-methoxypropene in the presence of a trace of HCl over the temperature range 0 to 22 °C then a chromatographically separable mixture of the isomeric, previously unreported ketals **12** (38%) and **13** (17%) was obtained. HMBC and ^{1}H–^{1}H COSY experiments were carried out (necessarily in C_6D_6 rather than $CDCl_3$ due to their high acid sensitivities) to differentiate between these regioisomeric products and key outcomes are shown in the Supporting Information. Protection of the single free hydroxyl group within compound **12** as the corresponding TBS ether was achieved under standard conditions and so affording compound **14** in 96% yield. Cleavage of the ketal residue associated with this last compound proved less straightforward and after examining a range of conditions, the most favourable outcome was achieved by briefly treating substrate **14** with oxalic acid and cerium trichloride heptahydrate in acetonitrile.[15] By such means, the required diol **15** was obtained in 87% yield.

Efforts to selectively protect the C3-hydroxyl group within compound **15** proved challenging, as evidenced by the preferential C2-benzoylation of this substrate under standard conditions and so affording ester **16** in 69% yield. This outcome is consistent with that reported by Kondo[16] for the highly selective C2-tosylation of methyl α-xylopyranoside. Ultimately, it was found that by treating a dichloromethane solution of compound **15** and pyridine maintained at –78 °C with ca. one equivalent of α-chloroacetyl chloride followed by two equivalents of acetyl chloride then the mixed di-ester **17** could be formed in 75% yield. Co-production of the bis-α-chloroacetate **18** was essentially avoided under the optimized reaction conditions eventually established for the conversion of **15** into **17**. Interestingly, single-crystal X-ray analysis of a crystalline product sample obtained from an unoptimized esterification revealed, as shown in Figure 1 of the Supporting Information, that a solid comprised of an 85:15 mixture of compounds **17** and **18** was formed in one instance.

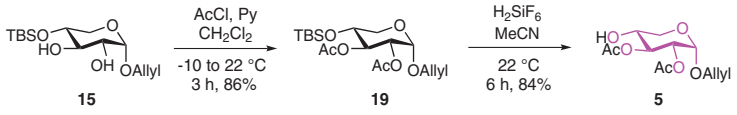
A range of conditions was then explored so as to affect the selective cleavage of the α-chloroacetate residue within compound **17**, and the most efficient means for doing so was achieved by treating this substrate with a combination of hydrazine dithiocarbonate (HDTC), 2,6-lutidine and acetic acid in ethanol/water[17] and so finally providing the target xylose derivative **3** as a single diastereoisomer in 90% yield. A series of HMBC and ^{1}H–^{1}H COSY NMR experiments (see the Supporting Information, Figure 3) provided support for the assigned structure of compound **3** but definitive confirmation of this came from a single-crystal X-ray analysis of a derivative (see below).



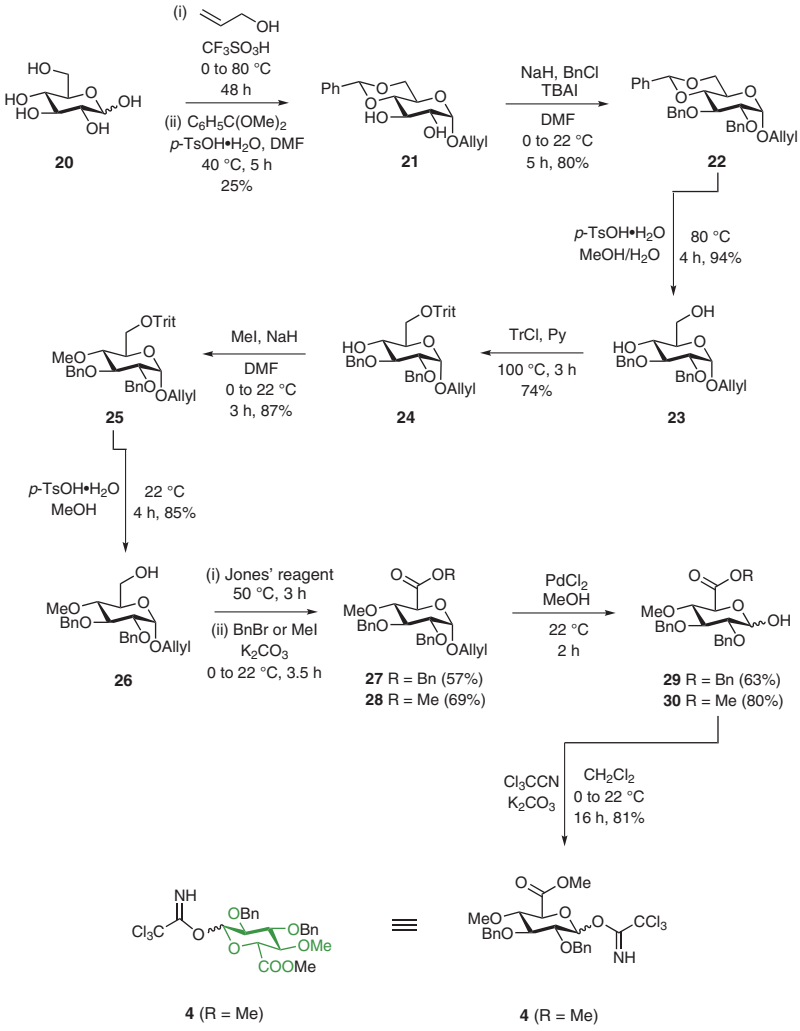
Scheme 2 Synthesis of xylose derivative **3**

The synthesis of the target 'capping' fragment **5** was very straightforward and simply involved, as shown in Scheme 3, converting diol **15** into the corresponding diacetate **19** (86%) under standard conditions and then treating the latter compound with aqueous fluorosilicic acid in acetonitrile (so as to affect cleavage of the TBS-ether). By such means compound **5** was obtained in 84% yield.

The synthesis of the glucuronic acid fragment **4** (R = Bn or Me) was more involved, with the ultimately successful route to this being shown in Scheme 4 and inspired by the work of Kosma *et al.*[18] To begin, D-glucose (**20**) was treated sequentially with allyl alcohol in the presence of triflic acid and then with benzaldehyde dimethyl acetal and *p*-toluenesulfonic acid monohydrate in DMF at 40 °C. As a result, the benzylidene acetal **21** was obtained in 25% yield and as a ca. 7:1 mixture of α- and β-anomers after chromatographic purification. Bis-*O*-benzylation of diol **21** under standard conditions then provided the fully protected glucose derivative **22** in 80% yield and again as a ca. 7:1 mixture of anomers. Hydrolytic cleavage of the benzylidene acetal residue associated with this last compound was achieved under standard conditions and so affording the new diol **23** (94%)



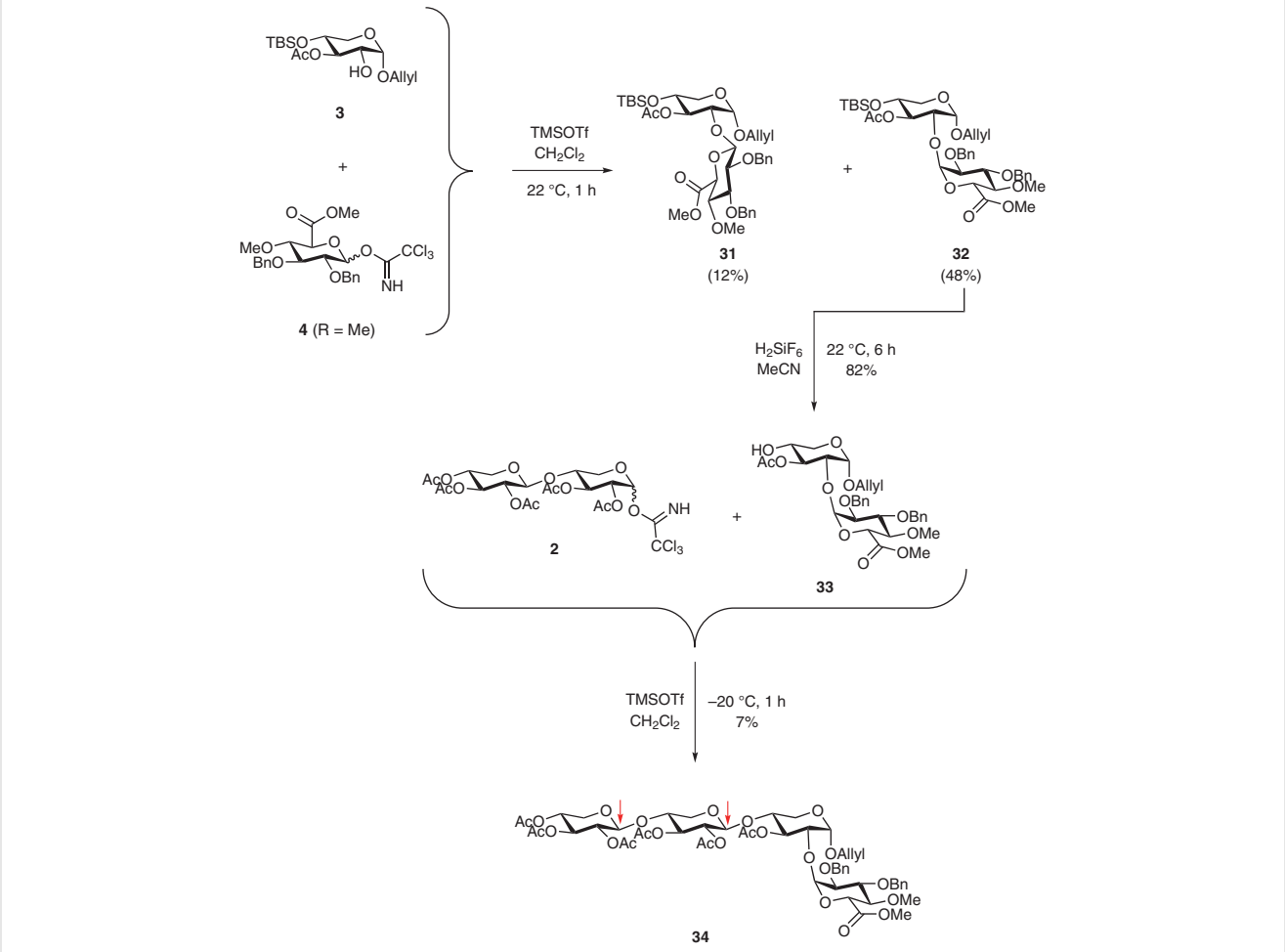
Scheme 3 Synthesis of xylose **5**



Scheme 4 Synthesis of glucuronic acid derivative **4** (R = Me)

and the 1°-hydroxyl group of which was selectively protected, again under standard conditions, as the corresponding trityl ether **24** (74%). *O*-Methylation of the single free hydroxyl group within compound **24** was affected using methyl iodide and sodium hydride and so delivering the anticipated product **25** (87%) as a ca. 7:1 mixture of α- and β-anomers. The trityl group associated with per-ether **25** was then selectively cleaved using *p*-toluenesulfonic acid monohydrate in methanol and the 1°-alcohol so revealed, oxidized to the corresponding carboxylic acid using Jones' reagent. This acid was then reacted, without purification, with either benzyl bromide or methyl iodide in the presence of potassium carbonate to afford the corresponding ester **27** (57%) or **28** (69%), respectively. Selective cleavage of the allyl protecting group at the anomeric centre within compound **27** proved challenging. When this ester was treated, as defined by Ogawa *et al.*,[18,19] with 3.7 mole equivalents of $PdCl_2$ in the presence of aqueous acetic acid and sodium acetate, then target alcohol **29** was only obtained in ca. 35% yield and accompanied by a range of difficult-to-separate impurities. By drastically reducing the amount of $PdCl_2$ used (to 0.2 equiv) as well as employing methanol as solvent, then compound **29** could be obtained in 63% yield.

While all the spectral data acquired on this product matched those recorded in the literature,[18] it was contaminated with varying quantities of the corresponding methyl ester **30** that arises through a transesterification reaction. In an attempt to circumvent this process, the deprotection reaction was run using benzyl alcohol as solvent, but little of the target product **29** was formed even after using extended reaction times and elevated temperatures. Furthermore, it proved very difficult to separate compound **29** from residual benzyl alcohol. The deprotection of compound **28** proved much more straightforward, and product **30** was obtained in 80% yield under the best of the conditions defined above. Finally, treatment of compound **30** with trichloracetonitrile, in the presence of potassium carbonate,[20] afforded the targeted trichloroacetimidate **4** (R = Me) in 81% yield and as a ca. 1:3 mixture of α- and β-anomers. All of the spectra data acquired on this compound

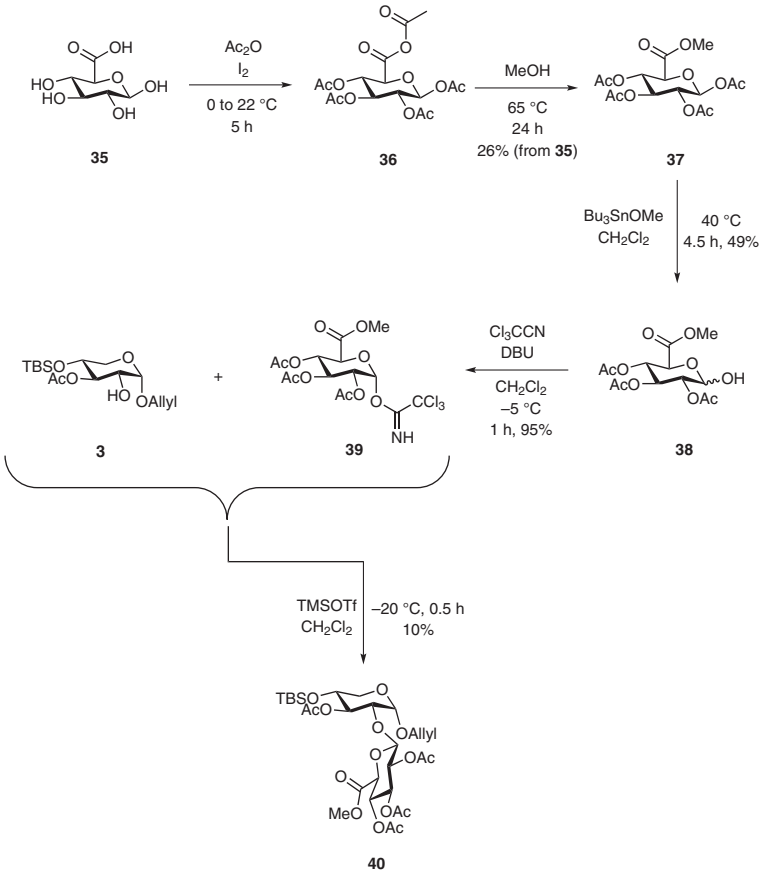


Scheme 5 Synthesis of coupling product **34**

were in accord with the assigned structure, with the ^{1}H NMR spectrum of the latter (predominant) anomer including a doublet at δ = 5.85 ppm that is assigned to H-1 and with the associated vicinal coupling to H-2 of 7.3 Hz being indicative of the α-configuration of the oxymethine hydrogen at C-1. In the α-anomer the analogous signal appeared as a doublet at δ = 6.43 ppm and the coupling constant was 3.5 Hz.

With the targeted building blocks **2**, **3**, **4** (R = Me) and **5** to hand, an initial study of their capacities to serve as coupling partners was undertaken. To such ends, and as shown in Scheme 5, a TMSOTf-mediated glycosylation reaction[13] was carried out at ambient temperatures using acceptor **3** and donor **4** and by such means a chromatographically separable mixture of the diastereoisomeric adducts **31** (12%) and **32** (48%) was obtained. While ESI mass spectrometric analyses of these compounds served to identify them as coupling products, their ^{1}H and HMBC NMR spectroscopic features, details of which are provided in the Supporting Information (Figure 5), allowed for the determination of the illustrated stereochemistries about the newly established glycosidic bonds. Treatment of disaccharide **32** with H_2SiF_6 in acetonitrile at ambient temperature[21] affected a smooth desilylation reaction and so delivering the alcohol **33** (82%) that was now coupled, at –20 °C, with an excess of donor **2** in the presence of TMSOTf. This conversion proved messy and extensive chromatographic operations were required to obtain the target product **34** in pure form and then only in 7% yield. Once again, ^{1}H and HMBC NMR spectroscopic experiments, as detailed in the Supporting Information (Figure 6), served to establish the illustrated stereochemical features, most particularly the β-configurations at highlighted anomeric centres (see red arrows) and α-configurations at the remaining two, including the one associated with the glucuronic acid residue.

In a complementary study allowing for the synthesis of a coupling product incorporating a β-configured glucoronic acid residue, commercially available glucuronic acid **35** (Scheme 6) was peracetylated using acetic anhydride and molecular iodine and so affording anhydride **36**[22] that, upon reaction with methanol, afforded methyl ester **37**[23] (26% from free acid). On reacting this last compound with a slight excess of tri-*n*-butyltin methoxide then hydrolysis took place at the anomeric centre to afford compound **38**[24] (49%) which was obtained as a ca. 5:1 mixture of α- and β-anomers. Treating a dichloromethane solution of acetal **38** with



Scheme 6 The stereocontrolled synthesis of the glycosylated xylose **40**

trichloroacetonitrile in the presence of DBU at –5 °C then gave trichloroacetimidate **39**[25] which was obtained in 95% yield and exclusively in the α-anomeric form. The reaction of this last compound with the keystone building block **3** in the presence of TMSOTf at –20 °C afforded, after extensive chromatographic purification of a complex product mixture, the crystalline coupling product **40**, albeit it in just 7% yield. The anticipated β-configured stereochemistry at the anomeric centre of the gluconic acid residue was evident from the derived NMR spectral data and confirmed by single-crystal X-ray analysis (see the Supporting Information).

The studies detailed here provide a means for assembling the key components of PPS so, when considered in conjunction with our recently developed methods for the *O*-sulfation of oligosaccharides,[10] the stereocontrolled synthesis of compound **1** and various of its congeners now seems possible. Work directed toward such ends is underway in our laboratories and results will be reported in due course.

Allyl 2,3-*O*-Isopropylidene-α-D-xylopyranoside (12) and Allyl 3,4-*O*-Isopropylidene-α-D-xylopyranoside (13)

Following a modification of a procedure reported by Stick *et al.*,[26] a magnetically stirred solution of allyl α-D-xylopyranoside (**11**)[14] (954 mg, 5.02 mmol) in DMF (8.0 mL) was treated with HCl in dioxane (40 µL of a 4 M aq. solution, 0.16 mmol). The ensuing mixture was cooled to –10 °C then treated with 2-methoxypropene (1.30 mL, 13.6 mmol) and stirring continued for 1 h. Thereafter, the cooling bath was removed and the reaction mixture stirred for a further 2 h at 22 °C before being diluted with water (10 mL) and extracted with chloroform (3 × 10 mL). The combined organic layers were washed sequentially with $NaHCO_3$ (5 mL of a sat. aq. solution) and brine (5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the residue thus obtained to flash column chromatography (silica, 40:1 v/v dichloromethane/methanol elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.2 in 20:1 v/v dichloromethane/methanol) afforded compound **12** (440 mg, 38%) as a white, crystalline solid.

Mp 73–75 °C; $[\alpha]_D$ +126 (*c* = 0.80, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ = 5.72 (m, 1 H), 5.23 (app. dq, *J* = 17.2, 1.7 Hz, 1 H), 5.03 (d, *J* = 3.0 Hz, 1 H), 4.99 (app dq, *J* = 10.5, 1.7 Hz, 1 H), 4.16 (app. t, *J* = 9.4 Hz, 1 H), 4.01 (m, 1 H), 3.86–3.74 (complex m, 2 H), 3.66 (dd, *J* = 11.2, 5.5 Hz, 1 H), 3.52–3.34 (complex m, 2 H), 2.40 (br s, 1 H), 1.42 (s, 3 H), 1.38 (s, 3 H).

^{13}C NMR (101 MHz, C_6D_6): δ = 134.3, 116.8, 110.5, 96.5, 77.9, 76.5, 70.6, 68.6, 63.2, 27.2, 26.7.

IR: 3437, 2986, 2934, 1372, 1225, 1103 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{18}O_5$·Na: 253.1052; found: 253.1046.

Concentration of fraction B (R_f = 0.4 in 20:1 v/v dichloromethane/methanol) afforded compound **13** (197 mg, 17%) as a clear, colourless oil.

$[\alpha]_D$ +57 (*c* = 0.40, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ = 5.65 (m, 1 H), 5.10 (app dq, *J* = 16.8, 1.5 Hz, 1 H), 4.97 (app. dq, *J* = 10.4, 1.5 Hz, 1 H), 4.76 (d, *J* = 2.8 Hz, 1 H), 3.94 (m, 1 H), 3.85–3.78 (complex m, 2 H), 3.76 (dd, *J* = 9.6, 4.6 Hz, 1 H), 3.70 (m, 1 H), 3.63 (app. t, *J* = 10.1 Hz, 1 H), 3.33 (m, 1 H), 2.52 (d, *J* = 7.5 Hz, 1 H), 1.39 (s, 3 H), 1.38 (s, 3 H).

^{13}C NMR (101 MHz, C_6D_6): δ = 134.3, 117.4, 110.5, 98.5, 80.0, 74.4, 72.5, 68.8, 61.8, 27.1, 26.7.

IR: 3459, 2986, 1372, 1228, 1022 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{18}O_5$·Na: 253.1052; found: 253.1053.

Allyl 2,3-*O*-Isopropylidene-4-*O*-*tert*-butyl-dimethylsilyl-α-D-xylopyranoside (14)

A magnetically stirred solution of alcohol **12** (240 mg, 1.04 mmol) in DMF (1.0 mL) was treated with imidazole (153 mg, 2.24 mmol) then cooled to 0 °C (ice-bath) before TBS-Cl (279 mg, 1.85 mmol) was added. Thereafter, the cooling bath was removed and the reaction mixture was stirred at 22 °C for 16 h then diluted with $NaHCO_3$ (3 mL of a sat. aq. solution) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (10 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residual oil was subjected to flash column chromatography (silica, 25:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.2) compound **14** (344 mg, 96%) as a clear, colourless oil.

$[\alpha]_D$+100 (*c* = 0.81, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94 (m, 1 H), 5.33 (app. dq, *J* = 17.2, 1.7 Hz, 1 H), 5.19 (app. dq, *J* = 10.6, 1.7 Hz, 1 H), 5.09 (d, *J* = 3.0 Hz, 1 H), 4.22 (app. ddt, *J* = 13.1, 5.2, 1.6 Hz, 1 H), 4.07 (app. ddt, *J* = 13.1, 5.8, 1.6 Hz, 1 H), 3.96–3.84 (complex m, 2 H), 3.65–3.56 (complex m, 1 H), 3.43–3.27 (complex m, 2 H), 1.44 (s, 3 H), 1.41 (s, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.0, 117.3, 110.1, 96.2, 77.3, 75.9, 71.2, 68.8, 63.6, 27.1, 26.5, 25.9, 18.3, –4.5, –4.8.

IR: 2931, 2858, 1094, 1022, 935, 778 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{32}O_5Si$·H: 345.2092; found: 345.2091.

Allyl 4-*O*-*tert*-Butyldimethylsilyl-α-D-xylopyranoside (15)

***Method A*:** Following a modification of a procedure reported by Xiao and Bai,[15] a magnetically stirred solution of acetonide **14** (3.47 g, 10.1 mmol) in acetonitrile (55.0 mL) was cooled to 0 °C then treated with $CeCl_3·7H_2O$ (7.50 g, 20.1 mmol). The resulting mixture was stirred for 5 min at 0 °C then oxalic acid (66.1 mg, 0.73 mmol) was added. After a further 10 min at 0 °C and then 10 min at 22 °C, the reaction was quenched with $NaHCO_3$ (5 mL of a sat. aq. solution) before concentrating the mixture under reduced pressure. The colourless residue so formed was diluted with water (20 mL) then extracted with EtOAc (3 × 20 mL) and the combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oil thus obtained was subjected to flash column chromatography (silica, 10:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.5), diol **15** (2.65 g, 87%) as a clear, colourless oil.

$[\alpha]_D$+99 (*c* = 0.80, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (m, 1 H), 5.30 (app. dq, *J* = 17.0, 1.5 Hz, 1 H), 5.21 (app. dq, *J* = 10.4, 1.5 Hz, 1 H), 4.85 (d, *J* = 3.8 Hz, 1 H), 4.21 (m, 1 H), 4.00 (app. ddt, *J* = 12.8, 6.2, 1.5 Hz, 1 H), 3.69–3.54 (complex m, 2 H), 3.54–3.44 (complex m, 3 H), 2.53 (d, *J* = 2.2 Hz, 1 H), 2.25 (d, *J* = 9.6 Hz, 1 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.8, 117.9, 97.5, 75.5, 72.4, 71.3, 68.6, 62.5, 25.9, 18.2, –4.47, –4.53.

IR: 3400, 2929, 2857, 1251, 1055, 835, 776 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{38}O_5Si{\cdot}Na$: 327.1598; found: 327.1599.

***Method B*:** Following minor modifications of a procedure reported by Reissig *et al.*,[27] a magnetically stirred solution of acetonide **14** (172 mg, 0.50 mmol) and $InCl_3$ (224 mg, 1.01 mmol) in acetonitrile (8.0 mL) containing a trace of water (40 μL) was stirred at 22 °C for 2 h. Conventional extractive work-up followed by flash chromatography then afforded compound **15** (90.1 mg, 60%) that was identical in all respects with that obtained by Method A.

Allyl 3-*O*-Benzoyl-4-*O*-*tert*-butyldimethylsilyl-α-D-xylopyranoside (16)

Following a procedure analogous to that reported by Hutchinson *et al.*,[28] a magnetically stirred solution of diol **15** (51.9 mg, 0.17 mmol) in pyridine (1.0 mL) was cooled to –10 °C then treated with benzoyl chloride (20 μL, 0.17 mmol). The ensuing mixture was warmed to 22 °C and stirred for 24 h before being diluted with dichloromethane (5 mL) and washed with HCl (3 mL of a 1 M aq. solution) followed by $NaHCO_3$ (3 mL of a sat. aq. solution). The combined aqueous phases were extracted with dichloromethane (3 × 5 mL) and the combined organic layers washed with ammonium chloride (3 mL of a sat. aq. solution) then $CuSO_4$ (3 mL of a 5% w/w aq. solution) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 4:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.5), alcohol **16** (48.1 mg, 69%) as a clear, colourless oil.

$[\alpha]_D$ +82 (*c* = 0.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (m, 2 H), 7.59 (m, 1 H), 7.45 (m, 2 H), 5.84 (m, 1 H), 5.28 (app. dq, *J* = 17.2, 1.7 Hz, 1 H), 5.13 (app. dq, *J* = 10.6, 1.7 Hz, 1 H), 5.10 (d, *J* = 3.7 Hz, 1 H), 4.94 (dd, *J* = 10.0, 3.7 Hz, 1 H), 4.19 (m, 1 H), 4.07 (dd, *J* = 10.0, 8.5 Hz, 1 H), 3.97 (m, 1 H), 3.74 (m, 1 H), 3.63–3.55 (complex m, 2 H), 2.28 (br s, 1 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.4, 133.9, 133.4, 130.0, 129.9, 128.5, 117.4, 95.7, 73.6, 72.6, 72.0, 68.5, 62.2, 25.9, 18.2, –4.4, –4.5.

IR: 3515, 2953, 2859, 1723, 1276, 1103, 1040, 838 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{32}O_6Si{\cdot}Na$: 431.1866; found: 431.1865.

Allyl 3-*O*-Acetyl-2-*O*-chloroacetyl-4-*O*-*tert*-butyldimethylsilyl-α-D-xylopyranoside (17)

A magnetically stirred solution of diol **15** (2.18 g, 7.16 mmol) in anhydrous dichloromethane (40.0 mL) was treated with pyridine (690 μL, 8.59 mmol) then cooled to –78 °C before being treated, dropwise, with α-chloroacetyl chloride (630 μL, 7.87 mmol). After 1.5 h pyridine (1.30 mL, 16.5 mmol) then acetyl chloride (1.00 mL, 14.3 mmol) were added to the reaction mixture that was then stirred at 22 °C for a further 3 h. Thereafter, the reaction mixture was poured into $NaHCO_3$ (10 mL of a sat. aq. solution) containing ice, then extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with ammonium chloride (15 mL of a sat. aq. solution) then $CuSO_4$ (15 mL of a 5% w/w aq. solution). The combined organic phases were then filtered through a short pad of Celite® contained in a sintered glass funnel. The pad was then washed with dichloromethane (10 mL) and the combined filtrates washed with brine (10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash column chromatography (silica, 7:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.6), compound **17** (2.46 g, 81%) as a clear, colourless oil.

$[\alpha]_D$ +84 (*c* = 0.88, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (m, 1 H), 5.37 (m, 1 H), 5.29 (app. dq, *J* = 16.8, 1.6 Hz, 1 H), 5.20 (m, 1 H), 4.99 (d, *J* = 3.7 Hz, 1 H), 4.78 (dd, *J* = 10.2, 3.7 Hz, 1 H), 4.18 (m, 1 H), 4.03 (s, 2 H), 3.96 (m, 1 H), 3.78 (ddd, *J* = 9.9, 8.9, 6.4 Hz, 1 H), 3.66–3.52 (complex m, 2 H), 2.03 (s, 3 H), 0.84 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8, 167.1, 133.5, 118.0, 94.8, 73.0, 72.5, 69.5, 68.5, 62.2, 40.7, 25.6, 21.1, 18.0, –4.6, –4.8.

IR: 2931, 2859, 1755, 1223, 1045, 837 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{31}{}^{35}ClO_7Si{\cdot}Na$: 445.1425; found: 445.1422.

Chromatographic fractions of compound **17** containing congener **18** were allowed to evaporate at 22 °C and so affording colourless crystals (mp 139–142 °C). This material was subjected to single-crystal X-ray analysis, details of which are provided in the Supporting Information.

Allyl 3-*O*-Acetyl-4-*O*-*tert*-butyldimethylsilyl-α-D-xylopyranoside (3)

***Method A*:** Using a minor modification of a procedure reported by van Boeckel and Beetz,[17] a magnetically stirred solution of hydrazine hydrate (730 μL, 15.0 mmol) in ethanol/water (30.0 of a 2:1 v/v mixture) maintained at 0 °C was treated with a solution of CS_2 (700 μL, 11.6 mmol) in 1,4-dioxane (6.0 mL). Di-isopropylethylamine (2.60 mL, 14.9 mmol) was then added dropwise and the ensuing mixture was stirred for 0.5 h and so providing a stock solution of HDTC. HDTC (3.40 mL of the stock solution, 0.985 mmol) was added to a magnetically stirred and ice-cold solution of chloroacetate **17** (133 mg, 0.314 mmol) and 2,6-lutidine (3.00 mL, 25.9 mmol) in acetic acid (1.00 mL, 17.5 mmol). The cooling-bath was then removed and the reaction mixture stirred at 22 °C for 1 h before being diluted with dichloromethane (10 mL) then washed with water (2 × 10 mL), $CuSO_4$ (20 mL of a 5% w/w aq. solution) and brine (10 mL). The separated organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a dark-brown oil that was subjected to flash column chromatography (silica, 7:3 v/v pet. spirit/EtOAc elution). Concentration of the appropriate fractions (R_f = 0.6) then gave compound **3** (98.3 mg, 90%) as a clear, colourless oil.

$[\alpha]_D$ +106 (*c* = 0.27, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (m, 1 H), 5.31 (app. dq, *J* = 17.2, 1.6 Hz, 1 H), 5.23 (app. dq, *J* = 10.3, 1.6 Hz, 1 H), 5.08 (app. t, *J* = 9.4 Hz, 1 H), 4.84 (d, *J* = 3.8 Hz, 1 H), 4.23 (m, 1 H), 4.01 (m, 1 H), 3.72 (m, 1 H), 3.60–3.43 (complex m, 3 H), 2.11 (s, 3 H), 2.08 (d, *J* = 11.6 Hz, 1 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 133.6, 118.1, 97.8, 76.3, 71.4, 69.0, 68.8, 62.7, 25.7, 21.4, 18.0, –4.6, –4.8.

IR: 3450, 2930, 2858, 1743, 1232, 1063, 1039, 836 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{30}O_6Si{\cdot}Na$: 369.1709; found: 369.1705.

***Method B*:** Following a procedure analogous to that reported by Banwell *et al.*,[29] a solution of chloroacetate **17** (2.42 g, 5.72 mmol) in MeOH (50.0 mL) maintained at 22 °C was treated with $Zn(OAc)_2{\cdot}2H_2O$ (1.28 g, 5.83 mmol). After 4 h, the reaction mixture was worked-up

and the residue subjected to chromatographic purification and so affording alcohol **3** (1.33 g, 67%) that was identical in all respects with that obtained by Method A.

Allyl 2,3-Di-*O*-acetyl-4-*O*-*tert*-butyldimethylsilyl-α-D-xylopyranoside (19)

A magnetically stirred solution of diol **15** (676 mg, 2.22 mmol) in dichloromethane (10 mL) was cooled to –10 °C then treated with pyridine (720 μL, 8.94 mmol) and acetyl chloride (480 μL, 6.75 mmol). Thereafter, the reaction mixture was warmed to 22 °C and after 3 h it was poured into ice-cold $NaHCO_3$ (10 mL of a sat. aq. solution) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were then washed with brine (10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash column chromatography (silica, 8:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.4), compound **19** (741 mg, 86%) as a clear colourless oil.

$[\alpha]_D$+84 (*c* = 0.84, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (m, 1 H), 5.39–5.26 (complex m, 2 H), 5.19 (app. dq, *J* = 10.4, 1.4 Hz, 1 H), 4.96 (d, *J* = 3.6 Hz, 1 H), 4.74 (dd, *J* = 10.3, 3.6 Hz, 1 H), 4.18 (m, 1 H), 3.97 (m, 1 H), 3.77 (ddd, *J* = 10.3, 8.9, 6.1 Hz, 1 H), 3.65–3.50 (complex m, 2 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 0.84 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 169.8, 133.7, 117.7, 95.1, 72.7, 71.4, 69.6, 68.4, 62.2, 25.6, 21.1, 20.9, 18.0, –4.5, –4.8.

IR: 2931, 2858, 1752, 1219, 1050, 837 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{32}O_7Si{\cdot}Na$: 411.1815; found: 411.1817.

Allyl 2,3-Di-*O*-acetyl-α-D-xylopyranoside (5)

Following a procedure due to Pilcher and DeShong,[21] a magnetically stirred solution of compound **19** (337 mg, 0.867 mmol) in acetonitrile (10 mL), and maintained at 22 °C in a falcon tube, was treated with fluorosilicic acid (610 μL of a 25% w/w aq. solution, 1.29 mmol). After 6 h the reaction mixture was treated with $CaCO_3$ (2 mL of a sat. aq. solution) and $NaHCO_3$ (2 mL of a sat. aq. solution) and after a further 0.25 h the reaction mixture was diluted with brine (10 mL) then extracted with EtOAc (2 × 15 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.4), compound **5** (199 mg, 84%) as a clear, colourless oil.

$[\alpha]_D$ +101 (*c* = 0.97, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (m, 1 H), 5.29 (app. dq, *J* = 17.3, 1.6 Hz, 1 H), 5.21 (m, 2 H), 4.97 (d, *J* = 3.7 Hz, 1 H), 4.79 (dd, *J* = 10.0, 3.7 Hz, 1 H), 4.18 (app. ddt, *J* = 13.2, 5.0, 1.6 Hz, 1 H), 3.97 (app. ddt, *J* = 13.2, 6.1, 1.6 Hz, 1 H), 3.82–3.68 (complex m, 2 H), 3.61 (m, 1 H), 2.80 (br s, 1 H), 2.09 (s, 3 H), 2.06 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 170.4, 133.5, 117.8, 94.9, 74.0, 70.7, 69.6, 68.4, 61.8, 21.0, 20.9.

IR: 3456, 2942, 2887, 1750, 1370, 1230, 1042 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}O_7{\cdot}Na$: 297.0950; found: 297.0950.

Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside (22)

Following a minor modification of a procedure reported by Kosma *et al.*,[18] a magnetically stirred solution of diol **21**[30] (5.55 g, 18.0 mmol) in anhydrous DMF (70 mL) was cooled to 0 °C then treated with NaH (2.18 g of a 60% dispersion in oil, 54.5 mmol). After 1 h benzyl chloride (4.56 mL, 40.0 mmol) was added, dropwise, to the reaction mixture and this was followed by the portion-wise addition of TBAI (702 mg, 2.18 mmol). The ensuing mixture was allowed to warm to 22 °C and after a further 4 h poured into ice-water (500 mL). Diethyl ether (200 mL) was then added and the organic phase separated. The aqueous phase was extracted with diethyl ether (3 × 200 mL) and combined organic phases then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow oil so obtained was subjected to flash column chromatography (silica, 9:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.2), compound **22** (7.01 g, 80%) as a white solid and a ca. 7:1 mixture of α- and β-anomers. The NMR spectral data recorded on this material match those reported in the literature.[18,31]

Benzyl (Allyl 2,3-di-*O*-benzyl-4-*O*-methyl-α-D-glucopyranosid)urinate (27)

In a minor modification of a procedure reported by Kosma *et al.*,[18] a magnetically stirred solution of compound **26** (950 mg, 2.29 mmol) in acetone (20 mL) maintained at 0 °C was treated, dropwise, with Jones' reagent (2.10 mL of a 3 M solution in aq. H_2SO_4, 6.30 mmol). The ensuing mixture was heated to 50 °C for 3 h then cooled before being poured into ice-water (100 mL) and extracted with chloroform (3 × 50 mL). The combined organic phases were washed with water until the washings were neutral and then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The viscous oil thus obtained was dissolved in DMF (30 mL) and the resulting, magnetically stirred solution was cooled to 0 °C (ice-bath) then treated with $KHCO_3$ (1.66 g, 16.5 mmol). After 0.5 h the reaction mixture was treated with benzyl bromide (550 μL, 4.63 mmol) then warmed to 22 °C. After a further 3 h the reaction mixture was poured into ice-water (100 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with $NaHCO_3$ (50 mL of sat. aq. solution) and water (50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica gel, 6:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the relevant fractions (R_f = 0.2), compound **27** (678 mg, 57%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.26 (complex m, 15 H), 5.92 (m, 1 H), 5.32 (app. dq, *J* = 17.1, 1.6 Hz, 1 H), 5.27–5.19 (complex m, 3 H), 4.92 (d, *J* = 10.8 Hz, 1 H), 4.84–4.74 (complex m, 3 H), 4.62 (d, *J* = 12.1 Hz, 1 H), 4.22–4.14 (complex m, 2 H), 4.02 (m, 1 H), 3.91 (m, 1 H), 3.54 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.43 (dd, *J* = 10.0, 9.0 Hz, 1 H), 3.35 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7, 138.8, 138.1, 135.4, 133.4, 128.7, 128.5(8), 128.5(6), 128.5(4), 128.4(9), 128.2, 128.0(9), 128.0(7), 127.8, 118.8, 96.2, 81.6, 81.5, 79.2, 75.9, 73.6, 70.5, 68.8, 67.3, 60.8.

IR: 3032, 2931, 1748, 1455, 1089 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{34}O_7{\cdot}Na$: 541.2202; found: 541.2208.

All the NMR, IR and MS data recorded on this material matched those reported previously.[18]

Methyl (Allyl 2,3-Di-*O*-benzyl-4-*O*-methyl-D-glucopyranosid)urinate (28)

Following the procedure detailed immediately above, a magnetically stirred solution of compound **26**[18] (2.79 g, 6.73 mmol) in acetone (56.0 mL) was cooled to 0 °C then treated, dropwise, with Jones' reagent (5.80 mL of a 3 M solution in aq. H_2SO_4, 17.4 mmol). The ensuing mixture was then heated at 50 °C for 3 h before being cooled, poured into ice-water (200 mL) then extracted with chloroform (3 × 100 mL). Further work-up in the manner detailed above afforded a clear, colourless oil that was dissolved in DMF (70 mL) with the resulting solution being reacted with $KHCO_3$ (4.53 g, 45.2 mmol) and then MeI (830 μL, 13.3 mmol). Work-up in the manner detailed above gave an oil that was subject to flash column chromatography (silica, 7:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.15), compound **28** (2.04 g, 69%) as a clear, colourless oil and a 6:1 mixture of α- and β-anomers.

$[\alpha]_D$+38 (*c* = 0.29, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (α-anomer) = 7.42–7.25 (complex m, 10 H), 5.92 (m, 1 H), 5.33 (app. dq, *J* = 17.1, 1.6 Hz, 1 H), 5.24 (app. dq, *J* = 10.3, 1.6 Hz, 1 H), 4.93 (d, *J* = 10.9 Hz, 1 H), 4.85–4.73 (complex m, 3 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.19 (m, 1 H), 4.15 (d, *J* = 10.0 Hz, 1 H), 4.01 (m, 1 H), 3.91 (app. t, *J* = 9.3 Hz, 1 H), 3.80 (s, 3 H), 3.54 (m, 1 H), 3.50 (s, 3 H), 3.44 (dd, *J* = 10.0, 9.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (α-anomer) = 170.4, 138.8, 138.1, 133.4, 128.6, 128.5(0), 128.4(9), 128.2, 128.1, 127.8, 118.8, 96.3, 81.6, 81.4, 79.2, 75.9, 73.6, 70.3, 68.7, 60.9, 52.7.

IR: 3031, 2930, 1749, 1078, 1027, 736, 697 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{30}O_7$·Na: 465.1889; found: 465.1885.

Benzyl (2,3-Di-*O*-Benzyl-4-*O*-methyl-D-glucopyranosyl)urinate (29)

Following a procedure due to Potter *et al.*,[32] a magnetically stirred solution of compound **27** (289 mg, 0.56 mmol) in anhydrous MeOH (10.0 mL) and protected from moisture using a $CaCl_2$ drying tube was cooled to 0 °C then treated with $PdCl_2$ (21.3 mg, 0.120 mmol). The ensuing mixture was allowed to warm, over 2 h, to 22 °C then filtered through a short pad of pad of Celite® contained in a sintered-glass funnel. The filtrate was concentrated under reduced pressure and the residue so-obtained subjected to flash column chromatography (silica, 3:1 *v*/*v* pet. spirit/EtOAc elution) to afford, after concentration of the relevant fractions (R_f = 0.3) compound **29** (167 mg, 63%) as a white gum and a 3:1 mixture of α- and β-anomers.

$[\alpha]_D$ +13 (*c* = 0.27, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (α-anomer) = 7.40–7.29 (complex m, 15 H), 5.21 (m, 3 H), 4.85 (d, *J* = 10.9 Hz, 1 H), 4.79 (d, *J* = 11.1 Hz, 1 H), 4.74 (m, 1 H), 4.65 (d, *J* = 11.8 Hz, 1 H), 4.41 (d, *J* = 9.6 Hz, 1 H), 3.94–3.83 (complex m, 1 H), 3.59–3.52 (complex m, 1 H), 3.49–3.40 (complex m, 1 H), 3.36 (s 3 H), 2.98 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (α-anomer) = 169.7, 138.5, 137.7, 135.3, 128.8, 128.7(2), 128.6(9), 128.6, 128.5, 128.2, 128.1, 127.9, 91.8, 81.3, 80.7, 79.0, 75.7, 73.7, 70.7, 67.4, 60.6 (one signal obscured or overlapping).

IR: 3420, 2937, 1744, 1454, 1076, 697 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{30}O_7$·Na: 501.1889; found 501.1897.

All the NMR, IR and MS data recorded on this material matched those reported previously.[18]

Methyl (2,3-Di-*O*-benzyl-4-*O*-methyl-D-glucopyranosyl)urinate (30)

A magnetically stirred solution of compound **28** (2.02 g, 4.57 mmol) in anhydrous MeOH (20 mL) and maintained at 0 °C while being protected from moisture, was treated with $PdCl_2$ (136 mg, 0.770 mmol). The ensuing mixture was allowed to warm, over 2 h, to 22 °C then filtered through a short pad of pad of Celite® contained in a sintered-glass funnel. The filtrate was concentrated under reduced pressure and the residue so-obtained subjected to flash column chromatography (silica, 5:2 v/v pet. ether/EtOAc elution) to afford, after concentration of the relevant fractions (R_f = 0.2), compound **30** (1.47 g, 80%) as a tan solid and a ca. 8:1 mixture of α- and β-anomers.

Mp 92–95 °C; $[\alpha]_D$+29 (*c* = 0.33, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (α-anomer) = 7.42–7.27 (complex m, 10 H), 5.20 (app. t, *J* = 3.2 Hz, 1 H), 4.89–4.81 (complex m, 2 H), 4.77 (d, *J* = 11.8 Hz, 1 H), 4.66 (d, *J* = 11.8 Hz, 1 H), 4.38 (d, *J* = 9.6 Hz, 1 H), 3.87 (app. t, *J* = 9.0 Hz, 1 H), 3.79 (s, 3 H), 3.56 (m, 1 H), 3.50 (s, 3 H), 3.46 (m, 1 H), 3.02 (br s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (α-anomer) = 170.3, 138.5, 137.7, 128.7, 128.6, 128.3, 128.1, 127.9, 91.8, 81.2, 80.6, 79.0, 75.7, 73.7, 70.5, 60.7, 52.7 (one signal obscured or overlapping).

IR: 3406, 2946, 1741, 1084, 1071, 734, 694 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{26}O_7$·Na: 425.1576; found: 425.1574.

Methyl (2,3-Di-*O*-benzyl-4-*O*-methyl-D-glucopyranosyltrichloroacetimidate)urinate [4 (R = Me)]

Following a procedure due to Das and Mukhopadhyay,[20] a magnetically stirred solution of acetal **30** (305 mg, 0.757 mmol) in dichloromethane (5.0 mL) maintained at 22 °C was treated with K_2CO_3 (523 mg, 3.79 mmol). After 0.5 h the reaction mixture was cooled to 0 °C then treated, dropwise, with trichloroacetonitrile (910 μL, 9.09 mmol). The mixture was then allowed to warm to 22 °C and after a further 16 h it was filtered through a pad of Celite® contained in a sintered-glass funnel and the filtrate concentrated under reduced pressure. The yellow residue so formed was subjected to flash column chromatography (silica, 3:1 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.3), compound **4** (R = Me) (336 mg, 81%) as a white, crystalline solid and a ca. 1:3 mixture of α- and β-anomers. Further chromatographic purification of a 10 mg sample of this mixture under the same conditions afforded an essentially pure sample of the β-anomer suitable for characterisation purposes.

Mp 84–86 °C; $[\alpha]_D$ +18 (*c* = 0.38, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (β-anomer) = 8.73 (s, 1 H), 7.36–7.27 (complex m, 10 H), 5.85 (d, *J* = 7.3 Hz, 1 H), 4.99–4.69 (complex m, 4 H), 4.01 (d, *J* = 9.1 Hz, 1 H), 3.81 (s, 3 H), 3.78–3.61 (complex m, 3 H), 3.51 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (β-anomer) = 168.9, 161.1, 138.3, 137.9, 128.5(4), 128.5(2), 128.1, 128.0, 127.9, 98.2, 90.8, 83.6, 80.9, 80.4, 75.6, 75.0, 74.8, 60.8, 52.8 (one signal obscured or overlapping).

IR: 3337, 3032, 2930, 1751, 1288, 1053, 797, 697 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{26}{}^{35}Cl_3O_7N$·Na: 568.0673; found: 568.0675.

Allyl 3-*O*-Acetyl-4-*O*-*tert*-butyl-dimethylsilyl-α-D-xylopyranosyl-(1→2)-methyl-(2,3-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosyl) (31) and Allyl 3-*O*-Acetyl-4-*O*-*tert*-butyl-dimethylsilyl-α-D-xylopyranosyl-(1→2)-methyl-(2,3-di-*O*-benzyl-4-*O*-methyl-α-D-glucopyranosyl)uronate (32)

Trichloroacetimidate **4** (R = Me) (336 mg, 0.61 mmol) and alcohol **3** (141 mg, 0.41 mmol) were placed in separate round-bottom flasks, each fitted with a stirrer bar and charged with activated 4 Å molecular sieves (100 mg). After each flask was sealed with a rubber septum, they were placed under high vacuum for 1 h and thereafter anhydrous dichloromethane (3.0 mL) was added to each flask and the resulting mixtures stirred at 22 °C for 2 h under an argon atmosphere. A solution of TMSOTf (24 μL in 220 μL of anhydrous dichloromethane, 0.13 mmol) was prepared, dried over activated 4 Å molecular sieves then added to the reaction mixture containing alcohol **3**. The solution containing the trichloroacetimidate **4** (R = Me) was then slowly added, *via* cannula, to the solution of the alcohol and the resulting yellow solution stirred at 22 °C for 1 h. Thereafter, the solution was quenched with triethylamine (3 drops) resulting in a colour change to pink. The reaction mixture was then concentrated under reduced pressure and the residue so-formed subjected to flash column chromatography (silica, 9:1 v/v dichloromethane/diethyl ether then 6:1 v/v pet. spirit/EtOAc elution) to give two fractions, A and B.

Concentration of fraction A (*R_f* = 0.3 in 5:1 v/v pet. spirit/EtOAc) afforded compound **32** (142 mg, 48%) as a clear, yellow oil.

$[\alpha]_D$+70 (*c* = 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.27 (complex m, 10 H), 5.88 (m, 1 H), 5.38 (dd, *J* = 10.0, 8.8 Hz, 1 H), 5.30 (app. dq, *J* = 16.9, 1.6 Hz, 1 H), 5.14 (app. dq, *J* = 10.4, 1.6 Hz, 1 H), 4.93 (d, *J* = 3.5 Hz, 1 H), 4.87 (m, 2 H), 4.79 (d, *J* = 11.0 Hz, 1 H), 4.71 (d, *J* = 11.9 Hz, 1 H), 4.63 (d, *J* = 11.9 Hz, 1 H), 4.17 (m, 2 H), 3.96 (m, 1 H), 3.85 (d, *J* = 9.3 Hz, 1 H), 3.81 (s, 3 H), 3.70 (m, 1 H), 3.60 (m, 2 H), 3.50 (m, 2 H), 3.44 (s, 3 H), 3.37 (m, 1 H), 2.07 (s, 3 H), 0.85 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 169.9, 138.7, 138.3, 134.0, 128.5(4), 128.4(8), 128.2, 128.0, 127.9, 127.7, 117.9, 97.2, 95.2, 81.8, 80.9, 78.6, 76.3, 75.7, 73.7, 73.1, 70.7, 69.9, 68.7, 62.3, 60.7, 52.7, 25.7, 21.3, 18.0, –4.5, –4.8.

IR: 2931, 2858, 1751, 1227, 1097, 1064, 1043 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{38}H_{54}O_{12}Si{\cdot}Na$: 753.3282; found: 753.3287.

Concentration of fraction B (*R_f* = 0.4 in 5:1 v/v pet. spirit/EtOAc) afforded compound **31** (35.0 mg, 12%) as a clear, yellow oil.

$[\alpha]_D$ +48 (*c* = 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (complex m, 10 H), 5.95 (m, 1 H), 5.47 (dd, *J* = 10.2, 8.4 Hz, 1 H), 5.36 (app. dq, *J* = 17.2, 1.7 Hz, 1 H), 5.20 (app. dq, *J* = 10.7, 1.7 Hz, 1 H), 4.97 (d, *J* = 3.6 Hz, 1 H), 4.86 (dd, *J* = 11.3, 3.6 Hz, 2 H), 4.76 (d, *J* = 10.9 Hz, 1 H), 4.65 (d, *J* = 11.7 Hz, 1 H), 4.50 (d, *J* = 7.6 Hz, 1 H), 4.21 (m, 1 H), 4.06 (m, 1 H), 3.81 (s, 3 H), 3.77 (dd, *J* = 6.8, 2.7 Hz, 1 H), 3.72 (m, 1 H), 3.65 (app. td, *J* = 10.3, 3.3 Hz, 2 H), 3.56–3.50 (complex m, 3 H), 3.48 (s, 3 H), 3.43 (m, 1 H), 1.86 (s, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9, 169.0, 138.5, 134.2, 128.4, 128.3, 128.2, 127.9, 127.7, 127.5, 117.0, 104.9, 98.0, 83.9, 81.1, 80.8, 77.7, 75.7, 74.6, 74.2, 73.9, 70.3, 68.9, 62.3, 60.8, 52.6, 25.7, 21.2, 18.0, –4.5, –4.9 (one signal obscured or overlapping).

IR: 2931, 2858, 1751, 1227, 1071, 1044, 1027, 838 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{38}H_{54}O_{12}Si{\cdot}Na$: 753.3282; found: 753.3287.

Allyl 3-*O*-Acetyl-α-D-xylopyranosyl-(1→2)-methyl-(2,3-di-*O*-benzyl-4-*O*-methyl-α-D-glucopyranosyl)urinate (33)

A magnetically stirred solution of disaccharide **32** (120 mg, 0.16 mmol) in acetonitrile (3.5 mL) and maintained at 22 °C in a falcon tube was treated with fluorosilicic acid (116 μL of a 25 wt % in H_2O solution, 0.25 mmol). After 6 h the reaction mixture was treated with $CaCO_3$ (2 mL of a sat. aq. solution) and $NaHCO_3$ (2 mL of a sat. aq. solution) and after a further 0.25 h the reaction mixture was diluted with brine (10 mL) then extracted with EtOAc (2 × 15 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:2 v/v pet. spirit/EtOAc elution) to afford, after concentration of the appropriate fractions (*R_f* = 0.6), compound **33** (83.1 mg, 82%) as a clear, colourless oil.

$[\alpha]_D$+63 (*c* = 0.80, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.26 (complex m, 10 H), 5.88 (m, 1 H), 5.30 (app. dq, *J* = 16.9, 1.6 Hz, 1 H), 5.18 (m, 2 H), 4.94 (dd, *J* = 7.1, 3.4 Hz, 2 H), 4.89 (d, *J* = 10.9 Hz, 1 H), 4.79 (d, *J* = 10.9 Hz, 1 H), 4.69 (m, 2 H), 4.30 (d, *J* = 10.0 Hz, 1 H), 4.20 (m, 1 H), 3.98 (m, 1 H), 3.87 (app. t, *J* = 9.3 Hz, 1 H), 3.81 (s, 3 H), 3.79–3.59 (complex m, 4 H), 3.52 (dd, *J* = 9.7, 3.5 Hz, 1 H), 3.46 (s, 3 H), 3.41 (dd, *J* = 10.0, 9.0 Hz, 1 H), 2.91 (br s, 1 H), 2.17 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 170.4, 138.7, 138.1, 133.7, 128.6, 128.5, 128.1(0), 128.0(8), 128.0, 127.8, 118.3, 96.3, 95.0, 81.6, 81.0, 78.5, 75.7, 75.5, 73.8, 73.2, 70.6, 70.0, 68.8, 62.4, 60.9, 52.7, 21.2.

IR: 3460, 2928, 1747, 1230, 1077, 1044, 744 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* $[M + Na]^+$ calcd for $C_{32}H_{40}O_{12}{\cdot}Na$: 639.2417; found: 639.2397.

2,3,2′,3′,4′-Penta-*O*-acetyl-β-D-xylobiosyl-(1→4)-allyl-3-*O*-acetyl-α-D-xylopyranosyl-(1→2)-methyl-(2,3-di-*O*-benzyl-4-*O*-methyl-α-D-glucopyranosyl)urinate (34)

A magnetically stirred mixture of trichloroacetimidate **2** (154 mg, 0.24 mmol) and activated 4 Å molecular sieves (100 mg), maintained under an atmosphere of argon, was treated with anhydrous dichloromethane (2.0 mL). In a separate flask, a magnetically stirred mixture of alcohol **33** (74.1 mg, 0.12 mmol) and activated 4 Å molecular sieves (100 mg) was also treated with anhydrous dichloromethane (2.0 mL). Both mixtures were then cooled to –20 °C [water/ethanol/CO_2(s)] and stirring continued for 2 h. TMSOTf (60 μL of a 0.62 M solution in dichloromethane, 0.036 mmol) was added to the reaction mixture containing alcohol **33** and then the solution of trichloroacetimidate **2** was added, slowly and *via* cannula, to the reaction mixture containing compound **33** and TMSOTf. Stirring of the mixture was continued at –20 °C for 1 h then the reaction was quenched by the addition of triethylamine (2 drops), this resulting in a colour change from yellow to pink. After warming to 22 °C, the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to successive flash column chromatographic purifications (silica, 1:2 *v*/*v* pet. spirit/EtOAc elution) to afford, after concentration of the relevant fractions (*R_f* = 0.2), compound **34** (8.8 mg, 7%) as a clear, colourless oil.

$[\alpha]_D$+13 (*c* = 0.77, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.27 (complex m, 10 H), 5.85 (m, 1 H), 5.41 (app. t, *J* = 9.1 Hz, 1 H), 5.29 (br dd, *J* = 16.5, 1.7 Hz, 1 H), 5.14 (br dd, *J* = 11.0, 1.7 Hz, 1 H), 5.09 (app. t, *J* = 7.8 Hz, 1 H), 5.05 (app. t, *J* = 8.1 Hz, 1 H), 4.92 (d, *J* = 3.5 Hz, 1 H), 4.89 (m, 1 H), 4.86 (d, *J* = 10.9 Hz, 1 H), 4.83 (d, *J* = 3.4 Hz, 1 H), 4.81 (m, 1 H), 4.78 (d, *J* = 10.9 Hz, 1 H), 4.71 (m, 2 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 6.0 Hz, 1 H), 4.48 (d, *J* = 6.0 Hz, 1 H), 4.17 (d, *J* = 10.1 Hz, 1 H), 4.14 (br. dd, *J* = 13.1, 5.7 Hz, 1 H), 4.09 (dd, *J* = 12.0, 4.7 Hz, 1 H), 3.95 (m, 2 H), 3.84

(app. t, J = 9.4 Hz, 1 H), 3.80 (s, 3 H), 3.78 (d, J = 8.1 Hz, 1 H), 3.69 (app. q, J = 9.1 Hz, 1 H), 3.60 (m, 3 H), 3.48 (m, 1 H), 3.43 (s, 3 H), 3.41–3.31 (complex m, 3 H), 2.06 (s, 3 H), 2.05(4) (s, 3 H), 2.05(1) (s, 3 H), 2.03(4) (s, 3 H), 2.03(2) (s, 3 H), 2.02(9) (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 170.5, 170.1, 169.9, 169.8, 169.5, 169.3, 138.8, 138.3, 133.8, 128.6, 128.5, 128.1, 127.9(8), 127.9(7), 127.7, 118.0, 100.6, 99.6, 97.3, 95.1, 81.8, 80.9, 78.7, 76.8, 76.1, 75.7, 74.3, 73.3, 71.9, 71.4, 71.2, 70.8, 70.7, 70.6, 68.8, 68.5, 62.4, 61.7, 60.7, 59.4, 52.6, 21.2, 20.9(3), 20.8(8), 20.8(1), 20.8(0), 20.7(8) (one signal obscured or overlapping).

IR: 2926, 2855, 1747, 1370, 1220, 1072, 1043, 752 cm^{-1}.

HRMS (ESI, +ve): m/z [M + Na]$^+$ calcd for $C_{52}H_{66}O_{25}$·Na: 1113.3791; found: 1113.3766.

Allyl 3-*O*-Acetyl-4-*O*-*tert*-butyl-dimethylsilyl-α-D-xylopyranosyl-(1→2)-methyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranuronate (40)

Trichloroacetimidate **39**[25] (282 mg, 0.59 mmol) and alcohol **3** (137 mg, 0.39 mmol) were placed in a round-bottom flask charged with a stirrer bar and activated 4 Å molecular sieves (100 mg). After being sealed with a rubber septum, the flask was placed under high vacuum for 1 h then refilled with argon before anhydrous dichloromethane (5 mL) was added. The resulting mixture was stirred at 22 °C for 2 h before being cooled to –20 °C then treated with a solution of TMSOTf in anhydrous dichloromethane (1.00 mL of a 0.12 M solution, 0.12 mmol) maintained at –20 °C under an atmosphere of argon. The resulting yellow solution was stirred at –20 °C for 1 h then quenched with triethylamine (3 drops) and so resulting in a colour change to pink. The reaction mixture was warmed to 22 °C then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 2:1 v/v pet. spirit/EtOAc elution then, separately, employing 9:1 v/v dichloromethane/diethyl ether elution and 5:2 v/v pet. spirit/EtOAc elution) to afford, after concentration of the relevant fractions (R_f = 0.2 in 5:2 v/v pet. spirit/EtOAc), compound **40** (26.3 mg, 10%) as a white solid. Slow evaporation of a solution of this material in diethyl ether at 22 °C afforded a crystalline solid suitable for single-crystal X-ray analysis.

Mp 140–142; $[\alpha]_D$ +17 (c = 0.38, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (m, 1 H), 5.37–5.29 (complex m, 2 H), 5.27–5.15 (complex m, 3 H), 4.98 (m, 1 H), 4.91 (d, J = 3.6 Hz, 1 H), 4.66 (d, J = 7.8 Hz, 1 H), 4.17 (m, 1 H), 4.05 (m, 1 H), 4.00 (d, J = 9.5 Hz, 1 H), 3.74 (s, 3 H), 3.68 (m, 1 H), 3.59 (m, 2 H), 3.50 (dd, J = 10.4, 5.6 Hz, 1 H), 2.09 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.4, 169.5, 169.4, 169.3, 167.1, 134.0, 117.3, 101.2, 97.6, 77.4, 74.2, 72.5, 72.4, 71.1, 70.0, 69.5, 69.1, 62.2, 53.0, 25.6, 21.4, 20.8, 20.6, 20.5, 18.0, –4.5, –4.9.

IR: 2933, 2858, 1748, 1374, 1217, 1042 cm^{-1}.

HRMS (ESI, +ve): m/z [M + Na]$^+$ calcd for $C_{29}H_{46}O_{15}Si$·Na: 685.2504; found: 685.2508.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2126-0346. Included are an outline of the general synthetic protocols employed in this study, plots derived from the single-crystal X-ray analyses of compounds **17**, **18** and **40** together with summaries of key NMR spectral data used to establish the structures of compounds **3**, **12** and **13**, **31** and **32** and **34**. Copies of the ^{1}H and ^{13}C NMR spectra of compounds **2**, **3**, **4** (R =Me), **5**, **7**, **9**, **11**–**17**, **19**, **21**–**34** and **36**–**40** are also provided.

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