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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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Abstract: Suitably protected mono- and di-saccharide residues associated with the glucuronic acid-containing repeat unit (1) 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 over-expression 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.\textsuperscript{4,5}

Pentosan polysulfate (PPS), a.k.a. sodium pentosan polysulfate or NaPPS\textsuperscript{6} and marketed under the brand name ELMIRON\textsuperscript{6,7}, 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.\textsuperscript{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 depolymerization, 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.\textsuperscript{9} The associated backbones of the constituent xylo-oligosaccharides are of varying length and with 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 \textbf{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.\textsuperscript{10}

**Figure 1:** The structure, 1, of the smallest repeat unit of PPS containing a glucuronic acid residue
Our ongoing interest\textsuperscript{10,11} in developing chemical techniques for the preparation of HS mimetics and related species for probing the mechanisms-of-actions of HPSE and 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.\textsuperscript{12}

\textbf{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 \( \beta \)-configured anomeric linkages between the backbone xylose residues and an \( \alpha \)-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\textsuperscript{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 readily separated, by flash chromatography, from the corresponding and accompanying derivatives of the higher-order oligomers. By such means compound 7\textsuperscript{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 anomic 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\textsuperscript{10} in 71% yield and as a ca. 3:1 mixture of α- and β-anomers. Finally, treatment of a dichloromethane solution of penta-acetate 9 with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at −5 °C afforded the targeted and previously reported\textsuperscript{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 following an established procedure,\textsuperscript{14} D-xylose (10) was treated with allyl alcohol in the presence at acetyl chloride and so affording ether 11\textsuperscript{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$_6$D$_6$ rather than CDCl$_3$ due to their high acid sensitivity) to differentiate between these regio-isomeric products and key outcomes are shown in the Supporting Information – SI). 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. 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-benzylation 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 15 → 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 SI, 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-lutidene and acetic acid in ethanol/water 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 Figure 3, SI) 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).

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 18 (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.\textsuperscript{18} To begin, 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%) 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.\textsuperscript{18,19} with 3.7 mole equivalents of PdCl\textsubscript{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\textsubscript{2} used (to 0.2 equiv.) as well as employing methanol as solvent then compound 29 could be obtained in 63% yield.
Scheme 4: Synthesis of glucuronic acid derivative 4 (R = Me).

While all the spectra data acquired on this product matched those recorded in the literature it was contaminated with varying quantities of the corresponding methyl ester 30 that arises through a trans-esterification 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\textsuperscript{20} afforded the targeted trichloroacetimidate 4 (R = Me) in 81\% yield and as a ca. 1:3 mixture of \(\alpha\)- and \(\beta\)-anomers. All of the spectra data acquired on this compound were in accord with the assigned structure, with the \(\text{\textsuperscript{1}}\text{H}\) NMR spectrum of the latter (predominant) anomer including a doublet at \(\delta 5.85\) that is assigned to H-1 and with the associated vicinal coupling to H-2 of 7.3 Hz being indicative of the \(\alpha\)-configuration of the oxymethine hydrogen at C-1. In the \(\alpha\)-anomer the analogous signal appeared as a doublet at \(\delta 6.43\) 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\textsuperscript{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 \(\text{\textsuperscript{1}}\text{H}\) and HMBC NMR spectroscopic features, details of which are provided in the SI (Figure 5), allowed for the determination of the illustrated stereochemistries about the newly established glycosidic bonds. Treatment of disaccharide 32 with H\(_2\)SiF\(_6\) in acetonitrile at ambient temperatures\textsuperscript{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, \(\text{\textsuperscript{1}}\text{H}\) and HMBC NMR spectroscopic experiments, as detailed in the Figure 6 of the SI, served to establish the illustrated stereochemical features, most particularly the \(\beta\)-configurations at highlighted anomeric centres (see red arrows) and \(\alpha\)-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 trichloroacetonitrile in the presence of DBU at \(-5^\circ C\) 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 SI).

Scheme 6: The stereo-controlled synthesis of the glycosylated xylose 40

The studies detailed here provide a means for assembling the key components of PPS and when considered in conjunction with our recently developed methods for the O-sulfation of oligosaccharides,\textsuperscript{10} the stereo-controlled synthesis of compound 1 and various of its congeners now seems possible. Work directed toward such ends is currently underway in our laboratories and results will be reported in due course.
Allyl 2,3-O-iso-Propylidene-α- D-xylopyranoside (12) and Allyl 3,4-O-iso-Propylidene-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 NaHCO₃ (1 × 5 mL of a sat. aq. solution) and brine (1 × 5 mL) before being dried (Na₂SO₄), 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 (Rₛ = 0.2 in 20:1 v/v dichloromethane/methanol) afforded compound 12 (440 mg, 38%) as a white, crystalline solid.

Mp 73-75 °C; [α]D +126 (c = 0.80, CHCl₃);

1H NMR (400 MHz, C₆D₆): δ = 5.72 (m, 1H), 5.23 (app. dq, J = 17.2, 1.7 Hz, 1H), 5.03 (d, J = 3.0 Hz, 1H), 4.99 (app dq, J = 10.5, 1.7 Hz, 1H), 4.16 (app t, J = 9.4 Hz, 1H), 4.01 (m, 1H), 3.86-3.74 (complex m, 2H), 3.66 (dd, J = 11.2, 5.5 Hz, 1H), 3.52-3.34 (complex m, 2H), 2.40 (br s, 1H), 1.42 (s, 3H), 1.38 (s, 3H);

13C NMR (101 MHz, C₆D₆): 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;


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

[α]D +57 (c = 0.40, CHCl₃);

1H NMR (400 MHz, C₆D₆): δ = 5.65 (m, 1H), 5.10 (app dq, J = 16.8, 1.5 Hz, 1H), 4.97 (app. dq, J = 10.4, 1.5 Hz, 1H), 4.76 (d, J = 2.8 Hz, 1H), 3.94 (m, 1H), 3.85-3.78 (complex m, 2H), 3.76 (dd, J = 9.6, 4.6 Hz, 1H), 3.70 (m, 1H), 3.63 (app t, J = 10.1 Hz, 1H), 3.33 (m, 1H), 2.52 (d, J = 7.5 Hz, 1H), 1.39 (s, 3H), 1.38 (s, 3H);

13C NMR (101 MHz, C₆D₆): 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-iso-Propylidene-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 NaHCO₃ (3 mL of a sat. aq. solution) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL) then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residual oil was subjected to flash column chromatography (silica, 25:1 v/v pet. spirit/ethyl acetate elution) to afford, after concentration of the appropriate fractions (Rᶠ = 0.2) compound 14 (344 mg, 96%) as a clear, colourless oil.

[α]D +100 (c = 0.81, CHCl₃);

¹H NMR (400 MHz, CDCl₃): δ = 5.94 (m, 1H), 5.33 (app. dq, J = 17.2, 1.7 Hz, 1H), 5.19 (app. dq, J = 10.6, 1.7 Hz, 1H), 5.09 (d, J = 3.0 Hz, 1H), 4.22 (app. ddt, J = 13.1, 5.2, 1.6 Hz, 1H), 4.07 (app. ddt, J = 13.1, 5.8, 1.6 Hz, 1H), 3.96-3.84 (complex m, 2H), 3.65-3.56 (complex m, 1H), 3.43-3.27 (complex m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H);

¹³C NMR (101 MHz, CDCl₃): 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 + Na]^+ calcd for C_{17}H_{32}O₅Si•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 CeCl₃•7H₂O (7.50 g, 20.1 mmol). The resulting mixture was stirred for 5 mins at 0 °C then oxalic acid (66.1 mg, 0.73 mmol) was added. After a further 10 mins at 0 °C and then 10 mins at 22 °C, the reaction mixture was quenched with NaHCO₃ (5 mL of a sat. aq. solution) before being concentrated under reduced pressure. The colourless residue so-formed was diluted with water (20 mL) then extracted with ethyl acetate (3 × 20 mL) and the combined organic phases were then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The oil thus obtained was subjected to flash column chromatography (silica, 10:1 v/v
pet. spirit/ethyl acetate elution) to afford, after concentration of the appropriate fractions \( (R_f = 0.5) \), diol 15 (2.65 g, 87%) as a clear, colourless oil.

\[ [\alpha]_D +99 \ (c = 0.80, \text{CHCl}_3); \]

\( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 5.92 \ (m, 1H) \), 5.30 (app. dq, \( J = 17.0 \), 1.5 Hz, 1H), 5.21 (app. dq, \( J = 10.4 \), 1.5 Hz, 1H), 4.85 (d, \( J = 3.8 \) Hz, 1H), 4.21 (m, 1H), 4.00 (app. ddt, \( J = 12.8 \), 6.2, 1.5 Hz, 1H), 3.69-3.54 (complex m, 2H), 3.54-3.44 (complex m, 3H), 2.53 (d, \( J = 2.2 \) Hz, 1H), 2.25 (d, \( J = 9.6 \) Hz, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H);

\( ^{13} \)C NMR (101 MHz, CDCl\(_3\)): \( \delta = 133.8, 117.9, 97.5, 75.5, 72.4, 71.3, 68.6, 62.5, 25.9, 18.2, −4.47, −4.53; \)

IR 3400, 2929, 2857, 1251, 1055, 835, 776 cm\(^{-1} \);

HRMS (ESI, +ve): \( m/z [M + Na]^+ \) calcd for C\(_{14}\)H\(_{38}\)O\(_5\)Si•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 In\(_3\)Cl \(_3\) (224 mg, 1.01 mmol) in acetonitrile (8.0 mL) containing a trace of water (40 \( \mu \)L) 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-butylidemethylsilyl-\( \alpha \)-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 \( \mu \)L, 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 (1 \( \times \) 3 mL of a 1 M aq. solution) followed by NaHCO\(_3\) (1 \( \times \) 3 mL of a sat. aq. solution). The combined aqueous phases were extracted with dichloromethane (3 \( \times \) 5 mL) and the combined organic layers washed with ammonium chloride (1 \( \times \) 3 mL of a sat. aq. solution) then CuSO\(_4\) (1 \( \times \) 3 mL of a 5% w/w aq. solution) before being dried (Na\(_2\)SO\(_4\)), filtered and concentrated under reduced pressure. The residue so-obtained was subjected to flash column chromatography (silica, 4:1 v/v pet. spirit/ethyl acetate elution) to afford, after concentration of the appropriate fractions \( (R_f = 0.5) \), alcohol 16 (48.1 mg, 69%) as a clear, colourless oil.

\[ [\alpha]_D +82 \ (c = 0.20, \text{CHCl}_3); \]

\( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.09 \ (m, 2H) \), 7.59 (m, 1H), 7.45 (m, 2H), 5.84 (m, 1H), 5.28 (app. dq, \( J = 17.2 \), 1.7 Hz, 1H), 5.13 (app. dq, \( J = 10.6 \), 1.7 Hz, 1H), 5.10 (d, \( J = 3.7 \) Hz, 1H), 4.94 (dd, \( J = 10.0, 3.7 \) Hz, 1H), 4.19 (m, 1H), 4.07 (dd, \( J = 10.0, 8.5 \) Hz, 1H), 3.97 (m, 1H),
3.74 (m, 1H), 3.63-3.55 (complex m, 2H), 2.28 (br s, 1H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 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$_6$Si•Na: 431.1866; found: 431.1865.

**Allyl 3-O-Acetyl-2-O-chloroacetyl-4-O-tert-butyldimethylsilyl-\(\alpha\)-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 $\mu$L, 8.59 mmol) then cooled to –78 °C before being treated, dropwise, with $\alpha$-chloroacetyl chloride (630 $\mu$L, 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 (1 × 15 mL of a sat. aq. solution) then CuSO$_4$ (1 × 15 mL of a 5% w/w aq. solution). The combined organic phases were then filtered through a short pad of Celite$^\circledR$ contained in a sintered glass funnel. The pad was then washed with dichloromethane (1 × 10 mL) and the combined filtrates washed with brine (1 × 10 mL) before being dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash column chromatography (silica, 7:1 v/v pet. spirit/ethyl acetate 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$_3$): $\delta =$ 5.86 (m, 1H), 5.37 (m, 1H), 5.29 (app. dq, $J =$ 16.8, 1.6 Hz, 1H), 5.20 (m, 1H), 4.99 (d, $J =$ 3.7 Hz, 1H), 4.78 (dd, $J =$ 10.2, 3.7 Hz, 1H), 4.18 (m, 1H), 4.03 (s, 2H), 3.96 (m, 1H), 3.78 (ddd, $J =$ 9.9, 8.9, 6.4 Hz, 1H), 3.66-3.52 (complex m, 2H), 2.03 (s, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta =$ 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$_{31}$ClO$_7$Si•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 SI.

**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 CS₂ (700 μL, 11.6 mmol) in 1,4-dioxane (6.0 mL). Di-iso-propylethylamine (2.60 mL, 14.9 mmol) was then added dropwise and the ensuing mixture 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), CuSO₄ (1 × 20 mL of a 5% w/w aq. solution) and brine (1 × 10 mL). The separated organic layer was then dried (Na₂SO₄), 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/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.6) then gave compound 3 (98.3 mg, 90%) as a clear, colourless oil.

|α|D| +106 (c = 0.27, CHCl₃);

**1**H NMR (400 MHz, CDCl₃): δ = 5.92 (m, 1H), 5.31 (app. dq, J = 17.2, 1.6 Hz, 1H), 5.23 (app. dq, J = 10.3, 1.6 Hz, 1H), 5.08 (app. t, J = 9.4 Hz, 1H), 4.84 (d, J = 3.8 Hz, 1H), 4.23 (m, 1H), 4.01 (m, 1H), 3.72 (m, 1H), 3.60-3.43 (complex m, 3H), 2.11 (s, 3H), 2.08 (d, J = 11.6 Hz, 1H), 0.85 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H);

**13**C NMR (101 MHz, CDCl₃): 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;


**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 methanol (50.0 mL) maintained at 22 °C was treated with Zn(OAc)₂•2H₂O (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 NaHCO₃ (10 mL of a sat. aq. solution) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were then washed with brine (1 × 10 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash column chromatography (silica, 8:1 v/v pet. spirit/ethyl acetate elution) to afford, after concentration of the appropriate fractions (RF = 0.4), compound 19 (741 mg, 86%) as a clear colourless oil.

[α]D +84 (c = 0.84, CHCl₃);

1H NMR (400 MHz, CDCl₃): δ = 5.87 (m, 1H), 5.39-5.26 (complex m, 2H), 5.19 (app. dq, J = 10.4, 1.4 Hz, 1H), 4.96 (d, J = 3.6 Hz, 1H), 4.74 (dd, J = 10.3, 3.6 Hz, 1H), 4.18 (m, 1H), 3.97 (m, 1H), 3.77 (ddd, J = 10.3, 8.9, 6.1 Hz, 1H), 3.65-3.50 (complex m, 2H), 2.04 (s, 3H), 2.03 (s, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H);

13C NMR (101 MHz, CDCl₃): 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;


**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 CaCO₃ (2 mL of a sat. aq. solution) and NaHCO₃ (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 ethyl acetate (2 × 15 mL). The combined organic phases were then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v pet. spirit/ethyl acetate
elution) to afford, after concentration of the appropriate fractions ($R_f = 0.4$), compound 5 (199 mg, 84%) as a clear, colourless oil. 
$\left[\alpha\right]_D +101 \ (c = 0.97, \text{CHCl}_3)$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 5.86 \ (m, 1H), 5.29 \ (\text{app. dq}, J = 17.3, 1.6 \ Hz, 1H), 5.21 \ (m, 2H), 4.97 \ (d, J = 3.7 \ Hz, 1H), 4.79 \ (\text{dd}, J = 10.0, 3.7 \ Hz, 1H), 4.18 \ (\text{app. ddt}, J = 13.2, 5.0, 1.6 \ Hz, 1H), 3.97 \ (\text{app. ddt}, J = 13.2, 6.1, 1.6 \ Hz, 1H), 3.82-3.68 \ (\text{complex m, 2H}), 3.61 \ (m, 1H), 2.80 \ (\text{br s, 1H}), 2.09 \ (s, 3H), 2.06 \ (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 172.1, 170.4, 133.5, 117.8, 94.9, 74.0, 70.7, 69.6, 68.4, 61.8, 21.0, 20.9$;

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

HRMS (ESI, $+ve$): $m/z$ [M + Na]$^+$ calced for C$_{12}$H$_{18}$O$_7$•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$_2$SO$_4$), filtered and concentrated under reduced pressure. The yellow oil so-obtained was subjected to flash column chromatography (silica, 9:1 v/v pet. spirit/ethyl acetate 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 $\alpha$- and $\beta$-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-$\alpha$-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$_2$SO$_4$, 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$_2$SO$_4$), filtered and concentrated under reduced pressure. The viscous oil thus obtained was dissolved in DMF (30 mL) and the resulting and magnetically stirred solution 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$_3$ (1 × 50 mL of sat. aq. solution) and water (1 × 50 mL) before being dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue so-obtained was subjected to flash column chromatography (silica gel, 6:1 v/v pet. spirit/ethyl acetate 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, 15H), 5.92 (m, 1H), 5.32 (app. dq, J = 17.1, 1.6 Hz, 1H), 5.27-5.19 (complex m, 3H), 4.92 (d, J = 10.8 Hz, 1H), 4.84-4.74 (complex m, 3H), 4.62 (d, J = 12.1 Hz, 1H), 4.22-4.14 (complex m, 2H), 4.02 (m, 1H), 3.91 (m, 1H), 3.54 (dd, J = 9.6, 3.6 Hz, 1H), 3.43 (dd, J = 10.0, 9.0 Hz, 1H), 3.35 (s, 3H);

$^{13}$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$_7$•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$_2$SO$_4$, 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/ethyl acetate 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 $\alpha$- and $\beta$-anomers.

$[\alpha]_D = +38$ ($c = 0.29$, CHCl$_3$);

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ ($\alpha$-anomer) = 7.42-7.25 (complex m, 10H), 5.92 (m, 1H), 5.33 (app. dq, $J = 17.1$, 1.6 Hz, 1H), 5.24 (app. dq, $J = 10.3$, 1.6 Hz, 1H), 4.93 (d, $J = 10.9$ Hz, 1H), 4.85-4.73 (complex m, 3H), 4.62 (d, $J = 12.0$ Hz, 1H), 4.19 (m, 1H), 4.15 (d, $J = 10.0$ Hz, 1H), 4.01 (m, 1H), 3.91 (app. $J = 9.3$ Hz, 1H), 3.80 (s, 3H), 3.54 (m, 1H), 3.50 (s, 3H), 3.44 (dd, $J = 10.0$, 9.0 Hz, 1H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ ($\alpha$-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]$^+$ calecd 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 methanol (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 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/ethyl acetate 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 $\alpha$- and $\beta$-anomers.

$[\alpha]_D = +13$ ($c = 0.27$, CHCl$_3$);

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ ($\alpha$-anomer) = 7.40-7.29 (complex m, 15H), 5.21 (m, 3H), 4.85 (d, $J = 10.9$ Hz, 1H), 4.79 (d, $J = 11.1$ Hz, 1H), 4.74 (m, 1H), 4.65 (d, $J = 11.8$ Hz, 1H), 4.41 (d, $J = 9.6$ Hz, 1H), 3.94-3.83 (complex m, 1H), 3.59-3.52 (complex m, 1H), 3.49-3.40 (complex m, 1H), 3.36 (s 3H), 2.98 (br s, 1H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ ($\alpha$-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]$^+$ calecd 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 methanol (20 mL), and maintained at 0 °C while being protected from moisture, was treated with PdCl₂ (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/ethyl acetate elution) to afford, after concentration of the relevant fractions (Rf = 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; [α]D +29 (c = 0.33, CHCl₃);

1H NMR (400 MHz, CDCl₃): δ (α-anomer) = 7.42-7.27 (complex m, 10H), 5.20 (app. t, J = 3.2 Hz, 1H), 4.89-4.81 (complex m, 2H), 4.77 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 9.6 Hz, 1H), 3.87 (app. t, J = 9.0 Hz, 1H), 3.79 (s, 3H), 3.56 (m, 1H), 3.50 (s, 3H), 3.46 (m, 1H), 3.02 (br s, 1H);

13C NMR (101 MHz, CDCl₃): 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;


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 K₂CO₃ (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/ethyl acetate elution) to afford, after concentration of the appropriate fractions (Rf = 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; [α]D +18 (c = 0.38, CHCl₃);
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (β-anomer) = 8.73 (s, 1H), 7.36-7.27 (complex m, 10H), 5.85 (d, $J = 7.3$ Hz, 1H), 4.99-4.69 (complex m, 4H), 4.01 (d, $J = 9.1$ Hz, 1H), 3.81 (s, 3H), 3.78-3.61 (complex m, 3H), 3.51 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ (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$_{26}$O$_4$N•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/ethyl acetate elution) to give two fractions, A and B.

Concentration of fraction A ($R_f = 0.3$ in 5:1 v/v pet. spirit/ethyl acetate) 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$_3$): $\delta$ = 7.41-7.27 (complex m, 10H), 5.88 (m, 1H), 5.38 (dd, $J = 10.0$, 8.8 Hz, 1H), 5.30 (app. dq, $J = 16.9$, 1.6 Hz, 1H), 5.14 (app. dq, $J = 10.4$, 1.6 Hz, 1H), 4.93 (d, $J = 3.5$ Hz, 1H), 4.87 (m, 2H), 4.79 (d, $J = 11.0$ Hz, 1H), 4.71 (d, $J = 11.9$ Hz, 1H),
4.63 (d, J = 11.9 Hz, 1H), 4.17 (m, 2H), 3.96 (m, 1H), 3.85 (d, J = 9.3 Hz, 1H), 3.81 (s, 3H), 3.70 (m, 1H), 3.60 (m, 2H), 3.50 (m, 2H), 3.44 (s, 3H), 3.37 (m, 1H), 2.07 (s, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H);

$^{13}$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, 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•Na: 753.3282; found: 753.3287.

Concentration of fraction B (R$_f$ = 0.4 in 5:1 v/v pet. spirit/ethyl acetate) afforded compound 31 (35.0 mg, 12%) as a clear, yellow oil.

[α]$_D$ +48 (c = 0.70, CHCl$_3$);

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.40-7.27 (complex m, 10H), 5.95 (m, 1H), 5.47 (dd, J = 10.2, 8.4 Hz, 1H), 5.36 (app. dq, J = 17.2, 1.7 Hz, 1H), 5.20 (app. dq, J = 10.7, 1.7 Hz, 1H), 4.97 (d, J = 3.6 Hz, 1H), 4.86 (dd, J = 11.3, 3.6 Hz, 2H), 4.76 (d, J = 10.9 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.50 (d, J = 7.6 Hz, 1H), 4.21 (m, 1H), 4.06 (m, 1H), 3.81 (s, 3H), 3.77 (dd, J = 6.8, 2.7 Hz, 1H), 3.72 (m, 1H), 3.65 (app. td, J = 10.3, 3.3 Hz, 2H), 3.56-3.50 (complex m, 3H), 3.48 (s, 3H), 3.43 (m, 1H), 1.86 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H);

$^{13}$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•Na: 753.3282; found: 753.3287.

Allyl 3-0-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$_2$O 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 ethyl acetate (2 × 15 mL). The combined organic phases were then dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography
(silica, 1:2 v/v pet. spirit/ethyl acetate 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$_3$): $\delta$ = 7.42-7.26 (complex m, 10H), 5.88 (m, 1H), 5.30 (app. dq, $J$ = 16.9, 1.6 Hz, 1H), 5.18 (m, 2H), 4.94 (dd, $J$ = 7.1, 3.4 Hz, 2H), 4.89 (d, $J$ = 10.9 Hz, 1H), 4.79 (d, $J$ = 10.9 Hz, 1H), 4.69 (m, 2H), 4.30 (d, $J$ = 10.0 Hz, 1H), 4.20 (m, 1H), 3.98 (m, 1H), 3.87 (app. t, $J$ = 9.3 Hz, 1H), 3.81 (s, 3H), 3.79-3.59 (complex m, 4H), 3.52 (dd, $J$ = 9.7, 3.5 Hz, 1H), 3.46 (s, 3H), 3.41 (dd, $J$ = 10.0, 9.0 Hz, 1H), 2.91 (br s, 1H), 2.17 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 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$_{12}$•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 reaction mixture was continued at −20 °C for 1 h then it 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/ethyl acetate 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\(_3\)): \(\delta = 7.34-7.27\) (complex m, 10H), 5.85 (m, 1H), 5.41 (app. t, \(J = 9.1\) Hz, 1H), 5.29 (br dd, \(J = 16.5, 1.7\) Hz, 1H), 5.14 (br dd, \(J = 11.0, 1.7\) Hz, 1H), 5.09 (app. t, \(J = 7.8\) Hz, 1H), 5.05 (app. t, \(J = 8.1\) Hz, 1H), 4.92 (d, \(J = 3.5\) Hz, 1H), 4.89 (m, 1H), 4.86 (d, \(J = 10.9\) Hz, 1H), 4.83 (d, \(J = 3.4\) Hz, 1H), 4.81 (m, 1H), 4.78 (d, \(J = 10.9\) Hz, 1H), 4.71 (m, 2H), 4.62 (d, \(J = 12.0\) Hz, 1H), 4.56 (d, \(J = 6.0\) Hz, 1H), 4.48 (d, \(J = 6.0\) Hz, 1H), 4.17 (d, \(J = 10.1\) Hz, 1H), 4.14 (br. dd, \(J = 13.1, 5.7\) Hz, 1H), 4.09 (dd, \(J = 12.0, 4.7\) Hz, 1H), 3.95 (m, 2H), 3.84 (app. t, \(J = 9.4\) Hz, 1H), 3.80 (s, 3H), 3.78 (d, \(J = 8.1\) Hz, 1H), 3.69 (app. q, \(J = 9.1\) Hz, 1H), 3.60 (m, 3H), 3.48 (m, 1H), 3.43 (s, 3H), 3.41-3.31 (complex m, 3H), 2.06 (s, 3H), 2.05(4) (s, 3H), 2.05(1) (s, 3H), 2.03(4) (s, 3H), 2.03(2) (s, 3H), 2.02(9) (s, 3H);

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 170.5, 170.1, 169.9, 169.8, 169.5, 169.3, 138.8, 138.3, 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-\(\alpha\)-\(D\)-xylopyranosyl-(1\(\rightarrow\)2)-methyl-2,3,4-tri-\(O\)-acetyl-\(\beta\)-\(D\)-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/ethyl acetate elution then, separately, employing 9:1 v/v dichloromethane/diethyl ether elution and 5:2 v/v pet. spirit/ethyl acetate elution) to afford, after concentration of the relevant fractions (\(R_f = 0.2\) in 5:2 v/v pet. spirit/ethyl acetate), 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; [α]D +17 (c = 0.38, CHCl₃);

1H NMR (400 MHz, CDCl₃): δ = 5.92 (m, 1H), 5.37-5.29 (complex m, 2H), 5.27-5.15 (complex m, 3H), 4.98 (m, 1H), 4.91 (d, J = 3.6 Hz, 1H), 4.66 (d, J = 7.8 Hz, 1H), 4.17 (m, 1H), 4.05 (m, 1H), 4.00 (d, J = 9.5 Hz, 1H), 3.74 (s, 3H), 3.68 (m, 1H), 3.59 (m, 2H), 3.50 (dd, J = 10.4, 5.6 Hz, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H);

13C NMR (101 MHz, CDCl₃): 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;


Conflicts of Interest
The authors declare no competing financial interest.

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Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/a-XXXX-XXXX. 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 ¹H and ¹³C NMR spectra of compounds 2, 3, 4 (R =Me), 5, 7, 9, 11-17, 19, 21-34 and 36-40 are also provided.
References and Notes


10. Recently we have shown that the exhaustive sulfation of compounds related to 1 results in the associated xylose residues preferentially adopting a $^1C_4$ conformation: Vo, Y.; Schwartz, B. D.; Onagi, H.; Ward, J. S.; Gardiner, M. G.; Banwell, M. G.; Nelms, K.; Malins, L. R. Chem. Eur. J. 2021, 27, 9830. However, for the sake of consistency with the prior literature concerned with such compounds, in this paper we show such residues in the $^4C_1$ conformation.


12. The realization of related objectives has recently been reported by Madsen et al., see: Underlin, E. N.; d’Errico, C.; Böhm, M.; Madsen, R. Eur. J. Org. Chem. 2020, 3050.


Supporting Information

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

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(ii) Figures 3-6: Key NMR spectral data used to establish the structures of compounds 3, 12 and 13, 31 and 32 and 34 ................................................................. S3
(iii) General experimental procedures .................................................................. S5
(iv) References and Notes ................................................................................. S7
(v) Copies of the 1H and 13C{1H} NMR spectra of compounds 2, 3, 4 (R =Me), 5, 7, 9, 11-17, 19, 21-34 and 37-40 ............................................................. S8
Figure 1: ORTEPs derived from a single-crystal X-ray analysis of an 85:15 mixture of compounds 17 (left) and 18 (right) (displacement ellipsoids show 50% probability levels) (CCDC No. 2256633). In both structures the allyl group was disordered over two positions in a 7:3 ratio.

Figure 2: ORTEP derived from a single-crystal X-ray analysis of compound 40 (displacement ellipsoids show 50% probability levels) (CCDC No. 2256634).
<table>
<thead>
<tr>
<th>Position</th>
<th>$^{13}$C NMR $\delta$ (ppm)</th>
<th>$^1$H NMR $\delta$ (ppm)</th>
</tr>
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<tr>
<td>1</td>
<td>97.8</td>
<td>4.84</td>
</tr>
<tr>
<td>2</td>
<td>71.4</td>
<td>3.60 – 3.43</td>
</tr>
<tr>
<td>3</td>
<td>76.3</td>
<td>5.08</td>
</tr>
<tr>
<td>OH</td>
<td>N/A</td>
<td>2.08</td>
</tr>
<tr>
<td>C=O</td>
<td>171.3</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Figure 3:** (left) HMBC and $^1$H-$^1$H COSY correlations used to establish the structure of the compound 3; (right) assignment of key resonances from the associated $^{13}$C and $^1$H NMR spectra

**Figure 4:** HMBC and $^1$H-$^1$H COSY correlations used to establish the structures of the regio-isomeric acetonides 12 and 13
Figure 5: HMBC correlations and key chemical shifts and proton-proton couplings observed for the epimeric disaccharides 31 and 32.

<table>
<thead>
<tr>
<th>Anomeric proton</th>
<th>1H NMR δ (ppm)</th>
<th>1H NMR δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ha</td>
<td>4.93 (J = 3.5 Hz)</td>
<td>4.97 (J = 3.5 Hz)</td>
</tr>
<tr>
<td>Hb</td>
<td>4.85 (J = 3.4 Hz)</td>
<td>4.50 (J = 7.6 Hz)</td>
</tr>
<tr>
<td>32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 6: (above) HMBC and 1H-1H COSY correlations used to establish the structure of the compound 34; (below) assignment of key resonances from the associated 1H NMR spectrum.

<table>
<thead>
<tr>
<th>Anomeric proton</th>
<th>1H NMR δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ha</td>
<td>4.92 (d, J = 3.5 Hz)</td>
</tr>
<tr>
<td>Hb</td>
<td>4.83 (d, J = 3.4 Hz)</td>
</tr>
<tr>
<td>Hc</td>
<td>4.48 (d, J = 6.4 Hz)</td>
</tr>
<tr>
<td>Hd</td>
<td>4.56 (d, J = 6.0 Hz)</td>
</tr>
</tbody>
</table>
General Procedures

$^1$H NMR spectra were recorded at 600 MHz or 400 MHz, using a Bruker AVANCE 600 or Bruker AVANCE 400 spectrometer. Residual solvent peaks were used as an internal reference (CHCl$_3$ δ 7.26 ppm, CD$_3$HD δ 7.16 ppm or DMSO-$d_5$ δ 2.50 ppm). Data from the $^1$H NMR spectra were reported as: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. In situations where first order multiplets arise due to coupling to two or more chemically distinct nuclei with the same coupling constant ($J$), the terminology ‘apparent (app.) multiplet’ is used [e.g., for a 1:2:1 apparent triplet integrating to one proton (dd with two equivalent $J$’s)]. $^{13}$C NMR spectra were recorded at 151 MHz or 101 MHz using a Bruker AVANCE 600 or Bruker AVANCE 400 spectrometer. Solvent peaks were similarly used as an internal reference (CDCl$_3$ δ 77.16 ppm, C$_6$D$_6$ δ 128.06 ppm or DMSO-$d_6$ δ 39.5 ppm). When a mixture of anomers was obtained, only the spectral data of the major anomer was reported in $^1$H and $^{13}$C NMR, as stated. Infrared spectra (ν$_{\text{max}}$) were recorded on a Perkin-Elmer “Spectrum Two” FTIR Spectrometer and samples were analysed neat. Low-resolution electrospray (ESI) mass spectra were recorded on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer. High-resolution electrospray mass spectra were recorded on either the above or an Orbitrap Velos Pro Mass Spectrometer with a resolution of 240,000. Melting points were measured on a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Optical rotations were measured in an Autopol I at the sodium-D line ($\lambda = 589$ nm) between 17 and 20 °C and at the concentrations ($c$, in g/100 mL) indicated using spectroscopic grade chloroform (CHCl$_3$) or methanol (CH$_3$OH) as solvent. Crystallographic data for all compounds were collected on an Oxford-Agilent SuperNova instrument with focused micro-source Cu Kα ($\lambda = 1.5418$ Å) radiation and Eos S2 CCD area detector, with data reduction performed using Crysalis PRO.$^1$ All structures were solved using direct methods with SHELXT and refined on $F^2$ using all data by full matrix least-squares procedures with SHELXL within OLEX2.$^{2-4}$ Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included in calculated positions with isotropic displacement parameters 1.2 times the isotropic equivalent of their carrier atoms. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F$_{254}$ plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). The retardation factor ($R_f$) values cited have been rounded to the second decimal point. Flash chromatographic separations were carried out according to protocols defined by Still et al.$^5$ with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were commercially available from Sigma–Aldrich, Merck, TCI, Strem, AK Scientific.
or Lancaster chemical companies and were used as supplied. Drying agents and other inorganic salts were purchased commercially from the AJAX, BDH or Unilab chemical companies. The pet. spirit used was 40-60 °C unless otherwise specified. Reactions were conducted under a positive pressure of dry nitrogen or argon in oven-dried glassware and, unless otherwise specified, at 22 °C.
References and Notes


400 MHz $^1$H NMR spectrum of compound 2 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 2 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 3 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 3 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 4 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 4 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 5 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 5 (recorded in CDCl$_3$)
4. $^1$H and $^{13}$C NMR spectra

600 MHz $^1$H NMR spectrum of compound 7 (recorded in CDCl$_3$)
151 MHz $^{13}$C NMR spectrum of compound 7 (recorded in CDCl$_3$).
400 MHz $^1$H NMR spectrum of compound 9 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 9 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 11 (recorded in DMSO-$d_6$)
101 MHz $^{13}$C NMR spectrum of compound 11 (recorded in DMSO-$d_6$)
400 MHz $^1$H NMR spectrum of compound 12 (recorded in C$_6$D$_6$)
101 MHz $^{13}$C NMR spectrum of compound 12 (recorded in C$_6$D$_6$)
400 MHz $^1$H NMR spectrum of compound 13 (recorded in C$_6$D$_6$)
101 MHz $^{13}$C NMR spectrum of compound 13 (recorded in $C_6D_6$)
400 MHz $^1$H NMR spectrum of compound 14 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 14 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 15 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 15 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 16 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 16 (recorded in CDCl$_3$)
$\text{H NMR spectrum of compound 17 (recorded in CDCl}_3$)
101 MHz $^{13}$C NMR spectrum of compound 17 (recorded in CDCl$_3$)
400 MHz $^1H$ NMR spectrum of compound 19 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 19 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 21 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 21 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 22 (recorded in CDCl$_3$)
101 MHz 13C NMR spectrum of compound 22 (recorded in CDCl₃)
400 MHz $^1$H NMR spectrum of compound 23 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 23 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 24 (recorded in CDCl$_3$)
$^{13}$C NMR spectrum of compound 24 (recorded in CDCl$_3$).
400 MHz $^1$H NMR spectrum of compound 25 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 25 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 26 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 26 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 27 (recorded in CDCl$_3$)
$^{13}$C NMR spectrum of compound 27 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 28 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 28 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 29 (recorded in CDCl$_3$)

$^1$H NMR spectrum of compound 29 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 29 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 30 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 30 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 31 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 31 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 32 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 32 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 33 (recorded in CDCl$_3$)
151 MHz $^{13}$C NMR spectrum of compound 33 (recorded in CDCl$_3$)
600 MHz $^1$H NMR spectrum of compound 34 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 34 (recorded in CDCl$_3$)
$400 \text{ MHz } {^1\text{H}} \text{ NMR spectrum of compound 37 (recorded in CDCl}_3$)
101 MHz $^{13}$C NMR spectrum of compound 37 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 38 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 38 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 39 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 39 (recorded in CDCl$_3$)
400 MHz $^1$H NMR spectrum of compound 40 (recorded in CDCl$_3$)
101 MHz $^{13}$C NMR spectrum of compound 40 (recorded in CDCl$_3$)