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An approach to the synthesis of α-(1-6)-*C*-disaccharides by tandem Tebbe methylenation and Claisen rearrangement

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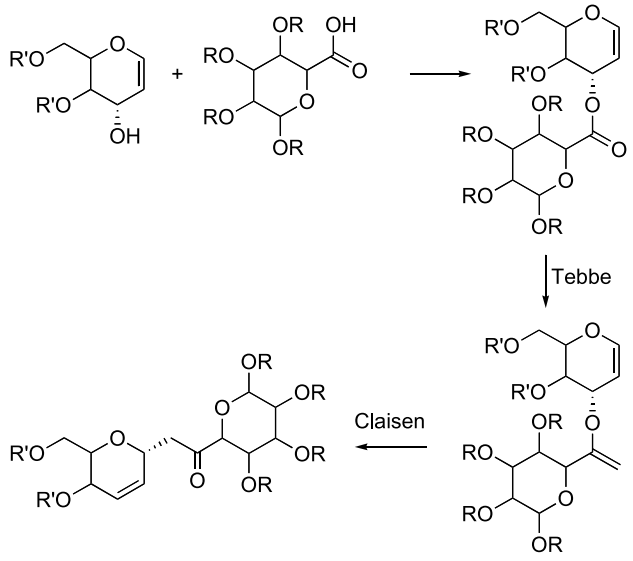
Abstract—Uronic acids, most efficiently synthesised from the corresponding alcohols by two step Dess-Martin and sodium chlorite mediated oxidation, may be used as coupling partners for esterification with an *allo* glycal as substrates for the tandem Tebbe/Claisen approach to the synthesis of 1-6 linked *C*-disaccharides. Whilst esters of glucuronic and mannuronic acids successfully undergo Tebbe methylenation, esters derived from galacturonic acids are unreactive under these conditions. Thermal Claisen rearrangement of vinyl ethers produced by methylenation yields α-*C*-disaccharides with complete control of anomeric stereochemistry.

1. Introduction

It is now well established that oligosaccharides play a huge number of crucially important roles in an enormously wide variety of fundamentally important biological systems.[1] It has also been long-proposed that carbohydrate mimetics[2] may be expected to display interesting biological activity either as enzyme inhibitors, for example, by inhibition of glycosidases or glycosyl tranferases, or as inhibitors or mediators of carbohydrate recognition events. Although the number of currently administered glycomimetic drugs is small, such molecules are expected to provide the basis of several new therapeutic strategies against a variety of disease states and infective agents in the future.[3]

Significant interest has recently, arisen in the synthesis of *C*-disaccharides,[4] in which the interglycosidic oxygen atom of a natural *O*-linked disaccharide is replaced by a methylene unit. These materials have been proposed as non-hydrolysable disaccharide mimetics, which may display interesting biological activity,[5] and therefore, perhaps therapeutic potential.

In principle the Tebbe/Claisen approach which, as recently, reported, allows stereospecific access to a wide range of *C*-glycoside materials,[6] could be advantageously applied to the synthesis of a variety of (1-6) linked *C*-disaccharides. This tandem approach initially involves esterification of a glycal possessing a free 3-hydroxyl group with a carboxylic acid. Tebbe methylenation[7] of the resultant ester can then be followed by [3,3] sigmatropic rearrangement[8,9] yielding the *C*-glycoside product in a predictable and entirely stereoselective fashion. One particular attraction of this approach is that carbohydrate-derived carboxylic acids may be used for the esterification step. In particular, selective oxidation of the primary hydroxyl of any one of the hexoses would readily provide access to suitable coupling partners. Tebbe methylenation of the resultant esters could then be followed



Scheme 1.

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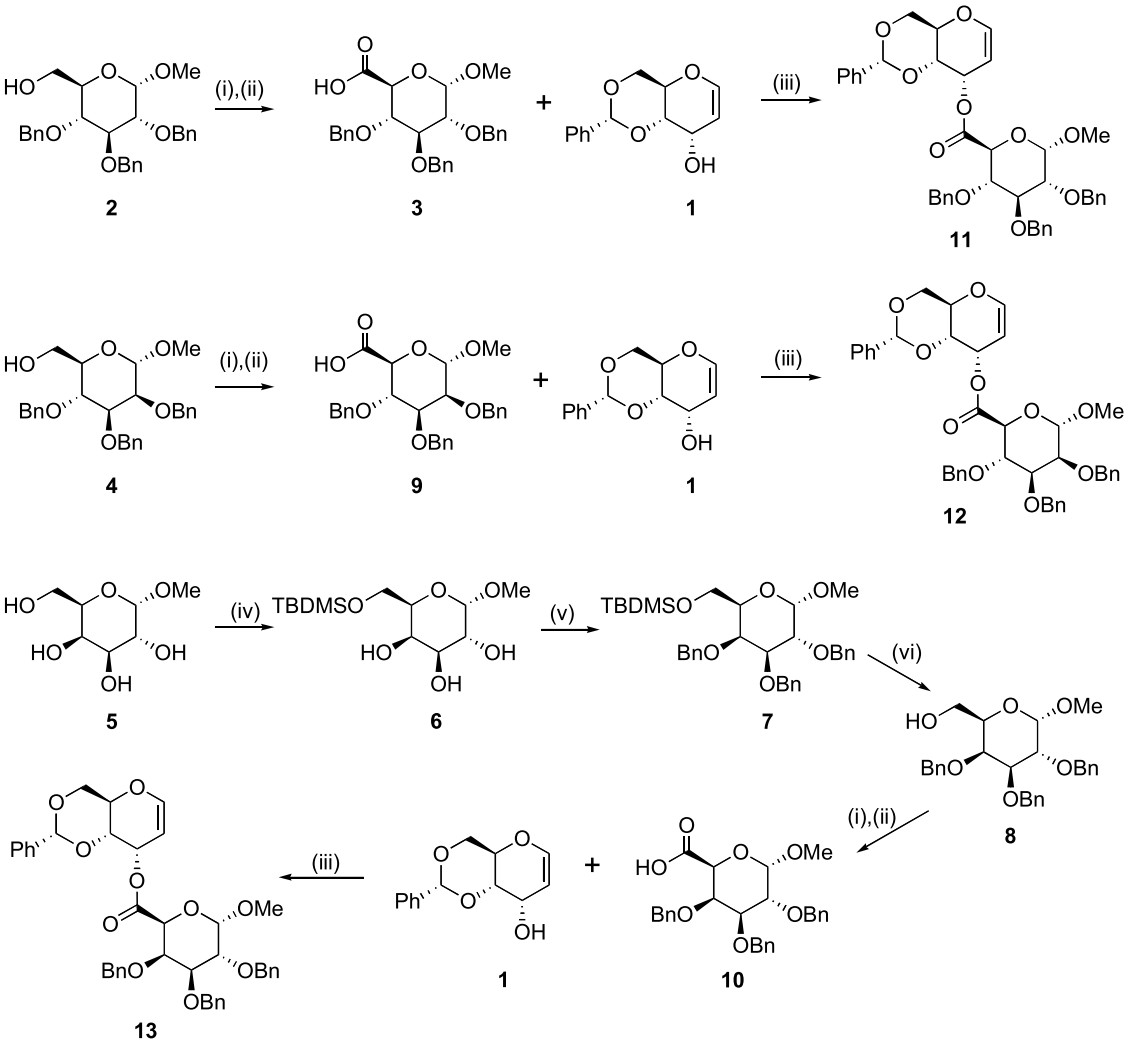
by Claisen rearrangement to yield 1-6-linked disaccharides, with complete control of anomeric stereochemistry (Scheme 1). This paper gives full details of investigations into the applicability of the tandem Tebbe/Claisen approach for the synthesis of a series of α-(1-6)-linked *C*-disaccharides.[10]

2. Results and discussion

2.1. Synthesis of uronic acid substrates and esterification

allo Glycal **1**, accessed using published synthetic routes,[11] was selected for esterification reactions, since sigmatropic rearrangement of a 3-*O* vinyl ether derived from **1** would produce a *C*-glycoside with the desired α-anomeric stereochemistry. It was envisaged that a series of uronic acids could be accessed via simple oxidation of the corresponding selectively protected alcohols in which only the primary OH-6 hydroxyl was free. The *gluco* alcohol **2** was synthesised using standard procedures[12] in order to provide a substrate for investigation of the most efficient and reliable method of achieving such an oxidation. Firstly several reagent combinations were investigated for effecting the one-pot oxidation directly to the carboxylic acid. Unfortunately the ruthenium trichloride/sodium periodate system,[13] which had proven to be an excellent method for oxidation of diacetone galactose to the corresponding galacturonic acid[6a] proved to be incompatible with the benzyl protection of the other hydroxyls of **2**. In addition, although a TEMPO[14] mediated oxidation with trichloroisocyanuric acid as co-oxidant did on one occasion provide the desired product **3** in 64% yield, the reaction proved unreliable and was unrepeatable. It was finally, concluded that in fact a two-step oxidation was the most efficient route to the desired product; sequential oxidation of alcohol **2** firstly by treatment with the Dess–Martin periodinane[15] and then immediate oxidation of the crude aldehyde product by treatment with sodium chlorite in the presence of 2-methyl-2-butene as a Cl^+ scavenger[16] yielded the desired acid **3**[17] in quantitative yield over two steps (Scheme 2).

With this optimised oxidation protocol in hand, further uronic acids were synthesised. The known *manno* alcohol **4**[18] was accessed by literature procedures. The corresponding *galacto* alcohol **8** was accessed from methyl



Scheme 2. Reagents and conditions: (i) Dess–Martin periodinane, DCM; (ii) $NaClO_2$, NaH_2PO_4, Bu^{t}OH, THF, H_2O, 2-methyl-2-butene, quantitative over two steps; (iii) DCC, DMAP, DCM; **11**, 83%; **12**, 76%; **13** 87%; (iv) TBDMSCl, imidazole, DMF, 0 °C, 92%; (v) BnBr, NaH, DMF, 84%; (vi) TsOH, MeCN, H_2O, 90%.

galactopyranoside **5** via a three-step reaction sequence. Thus, regioselective silylation of **5** with *tert*-butyldimethylsilylchloride and imidazole in DMF at 0 °C yielded the known silyl ether **6**[19] (92% yield). Benzylation of the remaining free hydroxyl groups by treatment of **6** with benzyl bromide and sodium hydride in DMF yielded completely protected galactoside **7** (84% yield). Finally, de-silylation by treatment of **7** with toluenesulfonic acid in aqueous acetonitrile[20] yielded the desired alcohol **8** (90% yield). Both *manno* and *galacto* alcohols were then oxidised smoothly to the desired carboxylic acids **9** and **10** by the two-step Dess–Martin/sodium chlorite procedure (both in quantitative yield over two steps). Finally, all three acids **3**, **9** and **10** were esterified by treatment with glycal **1** in the presence of dicyclohexylcarbodiimide (DCC) and dimethylamino pyridine (DMAP), in dichloromethane (DCM), to yield the corresponding *gluco*, *manno* and *galacto* esters **11**, **12** and **13** in 83, 76, and 87% yields, respectively, (Scheme 2).

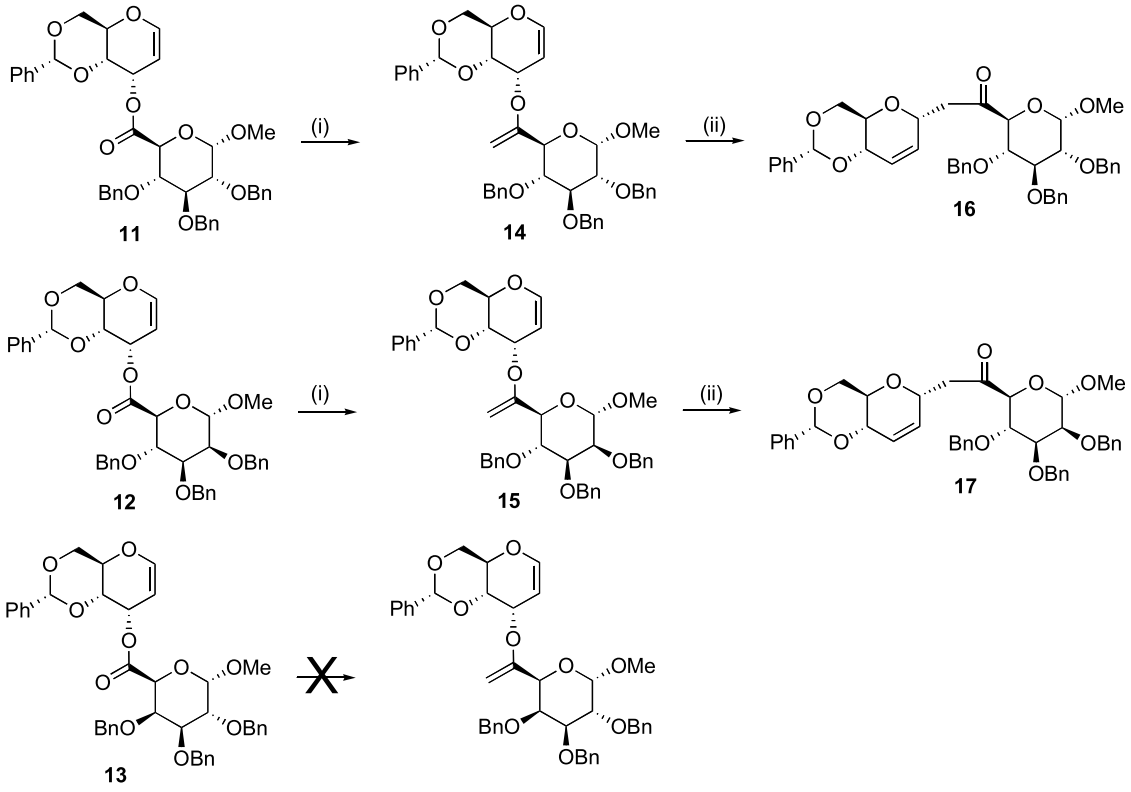
2.2. Tebbe methylenation and Claisen rearrangement

Methylenation reactions by the Tebbe reagent were attempted on the three esters **11**–**13**. Both *gluco* and *manno* esters **11** and **12** were smoothly methylenated by the Tebbe reagent to yield the desired enol ethers **14** and **15** in 82 and 76% yields, respectively, (Scheme 2). However, the corresponding *galacto* ester **13** was inert to methylenation under these conditions. Indeed despite protracted reaction times, and performing the reaction at room temperature the starting material was recovered in this case.[21]

With two substrates in hand Claisen rearrangement of both vinyl ethers **14** and **15** was undertaken. Mindful of previous studies[22] which had clearly demonstrated that in the case of α-*C*-glycosides the stereochemical purity of the product was dependent on the precise reaction conditions, thermal rearrangement of both substrates was undertaken in xylene in a sealed tube at 185 °C. Pleasingly under these conditions vinyl ethers **14** and **15** both underwent smooth stereocontrolled rearrangement to yield only the desired α-*C*-glycoside products **16** and **17** in 66 and 83% yields, respectively, (Scheme 3).

3. Conclusions

These studies demonstrate that the use of uronic acids, together with glycals in which the 3-hydroxyl group is not protected, allows access to (1-6)-linked *C*-disaccharide materials via the tandem Tebbe/Claisen approach. Uronic acid substrates for this reaction sequence were most efficiently obtained from selectively protected hexoses by a two-step oxidation process involving treatment of the alcohol firstly with the Dess–Martin periodinane and then immediate further, oxidation with sodium chlorite. The product carboxylic acids were readily esterified with the 3-hydroxyl group of the glycal. The efficiency of the Tebbe methylenation step was actually dependent on the stereochemistry of the uronic acid; whilst both *gluco* and *manno* esters readily underwent methylenation the *galacto* counterpart was resistant to reaction. Both *gluco* and *manno* vinyl ethers then underwent smooth thermal Claisen reaction to yield the desired α-*C*-disaccharide products with complete



Scheme 3. Reagents and conditions: (i) Tebbe reagent, THF, pyridine, −40 °C to rt, 16 h; **14**, 82%; **15**, 76%; (ii) 185 °C, xylene, sealed tube, 12 h; **16**, 66%; **17**, 83%.

control of stereochemistry. Further studies on the use of this tandem approach to *C*-disaccharide synthesis and in particular iteration of the process to allow access to (1-6)-linked *C*-oligosaccharides are currently in progress, and the results will be reported in due course.

4. Experimental

4.1. General

Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Bruker DPX 400 (400 MHz), or on a Bruker DQX 400 (400 MHz) spectrometer, and spectra were assigned using COSY and HMQC experiments. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Bruker DPX 400 (100.6 MHz), or on a Bruker DQX 400 (100.6 MHz) and were assigned using HMQC experiments. Multiplicities were assigned using DEPT or APT sequences. All chemical shifts are quoted on the δ-scale in parts per million (ppm) using residual solvent as internal standard. Infrared spectra were recorded on a Perkin-Elmer 150 Fourier Transform spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab20-250, Micromass Platform 1 APCI, or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionization (NH_3 DCI), electron impact (EI), electron spray ionisation (ESI), chemical ionization (NH_3 CI), atmospheric pressure chemical ionization (APCI), and fast atom bombardment (FAB) techniques as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalytical services of the Inorganic Chemistry Laboratory, Oxford. Thin layer chromatography (TLC) was carried out on Merck glass backed sheets, pre-coated coated with $60F_{254}$ silica. Plates were developed using 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and available reagents were dried and purified before use according to standard procedures; dichloromethane (DCM) was distilled from calcium hydride immediately before use. 4,6-*O*-Benzylidene-D-allal **1** was synthesised following literature procedures.[11]

4.2. General procedure A: esterification

Glycal (1.0 equiv) and carboxylic acid (1.2–1.5 equiv) were dissolved in anhydrous DCM, and *N*,*N*′-dimethyl-4-amino pyridine (0.2 equiv) and then dicyclohexylcarbodiimide (2.0 equiv) were added. The reaction mixture was stirred under an atmosphere of argon until TLC indicated the complete consumption of starting material. The reaction mixture was concentrated in vacuo, the residue taken up in ethyl acetate, and the suspension filtered through Celite®. The solution was concentrated in vacuo, and the residue purified by flash column chromatography.

4.3. General procedure B: Tebbe methylenation

The enol ether (1.0 equiv) was dissolved in a 4:1 mixture of anhydrous THF and anhydrous pyridine and the solution cooled to −40 °C under an atmosphere of argon. Tebbe reagent (0.5 M in toluene, 2.0–4.0 equiv depending on age and quality) was added drop-wise, and the reaction mixture allowed to warm to room temperature with stirring. After 16 h, when TLC indicated complete consumption of starting material, the reaction mixture was cooled to 0 °C and quenched by drop-wise addition of sodium hydroxide (0.5 M aqueous solution) until effervescence ceased. The mixture was diluted with petrol, stirred for 30 min, and sonicated for a further, 10 min. The mixture was poured onto a short column of silica and eluted (petrol and ether with 2% triethylamine), concentrated in vacuo and purified by flash column chromatography (silica; petrol and ether with 2% triethylamine).

4.3.1. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucuronic acid 3. Alcohol **2** (256 mg, 0.55 mmol) was dissolved in anhydrous DCM (15 ml) and Dess–Martin periodinane (350 mg, 0.83 mmol) was added. The mixture was stirred under an atmosphere of argon for 1 h, when TLC (petrol/ethyl acetate, 1:1) indicated consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.3). The mixture was diluted with ether (12 ml) and sodium bicarbonate (12 ml) and sodium thiosulphate (2 g) was added. The mixture was stirred for 1 h, and was then diluted with ether (50 ml) and the layers separated. The aqueous phase was extracted with ether (4×25 ml) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (50 ml) and water (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude aldehyde as a colourless oil; δ_H (400 MHz, $CDCl_3$)[23] 3.41 (3H, s, OCH_3), 3.53 (1H, dd, $J_{1,2}=3.4$ Hz, $J_{2,3}=9.7$ Hz, H-2), 3.60 (1H, at, $J=9.6$ Hz, H-4), 4.11 (1H, at, $J=9.1$ Hz, H-3), 4.19 (1H, d, $J_{4,5}=10.6$ Hz, H-5), 4.64–4.68 (3H, m, H-1, 2×PhCH), 4.81–4.85 (2H, m, 2×PhCH), 4.89 (1H, d, $J=10.6$ Hz, PhCH), 5.03 (1H, d, $J=10.6$ Hz, PhCH), 7.28–7.38 (15H, m, 15×Ar-H), 9.67 (1H, s, H-6).

The crude aldehyde was dissolved in a mixture of *tert*-butanol (7 ml), THF (3 ml), water (3 ml) and 2-methyl-2-butene (2 ml). Sodium dihydrogenphosphate (0.4 g) and then sodium chlorite (80%, 62 mg, 0.55 mmol) were added, and the mixture stirred under an atmosphere of argon for 16 h. After this time, TLC (petrol/ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.5) and formation of a major product (R_f 0.1). The mixture was quenched by addition of hydrochloric acid (10 ml of a 1 M aqueous solution). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (4×25 ml). The combined organic layers were washed with water (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the *gluco* acid **3** (319 mg, quant.) as a colourless oil; $[\alpha]_D^{22}$ +28.9 (*c*, 1.2 in $CHCl_3$) [lit. $[\alpha]_D^{20}$ +3 (*c*, in $CHCl_3$)];[17] δ_H (400 MHz, $CDCl_3$) 3.40 (3H, s, OCH_3), 3.57 (1H, dd, $J_{1,2}=3.4$ Hz, $J_{2,3}=9.9$ Hz, H-2), 3.70 (1H, dd, $J_{3,4}=9.1$ Hz, $J_{4,5}=10.2$ Hz, H-4), 4.01 (1H, at, $J=9.4$ Hz, H-3), 4.22 (1H, d, H-5), 4.60–4.66, 4.79–4.83 (6H, m, 5×PhCH, H-1), 4.97 (1H, d, $J=10.7$ Hz, PhCH), 7.20–7.36 (15H, m, 15×Ar-H).

4.3.2. Methyl 6-*O*-*tert*-butyldimethylsilyl-α-D-galacto-pyranoside 6. Methyl α-D-galactopyranoside **5** (5.07 g, 26.1 mmol) was dissolved in anhydrous DMF (60 ml) and

cooled to 0 °C. Imidazole (4.44 g, 65 mmol) and then *tert*-butyldimethylsilyl chloride (4.72 g, 31 mmol) were added to the solution, and the mixture was stirred for 19 h, when TLC (ethyl acetate) indicated complete consumption of starting material (R_f 0) and formation of a single product (R_f 0.3). The mixture was concentrated in vacuo and the residue taken up in ethyl acetate (400 ml). The solution was washed with water (2×200 ml) and brine (2×200 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate) to afford silyl ether **6** (7.41 g, 92%) as an amorphous white solid; $[\alpha]_D^{21}$ +102 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$)[19] 0.09 (6H, s, 2×$SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 3.41 (3H, s, OCH_3), 3.73–3.78 (2H, m, H-3, H-5), 3.80–3.90 (3H, m, H-2, H-6, H-6′), 4.04 (1H, br d, J= 2.9 Hz, H-4), 4.80 (1H, d, $J_{1,2}$=3.8 Hz, H-1).

4.3.3. Methyl 2,3,4-tetra-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α-D-galactopyranoside 7. Alcohol **6** (7.00 g, 23 mmol) was dissolved in anhydrous DMF (100 ml) and cooled to 0 °C. Benzyl bromide (12.2 ml, 102 mmol) and then sodium hydride (3.27 g, 82 mmol) were added and the reaction mixture stirred under an atmosphere of argon for 16 h, when TLC (petrol/ethyl acetate, 9:1) indicated consumption of starting material (R_f 0) and formation of a major product (R_f 0.3). The reaction mixture was quenched by drop-wise addition of methanol (10 ml), poured into water (500 ml) and extracted with ether (5×100 ml). The combined organic phases were washed with water (2×200 ml) and brine (2×200 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 19:1) to afford benzyl ether **7** (11.0 g, 84%) as a colourless oil; $[\alpha]_D^{21}$ +19.6 (*c*, 0.9 in $CHCl_3$); ν_{max} (thin film) no significant peak s; δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, 2×$SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 3.42 (3H, s, OCH_3), 3.61–3.70 (2H, m, H-6, H-6′), 3.74–3.78 (1H, m, H-5), 3.96–4.00 (2H, m, H-3, H-4), 4.09 (1H, dd, $J_{1,2}$=3.5 Hz, $J_{2,3}$=9.8 Hz, H-2), 4.65, 5.02 (2H, 2×d, J=11.3 Hz, $PhCH_2$), 4.73 (1H, d, H-1), 4.75, 4.88 (2H, 2×d, J= 12.0 Hz, $PhCH_2$), 4.79, 4.93 (2H, 2×d, J=12.0 Hz, $PhCH_2$), 7.27–7.46 (15H, m, 15×Ar-H); δ_C (100.6 MHz, $CDCl_3$) −5.4, −5.4 (2×q, 2×$SiCH_3$), 18.2 (s, $SiC(CH_3)_3$), 25.9 (q, $SiC(CH_3)_3$), 55.2 (q, OCH_3), 62.0 (t, C-6), 71.1 (d, C-5), 73.3, 73.6, 74.8 (3×t, 3×$PhCH_2$), 75.2 (d, C-4), 76.5 (d, C-2), 79.2 (d, C-3), 98.8 (d, C-1), 127.5, 127.7, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4 (8×d, 15× Ar-C), 138.6, 138.9, 138.9 (3×s, 3×Ar-C); *m/z* (ES^+) 637 ($M+NH_4^+ + CH_3CN$, 100), 601 ($M+Na^+$, 3%). (HRMS (ES^+) Calcd for $C_{34}H_{50}NO_6Si$ ($M+NH_4^+$) 596.3407. Found, 596.3408). (Found: C, 70.21; H, 8.33. $C_{34}H_{46}O_6Si$ requires C, 70.55; H, 8.01%).

4.3.4. Methyl 2,3,4-tetra-*O*-benzyl-α-D-galactopyranoside 8. Silyl ether **7** (8.57 g, 14.8 mmol) was dissolved in acetonitrile (100 ml). Water (20 ml) was added, and the pH of the solution adjusted to pH 3 by the addition of toluene sulphonic acid. The reaction mixture was stirred for 19 h, until TLC (petrol/ethyl acetate, 4:1) indicated consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.1). The reaction mixture was concentrated in vacuo and the residue taken up in ethyl acetate (300 ml). The solution was washed with saturated aqueous sodium bicarbonate (2×150 ml) and brine (150 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 2:1) to afford alcohol **8** (6.20 g, 90%) as an amorphous white solid; $[\alpha]_D^{21}$ +7.01 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disc) 3482 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.38 (3H, s, OCH_3), 3.49–3.52 (1H, m, H-6), 3.70–3.76 (2H, m, H-5, H-6′), 3.89 (1H, d, $J_{3,4}$=2.8 Hz, H-4), 3.96 (1H, dd, $J_{2,3}$=10.1 Hz, H-3), 4.07 (1H, dd, $J_{1,2}$=3.6 Hz, H-2), 4.66, 4.99 (2H, 2×d, J=11.6 Hz, $PhCH_2$), 4.72, 4.87 (2H, 2×d, J=11.9 Hz, $PhCH_2$), 4.73 (1H, d, H-1), 4.77, 4.92 (2H, 2× d, J=11.7 Hz, $PhCH_2$), 7.28–7.44 (15H, m, 15×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 55.4 (q, OCH_3), 60.4 (t, C-6), 70.2 (d, C-5), 73.6, 73.6, 74.4 (3×t, 3×$PhCH_2$), 75.0 (d, C-4), 76.5 (d, C-2), 79.1 (d, C-3), 98.8 (d, C-1), 127.6, 127.6, 127.8, 128.0, 128.1, 128.4, 128.4, 128.5, 128.6 (9×d, 15×Ar-C), 138.1, 138.4, 138.7 (3×s, 3×Ar-C); *m/z* (ES^+) 951 (2M+ Na^+, 3), 523 ($M+NH_4^+ + CH_3CN$, 100), 487 ($M+Na^+$, 5%). (HRMS (ES^+) Calcd for $C_{28}H_{32}O_6Na$ ($M+Na^+$) 487.2097. Found, 487.2087).

4.3.5. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannuronic acid 9. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **4** (435 mg, 0.81 mmol) was dissolved in anhydrous DCM (15 ml) and Dess–Martin periodinane (514 mg, 1.21 mmol) was added. The mixture was stirred under an atmosphere of argon for 3 h, when TLC (petrol/ethyl acetate, 1:1) indicated consumption of starting material (R_f 0.6) and formation of a single product (R_f 0.8). The mixture was diluted with ether (20 ml) and saturated aqueous sodium bicarbonate (20 ml) and sodium thiosulphate (2 g) were added. The mixture was stirred for 1 h, and was then diluted with ether (50 ml) and the layers separated. The aqueous phase was extracted with ether (4×25 ml) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (2× 50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude aldehyde as a colourless oil; δ_H (400 MHz, $CDCl_3$)[24] 3.40 (3H, s, OCH_3), 3.78 (1H, at, J=2.7 Hz, H-2), 3.96 (1H, dd, $J_{2,3}$=2.8 Hz, $J_{3,4}$=8.0 Hz, H-3), 4.05–4.12 (2H, m, H-4, H-5), 4.63 (2H, s, $PhCH_2$), 4.67 (1H, d, J= 11.2 Hz, PhCH), 4.73 (2H, s, $PhCH_2$), 4.84–4.87 (2H, m, H-1, PhCH), 7.22–7.51 (15H, m, 15×Ar-H), 9.75 (1H, s, H-6). The crude residue was dissolved in a mixture of *tert*-butanol (9 ml), THF (3 ml), water (3 ml) and 2-methyl-2-butene (2 ml). Sodium dihydrogenphosphate (0.4 g) and then sodium chlorite (80%, 91 mg, 0.81 mmol) were added, and the mixture was stirred under an atmosphere of argon for 16 h. After this time, TLC (petrol/ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.8) and formation of a major product (R_f 0.5). The mixture was quenched by addition of hydrochloric acid (30 ml of a 1 M aqueous solution). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (4×25 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate (4×30 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the *manno* carboxylic acid **9** (488 mg, quant.) as a colourless oil; $[\alpha]_D^{23}$ +15.0 (*c*, 1.2 in $CHCl_3$); ν_{max} (thin film) 3386 (br, OH), 1725 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.46 (3H, s, OCH_3), 3.79 (1H, at, J=3.2 Hz, H-2), 3.92 (1H, dd, $J_{2,3}$= 3.1 Hz, $J_{3,4}$=7.8 Hz, H-3), 4.23 (1H, at, J=7.8 Hz, H-4), 4.32 (1H, d, J=7.7 Hz, H-5), 4.61, 4.65 (2H, 2×d, J= 11.9 Hz, $PhCH_2$), 4.70–4.82 (4H, m, 4×PhCH), 4.97 (1H,

d, $J_{1,2}$=3.1 Hz, H-1), 7.18–7.64 (15H, m, 15×Ar-H), 8.72 (1H, br s, OH); δ_C (100.6 MHz, $CDCl_3$) 55.7 (q, OCH_3), 71.4 (d, C-5), 72.4, 73.0, 74.4 (3×t, 3×$PhCH_2$), 74.5 (d, C-2), 75.6 (d, C-4), 78.5 (d, C-3), 99.6 (d, C-1), 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5 (8×d, 15×Ar-C), 137.8, 138.0, 138.2 (3×s, 3×Ar-C), 174.0 (s, C-6); *m/z* (ES^+) 537 ($M+NH_4^+ + CH_3CN$, 100), 501 ($M+Na^+$, 20%). (HRMS (ES^+) Calcd for $C_{28}H_{34}NO_7$ ($M+NH_4^+$) 496.2335. Found, 496.2328).

4.3.6. Methyl 2,3,4-tri-*O*-benzyl-α-D-galacturonic acid 10. *Galacto* alcohol **8** (1.75 g, 3.8 mmol) was dissolved in anhydrous DCM (40 ml) and Dess–Martin periodinane (2.39 g, 5.6 mmol) was added. The mixture was stirred under an atmosphere of argon for 3 h, when TLC (petrol/ethyl acetate, 1:1) indicated consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.5). The mixture was diluted with ether (75 ml) and saturated aqueous sodium bicarbonate (75 ml) and sodium thiosulphate (3 g) were added. The mixture was stirred for 1 h, and the layers separated. The aqueous phase was extracted with ether (3×25 ml) and the combined organic layers were washed with brine (3×75 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give crude aldehyde as a colourless oil; δ_H (400 MHz, $CDCl_3$) 3.42 (3H, s, OCH_3), 3.98 (1H, dd, $J_{3,4}$=2.7 Hz, $J_{4,5}$=10.0 Hz, H-4), 4.10–4.14 (2H, m, H-2, H-5), 4.32 (1H, at, J=2.2 Hz, H-3), 4.57, 4.93 (2H, 2×d, J=11.1 Hz, $PhCH_2$), 4.72, 4.88 (2H, 2×d, J=11.9 Hz, $PhCH_2$), 4.77, 4.89 (2H, 2×d, J=11.7 Hz, $PhCH_2$), 4.83 (1H, d, $J_{1,2}$=3.5 Hz, H-1), 7.24–7.43 (15H, m, 15×Ar-H), 9.54 (1H, d, $J_{5,6}$=1.5 Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 55.9 (q, OCH_3), 73.5, 73.8, 74.9 (3×t, 3×$PhCH_2$), 75.6, 76.0, 76.1 (3×d, C-2, C-3, C-5), 78.1 (d, C-4), 99.3 (d, C-1), 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5 (9×d, 15×Ar-C), 137.9, 138.3, 138.4 (3×s, 3×Ar-C), 200.5 (d, C-6). The residue was dissolved in a mixture of *tert*-butanol (32 ml), THF (14 ml), water (14 ml) and 2-methyl-2-butene (9 ml). Sodium dihydrogenphosphate (1.8 g) and then sodium chlorite (80%, 425 mg, 3.8 mmol) were added, and the mixture stirred under an atmosphere of argon for 16 h. After this time, TLC (petrol/ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.6) and formation of a major product (R_f 0.1). The mixture was quenched by addition of hydrochloric acid (100 ml of a 1 M aqueous solution). The organic layer was separated, and the aqueous layer extracted with ethyl acetate (5×30 ml). The combined organic layers were washed with water (3×75 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the *galacto* acid **10** (1.82 g, quant.) as a white crystalline solid, mp 126–130 °C (ether/petrol); $[\alpha]_D^{21}$ +38.2 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disc) 3220 (br, OH), 1775 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.41 (3H, s, OCH_3), 4.01 (1H, dd, $J_{2,3}$=10.1 Hz, $J_{3,4}$=2.8 Hz, H-3), 4.08 (1H, dd, $J_{1,2}$=3.4 Hz, H-2), 4.34 (1H, at, J=2.1 Hz, H-4), 4.39 (1H, d, $J_{4,5}$=1.4 Hz, H-5), 4.62, 4.95 (2H, 2×d, J=11.0 Hz, $PhCH_2$), 4.68 (1H, d, J=12.3 Hz, PhCH), 4.77 (1H, d, J=11.5 Hz, PhCH), 4.78 (1H, d, H-1), 4.87 (2H, d, J=11.4 Hz, 2×PhCH), 7.24, 7.42 (15H, m, 15×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 56.2 (q, OCH_3), 70.4 (d, C-5), 73.4, 73.8, 75.2 (3×t, 3×$PhCH_2$), 75.5 (d, C-2), 76.4 (d, C-4), 77.9 (d, C-3), 99.4 (d, C-1), 127.5, 127.7, 127.7, 127.9, 128.1, 128.1, 128.2, 128.4, 128.5 (9×d, 15×Ar-C), 138.0, 138.2, 138.2 (3×s, 3×Ar-C), 171.2 (s, C-6); *m/z* (ES^+) 537 ($M+NH_4^+ + CH_3CN$, 100), 501 ($M+Na^+$, 5%). (HRMS (ES^+) Calcd for $C_{28}H_{34}NO_7$ ($M+NH_4^+$) 496.2335. Found, 496.2328).

4.3.7. Methyl 6-*O*-(4′,6′-*O*-benzylidene-3′-*O*-yl-D-allal)-2,3,4-tri-*O*-benzyl-α-D-glucuronic ester 11. *General procedure A*. 4,6-*O*-Benzylidene-D-allal **1**[11] (158 mg, 0.67 mmol), *gluco* acid **3** (558 mg, 1.0 mmol), *N*,*N*-dimethyl-4-amino pyridine (16 mg, 0.14 mmol), dicyclohexylcarbodiimide (278 mg, 1.4 mmol) in DCM (30 ml) gave ester **11** (388 mg, 83%) as a colourless oil; $[\alpha]_D^{21}$ +119 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1746 (s, C=O), 1636 (m, C=C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.45 (3H, s, OCH_3), 3.60 (1H, dd, $J_{1,2}$=3.5 Hz, $J_{2,3}$=9.9 Hz, H-2 Glc), 3.80–3.87 (2H, m, H-4 Glc, H-6 All), 4.00–4.05 (2H, m, H-4 All, H-3 Glc), 4.13–4.22 (1H, m, H-5 All), 4.27 (1H, d, $J_{4,5}$=9.8 Hz, H-5 Glc), 4.41 (1H, dd, $J_{5,6'}$=5.0 Hz, $J_{6,6'}$=10.6 Hz, H-6′ All), 4.67 (1H, d, $J_{1,2}$=3.4 Hz, H-1 Glc), 4.68 (1H, d, J=12.0 Hz, PhCH), 4.72, 4.76 (2H, 2×d, J=11.0 Hz, $PhCH_2$), 4.80 (1H, d, J=10.8 Hz, PhCH), 4.83 (1H, d, J=12.1 Hz, PhCH), 4.95 (1H, d, J=11.0 Hz, PhCH), 5.03 (1H, at, J=5.9 Hz, H-2 All), 5.46 (1H, dd, $J_{2,3}$=5.8 Hz, $J_{3,4}$=3.9 Hz, H-3 All), 5.62 (1H, s, $PhCHO_2$), 6.49 (1H, d, $J_{1,2}$=6.0 Hz, H-1 All), 7.21–7.54 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 55.5 (q, OCH_3), 63.6 (d, C-3 All), 64.9 (d, C-5 All), 68.5 (t, C-6 All), 70.5 (d, C-5 Glc), 73.6, 74.7, 75.8 (3×t, 3×$PhCH_2$), 75.8, 81.5 (2×d, C-4 All, C-3 Glc), 79.2, 79.4 (2×d, C-4 Glc, C-2 Glc), 97.8 (d, C-2 All), 98.6 (d, C-1 Glc), 101.6 (d, $PhCHO_2$), 126.2, 126.2, 127.4, 127.6, 127.6, 127.9, 128.0, 128.1, 128.2, 128.2, 128.3, 128.5, 129.1, 129.3 (14×d, 20×Ar-C), 137.0, 138.1, 138.2, 138.6 (4×s, 4×Ar-C), 147.8 (d, C-1 All), 168.9 (s, C-6 Glc); *m/z* (ES^+) 1447 ($2M+NH_4^+ + CH_3CN$, 3), 753 ($M+NH_4^+ + CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{41}H_{46}NO_{10}$ ($M+NH_4^+$) 712.3122. Found, 712.3112).

4.3.8. Methyl 6-*O*-(4′,6′-*O*-benzylidene-3′-*O*-yl-D-allal)-2,3,4-tri-*O*-benzyl-α-D-mannuronic ester 12. *General procedure A*. 4,6-*O*-Benzylidene-D-allal **1**[11] (408 mg, 1.74 mmol), *manno* acid **9** (1.25 g, 2.6 mmol), *N*,*N*-dimethyl-4-amino pyridine (43 mg, 0.35 mmol), dicyclohexylcarbodiimide (719 mg, 3.5 mmol) in DCM (30 ml) gave recovered 4,6-*O*-benzylidene-D-allal **1** (60 mg) and ester **12** (919 mg, 76%, 89% based on recovered starting material) as a colourless oil; $[\alpha]_D^{22}$ +147 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1748 (s, C=;O), 1636 (w, C=C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.52 (3H, s, OCH_3), 3.72 (1H, dd, $J_{1,2}$=4.9 Hz, $J_{2,3}$=3.0 Hz, H-2 Man), 3.81–3.87 (2H, m, H-3 Man, H-6 All), 4.00 (1H, dd, $J_{3,4}$=4.1 Hz, $J_{4,5}$=10.4 Hz, H-4 All), 4.20 (1H, dat, J=5.2, 10.3, 10.3 Hz, H-5 All), 4.27 (1H, at, J=6.3 Hz, H-4 Man), 4.38–4.46 (3H, m, PhCH, H-5 Man, H-6′ All), 4.52 (1H, d, J=11.7 Hz, PhCH), 4.62–4.72 (2H, m, 2×PhCH), 4.71 (1H, d, J=11.2 Hz, PhCH), 4.76 (1H, d, J=12.3 Hz, PhCH), 4.94 (1H, at, J=5.9 Hz, H-2 All), 5.06 (1H, d, H-1 Man), 5.30 (1H, dd, $J_{2,3}$=6.1 Hz, H-3 All), 5.60 (1H, s, $PhCHO_2$), 6.40 (1H, d, $J_{1,2}$=6.0 Hz, H-1 All), 7.19–7.48 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 56.0 (q, OCH_3), 63.5 (d, C-3 All), 64.9 (d, C-5 All), 68.6 (t, C-6 All), 72.2, 72.8 (2×t, 3×$PhCH_2$), 72.5 (d, C-5 Man), 74.8 (d, C-2 Man), 75.7, 75.8 (2×d, C-4 All, C-4 Man), 76.7 (d, C-3 Man), 98.1 (d, C-2 All), 99.4 (d, C-1 Man), 101.9 (d, $PhCHO_2$), 126.3, 127.5,

127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 129.2 (9×d, 20× Ar-C), 137.0, 138.0, 138.1, 138.4 (4×s, 4×Ar-C), 147.4 (d, C-1 All), 169.1 (s, C-6 Man); *m/z* (ES^+) 712 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{41}H_{46}NO_{10}$ ($M+NH_4^+$) 712.3122. Found, 712.3132). (Found: C, 70.51; H, 6.14. $C_{41}H_{42}O_{10}$ requires C, 70.88; H, 6.09%).

4.3.9. Methyl 6-*O*-(4′,6′-*O*-benzylidene-3′-*O*-yl-D-allal)-2,3,4-tri-*O*-benzyl-α-D-galacturonic ester 13. *General procedure A*. 4,6-*O*-Benzylidene-D-allal **1**[11] (168 mg, 0.72 mmol), *galacto* acid **10** (595 mg, 1.1 mmol), *N*,*N*-dimethyl-4-amino pyridine (18 mg, 0.14 mmol), dicyclohexylcarbodiimide (296 mg, 1.4 mmol) in DCM (30 ml) gave ester **13** (433 mg, 87%) as a white crystalline solid, mp 149–152 °C (ethyl acetate / petrol); $[\alpha]_D^{21}$ +140 (*c*, 1.2 in $CHCl_3$); ν_{max} (KBr disc) 1771 (s, C=O), 1637 (m, C=C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.41 (3H, s, OCH_3), 3.85 (1H, at, $J=10.5$ Hz, H-6 All), 4.00–4.04 (2H, m, H-3 Gal, H-4 All), 4.08 (1H, dd, $J_{1,2}=3.0$ Hz, $J_{2,3}=10.1$ Hz, H-2 Gal), 4.27 (1H, dat, $J=5.4$, 10.4, 10.4 Hz, H-5 All), 4.34 (1H, d, $J_{3,4}=1.4$ Hz, H-4 Gal), 4.41, 4.64 (2H, 2×d, $J=11.0$ Hz, $PhCH_2$), 4.43 (1H, s, H-5 Gal), 4.51 (1H, dd, $J_{5,6'}=5.0$ Hz, $J_{6,6'}=10.6$ Hz, H-6′ All), 4.66 (1H, d, $J=12.2$ Hz, PhCH), 4.73 (1H, d, $J=12.1$ Hz, PhCH), 4.80–4.84 (3H, m, 2×PhCH, H-1 Gal), 5.15 (1H, at, $J=5.9$ Hz, H-2 All), 5.31 (1H, at, $J=4.8$ Hz, H-3 All), 5.60 (1H, s, $PhCHO_2$), 6.49 (1H, d, $J_{1,2}=6.1$ Hz, H-1 All), 7.07–7.45 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 56.0 (q, OCH_3), 63.8 (d, C-3 All), 65.0 (d, C-5 All), 68.6 (t, C-6 All), 70.4 (d, C-5 Gal), 72.8, 73.7, 74.9 (3×t, 3×$PhCH_2$), 75.5, 75.6, 78.1 (3×d, C-2 Gal, C-3 Gal, C-4 All), 77.5 (d, C-4 Gal), 98.3 (d, C-2 All), 99.2 (d, C-1 Gal), 101.9 (d, $PhCHO_2$), 126.2, 127.0, 127.3, 127.4, 127.5, 127.8, 128.2, 128.2, 128.4, 129.2 (10×d, 20×Ar-C), 137.0, 138.3, 138.6, 138.8 (4×s, 4×Ar-C), 147.6 (d, C-1 All), 168.3 (s, C-6 Gal); *m/z* 1447 ($2M+NH_4^+ + CH_3CN$, 7), 753 ($M+NH_4^+ + CH_3CN$, 100%). (ES^+) Calcd for $C_{41}H_{46}NO_{10}$ ($M+NH_4^+$) 712.3122. Found, 712.3132).

4.3.10. Methyl 1,5-anhydro-6-*O*-(4′,6′-*O*-benzylidene-3′-yl-D-allal)-7-deoxy-2,3,4-tri-*O*-benzyl-α-D-*gluco*-hept-6-enopyranose 14. *General procedure B*. Ester **11** (R_f 0.2 (petrol/ethyl acetate, 4:1), 170 mg, 0.24 mmol), Tebbe reagent (0.5 M, 2.0 ml, 0.98 mmol) in THF (8 ml) and pyridine (2 ml) gave enol ether **14** (138 mg, 82%) as a pale yellow foam; (R_f 0.2 petrol/ethyl acetate, 4:1). This unstable compound was used in the next step without further, purification; ν_{max} (thin film) 1634 (sh, C=C–O) cm^{-1}; δ_H (400 MHz, C_6D_6) 3.16 (3H, s, OCH_3), 3.44–3.52 (2H, m, H-5 All, H-6 All), 3.58 (1H, dd, $J_{1,2}=3.5$ Hz, $J_{2,3}=9.5$ Hz, H-2 Glc), 4.08 (1H, at, $J=9.3$ Hz, H-4 Glc), 4.19 (1H, dd, $J_{5,6'}=5.4$ Hz, $J_{6,6'}=10.5$ Hz, H-6′ All), 4.22–4.27 (2H, m, H-3 Glc, C=C*H*H′), 4.31 (1H, d, $J_{4,5}=9.9$ Hz, H-5 Glc), 4.36, 4.48 (2H, 2×d, $J=11.8$ Hz, $PhCH_2$), 4.38–4.44 (3H, m, H-3 All, H-4 All, C=CH*H*′), 4.65 (1H, d, H-1 Glc), 4.74 (1H, at, $J=5.9$ Hz, H-2 All), 4.87, 4.98 (2H, 2×d, $J=11.2$ Hz, $PhCH_2$), 4.92, 4.95 (2H, 2×d, $J=11.3$ Hz, $PhCH_2$), 5.28 (1H, s, $PhCHO_2$), 6.04 (1H, d, $J_{1,2}=5.9$ Hz, H-1 All), 7.03–7.65 (20H, m, 20×Ar-H); δ_C (100.6 MHz, C_6D_6) 55.1 (q, OCH_3), 65.3, 65.9 (2×d, C-3 All, C-4 All), 68.8 (t, C-6 All), 73.1, 74.9, 75.9 (3×t, 3×$PhCH_2$), 74.1 (d, C-5 Glc), 77.3 (d, C-5 All), 80.1 (d, C-4 Glc), 81.3 (d, C-2 Glc), 82.2 (d, C-3 Glc), 89.1 (t, C=*C*H_2), 98.8, 98.8 (2×d, C-1 Glc, C-2 All), 101.9 (d, $PhCHO_2$), 127.1, 127.5, 127.6, 127.7, 127.9, 127.9, 128.1, 128.3, 128.4, 128.4, 128.5, 128.6, 129.1 (13×d, 20×Ar-C), 138.5, 139.5, 140.0, 140.0 (4×s, 4×Ar-C), 146.7 (d, C-1 All), 158.5 (s, C-6 Glc); *m/z* (ES^+) 751 ($M+NH_4^+ + CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3338).

4.3.11. Methyl 1,5-anhydro-2,3,4-tri-*O*-benzyl-6-*O*-(4′,6′-*O*-benzylidene-3′-yl-D-allal)-7-deoxy-α-D-*manno*-hept-6-enopyranoside 15. *General procedure B*. Ester **12** (R_f 0.2 (petrol/ethyl acetate, 4:1), 331 mg, 0.48 mmol), Tebbe reagent (0.5 M, 3.8 ml, 1.9 mmol) in THF (12 ml) and pyridine (3 ml) gave enol ether **15** (252 mg, 76%) as a pale yellow oil; (R_f 0.25, petrol/ethyl acetate, 4:1). This unstable compound was used in the next step without further, purification; ν_{max} (thin film) 1634 (m, C=C–O) cm^{-1}; δ_H (400 MHz, C_6D_6) 3.22 (3H, s, OCH_3), 3.59 (1H, at, $J=10.5$ Hz, H-6 All), 3.64 (1H, dd, $J_{3,4}=3.7$ Hz, $J_{4,5}=10.5$ Hz, H-4 All), 3.93 (1H, at, $J=2.5$ Hz, H-2 Man), 4.15 (1H, dd, $J_{2,3}=3.0$ Hz, $J_{3,4}=9.3$ Hz, H-3 Man), 4.30 (1H, dd, $J_{5,6'}=5.3$ Hz, $J_{6,6'}=10.3$ Hz, H-6′ All), 4.36 (1H, d, $J_{4,5}=9.5$ Hz, H-5 Man), 4.42 (1H, d, $J=1.7$ Hz, C=C*H*H′), 4.54 (1H, dat, $J=5.3$, 10.4, 10.4 Hz, H-5 All), 4.57–4.70 (6H, m, H-3 All, H-4 Man, C=CH*H*′, 3× PhCH), 4.78 (1H, d, $J=12.3$ Hz, PhCH), 4.88 (1H, d, $J_{1,2}=1.6$ Hz, H-1 Man), 4.91 (1H, at, $J=6.0$ Hz, H-2 All), 5.01 (2H, s, $PhCH_2$), 5.40 (1H, s, $PhCHO_2$), 6.16 (1H, d, H-1 All), 7.14–7.80 (20H, m, 20×Ar-H); δ_C (100.6 MHz, C_6D_6) 54.7 (q, OCH_3), 65.2 (d, C-5 All), 66.0 (d, C-3 All), 69.0 (t, C-6 All), 72.8, 73.1, 75.0 (3×t, 3×$PhCH_2$), 75.5 (d, C-5 Man), 76.2 (d, C-2 Man), 77.3 (d, C-4 Man), 77.6 (d, C-4 All), 80.5 (d, C-3 Man), 89.1 (t, C=*C*H_2), 99.0 (d, C-2 All), 100.0 (d, C-1 Man), 102.1 (d, $PhCHO_2$), 127.3, 127.5, 127.7, 127.7, 128.1, 128.4, 128.6, 128.7, 129.1 (9×d, 20× Ar-C), 138.6, 139.5, 139.7, 140.3 (4×s, 4×Ar-C), 146.6 (d, C-1 All), 159.1 (s, *C*=CH_2); *m/z* (ES^+) 710 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3329).

4.3.12. Methyl 8,12-anhydro-2,3,4-tri-*O*-benzyl-11,13-*O*-benzylidene-9,10-didehydro-6-oxo-7,9,10-trideoxy-α-D-*glycero*-D-*ido*-α-D-glucopyranoside 16. Enol ether **14** (125 mg, 0.18 mmol) was dissolved in xylene (3 ml) and stirred at 185 °C in a sealed tube under an atmosphere of argon. After 12 h, TLC (petrol/ethyl acetate, 4:1) indicated consumption of starting material (R_f 0.25) and formation of a major product (R_f 0.20). The solution was concentrated in vacuo, and the residue was purified by flash column chromatography (petrol/ethyl acetate, 4:1) to afford α-*C*-disaccharide **16** (83 mg, 66%) as a white foam; $[\alpha]_D^{21}$ +18.7 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1728 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.66 (1H, dd, $J_{7,7'}=17.2$ Hz, $J_{7,8}=4.9$ Hz, H-7), 3.14 (1H, dd, $J_{7',8}=8.2$ Hz, H-7′), 3.43 (3H, s, OCH_3), 3.51–3.57 (2H, m, H-2, H-12), 3.67 (1H, at, $J=9.3$ Hz, H-4), 3.75 (1H, at, $J=10.4$ Hz, H-13), 4.04 (1H, at, $J=9.4$ Hz, H-3), 4.12–4.17 (1H, m, H-11), 4.17 (1H, d, $J_{4,5}=10.0$ Hz, H-5), 4.21 (1H, dd, $J_{12,13'}=4.6$ Hz, $J_{13,13'}=10.4$ Hz, H-13′), 4.63 (1H, d, $J_{1,2}=3.3$ Hz, H-1), 4.64 (1H, d, $J=10.6$ Hz, PhCH), 4.68 (1H, d, $J=12.1$ Hz, PhCH), 4.82–4.87 (4H, m, H-8, 3×PhCH), 5.00 (1H, d, $J=10.9$ Hz, PhCH), 5.59 (1H, s, $PhCHO_2$), 5.70 (1H, dat, $J=2.6$, 2.6, 10.5 Hz, H-10), 6.03 (1H, d, $J_{9,10}=10.4$ Hz, H-9),

7.25–7.53 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 43.8 (t, C-7), 55.8 (q, OCH_3), 65.7 (d, C-12), 69.5 (t, C-13), 69.9 (d, C-8), 73.6, 75.1, 75.9 (3×t, 3×$PhCH_2$), 74.2, 75.0 (2×d, C-5, C-11), 78.7 (d, C-4), 79.4 (d, C-2), 81.7 (d, C-3), 98.7 (d, C-1), 101.9 (d, $PhCHO_2$), 126.2, 127.5, 127.7, 127.9, 127.9, 128.1, 128.1, 128.2, 128.3, 128.4, 128.5, 129.1 (12×d, C-9, 20×Ar-C), 129.6 (d, C-10), 137.4, 137.8, 137.9, 138.5 (4×s, 4×Ar-C), 203.8 (s, C-6); *m/z* (ES^+) 751 ($M+NH_4^+ +CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3328).

4.3.13. Methyl 8,12-anhydro-2,3,4-tri-*O*-benzyl-11,13-*O*-benzylidene-9,10-didehydro-6-oxo-7,9,10-trideoxy-α-D-*glycero*-D-*ido*-α-D-mannopyranoside 17. Enol ether **15** (151 mg, 0.22 mmol) was dissolved in xylene (3 ml) and stirred at 185 °C in a sealed tube under an atmosphere of argon. After 12 h, TLC (petrol/ethyl acetate, 2:1) indicated no change (R_f 0.5), but crude NMR indicated complete consumption of starting material and formation of a major product. The solution was concentrated in vacuo, and the residue was purified by flash column chromatography (toluene/ether, 19:1) to afford α-*C*-disaccharide **17** (125 mg, 83%) as a colourless oil; $[\alpha]_D^{21}$ +41.5 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1730 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.73 (1H, dd, $J_{7,7'}=17.2$ Hz, $J_{7,8}=5.0$ Hz, H-7), 3.26 (1H, dd, $J_{7',8}=8.6$ Hz, H-7′), 3.38 (3H, s, OCH_3), 3.56–3.62 (1H, m, H-12), 3.76 (1H, at, $J=10.4$ Hz, H-13), 3.79 (1H, at, $J=2.7$ Hz, H-2), 3.92 (1H, dd, $J_{2,3}=3.1$ Hz, $J_{3,4}=8.5$ Hz, H-3), 4.05–4.18 (3H, m, H-4, H-5, H-11), 4.27 (1H, dd, $J_{12,13'}=4.7$ Hz, $J_{13,13'}=10.2$ Hz, H-13′), 4.62, 4.66 (2H, 2×d, $J=11.9$ Hz, $PhCH_2$), 4.68, 4.81 (2H, 2×d, $J=9.9$ Hz, $PhCH_2$), 4.73, 4.79 (2H, 2×d, $J=12.0$ Hz, $PhCH_2$), 4.81 (1H, d, $J_{1,2}=2.3$ Hz, H-1), 4.89–4.93 (1H, m, H-8), 5.60 (1H, s, $PhCHO_2$), 5.75 (1H, dat, $J=2.4$, 2.4, 10.4 Hz, H-10), 6.03 (1H, d, $J_{9,10}=10.4$ Hz, H-9), 7.18–7.53 (20H, m, 20×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 42.8 (t, C-7), 55.5 (q, OCH_3), 65.8 (d, C-12), 69.7 (t, C-13), 70.1 (d, C-8), 72.5, 73.0, 74.9 (3×t, 3×$PhCH_2$), 74.5 (d, C-2), 75.1, 75.1, 76.8 (3×d, C-4, C-5, C-11), 79.4 (d, C-3), 99.8 (d, C-1), 102.0 (d, $PhCHO_2$), 125.4, 126.4, 127.4, 127.7, 127.8, 127.9, 127.9, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 129.2 (14×d, C-9, 20×Ar-C), 129.2 (d, C-10), 137.6, 138.2, 138.2, 138.4 (4×s, 4×Ar-C), 204.4 (s, C-6); *m/z* (ES^+) 1443 ($2M+NH_4^+ +CH_3CN$, 3), 751 ($M+NH_4^+ +CH_3CN$, 100%). (HRMS (ES^+) Calcd for $C_{42}H_{48}NO_9$ ($M+NH_4^+$) 710.3329. Found, 710.3315).

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model α-*C*-glycoside (derived from esterification of allal **1** with benzoic acid and then Tebbe methylenation and Claisen rearrangement) as follows. Complete ketone reduction was achieved via a three step reaction sequence involving; (a) reduction with sodium borohydride in ethanol to give a diastereomeric mixture of alcohols; (b) formation of a diastereomeric mixture of imidazole xanthates by subsequent reaction with thiocarbonyldiimidazole; (c) free radical reduction with triphenyltin hydride and AIBN in toluene at 80 °C. Diastereoselective *cis* dihydroxylation to give the *manno* configured product was then achieved by treatment with catalytic $K_2OsO_4 \cdot 2H_2O$ in an acetone/water mixture in the presence of quinuclidine, and methyl sulphonamide, with *N*-methyl morpholine *N*-oxide as stoichiometric oxidant.

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