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A *C*-linked Glycomimetic in the Gas Phase and in Solution: Synthesis and Conformation of the Disaccharide Manα(1,6)-*C*-ManαOPh

Ludovic Drouin,[a] E. Cristina Stanca-Kaposta,*[b, c] Priptal Saundh,[a] Antony J. Fairbanks,*[a] Sebastian Kemper,[a] Timothy D. W. Claridge,*[a] and John P. Simons[b]

Abstract: The intrinsic conformational preference of a newly synthesised glycomimetic, the *C*-linked disaccharide Manα(1,6)-*C*-ManαOPh (**1**), has been determined in the gas phase at about 10 K by infrared ion dip spectroscopy coupled with density functional theory and ab initio calculations, and compared with its dynamical conformation in aqueous solution at 298 K by NMR spectroscopy. Comparisons are also made between these conformations and those of the corresponding *O*-linked disaccharide **2** in the gas phase and the *C*-linked disaccharide Manα(1,6)-*C*-ManαOMe (**3**) in the gas phase and in aqueous solution. The *C*- and *O*-linked disaccharides **1** and **2** present quite distinct conformational preferences in the gas phase: inter-glycosidic hydrogen bonding, seen in one of the two conformers populated in **2**, is not seen in **1** which adopts a conformation (not populated in **2**) with glycosidic dihedral angles (ϕ, ψ, ω) of −72°, 52° and 66°; supported in part by an OH−π hydrogen bond. This conformer is also strongly populated in an aqueous solution of **1** (and very weakly, of **3**) together with a second conformer, with dihedral angles (ϕ, ψ, ω) of about −60°, 180° and 60°, not seen in the gas phase but by far the dominant conformer in an aqueous solution of **3.** The *C*-disaccharide **1** was tested as a potential inhibitor, but displayed no significant inhibitory activity against Jack Bean α-mannosidase.

Keywords: ab initio calculations · carbohydrates · conformational analysis · NMR spectroscopy · sigmatropic rearrangement

Introduction

Oligosaccharides play crucially important roles in an enormously wide variety of fundamentally important biological systems.[1] It has been long-proposed that carbohydrate mimetics[2] may be expected to display interesting biological activity either as enzyme inhibitors, or as agonists or antagonists of carbohydrate-mediated recognition events. Although the number of currently administered glycomimetic drugs is small, such molecules have for some time been expected to provide the basis of new therapeutic strategies against a variety of disease states and infective agents.[3] These possible applications have aroused interest in the synthesis of a wide variety of *C*-glycosides, including *C*-di-[4] and -oligosaccharides in which methylene units replace the interglycosidic oxygen atoms of natural *O*-linked di- or oligosaccharides. These materials were originally proposed as plausible non-hydrolysable saccharide mimetics that may display interesting biological activity[5] and perhaps future therapeutic potential.

Subsequently however, there has been considerable debate as to the ability of such *C*-saccharides to mimic their

[a] Dr. L. Drouin, P. Saundh, Dr. A. J. Fairbanks, S. Kemper, Dr. T. D. W. Claridge
Department of Chemistry, Chemistry Research Laboratory
University of Oxford
Mansfield Road, Oxford, OX1 3TA (UK)
Fax: (+44) 1865-285002
E-mail: antony.fairbanks@chem.ox.ac.uk
tim.claridge@chem.ox.ac.uk

[b] Dr. E. C. Stanca-Kaposta, Prof. J. P. Simons
Department of Chemistry
Physical and Theoretical Chemistry Laboratory
University of Oxford
South Parks Road, Oxford, OX1 3QZ (UK)

[c] Dr. E. C. Stanca-Kaposta
present address:
Institut für Experimentalphysik, Freie Universitaet Berlin
Arnimallee 14, 14195, Berlin (Germany)
Fax: (+49) 30-838-55567
E-mail: kaposta@physik.fu-berlin.de

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natural oxygen-linked counterparts; their conformational preferences in particular are of key interest since *C*-saccharides lack an exo anomeric effect, presumed to play a role in significantly favouring particular conformations of *O*-glycosides. Kishi et al.[6] were the first to investigate the solution-phase conformational preferences of *C*-glycomimetics by NMR spectroscopy and compare them with those of natural glycosides. More recently, Jiménez-Barbero and various co-workers have taken the lead in developing a more precise understanding of the conformational similarities of, and differences between, *O*- and *C*-glycosides and other glycomimetics.[7] In particular Skrydstrup and Jiménez-Barbero synthesised and investigated the conformation of the *C*-trisaccharide Manα(1,3)-*C*-[Manα(1,6)-*C*-]-ManαOMe and its constituent disaccharide building units through a combination of NMR spectroscopy, force-field calculations and for the trisaccharide time-averaged restrained molecular dynamics; several more conformers were populated in the *C*-trisaccharide than in the natural *O*-linked carbohydrate,[8] but despite its higher flexibility, the *C*-glycomimetic was recognised by three different lectins.

We address the conformational issue here through a three-pronged attack, focusing on comparisons between the *C*- and *O*-disaccharides, Manα(1,6)-*C*-ManαOPh (**1**), Manα-(1,6)ManαOPh (**2**) and Manα(1,6)-*C*-ManαOMe (**3**) (Figure 1). This approach includes a combination of synthesis; vibrational spectroscopy in the gas phase together with ab initio computation, to identify intrinsic conformational preferences at about 10 K; and NMR spectroscopy to identify conformational preferences in aqueous solution at about 300 K. A conformational analysis of the methyl glycoside **3**[9] in aqueous solution, undertaken by a combination of NMR spectroscopy and time-averaged restrained molecular dynamics, is already available[8] and the intrinsic conformational preferences of the *O*-disaccharide **2**, a key structural component of all *N*-glycan oligosaccharides, have also been reported recently.[10] Similar conformational investigations of the corresponding *C*-disaccharide Man-*C*-α(1,6)ManαOPh (**1**), both in solution and in the gas phase, would allow the conformational similarities, or differences of biologically important disaccharides and their *C*-linked counterparts to be assessed.

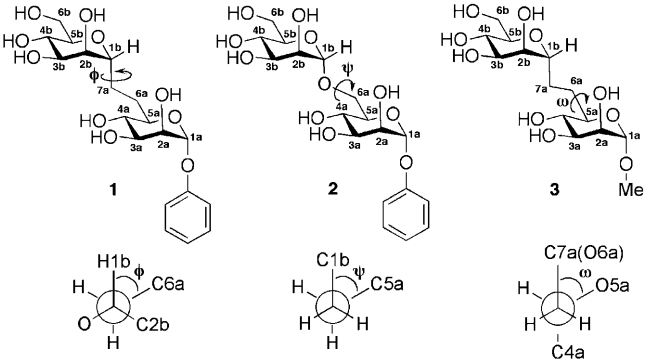


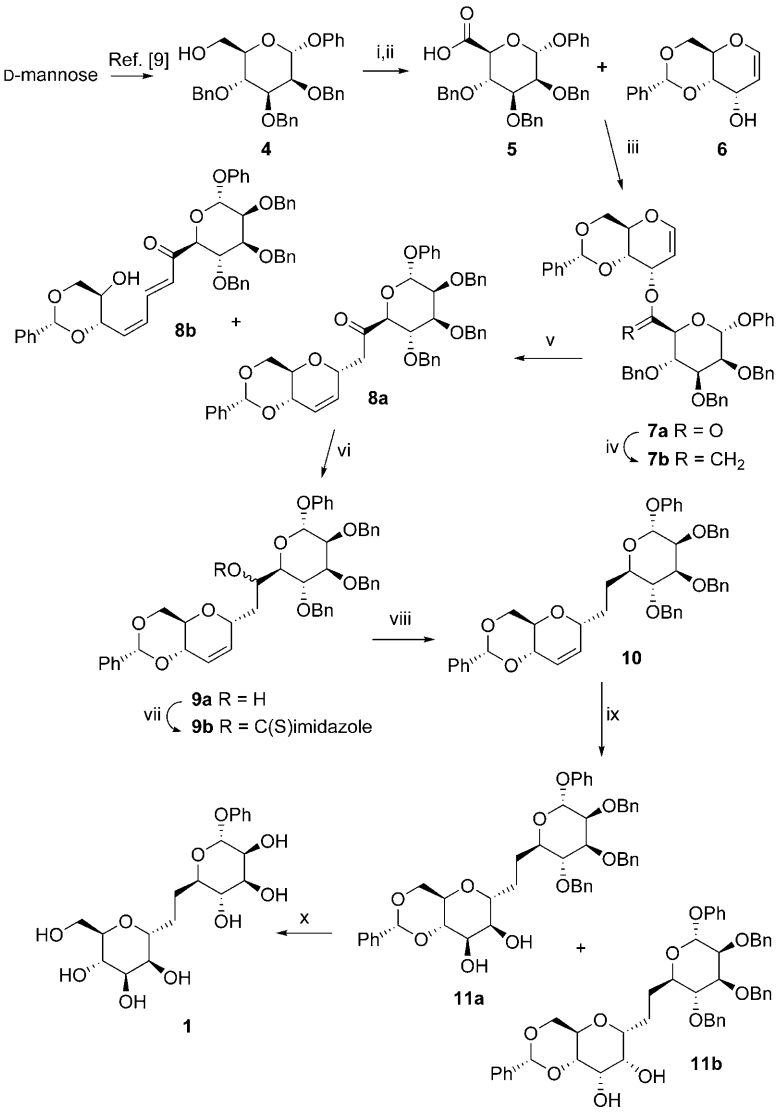
Figure 1. Structural formulae of *C*-disaccharide Manα(1,6)-*C*-ManαOPh (**1**), the corresponding natural *O*-linked disaccharide Manα-(1,6)ManαOPh (**2**), and the previously studied *C*-disaccharide Manα-(1,6)-*C*-ManαOMe (**3**). Torsion angles are defined as follows: ϕ: H1b-C1b-C7a(O6a)-C6a; ψ: C1b-C7a(O6a)-C6a-C5a; ω: C7a(O6a)-C6a-C5a-O5a.

Although stereospecific access to a range of *C*-glycoside materials, such as (1,6)-linked *C*-disaccharides can be provided by a tandem Tebbe methylenation/Claisen rearrangement approach,[11] the synthesis of the Manα(1,6)-*C*-Manα OPh *C*-disaccharide **1** on a large enough scale to provide sufficient material for gas-phase IR studies required further development of this basic methodology. Significant improvements of both the methylenation and sigmatropic rearrangement steps were needed, together with development of the final functional group transformations that were required to construct a fully oxygenated and de-protected *C*-disaccharide. The synthesis of **1** would also allow investigation of any biological activity, for example as a potential inhibitor of α-mannosidases.

Results and Discussion

Synthesis: Conformational analysis by ultraviolet resonant 2-photon ionisation and infrared ion dip spectroscopy required that the target *C*-disaccharide possess a chromophore for UV excitation, most simply achieved by the use of a phenyl aglycon. The primary alcohol **4**, previously used as a starting material for the synthesis and conformational investigation of the corresponding *O*-disaccharide was synthesised from D-mannose.[10] Oxidation to the mannuronic acid **5** was achieved in an optimised two-step sequential oxidation; firstly by treatment of **4** with *o*-iodoxybenzoic acid (IBX) in acetonitrile at reflux, followed by immediate oxidation of the crude aldehyde product by treatment with sodium chlorite in the presence of 2-methyl-2-butene as a Cl^+ scavenger[12] (quantitative yield over two steps, Scheme 1). Application of the methylenation/Claisen rearrangement sequence for formation of an α-*C*-disaccharide required an *allo*-configured glycal as the coupling partner. The 4,6-benzylidene-protected *allo*-glycal[13] **6** was therefore synthesised as previously described. Esterification of acid **5** with alcohol **6** was investigated under a variety of conditions, and was found to be most efficiently achieved by using 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) together with catalytic dimethylaminopyridine (DMAP), a combination which allowed production of the ester **7a** in a pure form on a large scale (86% yield on a ca. 25 g scale).

In previous applications[11] of the tandem methylenation/Claisen rearrangement approach for the synthesis of *C*-glycosides, methylenation of intermediate esters had been achieved by use of the Tebbe reagent.[14] However, despite the fact that this transformation could be effected, it was often difficult to reliably reproduce high-yielding product formation. Indeed when Tebbe methylenation was attempted on

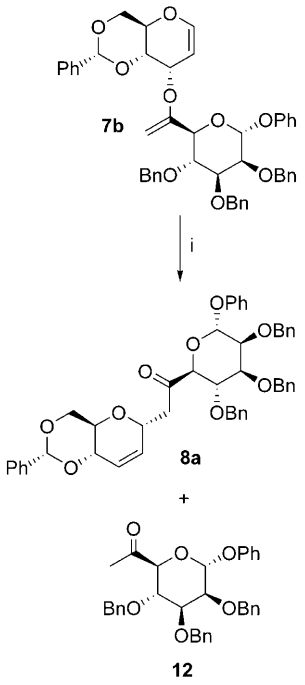


Scheme 1. i) IBX, MeCN, 80 °C; ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH/H_2O/THF (2:1:1), 4.5 h, 95% over two steps; iii) **6**, DMAP, EDCI·HCl, DCM, 0 °C to RT, 86%; iv) $TiCl_4$ (1 M in THF), TMEDA, Zn dust, $PbCl_2$, THF, then add **7a** and CH_2Br_2 in THF, RT to 62 °C, 64%; v) xylene, anion exchange resin, 300 W, 220 °C, 20 min, **8a**: 56%, **8b**: 17%; vi) $NaBH_4$, DCM/MeOH (1:1), 0 °C, 86%, (d.r. 57:43); vii) 1,1′-dithiocarbonyldiimidazole, toluene, reflux, 79%; viii) pentafluorophenol, Ph_3SnH, AIBN, toluene, reflux, 65%; ix) K_2OsO_4, $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, H_2O, *t*BuOH, THF, **11a**: 50%, **11b**: 5% ; x) H_2, Pd/C, MeOH, EtOAc, quantitative.

ester **7a**, the desired enol ether **7b** was only produced in 27% yield even after considerable optimisation of reaction conditions. As the use of the Petasis reagent[15] as an alternative also afforded the enol ether **7b** in low yield (35%), an alternative approach was sought. Re-investigation of other methods of ester methylenation revealed that the Takai procedure,[16] employing premixed $TiCl_4$, tetramethylethylenediamine (TMEDA), activated Zn dust, and crucially a catalytic quantity of $PbCl_2$ in THF, to which ester **7a** and CH_2Br_2 were added before heating to reflux, produced enol ether **7b** in 64% yield in a reliable and completely reproducible manner, which most importantly worked on a large (ca. 25 g) scale. It was concluded that the Takai approach was significantly superior to the previously applied Tebbe reagent, particularly with respect to scale up.

Claisen rearrangement of enol ether **7b** also required detailed investigation and optimisation. Previously the formation of α-*C*-glycosides using the tandem methylenation/Claisen approach had proved more problematic than for the corresponding β-compounds due to competitive ring-opening and re-closure reactions, which resulted in the formation of anomeric mixtures of products.[11b] Sigmatropic rearrangement of **7b** was investigated under a variety of conditions. Thermal rearrangement of a methyl glycoside, differing from phenyl glycoside **7b** only by the nature of the aglycon, had previously been achieved in good yield by heating in a sealed tube in xylene at 185 °C. However when phenyl glycoside **7b** was subjected to these conditions the desired product **8a** was formed in only 34% yield, and the ketone **12** was also produced (ca. 35% yield, Scheme 2). Lowering of the reaction temperature actually resulted in increased formation of the ketone **12** (isolated in up to 65% yield), and other variation of thermal parameters did not improve the efficiency of the process. A variety of Lewis acid catalysts were investigated as an alternative to thermal rearrangement, but all of these resulted in the concomitant formation of the undesired β-*C*-glycoside[17] as a side product, in line with previous observations.

In several recent disclosures the use of microwave irradiation has been reported to be distinctly advantageous to conventional heating for the promotion of certain sigmatropic rearrangements.[18] Irradiation of vinyl ether **7b** (300 W) at 180 °C in xylenes produced the desired *C*-disaccharide **8a** in 46% yield, but the ketone **12** was also formed (54% yield). Increasing the reaction temperature to 220 °C during irradiation (300 W) significantly improved the yield of **8a** (78% yield), and also decreased ketone formation. However when this reaction was performed at higher substrate concentra-



Scheme 2. i) Xylene, IRA-400 anionic exchange resin (HO^- form), microwave irradiation (300 W), 220 °C (41 psi), 20 min., **8a**: 80 %, **12**: 0 %.

tions that were required for the production of **8a** on a significant scale, the yield once again dropped, and ketone formation became more prevalent. Reasoning that formation of the by-product **12** was acid catalysed, the addition of acid scavengers to the microwave-mediated reaction was investigated. The addition of either propylene oxide[19] or potassium carbonate to the reaction mixture before irradiation did indeed preclude formation of the ketone **12**, though undesired β-*C*-glycoside was also formed in the former case and the isolated yields of **8a** were not greatly improved. Curtailment of the side reaction that resulted in formation of **11** indicated that the use of an acid scavenger was certainly advantageous. Finally, following further investigations, an optimised procedure was arrived upon involving the use of anionic ion exchange resin (IRA-400, HO^- form). Irradiation of **7b** (300 W) in xylenes at 220 °C (41 psi) in the presence of basic anion exchange resin for 15 min produced **8a** in 80 % yield (55 mg scale, Scheme 2).

Attention then turned to production of significant quantities of **8a** using this optimised procedure. Due to the limited scale of reactions that it was feasible to undertake in the microwave reactor this necessitated a 'batch' synthesis approach. Repetition of the above process and combination of the crude reaction products allowed production of >4 g of the desired α-*C*-glycoside **8a** (from 7.2 g of **7b**, overall 68 % yield), as a single anomer, together with some material identified as the ring-opened diene **8b**, which was easily separated by chromatography.

With large quantities of the *C*-glycoside **8a** in hand attention turned to the final functional group transformations required to access the fully oxygenated and de-protected α-*C*-disaccharide **1** (Scheme 1). The first objective was removal of the ketone functional group, the presence of which facilitated retro-Michael ring opening to **8b**, re-closure of which would result in epimerisation to the undesired β-*C*-glycoside. Reduction of the ketone **8a** to alcohols **9a** was achieved with sodium borohydride; no appreciable diastereoselectivity was observed and the two epimers of **9a** were formed in a 53:47 ratio. Conversion of these alcohols to the required methylene unit was achieved by a two-step free radical deoxygenation method. Firstly, reaction with thiocarbonyl diimidazole furnished the corresponding thiocarbamates **9b**. Free radical reduction was then attempted under a variety of conditions, and was most successfully achieved following the protocol reported by Beau, Skrydstrup, and co-workers,[20] by reduction with triphenyl tin hydride and azobisisobutyronitrile (AIBN) in refluxing toluene, crucially in the presence of pentafluorophenol, to yield **10**. *cis*-Dihydroxylation of **10**, required to fully re-oxygenate the carbon skeleton, was achieved by using catalytic potassium osmate, and proceeded with good stereocontrol (ca. 10:1) to give the desired *manno*-configured diol **11a** as the major product, together with minor amounts of the corresponding *allo* compound **11b**. Finally catalytic hydrogenation of **11a** in the presence of palladium on carbon resulted in removal of all protecting groups to yield the desired α-*C*-disaccharide **1**.

The overall synthesis from the known precursors **4** and **6** (longest linear sequence 10 steps) was performed on a large scale, and >200 mg of de-protected α-*C*-disaccharide **1** were synthesised providing ample quantities of material for gas-phase IR and NMR analysis. The de-protected α-*C*-disaccharide **1** was tested as a potential inhibitor of Jack bean α-mannosidase, using a spectrophotometric assay in which the rate of hydrolysis of *para*-nitrophenyl-α-D-mannoside at pH 5 was monitored by UVspectroscopy. *C*-Disaccharide **1** did not display any inhibitory effect at concentrations up to 1 mmol L^{-1}; swainsonine was used as a control inhibitor at a concentration of 0.2 mmol L^{-1}.

Conformational analysis: *Structure in the gas phase*: Ultraviolet resonant two-photon ionization (R2PI) and infrared ion dip (IRID) spectroscopy were used to investigate the gas-phase conformational preference of Manα(1,6)-*C*-ManOPh (**1**) in a cold molecular beam. The IRID technique is a double-resonance pump-probe method, which selectively depletes each selected conformer by removing population from its ground electronic state leading to a decrease of the total parent ion signal. Conformer-selective IR spectra can be measured by scanning the IR pump laser over a broad range of frequencies. The phenyl tag provides the UV chromophore necessary for detection via the resonant two photon ionization (probe) step in the IRID technique.[10,21]

Figure 2a and b show the R2PI and IRID spectra of Manα(1,6)-*C*-ManOPh (**1**) recorded in the gas phase in the parent ion mass channel, between 3350 cm^{-1} and 3700 cm^{-1}. The predicted vibrational spectra of its three most stable conformers are shown in Figure 2c–e. Although the R2PI spectrum displays a series of sharp features superimposed

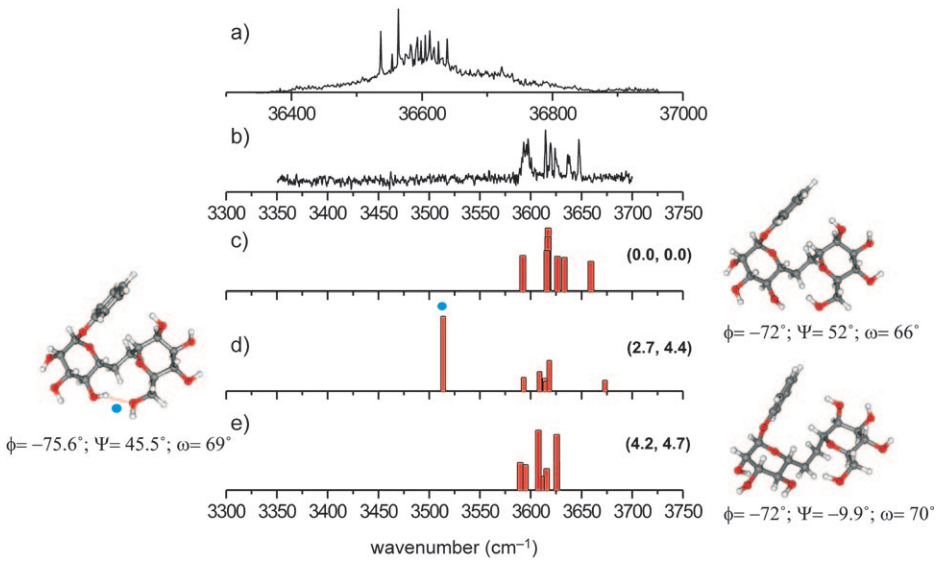


Figure 2. a) R2PI and b) IRID spectra of Manα(1,6)-*C*-ManOPh (**1**); c)–e) computed spectra at the B3LYP/6-31+G* level of theory of its three lowest energy conformers. The dots in (d) indicate the inter-ring OH→O hydrogen bond and the corresponding vibrational band. Predicted zero point corrected relative energies (0 K), and free energies (298 K) in kJ mol^{-1}, calculated at the MP2/6-311++G** level are shown in brackets; the glycosidic dihedral angles are defined as: ϕ: H1b-C1b-C7a-C6a; ψ: C1b-C7a-C6a-C5a; ω: C7a-C6a-C5a-O5a.

on an underlying continuum, the associated IRID spectrum was independent of the selected UV probe frequency, indicating the presence of only one major conformer—in contrast to the natural *O*-linked disaccharide, **2** where two conformers are strongly populated.[10] The underlying continuum in the R2PI spectrum can be attributed to the excitation of congested hot-band transitions.

The experimental IRID spectrum Figure 2b presents a cluster of bands between 3650 and 3596 cm^{-1} associated with OH stretching vibrational modes, moderately displaced towards lower wavenumber by hydrogen-bonded interactions; the most strongly displaced band at 3596 cm^{-1} is noticeably broader than the other features. No bands were observed below 3596 cm^{-1} however, indicating the absence of any strongly hydrogen-bonded OH groups. The predicted vibrational spectrum of the most stable conformer, shown in Figure 2c, also presents a distinctive cluster of bands lying above 3580 cm^{-1} and it provides the best agreement with experiment. There is no evidence of strong inter-ring, OH→O hydrogen bonding; were it to occur it would be signalled by a much larger spectral shift, compare, for example, the hydrogen-bonded structure and its associated spectrum shown in Figure 2d, where OH4a→OH6b hydrogen-bonding shifts one of the bands to 3513 cm^{-1}.

Figure 3 compares the vibrationally assigned experimental IRID spectra of the *C*-disaccharide **1** and the natural *O*-linked disaccharide **2** and their associated conformational structures. Interestingly replacement of the oxygen atom in the glycosidic linkage by CH_2, which might plausibly have been expected to result in a more flexible framework, actually leads to the opposite result.[22] In the gas phase only one conformer is populated in the *C*-disaccharide, whereas two are populated in the natural carbohydrate **2**, one of which displays an inter-ring OH→O hydrogen bond (see Figure 3b).[10] The vibrational spectrum associated with the other conformer (Figure 3c) appears to resemble that of the *C*-disaccharide **1** (Figure 3a), but the resemblance is decep-

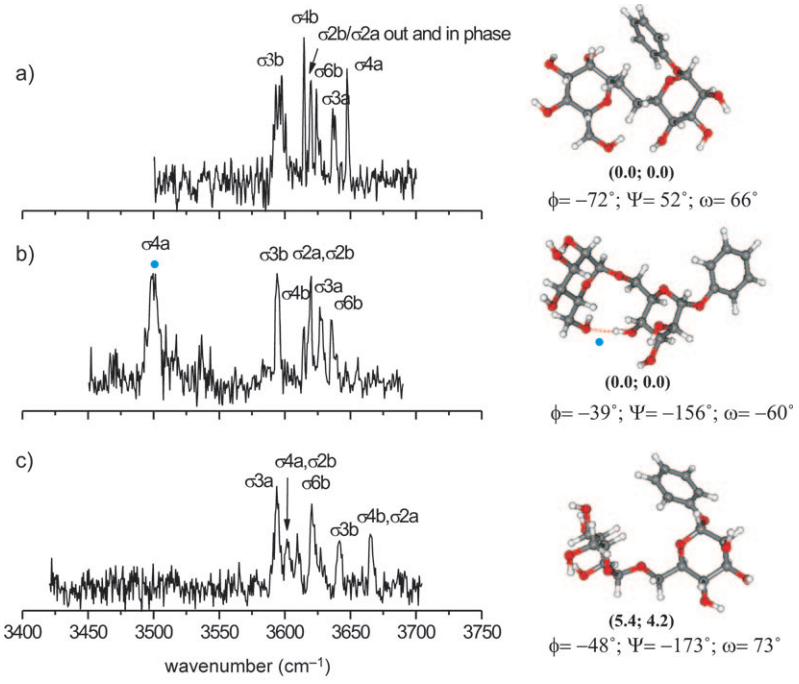


Figure 3. Experimental IRID spectra and vibrational assignments of a) Manα(1,6)-*C*-ManOPh (**1**) and b) and c) Manα(1,6)ManOPh (**2**); their corresponding conformational structures are shown on the right hand side of the figure. The assignments for Manα(1,6)ManOPh (**2**) are based on previous studies;[10] the blue dots identify the inter-ring hydrogen bond OH4a→OH6b and its associated (strongly displaced) vibrational band, σ4a. MP2 zero point (0 K) and free energy (298 K) corrected relative energies are given in brackets; glycosidic dihedral angles are defined as ϕ: H1b-C1b-C7a(O6a)-C6a; ψ: C1b-(C7a)O6a-C6a-C5a; ω: (C7a)O6a-C6a-C5a-O5a.

tive because the glycosidic angles and vibrational assignments are quite different. A conformer of **1** with dihedral angles similar to those of the non H-bonded conformer of **2** was identified computationally but its relative energy at 0 K and free energy at 298 K (calculated at the MP2/6-311++G** level) were 29.5 kJ mol^{-1} and 21.9 kJ mol^{-1}, respectively. The most stable conformer of **1** displays an OH2b–π interaction between the second mannose ring and the phenyl 'tag', not seen in **2**, accompanied by a change in the co-operative hydrogen bonding to a counter-clockwise orientation, OH4b-OH3b-OH2b-π. These changes discourage the formation of a strong OH→O inter-ring hydrogen bond across the glycosidic linkage and assist the stabilisation of a single major conformer in the gas phase.

To investigate the *un*perturbed conformational preference of the *C*-disaccharide, the phenyl tag in **1** was replaced by methyl to eliminate the OH2b-π interaction, and its relative low lying conformational energies were determined using the same methodology as for Manα(1,6)-*C*-ManOPh (**1**). These calculations included the most stable glycoside conformations found previously for **1** and also the lowest lying structures displaying inter-ring OH→O hydrogen bonding, but not an OH–π interaction. The results are shown in Figure 4. In contrast to the experimental and computational data for **1**, the most stable conformer of the methyl *C*-disaccharide **3** is predicted to present a strong OH→O hydrogen bond across the glycosidic linkage. The phenyl tag in Manα-(1,6)-*C*-ManOPh is therefore not "structurally benign" and it influences its conformational landscape.

Structure in solution: Solution-phase conformational analysis NMR spectra of the methyl *C*-disaccharide **3**, which lacks a potentially conformationally perturbing phenyl tag, had previously been undertaken by Jiménez-Barbero, Skrydstrup, and co-workers as part of their study of the *C*-trisaccharide Manα(1,3)-*C*-[Manα(1,6)-*C*-]-ManαOMe. The conformational preferences of **1** in aqueous solution were therefore investigated by ^{1}H NMR spectroscopy, and the results compared to data that were available for **3** (Table 1). Measurement of the ^3J ^{1}H–^{1}H coupling constants between protons at the C1b, C7a, C6a and C5a positions was achieved by iterative spectrum simulation[23] and comparison with the ^{1}H spectrum obtained for **1** at 298 K in D_2O (700 MHz, Figure 5 and Table 1).

Measured *J* values were interpreted following the previously described protocol;[8] conformational populations were assessed by comparison of the experimental $^3J_{H,H}$ values with those predicted by the Haasnoot–Altona variant of the Karplus equation for the possible staggered conformational energy minima, as previously reported.[8] Table 2 provides comparison between the conformational populations of the phenyl *C*-disaccharide **1** so determined, and methyl *C*-disaccharide **3**, for which three conformers had been identified by Jiménez-Barbero, Skrydstrup, and co-workers,[8] labelled D, E and F, with relative populations of 95:1:4 predicted from molecular mechanics calculations (Figure 6). The coupling constants observed in the C–C bridge of compound **1** between protons at positions 5a and 6a match closely the

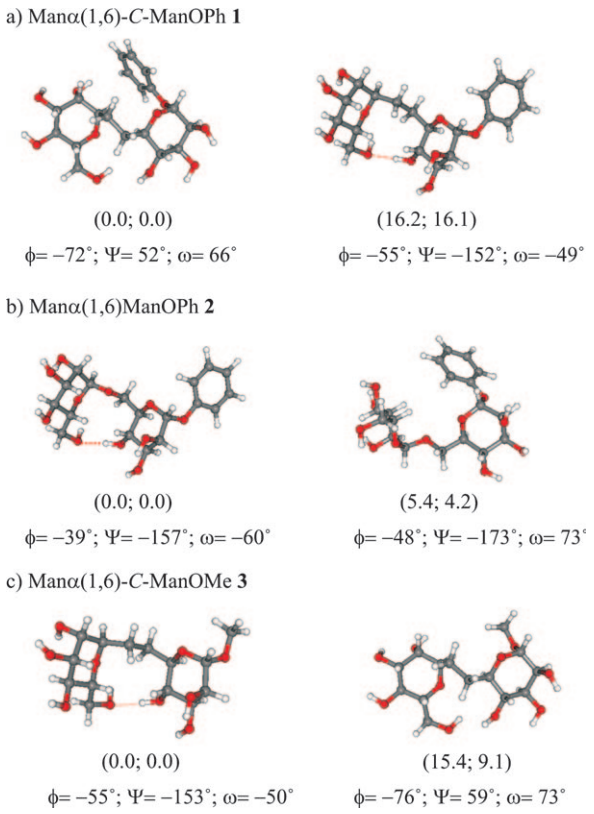


Figure 4. Computed structures comparing the most stable OH→O hydrogen-bonded and non hydrogen-bonded conformers of a) Manα(1,6)-*C*-ManOPh (**1**); b) Manα(1,6)ManOPh (**2**); c) Manα(1,6)-*C*-ManOMe (**3**). MP2 zero point (0 K) and free energy (298 K) corrected relative energies in kJ mol^{-1}, are given in brackets. Glycosidic dihedral angles as defined in the text are shown below each structure.

Table 1. Solution NMR $^3J_{H,H}$ coupling data for Manα(1,6)-*C*-ManOPh (**1**) compared to those reported for Manα(1,6)-*C*-ManOMe (**3**),[8] together with the predicted values for coupling constants across the C7a–C6a linkage for when Ψ = 180° or 60° (see text for discussion).

Protons	Related dihedral angle[a]	exp. J(**1**) [Hz]	exp. J(**3**) [Hz][b]	pred. J [Hz][b] Ψ = 180	pred. J [Hz][b] Ψ = 60
5a, 6aR	ω	1.8	2.6	–	–
5a, 6aS	ω	9.6	9.3	–	–
6aR, 7aR	ψ	7.7	small	1.9	13.8
6aR, 7aS	ψ	9.2	large	13.8	2.4
6aS, 7aR	ψ	8.8	large	13.8	2.2
6aS, 7aS	ψ	4.1	small	2.6	5.2
7aR, 1b	ϕ	4.3	4.3	–	–
7aS, 1b	ϕ	11.5	9.0	–	–

[a] C-linked glycosidic dihedral angles: ϕ: H1b-C1b-C7a-C6a; ψ: C1b-C7a-C6a-C5a; ω: C7a-C6a-C5a-O5a. [b] Ref. [8].

couplings found in compound **3**. According to the analysis of Jiménez-Barbero, Skrydstrup, and co-workers[8] these couplings are related to approximately 80% gt and approximately 20% gg conformations about the ω dihedral and hence these considerations also hold for **1**. Likewise, the couplings between protons at positions 7a and 1b are similar to those reported for **3** and correspond to a dominant Φ =

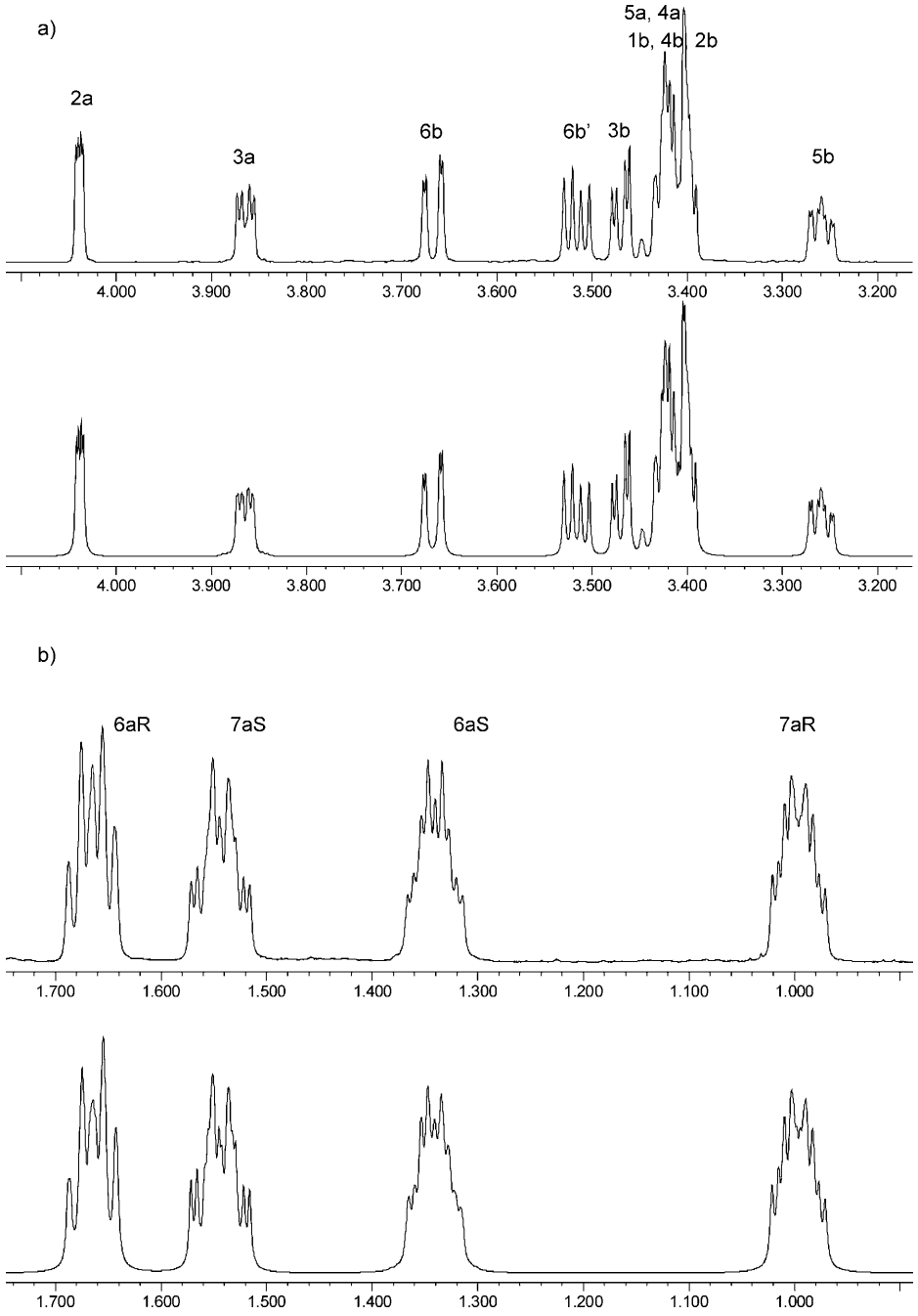


Figure 5. A comparison of experimental and simulated ^{1}H NMR spectra of Manα(1,6)-*C*-ManOPh (**1**). For both regions (a) and (b) the upper and lower traces present experimental and simulated spectra, respectively.

−60° angle. In this geometry the 7aS and 1b protons share an *anti* relationship, consistent with the large $^{3}J_{H,H}$ value. This arrangement in **1** was further supported by 2D NOESY data (see the Supporting Information) in which strong correlations were observed between the 7aS proton and both 3b and 5b protons.

Considering the Ψ angle, a high population of the −60° conformation could be excluded because of the low experimental value of the 6aS to 7aS coupling constant since in this conformation the coupling would be predicted to have a high value of around 14 Hz due to the *anti* arrangement of these protons. The predicted $^{3}J_{H,H}$ values for the alternative Ψ = 180° or 60° dihedral angles are given in Table 1. On consideration of the four observed 6a,7a coupling constants (Table 1), it is apparent that the values fall between those predicted for the 180° and 60° conformations, suggesting these to be populated to a similar extent; especially noteworthy is the mid-range coupling constant 6aR,7aR which would fall in this region only if the 60° conformation is populated to about 50%. These conformers correspond to the D and F Ψ forms defined by Jiménez-Barbero, Skrydstrup, and co-workers.[8] Compound **1** is therefore more flexible and would appear to adopt the Ψ = 60° F conformation more readily than compound **3** (in which conformer F was calculated to be only 4% populated). A significant population of conformer F is also consistent with the ^{1}H ring-current shifts observed for **1**, where, in particular the 1b, 2b, 7aR and 7aS protons show a very significant decrease in chemical shift relative to those of **3** (−0.77, −0.73, −0.91 and −0.76 ppm, respectively). The effect on the 1b, 2b and 7aR can be described well by conformer F, whereas in conformer D the phenyl group exhibits close proximity to only 7aR and 7aS. The substantial ring current shifts of 1b and 2b therefore provide further evidence for a substantial population of the −60°/60°/60° conformer. Attempts to identify supporting NOEs from phenyl protons to 1b and 2b were frustrated by extensive multiplet overlap where both 1b and 2b resonate (5 peaks within 0.05 ppm; see Figure 5). NOEs from the *ortho*-phenyl protons to this region were apparent and could be assigned to the 5a/4a and 1b/2b strongly-coupled pairs by comparison with 1D selective TOCSY experiments. However, these NOEs were insufficiently resolved, even in high-resolution 1D selective NOESY spectra, to reliably assign their intensities, although it was apparent that, unsurprisingly, the 5a/4a NOE was dominant.

Table 2. Glycosidic dihedral angles of Manα(1,6)-*C*-ManOPh (**1**) and Manα(1,6)-*C*-ManOMe (**3**) in aqueous solution and of Manα(1,6)-*C*-ManOPh (**1**) and Manα(1,6)ManOPh (**2**) isolated in the gas phase. C(O)-linked glycosidic dihedral angles: ϕ: H1b-C1b-C7a(O6a)-C6a; ψ: C1b-C7a(O6a)-C6a-C5a; ω: C7a(O6a)-C6a-C5a-O5a.

Technique	Compound	Conformations	ϕ, ψ, ω
NMR/aqueous[b]	Manα(1,6)-*C*-ManOPh (**1**)	D (ca. 50%)	−60, 180, 60[d]
		F (ca.50%)	−60, 60, 60[d]
NMR/aqueous[a]	Manα(1,6)-*C*-ManOMe (**3**)[a]	D (95%)	−60, 180, 60[d]
		E (1%)	60, 180, 60[d]
		F (4%)	−60, 60, 60[d]
gas phase IR/isolated[b]	Manα(1,6)-*C*-ManOPh (**1**)[b]	non-H-bonded (100%)	−72, 52, 66
		H-bonded (0%)	[−55, −152, −49]
gas phase IR/isolated[c]	Manα(1,6)-*O*-ManOPh (**2**)	non-H-bonded (major)	−48, −173, 73
		H-bonded (minor)	−39, −157, −60

[a] Ref. [8]. [b] This work. [c] Ref. [10]. [d] ω = 60 (80%); −60 (20%).

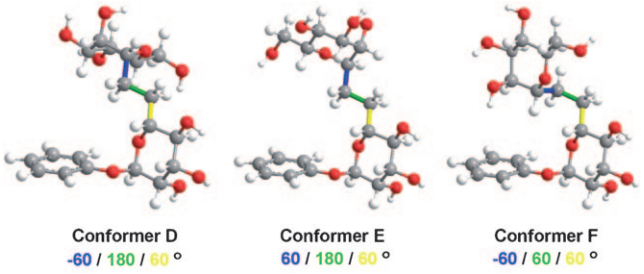


Figure 6. Conformers D, E and F, and their glycosidic dihedral angles with associated bonds coloured blue (*ϕ*), green (ψ) and yellow (ω; the ω dihedral angle is shown as the dominant (80%) 60° conformer in each case).

Table 2 also compares the glycosidic dihedral angles in the conformer of Manα(1,6)-*C*-ManOPh (**1**) populated in the gas phase at about 10 K, with those populated in the natural disaccharide **2**. The dihedral angles of the phenyl-tagged *C*-disaccharide **1** conformer populated in the gas phase are very similar to those of the solution-phase conformer, F, populated in aqueous solutions of Manα(1,6)-*C*-ManOPh (**1**) (but only in trace amounts in Manα(1,6)-*C*-ManOMe (**3**)). The second conformer, D, detected in the aqueous solution of **1**, was not populated in the gas phase. We therefore postulate that the enhanced population of conformer F of **1** in aqueous solution arises from its stabilisation by the presence of the OH2b–π interaction, as predicted by the gas-phase studies, which would not be possible in **3**.

Conclusions

Within this report we set out to synthesise and investigate the conformational preference of the *C*-glycosyl mimetic Manα(1,6)-*C*-ManOPh (**1**), in the gas phase and in solution, and compare it to that of the natural analogue studied previously. A convergent and reliable synthetic route to **1** was developed by employing a tandem methylenation and Claisen rearrangement approach; substantial methodological improvements were arrived upon by the use of Takai methylenation and microwave-mediated sigmatropic rearrangement in the presence of anionic exchange resin. Gas-phase results obtained in a cooled molecular beam at about 10 K were compared to solution-phase NMR spectroscopic findings at 298 K. The gas-phase results indicate the presence of only one conformer, whereas for the natural *O*-disaccharide **2**, two conformers have been observed. The higher flexibility of the glycosidic linkage in the glycomimetic allows the formation of an OH–π interaction with the aromatic ring of the phenyl chromophore. Such OH–π interactions between carbohydrates and aromatic rings have been studied previously,[24,25] and play an essential role in the molecular recognition of carbohydrates by proteins. The OH–π interaction formed in the *C*-disaccharide **1** accompanies a change of the conformational preference as indicated by calculations performed on the methylated analogue **3**. The NMR studies in aqueous solution indicate that **1** populates two dominant conformers, D and F, in approximately equal proportions. The gas-phase dihedral angles are similar to those derived from NMR spectroscopy for F, suggesting that similar conformations are populated at 10 K and in solution at 298 K. The enhanced population of conformer F of **1** in aqueous solution is associated, at least in part, by an interaction between the mannopyranoside and phenyl rings, including the OH2b–π bond identified in the gas-phase studies.

Experimental Section

General procedures: Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance (δH) spectra were recorded on a Bruker DPX 400 (400 MHz), or on a Bruker AV 400 (400 MHz) spectrometer, and spectra were assigned by using COSY and HMQC experiments. Carbon nuclear magnetic resonance (δC) spectra were recorded on a Bruker DPX 400 (100.6 MHz), or on a Bruker AV 400 (100.6 MHz) and were assigned by using HMQC experiments. Multiplicities were assigned by 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, by 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 per 100 mL. Microanalyses were performed by the microanalytical services of the Inorganic Chemistry Laboratory, Oxford. Thin-layer chromatography (t.l.c.) was carried out on Merck glass backed sheets, pre-coated coated with 60F254 silica. Plates were developed by 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. Microwave irradiations were performed in sealed tubes in a CEM Discover apparatus.

Phenyl 2,3,4-tri-*O*-benzyl-α-D-mannuronic acid (5): Primary alcohol **4**[10] (52.05 g, 98.83 mmol) and freshly prepared wet IBX (made from 2-iodobenzoic acid (80.40 g, 324.16 mmol)) were suspended in acetonitrile (660 mL) and the mixture was heated to 80 °C for 12 h, after which time, t.l.c. (petroleum ether/ethyl acetate 4:1) indicated the complete consumption of the starting material (R_f = 0.6). The reaction mixture was then cooled to room temperature, filtered and the solid was washed with acetonitrile (500 mL). The filtrate was concentrated under reduced pressure and the crude residue was suspended in a mixture of *tert*-butyl alcohol (250 mL), THF (250 mL) and 2-methyl-2-butene (100 mL), before a solution of $NaClO_2$ (259.54 g, 2.87 mol) and NaH_2PO_4 (200.30 g, 1.45 mol) in water (450 mL) was added slowly. The mixture was stirred and after 3 h, t.l.c (petroleum ether/ethyl acetate 1:1) indicated the formation of a major product (R_f 0.7). The reaction mixture was then acidified by addition of an aqueous solution of hydrochloric acid (1 M, 250 mL) and was then extracted with ethyl acetate (4×750 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Filtration through a plug of silica (petroleum ether/diethyl ether 1:1) provided the mannuronic acid **5** (79.92 g, 95 %) as a colourless oil. R_f = 0.7 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{20}$ = +17 (c = 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ = 3.85 (bat, ^3J(H,H) = 4.0, 3.0 Hz, 1H; 2-H), 3.88 (dd, ^3J(H,H) = 6.5, 3.0 Hz, 1H; 3-H), 4.15 (at, ^3J-(H,H) = 6.5, 6.5 Hz, 1H; 4-H), 4.25 (d, ^3J(H,H) = 6.5 Hz, 1H; 5-H), 4.44–4.62 (m, 6H; 3CH_2Bn), 5.76 (d, ^3J(H,H) = 4.0 Hz, 1H; 1-H), 6.86–7.26 ppm (m, 20H; 20ArH); ^{13}C NMR (100.6 MHz, CD_3OD): δ = 73.3 (*C*H_2Bn), 74.2 (*C*H_2Bn), 74.6 (*C*H_2Bn), 75.1 (C-5), 76.2 (C-2), 77.2 (C-4), 78.5 (C-3), 97.5 (C-1), 117.6, 123.3, 128.7, 128.8, 129.1, 129.3, 129.3, 129.4, 129.4, 130.5 (20ArCH), 139.5, 139.5, 139.6, 158.2 (4ArC), 174.7 ppm (C-6); IR (film): $\tilde{\nu}$ = 3406 (br, ν(OH)), 1721 (s, ν(C=O)) 1598, 1495, 1454 (m, ν(C=C)), 1363, 1225, 1114, 1028 cm^{-1} (s, ν(C–O)); ESI$^+$-HRMS: m/z: calcd for $C_{33}H_{32}O_7Na$: 563.2040 $[M+Na]^+$, found: 563.2035.

1b,5b-Anhydro-4b,6b-*O*-benzylidene-2b-deoxy-D-ribo-hex-1-en-3b-yl-(phenyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside) uronate (7a): Under an atmosphere of argon, glycal **6**[13] (9.03 g, 38.59 mmol), mannuronic acid **5** (30.18 g, 55.89 mmol) and DMAP (1.04 g, 8.48 mmol), were dissolved in anhydrous DCM (190 mL) and the reaction mixture was cooled to 0 °C. After the mixture had been stirred for 15 min, EDCI·HCl (20.98 g, 109.44 mmol) was added and the mixture was stirred for a further 12 h, after which time, t.l.c (petroleum ether/ethyl acetate 1:1) indicated the formation of a major product (R_f = 0.9). The mixture was partitioned between DCM (400 mL) and a 10 % aqueous solution of ammonium chloride (100 mL). The organic layer was separated, washed with 10 % aqueous solution of ammonium chloride (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was then purified by flash column chromatography (petroleum ether/ethyl acetate 9:1 to 1:1) to afford ester **7a** (25.18 g, 86 %) as a white foam. R_f = 0.9 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{19}$ = +120 (c = 1.5 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ = 3.34 (dd, ^3J(H,H) = 10.5, 4.0 Hz, 1H; 4b-H), 3.39 (at, ^3J(H,H) = 9.5 Hz, ^2J(H,H) = 9.5 Hz, 1H; 6b-H), 4.00 (dd, ^3J(H,H) = 5.0, 2.5 Hz, 1H; 3a-H), 4.11–4.19 (m, 3H; 2a-H, 5b-H, 6′b-H), 4.31 (brd, ^2J(H,H) = 10.0 Hz, 1H; C*H*$_2$Bn), 4.37 (d, ^2J-(H,H) = 12.0 Hz, 1H; C*H*$_2$Bn), 4.47–4.53 (m, 4H; 4a-H, 3C*H*$_2$Bn), 4.66 (d, ^3J(H,H) = 3.5 Hz, 1H; 5a-H), 4.74 (at, ^3J(H,H) = 6.0, 6.0 Hz, 1H; 2b-H), 4.75 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*$_2$Bn), 5.15 (s, 1H; 7b-H), 5.24 (dd, ^3J(H,H) = 6.0, 4.0 Hz, 1H; 3b-H), 5.96 (d, ^3J(H,H) = 6.0 Hz, 1H; 1b-H), 6.34 (brs, 1H; 1a-H), 6.90 (at, ^3J(H,H) = 7.5 Hz, 1H, ArH), 7.04–7.26 (m, 20H; 20ArH), 7.49–7.51 (m, 2H; 2ArH), 7.58–7.60 ppm (m, 2H; 2ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ = 63.7 (C-3b), 65.2 (C-5b), 68.6 (C-6b), 72.8 (2CH_2Bn), 73.4 (*C*H_2Bn), 73.5 (C-5a), 75.9 (C-2a), 75.9 (C-4b), 76.3 (C-4a), 77.6 (C-3a), 97.4 (C-1a), 98.4 (C-2b), 102.0 (C-7b), 117.3 (ArCH), 122.5 (ArCH), 126.8 (2ArCH), 127.6 (2ArCH), 127.9 (2ArCH), 127.9 (2ArCH), 128.0 (2ArCH), 128.0 (2ArCH), 128.3 (ArCH), 128.4 (2ArCH), 128.4 (2ArCH), 128.6 (2ArCH), 129.2 (ArCH), 129.8 (2-ArCH), 137.9 (ArC), 138.3 (ArC), 138.8 (ArC), 139.2 (ArC), 147.3 (C-1b), 158.2 (ArC), 169.3 ppm (C=O); IR (film): $\tilde{\nu}$ = 3032 (m, ν(CHAr)), 2866 (m, ν(CH)), 1747 (s, ν(C=O)), 1636 (m, ν(C=C)), 1590, 1588, 1496 (m, ν(C=CAr)), 1455 (m, δ(CH)) ,1242, 1089 (s, ν(CO)), 754, 697 cm^{-1} (m, δ(CH)); ESI$^+$-HRMS: m/z: calcd for $C_{46}H_{44}NaO_{10}$: 779.2827 $[M+Na]^+$, found 779.2838.

Phenyl 6-*O*-(1b,5b-Anhydro-4b,6b-*O*-benzylidene-2b-deoxy-D-ribo-hex-1-en-3b-yl)-7-deoxy-2,3,4-tri-*O*-benzyl-α-D-*gluco*-hept-6-enopyranoside (7b): Under an atmosphere of argon, $TiCl_4$ (99 %, 92.5 mL, 843.5 mmol) in solution in anhydrous DCM (250 mL) was added by using a cannula to anhydrous THF (790 mL) cooled to 0 °C, and the mixture was stirred for 15 min. TMEDA (229.0 mL, 1.52 mol) was then added to the yellow solution, and the mixture was then warmed to room temperature and stirred for a further 15 min. Activated Zn dust (128.04 g, 1.85 mol) and $PbCl_2$ (2.28 g, 8.19 mmol) were added, and the reaction mixture was stirred for a further 20 min., when a green then blue-green colour appeared. A solution of ester **7a** (35.58 g, 47.01 mmol) and CH_2Br_2 (31.4 mL, 445.91 mmol), in anhydrous THF (240 mL) was added by using a cannula to the green solution and the reaction mixture was then heated to 62 °C. After 1 h 30 min., t.l.c (petroleum ether/ethyl acetate 7:3) indicated complete consumption of the starting material (R_f = 0.5) and the formation of a major product (R_f = 0.6). The mixture was then cooled to 0 °C and the reaction mixture was poured into a mixture of saturated aqueous solution of sodium hydrogencarbonate (30 mL) and DCM (100 mL). The resulting mixture was stirred for 30 min. before it was filtered through a Celite/alumina pad. The solid residue was then washed three times with DCM (400 mL + 3 % Et_3N). The filtrates were combined, concentrated under reduced pressure, and the residue was then dry-loaded on silica and purified by flash column chromatography (petroleum ether/ethyl acetate 95:5 to 4:1, 2 % Et_3N) to afford vinyl ether **7b** (22.63 g, 64 %) as translucent orthorhombic crystals. R_f = 0.6 (petroleum ether/ethyl acetate 7:3); m.p. 145–146 °C; $[\alpha]_D^{19}$ = +129 (c = 1.0 in $CHCl_3$), $[\alpha]_D^{21}$ = +120 (c = 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ = 3.46 (at, ^3J(H,H) = 10.5 Hz, ^2J-(H,H) = 10.5 Hz, 1H; 6b-H), 3.49 (dd, ^3J(H,H) = 10.5, 3.5 Hz, 1H; 4b-H), 3.97 (at, ^3J(H,H) = 2.5, 2.5 Hz, 1H; 2a-H), 4.17 (dd, ^2J(H,H) = 10.5 Hz, ^3J-(H,H) = 5.5 Hz, 1H; 6′b-H), 4.19 (d, ^3J(H,H) = 2.0 Hz, 1H; 7a-H), 4.25 (dd, ^3J(H,H) = 9.5 2.5 Hz, 1H; 3a-H), 4.34 (d, ^3J(H,H) = 2.0 Hz, 1H; 7′a-H), 4.38–4.43 (m, 2H; 5b-H, 3b-H), 4.47 (d, ^3J(H,H) = 9.5 Hz, 1H; 5a-H), 4.50 (d, ^2J(H,H) = 13.5 Hz, 1H; C*H*$_2$Bn), 4.56 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*$_2$Bn), 4.61 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*$_2$Bn), 4.64 (d, ^2J(H,H) = 13.5 Hz, 1H; C*H*$_2$Bn), 4.69 (at, ^3J(H,H) = 9.5, 9.5 Hz, 1H; 4a-H), 4.72 (at, ^3J(H,H) = 6.0, 6.0 Hz, 1H; 2b-H), 4.90 (d, ^2J(H,H) = 12.0 Hz, 1H, C*H*$_2$Bn), 4.93 (d, ^2J(H,H) = 12.0 Hz, 1H; C*H*$_2$Bn), 5.29 (s, 1H; 7b-H), 5.67 (d, ^3J(H,H) = 2.5 Hz, 1H; 1a-H), 6.01 (d, ^3J(H,H) = 6.0 Hz, 1H; 1b-H), 6.86 (brat, ^3J(H,H) = 7.5 Hz, 1H; ArH), 7.03–7.21 (m, 16H; 16ArH), 7.34 (brat, ^3J(H,H) = 7.5 Hz, 4H; 4ArH), 7.40 (brd, ^3J(H,H) = 7.5 Hz, 2H; 2ArH), 7.71 ppm (brd, ^3J(H,H) = 8.5 Hz, 2H; 2ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ = 65.0 (C-3b or C-5b), 65.6 (C-5b or C-3b), 68.8 (C-6b), 72.7 (CH_2), 73.0 (CH_2), 74.9 (CH_2), 76.0 (C-2a), 76.1 (C-5a), 76.7 (C-4a), 77.2 (C-4b), 80.0 (C-3a), 89.0 (C-7a), 97.6 (C-1a), 98.7 (C-2b), 101.9 (C-7b), 117.0 (2ArCH), 122.5 (ArCH), 127.2 (2ArCH), 127.4 (ArCH), 127.6 (ArCH), 127.6 (ArCH), 127.8 (2ArCH), 127.8 (3ArCH), 128.2 (2ArCH), 128.3 (3ArCH), 128.5 (2ArCH), 128.5 (2ArCH), 129.0 (ArCH), 129.8 (2ArCH), 138.4 (ArC), 139.1 (ArC), 139.4 (ArC), 140.0 (ArC), 146.4 (C-1b), 157.3 (Cq), 158.0 ppm (Cq); IR (KBr): $\tilde{\nu}$ = 3020 (m, ν(CHAr)), 2863 (m, ν(CH)), 1632 (s, ν(C=C)), 1597, 1595, 1497, 1495 (m, ν(C=CAr)), 1455 (m, δ(CH)) ,1141, 1088 (s, ν(CO)), 735, 695 cm^{-1} (m, δ(CH)); ESI$^+$-HRMS: m/z: calcd for $C_{47}H_{46}NaO_9$: 772.3480 $[M+Na]^+$, found 772.3474; elemental analysis calcd (%) for $C_{47}H_{46}O_9$: C 74.80, H 6.15; found C 74.78, H 6.14.

Phenyl 6a-*C*-(2b,6b-Anhydro-5b,7b-*O*-benzylidene-1,3,4-trideoxy-α-D-*glycero*-D-*manno*-heptit-3-en-1-yl)-2,3,4-tri-*O*-benzyl-6-deoxy-6-oxo-α-D-mannopyranoside (8a) and phenyl 2,3,4-tri-*O*-benzyl-6-[4-(buta-1′*Z*,3′*E*-dienyl)-2-phenyl-1,3-dioxan-5-olyl]-6-deoxy-6-oxo-α-D-mannopyranoside (8b): The following reaction sequence was performed in 15 batches, which were then combined for purification. Vinyl ether **7b** (7.20 g, 9.54 mmol, divided into 15 batches) and anion-exchange resin (IRA-400, HO^-, 385.9 mg, divided into 15 batches) were suspended in xylene (105.0 mL, 7 mL per batch) and the mixture was irradiated with microwaves (300 W) at 220 °C for 20 min. After this time, t.l.c (toluene/diethyl ether 9:1) indicated complete consumption of the starting material (R_f = 0.6) and the formation of a major product (R_f = 0.5). After combination of the different batches, filtration, and concentration, purification by flash column chromatography (toluene/diethyl ether 19:1) gave ring-opened diene **8b** (1.24 g, 17 % vide infra) as a colourless oil, and the de-

sired α-*C*-glycoside **8a** (4.06 g, 56%) as a colourless oil. R_f=0.5 (toluene/ether 9:1); $[\alpha]_D^{20}$=+35 (c=0.8 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ=2.18 (dd, ^2J(H,H)=16.5 Hz, ^3J(H,H)=4.5 Hz, 1H; 7a-H), 2.98 (dd, ^2J-(H,H)=16.5 Hz, ^3J(H,H)=9.0 Hz, 1H, 7′a-H), 3.46 (at, ^2J(H,H)= 10.5 Hz, ^3J(H,H)=10.0 Hz, 1H; 6b-H), 3.55 (ddd, ^3J(H,H)=10.0, 8.0, 4.5 Hz, 1H; 5b-H), 3.83 (ddd, ^3J(H,H)=8.0, 4.0, 2.5 Hz, 1H; 4b-H), 3.91 (at, ^3J(H,H)=3.0, 3.0 Hz, 1H; 2a-H), 4.18 (dd, ^3J(H,H)=8.5, 3.0 Hz, 1H; 3a-H), 4.20 (dd, ^2J(H,H)=10.5 Hz, ^3J(H,H)=4.5 Hz, 1H; 6′b-H), 4.36 (d, ^3J(H,H)=8.5 Hz, 1H; 5a-H), 4.45 (at, ^3J(H,H)=8.5, 8.5 Hz, 1H; 4a-H), 4.49 (d, ^2J(H,H)=9.5 Hz, 1H; CH_2Bn), 4.51 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.54 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.59 (d, ^2J(H,H)= 12.0 Hz, 1H; CH_2Bn), 4.76–4.82 (m, 3H; 1b-H, CH_2Bn), 5.22 (dat, ^3J-(H,H)=10.5, 2.5, 2.5 Hz, 1H; 2b-H), 5.28 (s, 1H; 7b-H), 5.70 (d, ^3J-(H,H)=1.5 Hz, 1H; 1a-H), 5.82 (brd, ^3J(H,H)=10.5 Hz, 1H; 3b-H), 7.04–7.60 ppm (m, 25H; 25ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ=42.9 (C-7a), 66.0 (C-5b), 69.7 (C-6b), 70.4 (C-1b), 72.8 (*C*H$_2$Bn), 73.4 (*C*H$_2$Bn), 74.8 (*C*H$_2$Bn), 75.2 (C-4b), 75.2 (C-4a), 75.5 (C-2a), 77.3 (C-5a), 79.5 (C-3a), 97.1 (C-1a), 101.9 (C-7b), 116.8 (2ArCH), 126.8 (2ArCH), 127.5 (ArCH), 127.8 (C-3b), 127.9 (ArCH), 127.9 (2-ArCH), 128.0 (ArCH), 128.1 (2-ArCH), 128.2 (2-ArCH), 128.3 (2-ArCH), 128.4 (2ArCH), 128.5 (2ArCH), 128.6 (2ArCH), 128.7 (2ArCH), 128.9 (ArCH), 130.0 (C-2b), 130.0 (ArCH), 138.6 (ArC), 138.7 (ArC), 138.9 (ArC), 139.0 (ArC), 156.5 (ArC), 202.5 ppm (C=O); IR (film): $\tilde{\nu}$=3032 (m, ν(CHAr)), 2870 (m, ν(CH)), 1750–1955 (w, δ(CHAr harmonic)), 1721 (s, ν(C=O)), 1598, 1590; 1495 (s, ν(C=CAr)), 1455 (m, δ(CH)), 1222, 1096 (s, ν(CO)), 753, 697 cm^{-1} (m, δ(CH)); ESI$^+$-HRMS: m/z: calcd for $C_{47}H_{46}NaO_9$: 777.3034 $[M+Na]^+$, found 777.3021. Ring-opened diene **8b**: R_f=0.0 (toluene/diethyl ether 9:1); $[\alpha]_D^{22}$=−43 (c=1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ=1.15 (d, ^3J(H,H)=5.0 Hz, 1H; OH), 3.15–3.20 (m, 1H; 5b-H), 3.22 (at, ^2J(H,H)=10.0 Hz, ^3J(H,H)= 10.0 Hz, 1H; 6b-H), 3.95 (at, ^3J(H,H)=2.5, 2.5 Hz, 1H; 2a-H), 3.99 (dd, ^2J(H,H)=10.0 Hz, ^3J(H,H)=4.5 Hz, 1H; 6′b-H), 4.14 (at, ^3J(H,H)=8.0, 8.0 Hz, 1H; 4b-H), 4.26 (dat, ^3J(H,H)=6.0, 2.5 Hz, 1H; 3a-H), 4.48 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.56 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.57 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.63 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.68–4.70 (m, 2H; 4a-H, 5a-H), 4.81 (d, ^2J(H,H)=11.0 Hz, 1H; CH_2Bn), 4.86 (d, ^2J(H,H)=11.0 Hz, 1H; CH_2Bn), 5.18 (s, 1H; 7b-H), 5.68 (dd, ^3J(H,H)=11.0, 8.0 Hz, 1H; 3b-H), 5.72 (d, ^3J(H,H)=2.5 Hz, 1H; 1a-H), 5.91 (at, ^3J(H,H)=11.0, 11.0 Hz, 1H; 2b-H), 6.43 (d, ^3J-(H,H)=15.5 Hz, 1H; 7a-H), 6.85 (atat, ^3J(H,H)=7.0, 7.0, 1.0, 1.0 Hz, 1H; ArH), 7.01–7.35 (m, 22H, 22ArH), 7.64–7.65 (m, 2H, 2ArH), 7.87 ppm (ddd, ^3J(H,H)=15.5, 11.0, 1.0 Hz, 1H; 1b-H); ^{13}C NMR (125.8 MHz, C_6D_6): δ=65.7 (C-5b), 71.2 (C-6b), 73.1 (*C*H$_2$Bn), 73.8 (*C*H$_2$Bn), 75.3 (*C*H$_2$Bn), 76.0, 76.1 (C-2a, C-4a, C-5a), 79.3 (C-4b), 800.1 (C-3a), 98.1 (C-1a), 101.0 (C-7b), 117.2 (2ArCH), 123.3 (ArCH), 126.0 (2ArCH), 127.1 (2ArCH), 128.1 (ArCH), 128.3 (ArCH), 128.3 (ArCH), 128.3 (ArCH), 128.4 (2ArCH), 128.7 (2ArCH), 128.7 (2ArCH), 128.8 (2ArCH), 129.0 (2ArCH), 129.0 (2ArCH), 129.7 (C-7a), 130.4 (2ArCH), 130.9 (C-2b), 138.0 (C-3b), 138.9 (ArC), 139.1 (ArC), 139.4 (ArC), 139.4 (ArC), 139.6 (C-1b), 157.4 (ArC), 194.7 ppm (C-6a); IR (film): ν=3457 (w, ν(OH)), 3031 (w, ν(CHAr)), 2868 (w, ν(CH)), 1693 (w, ν(C=O)), 1590, 1495; 1454 (s, ν(C=CAr)), 1082 (s, ν(C−O)), 754, 698 cm^{-1} (s, δ(CH)); ESI$^+$-HRMS: m/z: calcd for $C_{47}H_{46}O_9Na$: 777.3034 $[M+Na]^+$, found: 777.3034.

Phenyl 6a-*C*-(2b,5b-Anhydro-5b,7b-*O*-benzylidene-1,3,4-trideoxy-α-D-*glycero*-D-*manno*-heptit-3-en-1-yl)-2,3,4-tri-*O*-benzyl-6-deoxy-6-(*R*,*S*)-hydroxy-α-D-mannopyranoside (9a): *C*-Glycoside **8a** (4.26 g, 5.64 mmol) was dissolved in DCM/methanol (1:1, 112 mL) and the solution was cooled to 0°C. After 15 min, $NaBH_4$ (1.09 g, 28.83 mmol) was added portion-wise and the reaction mixture was stirred at room temperature. After 45 min, t.l.c (toluene/diethyl ether 9:1) indicated complete consumption of the starting material (R_f=0.6) and the formation of two products (R_f=0.3, R_f=0.2). The mixture was diluted with DCM (250 mL), and the reaction was quenched with a saturated aqueous solution of sodium hydrogencarbonate (250 mL). After re-extraction of the aqueous layer with DCM (100 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (toluene/diethyl ether 100:1 to 7:3) gave alcohols **9a** (3.66 g, 86%) as a diastereoisomeric mixture (57:43). IR (film): $\tilde{\nu}$=3432 (br, ν(OH)), 3027 (m, ν(CHAr)), 2900 (m, ν(CH)), 1700–2000 (δ(CHAr harmonic)), 1600, 1585, 1500 (s, ν(C=C)), 1450 (m, δ(CH)), 1100, 1230 (s, ν(CO)), 720, 810 cm^{-1} (m, δ(CH)); ESI$^+$-HRMS: m/z: calcd for $C_{47}H_{52}NO_9$: 774.3637 $[M+NH_4]^+$, found 774.3627; elemental analysis calcd (%) for $C_{47}H_{48}O_9$: C 74.58, H 6.39; found: C 74.17, H 6.32. Diastereomer 1: 43%, colourless oil; R_f=0.2 (toluene/diethyl ether 9:1); ^{1}H NMR (500 MHz, C_6D_6): δ=1.29 (ddd, ^2J(H,H)=14.0 Hz, ^3J-(H,H)=6.5, 4.5 Hz, 1H; 7a-H), 2.06 (ddd, ^2J(H,H)=14.0 Hz, ^3J(H,H)= 10.5, 7.5 Hz, 1H; 7′a-H), 2.35 (brd, ^3J(H,H)=4.5 Hz, 1H; OH), 3.45 (at, ^2J(H,H)=10.0 Hz, ^3J(H,H)=10.0 Hz, 1H; 6b-H), 3.57 (ddd, ^3J(H,H)= 10.0, 8.0, 4.5 Hz, 1H; 5b-H), 3.78 (brd, ^3J(H,H)=9.5 Hz, 1H; 5a-H), 3.83 (brdd, ^3J(H,H)=8.0, 1.5 Hz, 1H; 4b-H), 3.95 (at, ^3J(H,H)=2.5, 2.5 Hz, 1H; 2a-H), 3.92–3.97 (m, 1H; 1b-H), 4.04 (dd, ^2J(H,H)=10.0 Hz, ^3J-(H,H)=4.5 Hz, 1H; 6′b-H), 4.21–4.25 (m, 1H; 6a-H), 4.24 (dd, ^3J(H,H)= 9.5, 2.5 Hz, 1H; 3a-H), 4.52 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.55 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.62 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.63 (at, ^3J(H,H)=9.5, 9.5 Hz, 1H; 4a-H), 4.70 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.86 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 5.07 (d, ^2J(H,H)= 11.5 Hz, 1H; CH_2Bn), 5.17 (dat, ^3J(H,H)=10.5, 2.5, 2.5 Hz, 1H; 2b-H), 5.29 (s, 1H; 7b-H), 5.64 (d, ^3J(H,H)=2.5 Hz, 1H; 1a-H), 5.84 (brd, ^3J-(H,H)=10.5 Hz, 1H; 3b-H), 6.84 (at, ^3J(H,H)=7.5, 7.5 Hz, 1H; ArH), 6.96–7.21 (m, 17H; 17ArH), 7.34–7.38 (m, 5H; 5ArH), 7.60–7.62 ppm (m, 2H; 2ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ=36.7 (C-7a), 65.5 (C-5b), 67.4 (C-3a), 69.6 (C-6b), 72.6 (C-1b or C-2a), 72.6 (*C*H$_2$Bn), 73.5 (*C*H$_2$Bn), 73.9 (C-5a), 75.1 (C-4a), 75.4 (*C*H$_2$Bn), 75.4 (C-4b), 75.8 (C-2a or C-1b), 80.6 (C-6a), 96.6 (C-1a), 102.0 (C-7b), 116.6 (2ArCH), 122.5 (ArCH), 126.8 (C-3b), 126.9 (2ArCH), 127.6 (ArCH), 127.7 (ArCH), 127.8 (2ArCH), 127.9 (ArCH), 127.9 (2ArCH), 127.9 (2ArCH), 128.2 (2ArCH), 128.4 (2ArCH), 128.6 (2ArCH), 128.6 (2ArCH), 128.9 (ArCH), 129.7 (2ArCH), 130.4 (C-2b), 138.7 (ArC), 138.9 (ArC), 139.2 (ArC), 139.6 (ArC), 156.2 ppm (ArC). Diastereomer 2: 57%, yellow oil; R_f=0.3 (toluene/diethyl ether 9:1); ^{1}H NMR (500 MHz, C_6D_6): δ=1.62 (ddd, ^2J(H,H)=14.0 Hz, ^3J(H,H)=10.5, 2.5 Hz, 1H; 7a-H), 2.06–2.09 (m, 1H; 7′a-H), 2.38 (d, ^3J(H,H)=4.5 Hz, 1H; OH), 3.50 (at, ^2J(H,H)= 10.0 Hz, ^3J(H,H)=10.0 Hz, 1H; 6b-H), 3.58–3.61 (m, 1H; 5b-H), 3.92–3.99 (m, 2H; 2a-H, 4b-H), 4.01 (dd, ^2J(H,H)=10.0 Hz, ^3J(H,H)=4.0 Hz, 1H; 6′b-H), 3.99–4.02 (m, 1H; 5a-H), 4.20–4.22 (m, 2H; 4a-H, 3a-H), 4.38 (brd, ^3J(H,H)=10.0 Hz, 1H; 6a-H), 4.43 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.47 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.49 (d, ^2J(H,H)= 11.0 Hz, 1H; CH_2Bn), 4.52 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.59 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.75 (dat, ^3J(H,H)=10.5, 2.5, 2.5 Hz, 1H; 1b-H), 4.94 (d, ^2J(H,H)=11.0 Hz, 1H; CH_2Bn), 5.31 (s, 1H; 7b-H), 5.37 (dat, ^3J(H,H)=10.5, 2.5, 2.5 Hz, 1H; 2b-H), 5.61 (d, ^3J(H,H)= 2.0 Hz, 1H; 1a-H), 5.91 (brd, ^3J(H,H)=10.5 Hz, 1H; 3b-H), 6.87 (dat, ^3J-(H,H)=6.0, 6.0, 2.0 Hz, 1H; ArH), 7.00–7.66 ppm (m, 24H, 24ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ=35.7 (C-7a), 65.5 (C-5b), 68.9 (C-6a), 69.9 (C-6b), 71.1 (C-1b), 72.3 (*C*H$_2$Bn), 73.3 (*C*H$_2$Bn), 74.9 (*C*H$_2$Bn), 75.7, 75.8 (C-2a, C-4b, C-5a), 76.8, 80.6 (C-4a, C-3a), 97.3 (C-1a), 101.9 (C-7b), 117.1 (2ArCH), 122.9 (ArCH), 126.8 (C-3b), 126.9 (2ArCH), 127.8 (2ArCH), 127.9 (ArCH), 127.9 (2ArCH), 128.0 (2ArCH), 128.0 (ArCH), 128.2 (2ArCH), 128.3 (ArCH), 128.6 (4ArCH), 128.7 (2ArCH), 128.9 (ArCH), 129.9 (2ArCH), 131.7 (C-2b), 138.7 (ArC), 138.8 (ArC), 138.8 (ArC), 138.9 (ArC), 156.8 ppm (ArC).

Phenyl 6a-*C*-(2b,5b-Anhydro-5b,7b-*O*-benzylidene-1,3,4-trideoxy-α-D-*glycero*-D-*manno*-heptit-3-en-1-yl)-2,3,4-tri-*O*-benzyl-6-deoxy-6-((*R*,*S*)-1-thiocarbonylimidazoyl)-α-D-mannopyranoside (9b): Under an atmosphere of argon, alcohols **9a** (3.66 g, 4.83 mmol) and 1,1′-thiocarbonyldiimidazole (8.81 g, 49.40 mmol) were dissolved in anhydrous toluene (65 mL) and then the mixture was heated under reflux. After 18 h, t.l.c (petroleum ether/ethyl acetate 3:2) indicated complete consumption of the starting material (R_f=0.7) and the appearance of two products (R_f= 0.6, R_f=0.4). The reaction mixture was then cooled to room temperature, and filtered through a silica pad (eluting with ethyl acetate/petroleum ether 3:2). After concentration to dryness, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate 7:3) to afford thiocarbonates **9b** (3.30 g, 79%) as a diastereomeric mixture (58:42). IR (film): $\tilde{\nu}$=3032 (m, ν(CHAr)), 2930 (m, ν(CH)), 1811, 1880, 1955 (w, δ(CHAr harmonic)), 1763 (m, ν(C=S)), 1598, 1590 (s, ν(C=CAr)), 1495 (m, δ(CH)), 1388, 1285 (m, ν(CN)), 1097, 1231 (s, ν(CO)),

698, 753 cm^{-1} (m, δ(CH)); ESI$^+$-HRMS: *m/z*: calcd for $C_{51}H_{51}N_2O_9S$: 867.3310 $[M+H]^+$, found: 867.3315. Diastereomer 1; 42%, yellowish oil; R_f=0.4 (petroleum ether/ethyl acetate 3:2); $[\alpha]_D^{20}$=+48 (*c*=0.9 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ=2.06 (ddd, ^2J(H,H)=15.5 Hz, ^3J(H,H)=9.5, 2.0 Hz, 1H; 7a-H), 2.25 (ddd, ^2J(H,H)=15.5 Hz, ^3J(H,H)=11.0, 2.0 Hz, 1H; 7′a-H), 3.37 (at, ^2J(H,H)=10.0 Hz, ^3J(H,H)=10.0 Hz, 1H; 6b-H), 3.48 (ddd, ^3J(H,H)=10.0, 8.0, 4.5 Hz, 1H; 5b-H), 3.84 (brdd, ^3J(H,H)=8.0, 2.5 Hz, 1H; 4b-H), 3.88 (dd, ^3J(H,H)=3.0, 2.0 Hz, 1H; 2a-H), 3.96 (dd, ^2J(H,H)=10.0 Hz, ^3J(H,H)=4.5 Hz, 1H; 6′b-H), 4.10 (at, ^3J(H,H)=9.5, 9.5 Hz, 1H; 4a-H), 4.16 (dd, ^3J(H,H)=9.5, 3.0 Hz, 1H; 3a-H), 4.29 (brdat, ^3J(H,H)=11.0, 11.0, 2.0 Hz, 1H; 1b-H), 4.39 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 4.43 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 4.50 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.51 (dd, ^3J(H,H)=9.5, 2.0 Hz, 1H; 5a-H), 4.56 (d, ^2J(H,H)=11.0 Hz, 1H; CH_2Bn), 4.62 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.90 (d, ^2J(H,H)=11.0 Hz, 1H; CH_2Bn), 5.22 (dat, ^3J(H,H)=11.0, 2.5, 2.5 Hz, 1H; 2b-H), 5.25 (s, 1H; 7b-H), 5.56 (d, ^3J(H,H)=2.0 Hz, 1H; 1a-H), 5.89 (brd, ^3J(H,H)=11.0 Hz, 1H; 3b-H), 6.38 (dat, ^3J(H,H)=9.5, 2.0, 2.0 Hz, 1H; 6a-H), 6.80 (at, ^3J(H,H)=7.0, 7.0 Hz, 1H; ArH), 6.86 (brs, 1H; ArH), 6.92–6,94 (m, 2H; 2ArH), 6.98–7.02 (m, 2H; 2ArH), 7.05–7.24 (m, 13H; 13ArH), 7.30–7.35 (m, 4H; 4ArH), 7.46–7.48 (m, 2H; 2ArH), 7.59–7.61 (m, 2H; 2ArH), 8.14 ppm (s, 1H; ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ=31.3 (C-7a), 65.5 (C-5b), 69.5 (C-6b), 70.5 (C-1b), 72.5 (C-5a), 72.5 (*C*H_2Bn), 73.5 (*C*H_2Bn), 75.0 (*C*H_2Bn), 75.3 (C-4a), 74.3 (C-4b), 75.5 (C-2a), 79.7 (C-6a), 80.5 (C-3a), 96.7 (C-1a), 101.9 (C-7b), 116.8 (2ArCH), 118.4 (ArCH), 123.2 (ArCH), 126.8 (2ArCH), 127.9 (C-3b), 127.9 (ArCH), 128.0 (2ArCH), 128.0 (ArCH), 128.1 (2ArCH), 128.2 (ArCH), 128.3 (2ArCH), 128.4 (2ArCH), 128.7 (2ArCH), 128.7 (2ArCH), 128.7 (2ArCH), 128.9 (ArCH), 129.7 (2ArCH), 130.0 (C-2b), 131.1 (ArCH), 136.4 (ArCH), 138.5 (ArC), 138.6 (ArC), 138.6 (ArC), 138.8 (ArC), 155.8 (ArC phenyl), 183.4 ppm (C=S). Diastereomer 2; 58% yield, colourless oil; R_f=0.6 (petroleum ether/ethyl acetate 3:2); $[\alpha]_D^{20}$=+2 (*c*=0.7 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ=1.69 (ddd, ^2J(H,H)=13.5 Hz, ^3J(H,H)=10.0, 2.5 Hz, 1H; 7a-H), 2.24 (dat, ^2J(H,H)=13.5 Hz, ^3J(H,H)=13.5, 4.5 Hz, 1H; 7′a-H), 3.54 (at, ^2J(H,H)=10.0 Hz, ^3J(H,H)=10.0 Hz, 1H; 6b-H), 3.68 (dat, ^3J(H,H)=13.5, 2.5, 2.5 Hz, 1H; 1b-H), 3.83 (dat, ^3J(H,H)=10.0, 3.0, 3.0 Hz, 1H; 5b-H), 3.80–3.85 (m, 2H; 2a-H, 4b-H), 4.05 (brd, ^3J(H,H)=9.5 Hz, 1H; 5a-H), 4.10 (at, ^3J(H,H)=9.5, 9.5 Hz, 1H; 4a-H), 4.18 (dd, ^3J(H,H)=3.0, 9.5 Hz, 1H; 3a-H), 4.38 (dd, ^2J(H,H)=10.0 Hz, ^3J(H,H)=3.0 Hz, 1H; 6′b-H), 4.42 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 4.46–4.49 (m, 2H; CH_2Bn), 4.48 (d, ^2J(H,H)=10.5 Hz, 1H; CH_2Bn), 4.67 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 4.78 (d, ^2J(H,H)=10.5 Hz, 1H; CH_2Bn), 5.05 (dat, ^3J(H,H)=10.5, 2.5, 2.5 Hz, 1H; 2b-H), 5.31 (s, 1H; 7b-H), 5.61 (d, ^3J(H,H)=2.0 Hz, 1H; 1a-H), 5.88 (brd, ^3J(H,H)=10.5 Hz, 1H; 3b-H), 6.27 (brdd, ^3J(H,H)=10.0, 4.5 Hz, 1H; 6a-H), 6.82–6.87 (m, 2H; 2ArH), 6.91 (brs, 1H; ArH), 7.04–7.07 (m, 2H; 2ArH), 7.09–7.20 (m, 12H; 12ArH), 7.23–7.26 (m, 2H; 2ArH), 7.30–7.37 (m, 5H; 5ArH), 7.59–7.63 (m, 3H; 3ArH), 8.61 ppm (s, 1H, ArH); ^{13}C NMR (125.8 MHz, C_6D_6) δ=31.4 (C-7a), 65.6 (C-5b), 69.6 (C-6b), 70.4 (C-1b), 70.6 (C-5a), 72.4 (*C*H_2Bn), 73.8 (*C*H_2Bn), 74.0 (C-4a), 75.2 (C-4b), 75.3 (C-2a), 75.4 (*C*H_2Bn), 78.5 (C-6a), 80.7 (C-3a), 95.6 (C-1a), 102.1 (C-7b), 116.5 (2ArCH), 118.1 (2ArCH), 122.7 (2ArCH), 126.9 (C-3b), 127.4 (ArCH), 127.9 (2ArCH), 127.9 (ArCH), 128.0 (ArCH), 128.2 (ArCH), 128.2 (2ArCH), 128.3 (2ArCH), 128.4 (2ArCH), 128.4 (2ArCH), 128.7 (2ArCH), 128.8 (2ArCH), 128.9 (ArCH), 129.7 (ArCH), 129.8 (C-2b), 131.6 (ArCH), 137.4 (ArCH), 138.5 (ArC), 138.6 (ArC), 138.6 (ArC), 138.8 (ArC), 155.5 (ArC phenyl), 183.6 ppm (C=S).

Phenyl 6a-*C*-(2b,6b-Anhydro-5b,7b-*O*-benzylidene-1,3,4-trideoxy-α-D-*glycero*-D-*manno*-heptit-3-en-1-yl)-2,3,4-tri-O-benzyl-6-deoxy-α-D-mannopyranoside (10): Under an atmosphere of argon, thiocarbonates **9b** (3.30 g, 3.80 mmol) were suspended in anhydrous degassed toluene (180 mL). Pentafluorophenol (1.84 g, 9.98 mmol) and Ph_3SnH (4.45 g, 12.69 mmol) were added, followed by a catalytic amount of AIBN (96.4 mg, 587.5 μmol) and the reaction mixture was then refluxed in the dark room. After 1 h 30 min., t.l.c (petroleum ether/ethyl acetate 1:1) indicated complete consumption of the starting material (R_f=0.6, R_f=0.4) and the formation of a major product (R_f=0.9). The reaction mixture was then cooled to room temperature, and concentrated in vacuo. The residue was dissolved in acetonitrile (180 mL), and washed with pentane (3×90 mL). After concentration to dryness, purification by flash column chromatography (petroleum ether/ethyl acetate, gradient elution) gave alkene 10 (1.83 g, 65%) as a colourless oil. R_f=0.9 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{20}$=+30 (*c*=0.4 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ=1.30–1.37 (m, 1H; 7a-H), 1.75–1.84 (m, 2H; 6a-H, 7′a-H), 1.93–1.99 (m, 1H; 6′a-H), 3.52 (at, ^2J(H,H)=10.0 Hz, ^3J(H,H)=10.0 Hz, 1H; 6b-H), 3.58 (ddd, ^3J(H,H)=14.5, 10.0, 4.0 Hz, 1H; 5b-H), 3.86–3.94 (m, 4H; 2a-H, 5a-H, 1b-H, 4b-H), 3.96 (at, ^3J(H,H)=9.0, 9.0 Hz, 1H; 4a-H), 4.11 (dd, ^2J(H,H)=10.0 Hz, ^3J(H,H)=4.0 Hz, 1H; 6′b-H), 4.20 (dd, ^3J(H,H)=9.0, 3.0 Hz, 1H; 3a-H), 4.47 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 4.50 (d, ^2J(H,H)=13.5 Hz, 1H; CH_2Bn), 4.50 (d, ^2J(H,H)=13.5 Hz, 1H; CH_2Bn), 4.53 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.62 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.96 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 5.21 (dat, ^3J(H,H)=10.5, 2.5, 2.5 Hz, 1H; 2b-H), 5.31 (s, 1H; 7b-H), 5.64 (d, ^3J(H,H)=1.5 Hz, 1H; 1a-H), 5.87 (d, ^3J(H,H)=10.5 Hz, 1H; 3b-H), 6.83 (atat, ^3J(H,H)=7.0, 7.0 Hz, 1.0 Hz, 1.0 Hz, 1H; ArH), 7.04–7.19 (m, 16H; 16ArH), 7.30–7.36 (m, 6H; 6ArH), 7.60–7.62 ppm (m, 2H; 2ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ=28.2 (C-6a), 28.9 (C-7a), 65.5 (C-5b), 69.9 (C-6b), 71.9 (C-2a), 72.4 (*C*H_2Bn), 73.4 (*C*H_2Bn, C-1b), 75.3 (*C*H_2Bn), 75.8 (C-5a), 75.9 (C-4b), 79.0 (C-4a), 80.7 (C-3a), 96.4 (C-1a), 102.0 (C-7b), 116.7 (2ArCH), 122.5 (ArCH), 126.6 (C-3b), 126.9 (2ArCH), 127.7 (ArCH), 127.8 (ArCH), 127.9 (2ArCH), 127.9 (2ArCH), 128.0 (2ArCH), 128.2 (2ArCH), 128.3 (2ArCH), 128.5 (2ArCH), 128.6 (2ArCH, ArCH), 128.9 (ArCH), 129.8 (2ArCH), 131.2 (C-2b), 138.7 (ArC), 138.8 (ArC), 139.1 (ArC), 139.3 (ArC), 156.5 ppm (ArC phenyl); IR (film): $\tilde{\nu}$=3064 (m, ν(CHAr)), 2926 (m, ν(CH)), 1954, 1879, 1812 (w, δ(CHAr harmonic)), 1598, 1496 (s, ν(C=CAr)), 1454 (m, δ(CH)), 1225, 1096 (s, ν(CO)), 753, 697 cm^{-1} (m, δ(CH)); ESI$^+$-HRMS: *m/z*: calcd for $C_{47}H_{48}O_8Na$: 763.3241 $[M+Na]^+$, found 763.3244; elemental analysis calcd (%) for $C_{47}H_{48}O_8$: C 76.19, H 6.53; found: C 76.32, H 6.52.

Phenyl 6a-*C*-(2b,6b-Anhydro-5b,7b-*O*-benzylidene-1-deoxy-α-D-*glycero*-D-*talo*-heptit-1-yl)-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-mannopyranoside (11a): Alkene **10** (563.9 mg, 761.6 μmol) was dissolved in THF (3 mL) and water (3.6 mL), and potassium carbonate (319.4 mg, 2.31 mmol) was then added followed by methanesulfonamide (83.0 mg, 0.87 mmol), $K_3Fe(CN)_6$ (753.3 mg, 2.29 mmol), and *t*BuOH (3.6 mL). An aqueous solution of potassium osmate dihydrate (302.9 mg, 0.82 mmol in 2 mL) was then added drop-wise. After 20 h, t.l.c (petroleum ether/ethyl acetate 1:1) showed complete consumption of the starting material (R_f=0.9) and the appearance of a major product (R_f=0.2) and a minor product (R_f=0.3). The reaction was quenched by the addition of sodium sulfite (2.69 g) and the mixture was then stirred for a further 30 min. The mixture was then partitioned between ethyl acetate (200 mL) and water (200 mL), and the aqueous layer was re-extracted with ethyl acetate (200 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 1:1 to 0:1) gave the *manno*-*C*-disaccharide **11a** (292.26 mg, 50%) as a white amorphous solid and the *allo*-*C*-disaccharide **11b** (31.44 mg, 5%) as a yellow oil. IR (film): $\tilde{\nu}$=3421 (m, ν(OH)), 3032 (m, ν(CHAr)), 2964 (m, ν(CH)), 1700–2000 (w, δ(CHAr harmonic)), 1598, 1495 (s, ν(C=CAr)), 1454 (m, δ(CH)), 1262, 1095 (s, ν(CO)), 801, 696 cm^{-1} (m, δ(CH)).

11a: R_f=0.2 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{19}$=+41 (*c*=0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ=1.03–1.09 (m, 1H; 7a-H), 1.60–1.74 (m, 2H; 6a-H, 7′a-H), 1.79–1.84 (m, 1H; 6′a-H), 2.05 (s, 1H; 2b-OH), 2.13 (s, 1H; 3b-OH), 3.40 (d, ^3J(H,H)=2.5 Hz, 1H; 2b-H), 3.51–3.55 (m, 1H; 5b-H), 3.55 (dd, ^2J(H,H)=16.0 Hz, ^3J(H,H)=9.5 Hz, 1H; 6b-H), 3.67–3.69 (m, 2H; 1b-H, 3b-H), 3.79 (brat, ^3J(H,H)=9.0, 9.0 Hz, 1H; 4b-H), 3.83 (dat, ^3J(H,H)=9.5, 9.5, 2.0 Hz, 1H; 5a-H), 3.94 (dd, ^3J(H,H)=3.0, 2.0 Hz, 1H; 2a-H), 3.94 (at, ^3J(H,H)=9.5, 9.5 Hz, 1H; 4a-H), 4.11 (dd, ^2J(H,H)=16.0 Hz, ^3J(H,H)=10.5 Hz, 1H; 6′b-H), 4.18 (dd, ^3J(H,H)=9.5, 3.0 Hz, 1H; 3a-H), 4.47 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.51 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 4.53 (d, ^2J(H,H)=12.0 Hz, 1H; CH_2Bn), 4.55 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.63 (d, ^2J(H,H)=12.5 Hz, 1H; CH_2Bn), 4.99 (d, ^2J(H,H)=11.5 Hz, 1H; CH_2Bn), 5.27 (s, 1H; 7b-H), 5.64 (d, ^3J(H,H)=2.0 Hz, 1H; 1a-H), 6.84 (at, ^3J(H,H)=7.5 Hz, 1H; ArH), 6.99–7.58 ppm (m, 24H; 24ArH); ^{13}C NMR (125.8 MHz, C_6D_6): δ=23.9 (C-7a), 27.4 (C-6a), 64.6 (C-5b), 69.2 (C-1b or C-3b), 69.4 (C-6b), 71.8 (C-5a), 72.4 (*C*H_2Bn), 72.5 (C-2b), 73.5

(CH_2Bn), 75.3 (CH_2Bn), 75.9 (C-2a), 77.6 (C-3b or C-1b), 79.0 (C-4a), 79.9 (C-4b), 80.8 (C-3a), 96.2 (C-1a), 102.3 (C-7b), 116.7 (2ArCH), 122.4 (ArCH), 126.9 (2ArCH), 127.7 (ArCH), 127.7 (ArCH), 127.8 (2ArCH), 127.9 (2ArCH), 127.9 (ArCH), 128.0 (2ArCH), 128.2 (2ArCH), 128.5 (2ArCH), 128.6 (2ArCH), 128.6 (2ArCH), 129.0 (ArCH), 129.8 (2ArCH), 138.7 (ArC), 138.8 (ArC), 139.1 (ArC), 139.3 (ArC), 156.4 ppm (ArC phenyl); ESI$^+$-HRMS: m/z: calcd for $C_{47}H_{50}NaO_{10}$: 797.3296 $[M+Na]^+$, found 797.3302; elemental analysis calcd (%) for $C_{47}H_{50}O_{10}$: C 72.85, H 6.50; found C, 72.45; H, 6.67.

11b : $R_f = 0.3$ (petroleum ether/ethyl acetate 1:1); ^{1}H NMR (500 MHz, C_6D_6): $\delta = 1.71$–1.79 (m, 1H; 7′a-H), 1.84–1.91 (m, 1H; 6a-H), 1.92–1.99 (m, 1H; 6′a-H), 2.32–2.40 (m, 1H; 7a-H), 2.90 (dd, ^3J(H,H) = 9.5, 3.0 Hz, 1H; 4b-H), 3.35 (at, ^2J(H,H) = 9.5 Hz, ^3J(H,H) = 9.5 Hz, 1H; 6b-H), 3.53 (dd, ^3J(H,H) = 6.5, 3.0 Hz, 1H; 2b-H), 3.76 (ddd, ^3J(H,H) = 12.0, 6.5, 3.5 Hz, 1H; 1b-H), 3.90 (dat, ^3J(H,H) = 9.5, 9.5, 5.0 Hz, 1H; 5b-H), 3.92 (at, ^3J(H,H) = 3.0, 3.0 Hz, 1H; 3b-H), 3.95 (dd, ^3J(H,H) = 3.0, 2.0 Hz, 1H; 2a-H), 4.00–4.05 (m, 1H; 5a-H), 4.03 (at, ^3J(H,H) = 9.0, 9.0 Hz, 1H; 4a-H), 4.16 (dd, ^2J(H,H) = 9.5, ^3J(H,H) = 5.0 Hz, 1H; 6′b-H), 4.21 (dd, ^3J-(H,H) = 9.0, 3.0 Hz, 1H; 3a-H), 4.46 (d, ^2J(H,H) = 11.5 Hz, 1H; CH_2Bn), 4.51 (d, ^2J(H,H) = 11.5 Hz, 1H; CH_2Bn), 4.53 (d, ^2J(H,H) = 12.0 Hz, 1H; CH_2Bn), 4.56 (d, ^2J(H,H) = 11.5 Hz, 1H; CH_2Bn), 4.60 (d, ^2J(H,H) = 12.0 Hz, 1H; CH_2Bn), 5.00 (d, ^2J(H,H) = 11.5 Hz, 1H; CH_2Bn), 5.23 (s, 1H; 7b-H), 5.67 (d, ^3J(H,H) = 2.0 Hz, 1H; 1a-H), 6.87–7.55 ppm (m, 25H; 25ArH); ^{13}C NMR (125.8 MHz, C_6D_6): $\delta = 21.7$ (C-7a), 27.9 (C-6a), 58.2 (C-5b), 68.7 (C-2b), 69.9 (C-6b), 69.9 (C-3b), 71.9 (C-5a), 72.4 (CH_2Bn), 73.3 (CH_2Bn), 75.3 (CH_2Bn), 75.7 (C-1b), 76.0 (C-2a), 79.2 (C-4b), 79.3 (C-4a), 80.8 (C-3a), 96.6 (C-1a), 101.6 (C-7b), 117.0 (2ArCH), 122.3 (ArCH), 126.7 (2ArCH), 127.5 (ArCH), 127.6 (ArCH), 127.7 (ArCH), 127.7 (2ArCH), 127.8 (2ArCH), 127.8 (2ArCH), 127.9 (2ArCH), 128.4 (2ArCH), 128.5 (2ArCH), 128.5 (2ArCH), 128.9 (2ArCH), 129.9 (2ArCH), 138.5 (ArC), 138.9 (ArC), 139.2 (ArC), 139.5 (ArC), 156.8 ppm (ArC Phenyl).

Phenyl 6a-*C*-(2b,6b-Anhydro-1-deoxy-α-D-*glycero*-D-*talo*-heptit-1-yl)-6-deoxy-α-D-mannopyranoside (1): Protected *C*-disaccharide **11a** (350.9 mg, 453.1 μmol) was dissolved in a mixture of methanol (10 mL) and EtOAc (8 mL). Pd/C (10%, 244.6 mg) was suspended in EtOAc and then added to the reaction vessel. The reaction mixture was then stirred at room temperature under an atmosphere of hydrogen. After 3 h, t.l.c (petroleum ether/ethyl acetate 3:2) indicated complete consumption of the starting material ($R_f = 0.2$) and the formation of a single product at the baseline ($R_f = 0.7$ in CH_2Cl_2/MeOH 1:1). The reaction mixture was then filtered through a Celite pad, which was then washed with methanol/EtOAc (1:1). Removal of the solvent in vacuo then gave the deprotected *C*-disaccharide **1** (189 mg, quant.), as a white amorphous solid. $R_f = 0.7$ (CH_2Cl_2/MeOH 1:1); $[\alpha]_D^{21} = +51$ ($c = 0.8$ in MeOH), $[\alpha]_D^{21} = +62$ ($c = 0.5$ in MeOH); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 1.15$–1.21 (m, 1H; 7a-H), 1.55–1.61 (m, 1H; 6a-H), 1.79–1.87 (m, 2H; 6′a-H, 7′a-H), 3.35 (brat, ^3J(H,H) = 6.0, 6.0 Hz, 1H; 2b-H), 3.46–3.58 (m, 5H; 4a-H, H-5a, 3b-H, 4b-H, 5b-H), 3.65 (dd, ^2J(H,H) = 11.5 Hz, ^3J(H,H) = 5.5 Hz, 1H, 6b-H), 3.63–3.68 (m, 1H; 1b-H), 3.75 (dd, ^2J(H,H) = 11.5 Hz, ^3J(H,H) = 2.5 Hz, 1H; 6′b-H), 3.82 (dd, ^3J(H,H) = 9.0, 3.5 Hz, 1H; 3a-H), 3.98 (dd, ^3J(H,H) = 1.5, 3.5 Hz, 1H; 2a-H), 5.47 (d, ^3J(H,H) = 1.5 Hz, 1H; 1a-H), 6.98 (at, ^3J(H,H) = 7.5, 7.5 Hz, 1H; ArH), 7.04 (d, ^3J(H,H) = 8.0 Hz, 2H; 2ArH), 7.28 ppm (dd, ^3J(H,H) = 8.0, 7.5 Hz, 2H; 2ArH); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 25.3$ (C-7a), 28.3 (C-6a), 63.2 (C-6b), 69.3 (C-5b), 72.0 (CH), 72.2 (CH), 72.6 (C-3a), 72.9 (CH), 73.2 (C-2a), 73.5 (C-5a), 75.3 (C-2b), 78.4 (C-1b), 99.4 (C-1a), 117.6 (2ArCH), 123.2 (ArCH), 130.6 (2ArCH), 157.5 ppm (ArC); IR (KBr): $\tilde{\nu} = 3422$ (s, ν(OH)), 2926 (m, ν(CH)), 1597, 1493 (s, ν(C=CAr)), 1226, 1070 (s, ν(CO)), 758, 692 cm^{-1} (m, δ(CH)); ESI$^-$-HRMS: m/z: calcd for $C_{19}H_{27}O_{10}$: 415.1599 $[M-H]^+$, found 415.1598.

Gas-phase spectroscopy: A detailed description of the experimental instrumentation is already available.[26] Briefly, the carbohydrate sample was mixed with graphite powder (mass ratio 1:10), deposited as a thin, homogenous layer on a graphite surface located close to the nozzle (0.8 mm diameter) of a pulsed valve (Jordan Valve). The molecules were desorbed from the surface using the fundamental of a Nd:YAG laser (1–2 mJ), into a supersonic argon jet expansion which subsequently passed through a 2 mm skimmer to form a collimated molecular beam which was intersected by UV and IR laser beams. The carbohydrate was ionized in the acceleration region of a linear time-of-flight mass spectrometer (Jordan) using the radiation emitted by a Nd:YAG pumped dye laser (Continuum Powerlite II/Sirah PS-G, 1–3 mJ/pulse UV operating at 10 Hz) and its mass-selected resonant two-photon ionization (R2PI)[10,21,24–26,30] spectrum was recorded. Conformer selective infrared (IR) spectra were then recorded by using the infrared ion dip (IRID) double resonance technique. IR excitation was performed using radiation between 3100–3800 cm^{-1} obtained through difference frequency mixing of the fundamental of a Nd:YAG laser with the output of a dye laser in a $LiNbO_3$ crystal (Continuum Powerlite 8010/ND6000/IRP module) with a pulse duration of approximately 10 ns. The delay between the pump and the probe laser was approximately 150 ns.

Computation: Conformational and structural assignments of the experimental IR spectra were performed through comparison with calculations using a combination of molecular mechanics, ab initio and density functional theory (DFT) methods. Initial structures were generated by an extensive molecular mechanics conformational search using the Monte Carlo multiple minimization procedure as implemented in the MacroModel software (MacroModel v.8.5, Schrödinger, LLC21).[27] Relevant structures, filtered on the basis of their relative energies, information gained from previous studies on carbohydrates and their experimental vibrational signatures, were selected for geometry optimisations using the HF/6–31+G* method, as implemented in the Gaussian 03 program package.[28] The most stable conformers were re-optimized at the B3LYP/6-31+G* level. Their relative energies were subsequently calculated more accurately, at the MP2/6-311++G** level of theory, to take proper account of dispersion interactions. Zero-point and free energy corrections were performed using the harmonic frequency calculations performed on the B3LYP structures; for comparison with the experiments, the frequencies predicted for the O–H modes were scaled by a factor of 0.9734.

NMR spectroscopy: NMR data were collected on a sample of Manα-(1,6)-*C*-ManOPh (**1**; 3 mg) in D_2O (0.5 mL) on a Bruker AVIII 700 NMR spectrometer equipped with a TCI cryoprobe regulated at 298 K. Assignments were made from 2D HSQC and 1D TOCSY experiments with the TOCSY sequences incorporating Keeler–Thrippleton zero-quantum suppression elements.[29] Precise values for ^{1}H coupling constants were determined by a full lineshape simulation performed with the gNMR (v 5.0) program. 2D NOESY spectra were recorded with mixing times between 100 and 700 ms in steps of 100 ms. Full details including all experimental and simulated spectra are provided in the Supporting Information.

Notation: The nomenclature for carbohydrates has been described previously.[30] The OH groups are numbered in clockwise direction starting with the anomeric C atom. Atoms in the pyranose ring with the attached phenyl chromophore are labelled with a, those associated with the ring further away from the phenyl group are labelled with b.

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