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N-Iodosuccinimide-mediated intramolecular aglycon delivery

S. C. Ennis, A. J. Fairbanks,* C. A. Slinn, R. J. Tennant-Eyles and H. S. Yeates

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, UK

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Abstract—Enol ethers may be accessed via Tebbe methylenation of either 2-*O* acetates or *para*-methoxybenzoates. *N*-Iodosuccinimide may then be employed to achieve both tethering and thioglycoside activation allowing the stereoselective synthesis of α-glucosides and β-mannosides, either in a one or two step procedure.

1. Introduction

Glycosides may be subdivided into two categories depending on whether the 2-hydroxyl group is *cis* or *trans* to the anomeric substituent. Whilst the use of participating protecting groups on the 2-hydroxyl of the glycosyl donor readily allows the formation of 1,2-*trans* linkages,[1] the stereoselective formation of 1,2-*cis* linkages is considerably more difficult. Whilst there are several potential solutions to this problem,[2] one of the most ingenious is to temporarily tether the glycosyl acceptor to the C-2 hydroxyl of the glycosyl donor. This process can then be followed by a stereospecific intramolecular glycosylation, or intramolecular aglycon delivery (IAD), wherein the aglycon is delivered to the same face of the glycosyl donor as the C-2 hydroxyl, hence forming a 1,2-*cis* linkage. At least initially the development of IAD was motivated by the ubiquity of the β-*manno* linkage in the N-glycan core pentasaccharide. The most notable applications of IAD of the synthesis of β-mannosides have arisen from the laboratories of Hindsgaul[3], Stork,[4] and Ogawa,[5] whilst Bols extended the Stork silicon tether approach to the synthesis of α-glucosides.[6]

We recently reported[7] a modification and extension of the original Hindsgaul mixed ketal approach,[3] which we applied to the synthesis of a series of β-mannnosides and α-glucosides. Whilst considering potential further modifications and improvements to the mixed ketal methodology, we were mindful of the particular limitation observed in Hindsgaul's initial investigations, namely the low yields observed for glycosylations with bulky aglycons. In contrast the Ogawa *para*-methoxybenzyl derived system[5] does not suffer from the same problem. It therefore seemed prudent to additionally investigate a hybrid situation, involving a combination of the Ogawa PMB and the Hindsgaul mixed ketal systems. In this paper we would like to give full details of both of our investigations into NIS mediated variants of the acetate derived enol ether system, and into a new hybrid Ogawa/Hindsgaul system, which is derived via Tebbe methylenation of a 2-O-*para*-methoxybenzoyl protected glycosyl donor.

2. Results and discussion

2.1. Synthesis of glycosyl donors

Investigations focussed on the use of thiophenyl glycosides as donors since it was envisaged that *N*-iodosuccinimide could be used for both tethering and activation steps, allowing the potential development of a one-pot approach which would obviate the need for the handling of sensitive mixed ketal intermediates. The required *manno* **1**[8] and *gluco* **2**[9] acetate substrates for Tebbe methylenation were readily synthesised according to reported literature procedures (**1**: 4 steps from mannose α-pentaacetate, 33% overall yield; **2**: 4 steps from glucose β-pentacetate, 43% overall yield). Tebbe methylenation then provided the corresponding *manno* and *gluco* enol ethers **3** and **4** (70% and 68% yields respectively, Scheme 1). The corresponding 2-*O*-*para*-methoxybenzoyl protected *gluco* thioglycoside **5** was simply accessed by deacetylation of the *gluco* acetate **2**, by treatment with catalytic sodium methoxide in methanol to yield the known[10] alcohol **6** (94% yield). Alcohol **6** was then esterified by treatment with *p*-anisic acid and dicyclohexylcarbodiimide to yield the *gluco para*-methoxy benzoate **5** (52% yield). Tebbe methylenation of **5** then yielded the required *para*-methoxyphenyl enol ether **7** (66% yield).

2.2. Investigations of two step NIS mediated tethering and glycosylation reactions

gluco Donor: Initial attempts at tethering using catalytic acid in the *gluco* series (following the reported procedure[3]

Keywords: carbohydrates; glycosidation; stereocontrol; thioglycosides.

* Corresponding author. Tel.: +44-1865-275-647; fax: +44-1865-275-674; e-mail: antony.fairbanks@chem.ox.ac.uk

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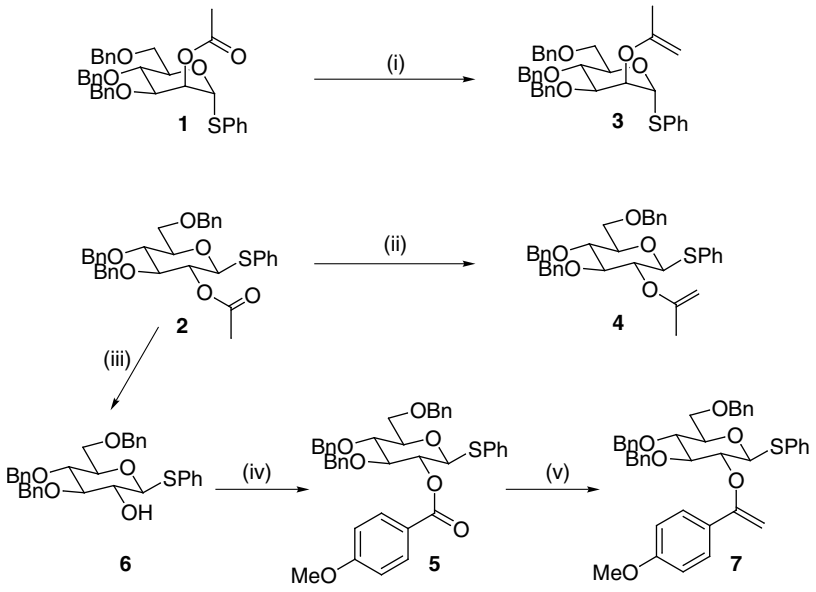
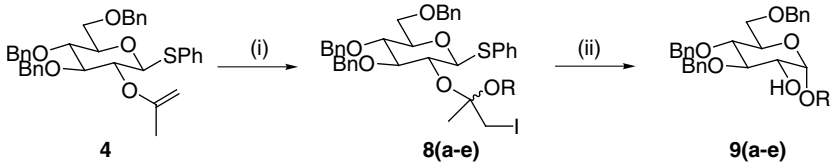


Scheme 1. (i) Tebbe reagent, pyridine, THF, −40°C to RT, 2 h, 70%; (ii) Tebbe reagent, pyridine, THF, −40°C to RT, 2 h, 68%; (iii) Na, MeOH, RT, 18 h, 94%; (iv) *p*-anisic acid, DCCI, THF, DMAP, reflux, 18 h, 52%; (v) Tebbe reagent, pyridine, THF, −78°C to RT, 18 h, 66%.

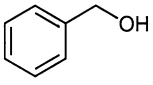
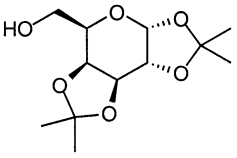
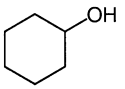
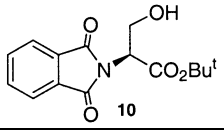
for the *manno* series) lead only to hydrolysis of the enol ether. Therefore attention turned to the use of other electrophiles for this initial step. Although it was found that iodine could successfully tether methanol to enol ether **4** (92% yield), attention focussed on the use of *N*-iodosuccinimde (NIS), driven by the prospect of the development of a one-pot procedure, wherein tethering and glycosylation were achieved sequentially in a single reaction vessel. Thus treatment of the enol ether **4** with a variety of alcohols and NIS in THF at low temperature, produced good to excellent yields of mixed ketal intermediates **8(a–e)** which could each be isolated as an inseparable mixture of diastereomers after flash chromatography on silica (Scheme 2, Table 1).

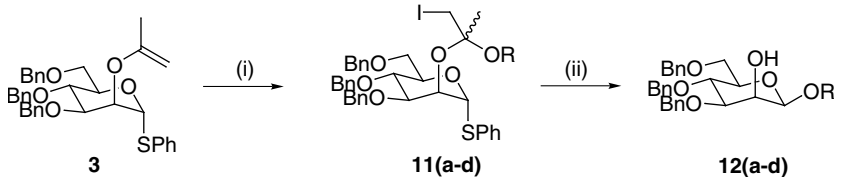
Subsequent attempted NIS mediated intramolecular



Scheme 2. (i) ROH, NIS (3 equiv.), THF, −78°C to RT; (ii) NIS (5 equiv.), DTBMP, CH_2Cl_2, 0°C to RT.

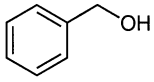
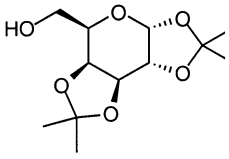
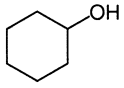
Table 1. *gluco* Tethering and glycosidation

Entry	Alcohol ROH	Product /Yield of Mixed Ketals	Product /Yield of Glycosidation
a)	MeOH	**8a** / 96%	**9a**/ 75%
b)		**8b**/ 76%	**9b**/ 75%
c)		**8c**/ 82%	**9c**/ 86%
d)		**8d**/ 82%	**9d**/ 65%
e)	 **10**	**8e**/ 56%	**9e**/ 55%



Scheme 3. (i) ROH, NIS (3 equiv.), THF, −78°C to RT; (ii) NIS (5 equiv.), DTBMP, CH_2Cl_2, 0°C to RT.

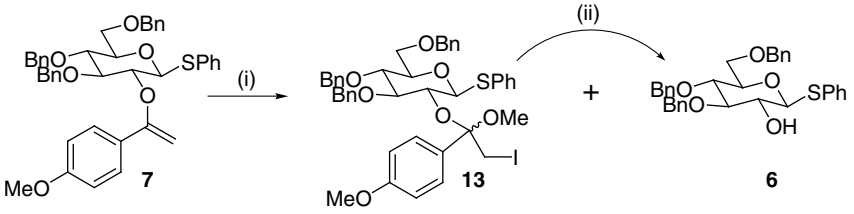
Table 2. *manno* Tethering and glycosidation

Entry	Alcohol ROH	Product / Yield of Mixed Ketals	Product / Yield of Glycosidation
a)	MeOH	**11a** / 92%	**12a** / 70%
b)		**11b** / 66%	**12b** / 88%
c)		**11c** / 95%	**12c** / 63%
d)		**11d** / 76%	**12d** / quantitative

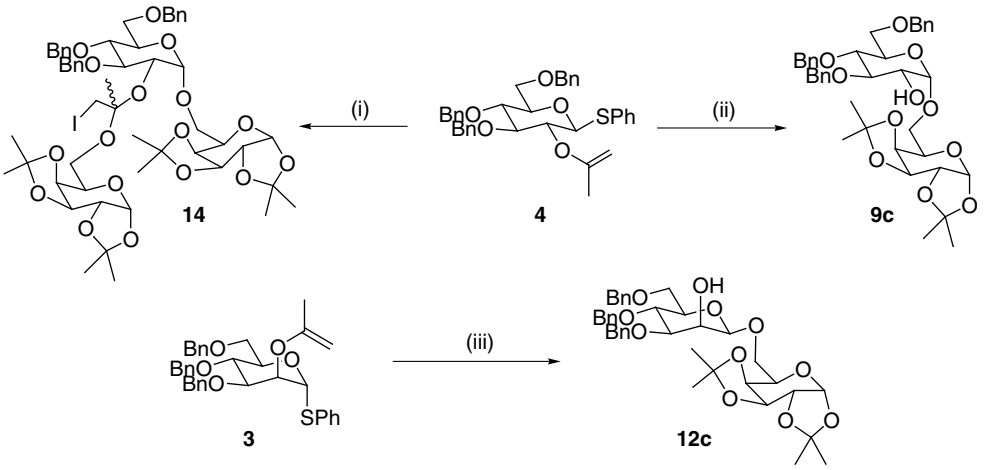
glycosylation of these mixed ketals in THF as the solvent gave only moderate yields of products. However glycosylation in dichloromethane at room temperature, with the addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) produced clean high yielding reactions (Table 1). As can be seen the yields for both tethering and glycosylation when performed in these two different solvents are good with primary alcohols, and in all cases only the α products (**9a–e**) were observed. Cyclohexanol also produced good results (entry d). Particularly noteworthy is the reaction of **4** with the protected serine derivative **10**,[11] which, after sequential tethering and activation yielded the α-glycosyl amino acid **9e**.[12] This approach may therefore be useful for the stereoselective synthesis of α-*O*-linked glycopeptides.

manno Donor. A similar set of reactions were performed in the analogous *manno*series (Scheme 3). NIS mediated tethering in THF with a similar series of alcohols again produced good yields of mixed ketals **11(a–d)** and subsequent NIS mediated glycosylation in dichloromethane cleanly produced the corresponding glycosides **12(a–d)** (Table 2). Again yields for both tethering and glycosylation were good, and in all cases only β-mannnoside products were isolated.[13]

p-Methoxybenzoyl derived donor. Initial tethering experiments revealed that reaction of the PMBz derived enol ether with NIS was extremely rapid at −40°C in dichloroethane, but that yields were low. This lead to a change of reaction solvent to dichloromethane, since tethering could then be achieved at −78°C. Tethering experiments using the PMBz derived enol ether **7** in dichloromethane quickly revealed that the intermediate mixed ketals were much more labile than in the acetate derived cases. For example although reaction of enol ether **7** with methanol and NIS at −78°C in dichloromethane was complete by TLC after 10 minutes, attempted work-up produced large amounts of hydrolysed material **6**, together with a small amount of a mixture of two compounds, the structures of which were tentatively assigned[14] as the mixed ketals **13** (Scheme 4). Simple stirring of **13** with acidic ion exchange resin rapidly resulted in the formation of the hydrolysed material **6** as the sole isolable product. It was clear that the mixed ketal intermediates in this PMBz derived system were extremely sensitive and underwent hydrolysis very rapidly. Since in this case a two-step procedure would probably not be either high yielding or facile, attention turned to the development of an operationally simple one-pot approach, which would avoid the isolation or handling of these intermediates, along the lines of that developed for the acetate derived system (vide infra).



Scheme 4. (i) MeOH, NIS (3 equiv.), DCM, −78°C, 10 min; (ii) acidic ion exchange resin, MeOH, RT.



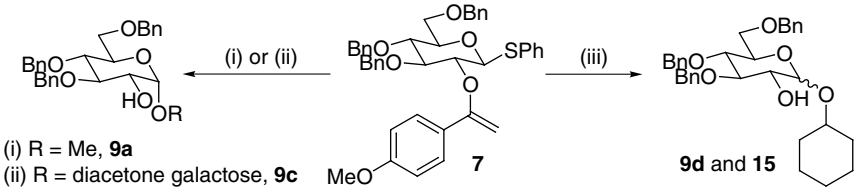
Scheme 5. (i) diacetone galactose (3 equiv.), NIS (3 equiv.), DCE, −40°C to RT, 79%; (ii) diacetone galactose, NIS, DTBMP, DCE, −40°C to RT, then Dowex H^+/MeOH, 68%; (iii) diacetone galactose, NIS, DTBMP, DCE, −40°C to RT, then Dowex H^+/MeOH, 84%.

2.3. One-Pot Approach

The success of the tethering reactions in the acetate derived series detailed above clearly demonstrated the order of magnitude difference in reactivity between the enol ether and the anomeric sulphur. Therefore in theory it should be a simple matter to effect both tethering and glycosylation in a single step, though early indications were that the choice of reaction solvent was important. A screen to find a solvent which produced clean, high-yielding reactions for the glycosylation step, led us to investigate the use dichloroethane for the one-pot reaction.

Stirring the *gluco*acetate derived donor **4** with diacetone galactose and 3 equivalents of NIS in dichloroethane (−40°C to RT, overnight), produced an inseparable mixture of products, which were identified as the α-glucoside ketals **14**, in a combined 79% yield (Scheme 5). Production of **14** presumably occurred by trapping of the oxonium ion produced subsequently to glycosylation by the excess of glycosyl acceptor present in solution. Since in this case no β-products were observed it can be concluded that the intramolecular process competed effectively with the possible intermolecular reaction for this donor in this solvent. This was confirmed by a competitive control reaction, whereby glycosylation of the diacetone galactose mixed ketals **8c** was undertaken in dichloroethane in the presence of 3 equivalents of methanol as intermolecular nucleophile; no methyl glycoside products were observed. However it is clear that the choice of reaction solvent is important to ensure that intramolecular reaction is entirely competitive, since when ether was used for the attempted one-pot reaction, very small amounts of β-*gluco* products were occasionally observed. A slight modification of the experimental procedure, involving the addition of the DTBMP and further NIS immediately after tethering was complete (~15 minutes at −40°C as monitored by TLC), together the use of an acidic work-up procedure involving stirring of the crude reaction product with acidic ion exchange resin (Dowex 50WX8-100, H^+) in methanol, allowed the formation of the α-disaccharide **9c** in a single manipulation, in a very satisfactory 68% yield (Scheme 5). This completely stereoselective glycosylation was in direct contrast with a control reaction using phenyl 2,3,4,6 tetra-*O*-benzyl-1-thio-α-D-glucopyranoside as the glycosyl donor, which under similar reaction conditions produced a 1:1 mixture of the α-and β-anomers. A similar one-pot transformation was performed in the *manno* series, again with dichloroethane as the solvent. In this case the reaction was even more efficient, allowing the synthesis of the β-*manno* disaccharide **12c** in a single operation in an excellent 84% yield (Scheme 5).

On the basis of these successful developments one-pot tethering and glycosyation was attempted in the PMBz derived system. Using the optimised reaction conditions one-pot tethering and glycosylation of enol ether **7** was undertaken in dichloromethane with both methanol and diacetone galactose as glycosyl acceptors. In both cases reaction was successful, though less efficient than in the acetate derived case; the α-glycosides **9a** and **9c** were obtained in 55% and 49% yields respectively. Again no β-glucoside products were observed. However when one-pot reaction of **7** was attempted with cyclohexanol in



Scheme 6. (i) MeOH, NIS, DTBMP, CH_2Cl_2, −78°C to RT, then Dowex H^+/MeOH, 55%; (ii) diacetone galactose, NIS, DTBMP, CH_2Cl_2, −78°C to RT, then Dowex H^+/MeOH, 49%; (iii) cyclohexanol, NIS, DTBMP, CH_2Cl_2, −78°C to RT, then Dowex H^+/MeOH, 51%, α:β 3:1.

dichloroethane surprisingly an α/β mixture of glycoside products **9d** and **15** was observed, in a combined 51% yield (Scheme 6). This was perplexing since all of the previously investigated reactions in dichloroethane had been completely stereoselective. In light of this result it was concluded that in the case of the PMBz derived system intermolecular reaction could occur competitively, limiting the synthetic utility of this approach. This is probably due to the inherent low stability of the *para*-methoxyphenyl mixed ketal intermediates, which decompose during the reaction, leaving intermolecular reaction as the only possibility.

3. Summary and conclusion

In summary we have demonstrated that *N*-iodosuccinimide can be used to effect both tethering and glycosylation steps implicit in the Hindsgaul mixed ketal approach to 1,2-*cis* glycosides, and that this methodology allows the stereoselective synthesis of a number of α-glucosides as well as of β-mannosides. Moreover the use of dichloroethane as solvent permits a one-pot approach, whereby both tethering and glycosylation are achieved in a single manipulation. However the PMBz derived system, which can be considered as a hybrid of the Hindsgaul and Ogawa approaches has less synthetic utility. The mixed ketal intermediates in this case are particularly unstable, and the utility of a one-pot approach is diminished by the finding that intermolecular reaction can be competitive leading to the formation of an α/β product mixture in the case of a secondary alcohol acceptor.

Further development and refinement of the one-pot procedure, extensions to other enol ether systems, and investigations into the applicability of this methodology to hindered secondary carbohydrate alcohols are currently in progress, and will be reported in due course.

4. Experimental

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 AMX 500 (500 MHz) spectrometer. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Bruker AC 200 (50.3 MHz), or on a Bruker DPX 400 (100.6 MHz) spectrometer. Multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale in parts per million (ppm). Infrared spectra were recorded on a Perkin–Elmer 150 Fourier Transform spectrophotometer. Low resolution mass spectra were recorded a Micromass Platform 1 APCI using atmospheric pressure chemical ionisation (APCI). High reolsution mass spectra (electrospray) were performed on a Waters 2790-Micromass LCT electrospray ionisation mass specrometer, or by the EPSRC Mass Spectrometry Service Centre, Department of Chemistry, University of Wales, Swansea on a MAT900 XLT electrospray ionisation mass specrometer. 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 Kieselfel 0.220.25 mm thickness glassbacked sheets, pre-coated with $60F_{254}$ silica. Plates were developed using 0.2% w/v cerium (IV) sulfate and 5% w/v ammonium molybdate in 2 M sulphuric acid. Flash column chromatography was carried out using Sorbsil C60 40/60 silica or basic alumina. Solvents and reagents were dried and purified before use according to standard procedures; methanol was distilled from sodium hydride, dichloromethane (DCM) was distilled from calcium hydride, pyridine was distilled from calcium hydride and stored over potassium hydroxide and tetrahydrofuran was distilled from a solution of sodium benzophenone ketyl immediately before use. Petrol was distilled between 40 and 60°C before use to remove involatile fractions.

4.1. Phenyl-3,4,6-tri-O-benzyl-2-O-(2-propenyl)-1-thio-β-D-mannopyranoside 3

Acetate **1**[8] (100 mg, 0.17 mmol) was dissolved in THF (4 ml) and pyridine (0.1 ml). Tebbe reagent (0.5 M in toluene, 0.68 ml, 0.34 mmol) was added at −40°C, and the reaction mixture was allowed to warm to −10°C. After 2 h, TLC (petrol:ethyl acetate, 5:1) indicated the consumption of starting material (R_f 0.4) and the formation of a major product (R_f 0.6). The reaction was quenched by the careful addition of ether (5 ml), and 1 M aqueous NaOH (0.1 ml), filtered through Celite® and washed with more ether until the filtrate was colourless. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The deep red residue was purified by column chromatography (petrol:ethyl acetate, 5:1, 0.1% triethylamine) to yield enol ether **3** (70 mg, 70%) as a pale yellow crystalline solid; mp 63–65°C (ether/petrol); $[\alpha]_D^{24}=+106$ (*c*, 0.95 in $CHCl_3$); ν_{max} (KBr disc) 1650 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.90 (3H, s, C*H*$_3$), 3.77–3.74 (2H, m, H-6′, C=CH*H*), 3.87 (1H, dd, $J_{5,6}$=4.9 Hz, $J_{6,6'}$=10.9 Hz, H-6), 3.98–3.95 (2H, m, H-3, C=C*H*H), 4.11 (1H, a-t, $J_{3,4}=J_{4,5}$= 9.5 Hz, H-4), 4.31 (1H, ddd, $J_{4,5}$=9.7 Hz, $J_{5,6}$=4.7 Hz, $J_{5,6'}$=1.6 Hz, H-5), 4.49 (1H, d, *J*=11.9 Hz, PhC*H*$_2$), 4.70–4.66 (3H, m, PhC*H*$_2$), 4.57–4.55 (2H, m, PhC*H*$_2$, H-2), 4.95, (1H, d, *J*=10.7 Hz, PhC*H*$_2$), 5.76 (1H, d, $J_{1,2}$=0.8 Hz, H-1), 7.42–7.23 (18H, m, Ar*H*), 7.50–7.47 (2H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 21.1 (q, *C*H$_3$), 69.1, 72.0, 73.3, 75.3 (4×t, 3×Ph*C*H$_2$, C-6), 72.4, 75.4, 74.7, 79.0, 84.2 (5×d, C-1, C-2, C-3, C-4, C-5), 83.0 (t, C=*C*H$_2$), 127.7, 127.9, 128.2, 128.5, 128.6, 128.7, 129.3, 129.6, 131.9 (9×d, 20×Ar*C*H), 134.2, 138.2, 138.5, 138.7 (4×s, 4×Ar*C*), 158.6 (s, *C*=CH$_2$); *m/z* (APCI$^+$) 604.8 (M+Na$^+$, 17%), 583.0 (M+H$^+$, 15), 638 (18), 417.1 (43), 341.1 (84), 309.1 (24), 120.8 (100), 106.7 (21). (Found: C, 74.25; H, 6.37. $C_{36}H_{38}O_5S$ requires: C, 74.20; H, 6.57%). (HRMS Calcd. For $C_{36}H_{39}O_5S$ (M+H$^+$) 583.2518. Found 583.2515).

4.2. Phenyl 2,3,6-tri-O-benzyl-2-O-(2-propenyl)-1-thio-β-D-glucopyranoside 4

To a stirred solution of acetate **2**[9] (3 g, 5.1 mmol) in THF (50 ml) and toluene (25 ml) was added pyridine (1 ml), followed by Tebbe Reagent (0.5 M solution in toluene, 19 ml, 9.9 mmol) portionwise, at −40°C, under argon. After the addition of Tebbe Reagent was completed, the

reaction was allowed to reach −10°C. After 1.5 h, TLC (petrol:ethyl acetate, 3:1) indicated complete conversion of starting material (R_f 0.8) to a major product (R_f 0.9). 1 M Aqueous NaOH (0.1 ml) was added carefully to the reaction mixture (vigorous methane evolution). After the gas evolution subsided, the reaction mixture was allowed to reach room temperature, followed by a further addition of 1M aqueous NaOH (0.5 ml). The deep red mixture was filtered through Celite®, the filtrate washed with ether until colourless and concentrated in vacuo. The resulting residue was purified by column chromatography (petrol:ethyl acetate, 7:1) to give enol ether **4** (2.0 g, 68%) as a pale yellow crystalline powder; mp 78°C (ether/petrol); $[\alpha]_D^{23}$=−30 (*c*, 1.2 in $CHCl_3$); ν_{max} (KBr disc) 1657 cm^{-1} (C=C); δ_H (400 MHz + COSY, $CDCl_3$) 1.82 (3H, s, C*H*$_3$), 3.46 (1H, ddd, $J_{4,5}$=9.6 Hz, $J_{5,6}$=4.7 Hz, $J_{5,6'}$=1.8 Hz, H-5), 3.58 (1H, a-t, $J_{3,4=4,5}$=9.6 Hz, H-4), 3.63–3.70 (2H, m, H-3, H-6), 3.71 (1H, dd, $J_{6,6'}$=10.9 Hz, H-6′), 4.03 (1H, d, *J*=1.4 Hz, C=C*H*H), 4.07 (1H, a-t, $J_{1,2=2,3}$=9.3 Hz, H-2), 4.12 (1H, d, C=CH*H*) 4.44 (1H, d, *J*=12.0 Hz, PhC*H*$_2$), 4.48 (1H, d, *J*=10.3 Hz, PhC*H*$_2$), 4.51 (1H, d, PhC*H*$_2$), 4.60 (1H, d, $J_{1,2}$=9.7 Hz, H-1), 4.62 (1H, d, *J*=10.7 Hz, PhC*H*$_2$), 4.74 (1H, d, PhC*H*$_2$), 4.76 (1H, d, PhC*H*$_2$), 7.11–7.57 (20 H, m, Ar*H*); δ_C (50.3 MHz + DEPT, $CDCl_3$): 21.3 (q, *C*H$_3$), 69.1, 73.4, 75.1, 75.4, 85.1 (5×t, C-6, 3×Ph*C*H$_2$, C=*C*H$_2$), 77.2, 77.4, 79.2, 86.1, 87.2 (5×d, C-1, C-2, C-3, C-4, C-5), 127.6, 127.8, 127.9, 128.1, 128.5, 129.0, 132.2 (7×d, Ar*C*H), 134.0, 138.4, 138.5 (3×s, Ar*C*); *m/z* (APCI +ve) 605 (M+Na^+, 20%), 525 (100). (Found: C, 74.07; H, 6.52. $C_{36}H_{38}O_5S$ requires: C, 74.20; H, 6.52%).

4.3. Phenyl 3,4,6-tri-O-benzyl-1-thio-β-D-glucopyranoside 6[10]

A solution of sodium (440 mg) in methanol (50 ml) was added to a stirred solution of the acetate **2**[9] (2.02 g, 3.46 mmol) in methanol (100 ml) under argon. After 18 h, TLC (petrol:ethyl acetate, 3:1) indicated complete conversion of starting material (R_f 0.5) to a major product (R_f 0.4). DCM (100 ml) was added to the reaction mixture, which was then washed with dilute aqueous HCl (1 M, 100 ml). The organic phase was then dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was purified by recrystallisation (ether/petrol) to give the alcohol **6** (1.77 g, 94%) as a white crystalline solid; mp 72–75°C (ether/petrol); $[\alpha]_D^{22}$=−11.2 (*c*, 1.0 in $CHCl_3$), [Lit.,[10] mp 71–73°C; $[\alpha]_D^{25}$−11.5 (*c*, 1.4 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.42 (1H, d, $J_{2,OH}$=1.8 Hz, O*H*), 3.49–3.57 (2H, m, H-2, H-5), 3.59–3.65 (2H, m, H-3, H-4), 3.75 (1H, dd, $J_{5,6}$=4.3 Hz, $J_{6,6'}$=11.0 Hz, H-6), 3.81 (1H, dd, $J_{5,6'}$ 1.9 Hz, H-6′), 4.52 (1H, d, $J_{1,2}$=9.6 Hz, H-1), 4.55–4.94 (6H, m, 3×PhC*H*$_2$), 7.20–7.60 (20H, m, Ar*H*).

4.4. Phenyl 3,4,6-tri-O-benzyl-2-O-*para*-methoxybenzoyl-1-thio-β-D-glucopyranoside 5

Dicyclohexylcarbodiimide (1.19 g, 5.74 mmol) was added to a stirred solution of the alcohol **6** (857 mg, 1.58 mmol) in THF (15 ml) at room temperature. After 30 min., *p*-anisic acid (1.21 g, 7.95 mmol) and then DMAP (51 mg, 0.42 mmol) were added. The resulting reaction mixture was refluxed under argon, and after 18 h, TLC (petrol:ethyl acetate, 2:1) indicated complete conversion of starting material (R_f 0.7) to a major product (R_f 0.5). The reaction mixture was filtered through Celite®, the filtrate was washed with DCM (150 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 7:2) to give ester **5** (0.50 g, 52%) as a white crystalline solid; mp 110–111°C (ether/petrol); $[\alpha]_D^{22}$ =+45 (*c*, 0.9 in $CHCl_3$); ν_{max} (KBr disc) 1712 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.63–3.67 (1H, m, H-5), 3.76 (1H, a-t, $J_{3,4}$=$J_{4,5}$=9.0 Hz, H-4), 3.78 (1H, dd, $J_{5,6}$=4.7 Hz, $J_{6,6'}$=11.1 Hz, H-6), 3.86 (1H, dd, $J_{5,6'}$=1.6 Hz, H-6′), 3.86–3.91 (1H, m, H-3), 3.90 (3H, s, C*H*$_3$), 4.59, 4.65 (2H, ABq, *J*=11.9 Hz, PhC*H*$_2$), 4.62, 4.85 (2H, ABq, *J*=11.3 Hz, PhC*H*$_2$), 4.69, 4.75 (2H, ABq, *J*=10.9 Hz, PhC*H*$_2$), 4.82 (1H, d, $J_{1,2}$=10.1 Hz, H-1), 5.32 (1H, dd, $J_{2,3}$=9.2 Hz, H-2), 6.95–6.98, 8.03–8.07 (4H, 2×m, $CH_3OC_6H_4$), 7.14–7.53 (20H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 55.5 (q, *C*H$_3$), 69.0, 73.5, 75.1, 75.3 (4×t, C-6, Ph*C*H$_2$), 72.2, 77.7, 79.4, 84.4, 86.3 (5×d, C1, C-2, C-3, C4, C-5), 113.1 (d, Ar*C*H), 122.2 (s, Ar*C*), 127.6. 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.4, 128.8, 132.0, 132.4, 132.8, 133.1, 137.7, 137.9, 137.9, 138.2 (17×d, 30×Ar*C*H), 133.3, 137.7, 137.9, 138.2 (4×s, 4×Ar*C*), 163.6, 164.9 (2×s, Ar*C*, *C*=O); *m/z* (APCI$^+$) 700 (M+Na^+, 24%), 568 (M-SPh, 28), 135 ($MeOC_6H_4CO$, 100). (Found: C, 72.90%; H, 5.99%. $C_{41}H_{40}O_7S$ requires: C, 72.76%; H, 5.96%).

4.5. Phenyl 3,4,6-tri-O-benzyl-2-O-(1-*para*-methoxyphenyl-ethenyl)-1-thio-β-D-glucopyranoside 7

Tebbe reagent (0.5 M in toluene, 1.75 ml, 0.88 mmol) was added to a stirred solution of the ester **5** (298 mg, 0.44 mmol) in anhydrous pyridine (0.4 ml), and anhydrous THF (2 ml) at −78°C under argon. The reaction was then allowed to warm to room temperature and after 18 h, TLC (petrol:ethyl acetate, 1:1) showed conversion of starting material (R_f 0.5) to a major product (R_f 0.6). The reaction mixture was diluted with ether (5 ml), cooled to 0°C and quenched by the addition of aqueous sodium hydroxide (1.0 M, 2 ml) until vigorous gas evolution ceased. The resulting residue was filtered though Celite®, washing with ether (250 ml). The filtrate was dried (magnesium sulfate) and concentrated in vacuo. The resulting residue was purified by flash column chromatography on basic alumina (petrol:ethyl acetate, 5:1) to give the vinyl ether **7** (197 mg, 66%, 78% based on recovered starting material) as an unstable brown syrup; $[\alpha]_D^{22}$ −1.9 (*c*, 0.7 in $CHCl_3$); ν_{max} (thin film) 1684 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.62–3.65 (1H, m, H5), 3.72 (1H, a-t, $J_{3,4}$=$J_{4,5}$ 9.3 Hz, H-4), 3.78 (1H, dd, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 10.8 Hz, H-6), 3.83–3.89 (5H, m, H3, H-6′, C*H*$_3$), 4.32 (1H, a-t, $J_{1,2}$=$J_{2,3}$=9.5 Hz, H-2) 4.48, 4.74 (2H, 2×d, *J*=2.8 Hz, C=C*H*$_2$), 4.58, 4.64 (2H, ABq, *J*=11.9 Hz, PhC*H*$_2$), 4.60, 4.87 (2H, ABq, *J*=11.2 Hz, PhC*H*$_2$), 4.67, 4.83 (2H, ABq, *J*=10.5 Hz, PhC*H*$_2$), 4.83 (1H, d, H-1), 6.87–6.97, 7.69–7.71 (4H, m, $CH_3OC_6H_4$), 7.20–7.38, 7.54–7.56 (20H, m, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 55.5 (q, *C*H$_3$), 69.0, 73.4, 75.1, 75.2, 84.4 (5×t, C-6, 3×Ph*C*H$_2$, C=*C*H$_2$), 77.4, 77.6, 79.2, 86.2, 87.0 (5×d, C-1, C-2, C-3, C-4, C-5), 113.4, 113.7, 113.7, 127.4, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.3, 128.3, 128.3, 128.4, 128.4, 128.5, 128.7, 129.0, 132.5, 132.9 (22×d, 24×Ar*C*H), 130.6 (s, Ar*C*),

133.2, (s, Ar*C*) 138.1, 138.2 (2×s, Ar*C*), 159.1, 160.0 (2×s, Ar*C*, *C*=CH_2); *m/z* (APCI$^+$) 692 (M+NH_4^+, 100%).

4.6. General procedure for two stage tethering and glycosylation

A mixture of either the *gluco* **4** or *manno* **3** enol ether (typically 100 mg, 0.17 mmol), the alcohol (3 equivalents) and 4Å molecular sieves (200 mg, powdered) in THF (3 ml) was stirred at −78°C, under argon. *N*-Iodosuccinimide (124 mg, 0.51 mmol) was added and the resulting reaction mixture was allowed to reach 0°C. After 18 h, DCM (50 ml) was added to the reaction mixture, which was then filtered through Celite®, the filtrate washed with 10% aq. sodium thiosulfate (25 ml), the organic phase dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was purified by column chromatography (petrol:ethyl acetate, 4:1, 0.1% triethylamine) to give the mixed ketals, as a colourless oil. A solution of this mixture (typically 100 mg, 0.12 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (5 equivalents) in DCM (5 ml) was stirred at 0°C, under argon. *N*-Iodosuccinimide (5 equivalents) was then added and the resulting reaction mixture was allowed to reach room temperature. After 18 h, TLC (petrol:ethyl acetate, 3:1) indicated complete conversion of starting material to a major product. DCM (50 ml) was added to the reaction mixture, which was then washed with dilute aqueous HCl (1.0 M, 50 ml). The organic phase was further washed with 10% aq. sodium thiosulfate (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was purified by column chromatography (petrol: ethyl acetate, 3:1) to give either the α-glucoside **9a–e** or β-mannoside **12a–d** respectively.

4.7. Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 9a

The *gluco* enol ether **4** (150 mg, 0.26 mmol), and methanol (0.03 ml, 0.78 mmol) gave the α-methyl glycoside **9a** as a colourless crystalline solid; m.p 89–90°C (petrol/ethyl acetate); $[\alpha]_D^{23}$=+90 (*c*, 1.1 in $CHCl_3$), [lit.[15] mp 87–88°C; $[\alpha]_D^{20}$=+98 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz + COSY, $CDCl_3$) 2.15 (1H, d, $J_{2,OH}$=7.5 Hz, O*H*), 3.43 (3H, s, OMe), 3.63–3.79 (6H, m, H-2, H-3, H-4, H-5, H-6 and H-6′), 4.81 (1H, d, $J_{1,2}$=3.3 Hz, H-1), 4.49–4.93 (6H, 6×d, 3×PhCH_2), 7.15–7.39 (15H, m, Ar*H*).

4.8. Benzyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 9b

The *gluco* enol ether **4** (100 mg, 0.17 mmol) and benzyl alcohol (0.05 ml, 0.51 mmol) gave the α-benzyl glucoside **9b** as a colourless oil; $[\alpha]_D^{24}$=+88 (*c*, 0.76 in $CHCl_3$), [lit.[16] $[\alpha]_D^{20}$=+105 (*c*, 1.8 in $CHCl_3$)]; δ_H (400 MHz+ COSY, $CDCl_3$) 3.58–3.85 (6H, m, H-2, H-3, H-4, H-5, H-6 and H-6′), 4.49–4.96 (8H, 8×d, 4×PhCH_2), 5.03 (1H, d, $J_{1,2}$=3.5 Hz, H-1), 7.13–7.54 (20H, m, Ar*H*).

4.9. 3,4,6-Tri-O-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 9c

The *gluco* enol ether **4** (100 mg, 0.17 mmol) and diacetone galactose (177 mg, 0.68 mmol) gave the α-disaccharide **9c** as a colourless oil; $[\alpha]_D^{24}$=+29 (*c*, 0.9 in $CHCl_3$), [lit.[15] $[\alpha]_D^{20}$=+26 (*c*, 0.5, $CHCl_3$)]; δ_H (400 MHz+COSY, $CDCl_3$) 1.34, 1.35, 1.45, 1.53 (12H, 4×s, 4×CH_3), 3.63–3.78 (6H, m, H-2′, H-3′, H-4′, H-6a′, H-6b′, H-6′), 3.85 (1H, ddd, $J_{4',5'}$=9.6 Hz, $J_{5',\ 6a'}$=2.8 Hz, $J_{5,6b'}$=1.9 Hz, H-5′), 3.91 (1H, dd, $J_{5,6}$=6.9 Hz, $J_{6,6'}$=10.3 Hz, H-6), 3.99 (1H, ddd, $J_{4,5}$=10.1 Hz, $J_{5,6'}$=1.9 Hz, H-5), 4.25 (1H, dd, H-4), 4.33 (1H, dd, $J_{1,2}$=2.5 Hz, $J_{2,3}$=5.0 Hz, H-2), 4.47–4.57 (2H, 2×d, PhCH_2), 4.61–4.65 (2H, m, H-3, PhCH_2), 4.81–4.84 (2H, 2×d, PhCH_2), 4.93 (1H, d, $J_{1',2'}$=3.4 Hz, H-1′), 4.98 (1H, d, PhCH_2), 5.52 (1H, d, $J_{1,2}$=5.0 Hz, H-1), 7.13–7.53 (15H, m, Ar*H*).

4.10. Cyclohexyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 9d

The *gluco* enol ether **4** (100 mg, 0.17 mmol) and cyclohexanol (0.1 ml, 0.85 mmol) gave the α-cyclohexyl glucoside **9d** as a colourless oil; $[\alpha]_D^{24}$=+60 (*c*, 0.6 in $CHCl_3$); ν_{max} (thin film) 3470 (br, OH) cm^{-1}; δ_H (400 MHz+COSY, $CDCl_3$) 1.19–1.89 (10H, m, OCH(CH_2)$_5$), 2.05 (1H, d, $J_{2,OH}$=9.3 Hz, O*H*), 3.59–3.90 (7H, m, H-2, H-3, H-4, H-5, H-6, H-6′,OC*H*(CH_2)$_5$), 4.45–5.00 (6H, 6×d, 3×PhCH_2), 5.03 (1H, d, $J_{1,2}$=3.5 Hz, H-1), 7.14–7.42 (15H, m, Ar*H*); δ_C (125 MHz+DEPT, $CDCl_3$) 23.9, 24.1, 25.3, 31.7, 33.4 (5×t,OCH(*C*H_2)$_5$), 68.5, 73.4, 75.1, 75.3 (4×t, C-6, 3×Ph*C*H_2), 70.4, 73.0, 76.1, 77.2, 83.8 (5×d, C-2, C-3, C-4, C-5,OCH(CH$_2$)$_5$), 96.8 (d, C-1), 127.6, 127.65, 127.7, 127.8, 128.0, 128.5, 128.6, 128.7 (8×d, Ar*C*H), 137.9, 138.1, 138.5 (3×s, Ar*C*); *m/z* (APCI+ve) 555 (M+Na^+, 25%). (HRMS Calcd. For $C_{33}H_{44}NO_6$ (M+NH_4^+) 550.3169. Found 550.3169).

4.11. *N*-(Phthaloyl)-O^3-(3,4,6-tri-O-benzyl-α-D-glucopyranosyl)-L-serine-tert butyl ester 9e

The *gluco* enol ether **4** (80 mg, 0.14 mmol) and *N*-phthaloyl-L-serine-*tert*-butyl ester **10**[11] (122 mg, 0.42 mmol) gave the α-glucosyl amino acid **9e** as a colourless oil; $[\alpha]_D^{24}$=+43 (*c*, 0.25 in $CHCl_3$); ν_{max} (thin film) 3480 (br, OH), 1778 ($CO_2{}^tBu$), 1716 (C=O) cm^{-1}; δ_H (400 MHz+COSY, C_6D_6) 1.35 (9H, s, C(CH_3)$_3$), 2.54 (1H, d, $J_{OH,2}$=9.9 Hz, O*H*), 3.68 (1H, dd, $J_{5,6}$=1.7 Hz, $J_{6,6}$=10.8 Hz, H-6), 3.71–3.79 (3H, m, H-2, H-4, H-6′), 3.92 (1H, a-t, $J_{2,3=3,4}$=9.1 Hz, H-3), 4.03 (1H, m, H-5), 4.31–4.36 (2H, m, H-2aa, H-2′aa), 4.40 (1H, d, *J* 12.2 Hz, PhCH_2), 4.50 (1H, d, PhCH_2), 4.63 (1H, d, *J*=11.3 Hz, PhCH_2), 4.87 (1H, d, *J*=11.4 Hz, PhCH_2), 4.96 (1H, d, PhCH_2), 4.97 (1H, d, $J_{1,2}$=3.9 Hz, H-1), 5.07 (1H, d, PhCH_2), 5.21 (1H, dd, $J_{1aa,2aa}$=5.0 Hz, $J_{1aa,2'aa}$=6.5 Hz, H-1aa), 6.83–7.49 (19 H, m, Ar*H*); δ_C (125 MHz+DEPT, $CDCl_3$) 27.8 (q, C(*C*H$_3$)$_3$), 53.2, 71.0, 73.2, 77.1, 83.3 (5×d, C-2, C-3, C-4, C-5, C-1aa), 66.3, 68.5, 73.5, 74.9, 75.2 (5×t, C-6, C-2aa, 3×Ph*C*H$_2$), 83.5 (s, *C*(CH$_3$)$_3$), 100.2 (d, C-1), 123.6, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 134.3 (10×d, Ar*C*H), 131.8, 138.1, 138, 3, 138.8 (4×s, Ar*C*), 165.7, 167.7 (2×s, 2×*C*=O); *m/z* (APCI +ve) 747 (M+Na^+, 50%), 488 (15), 473 (15), 209 (100), 181 (50, 122 (90). (HRMS Calcd. For $C_{42}H_{49}N_2O_{10}$ (M+NH_4^+) 741.3387. Found 741.3386).

4.12. Methyl 3,4,6-Tri-O-benzyl-β-D-mannopyranoside 12a

The *manno* enol ether **3** (100 mg, 0.17 mmol) and anhydrous

methanol (20.8 μl, 0.51 mmol) gave the β-methyl mannoside **12a** as a colourless oil; $[\alpha]_D^{24}=-13$ (*c*, 1.0 in $CHCl_3$) [lit.[15] −13 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.43 (1H, s, O*H*), 3.44 (1H, m, H-5), 3.57 (3H, s,OCH_3), 3.59 (1H, dd, $J_{2,3}$=3.1 Hz, $J_{3,4}$=9.4 Hz, H-3), 3.73 (1H, dd, $J_{5,6'}$=5.2 Hz, $J_{6,6'}$ 10.8 Hz, H-6′), 3.80 (1H, dd, $J_{5,6}$= 2.0 Hz, Hz, H-6), 3.87 (1H, at, $J_{3,4}=J_{4,5}$=9.4 Hz, H-4), 4.10 (1H, dd, $J_{1,2}$=0.8 Hz, H-2), 4.34 (1H, d, H-1), 4.57, 4.64 (2H, 2×d, *J*=12.2 Hz, PhCH_2), 4.69, 4.77 (2H, 2×d, *J*=11.9 Hz, PhCH_2), 4.54, 4.89 (2H, 2×d, *J*=10.8 Hz, PhCH_2), 7.18–7.41 (15H, m, Ar*H*).

4.13. Benzyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside 12b

The *manno* enol ether **3** (100 mg, 0.17 mmol) and anhydrous benzyl alcohol (43 μl, 0.41 mmol) gave the β-benzyl mannoside **12b** as a colourless oil; $[\alpha]_D^{24}$ −40 (*c*, 0.4 in $CHCl_3$), [lit.[17] −43 (*c*, 1.3 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.49 (1H, s, O*H*), 3.43 (1H, m, H-5), 3.56 (1H, dd, $J_{2,3}$=3.1 Hz, $J_{3,4}$=9.0 Hz, H-3), 3.75 (1H, dd, $J_{5,6'}$=5.3 Hz, $J_{6,6'}$=10.7 Hz, H-6′), 3.81 (1H, dd, $J_{5,6}$=2.1 Hz, H-6), 3.89 (1H, a-t, $J_{3,4}=J_{4,5}$=9.4 Hz, H-4), 4.12 (1H, dd, $J_{1,2}$=0.6 Hz, $J_{2,3}$=2.8 Hz, H-2), 4.46 (1H, d, H-1), 4.55–4.96 (8H, 8×d, 3×CH_2Ph), 7.19–7.22 (2H, m, Ar*H*), 7.38–7.27 (18H, m, Ar*H*).

4.14. 3,4,6-Tri-O-benzyl-β-D-mannopyranosyl-(1→6)-1,2,3,4-di-O-isopropylidene-D-galactopyranose 12c

The *manno* enol ether **3** (100 mg, 0.17 mmol) and diacetone galactose (134 mg, 0.52 mmol) gave the β-disaccharide **12c** as a colourless oil; $[\alpha]_D^{24}=-53$ (*c*, 1.3 in $CHCl_3$); ν_{max} (thin film) 3584 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.57 (1H, s, O*H*), 3.40–3.44 (1H, ddd, $J_{4',5'}$=9.7 Hz, $J_{5',6'}$=4.5 Hz, $J_{5',6'a}$=2.2 Hz, H-5′), 3.55–3.58 (1H, dd, $J_{2',3'}$=3.0 Hz, $J_{3',4'}$=9.1 Hz, H-3′), 3.70–3.78 (3H, m, H-6a, H-6′, H-6′a), 3.89–3.94 (1H, a-t, $J_{3',4'}=J_{4',5'}$=9.4 Hz, H-4′), 4.02–4.05 (1H, m, H-5), 4.12–4.16 (1H, dd, $J_{5,6}$=2.9 Hz, $J_{6,6a}$=11.2 Hz, H-6), 4.21–4.23 (2H, m, H-2′, H-4), 4.32–4.33 (1H, dd, $J_{2,3}$=2.4 Hz, $J_{1,2}$=5.0 Hz, H-2), 4.50–4.56 (3H, m, H-1′, PhCH_2), 4.59–4.67 (3H, m, PhCH_2, H-3), 4.80 (1H, d, *J*=11.9 Hz, PhCH_2), 4.91 (1H, d, *J*=10.8 Hz, PhCH_2), 5.55 (1H, $J_{1,2}$=5.0 Hz, H-1), 7.18–7.39 (15H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 24.3, 24.9, 25.9, 26.1 (4×q, *C*H_3), 69.0, 69.1, 71.1, 75.1 (4×t, 3×Ph*C*H_2, C-6, C-6′), 67.7, 67.9, 70.3, 70.7, 71.4, 74.1, 75.2, 81.2 (8×d, C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 96.3 (d, C-1), 100.2 (d, $J_{C\text{-}1',H\text{-}1'}$=157.8 Hz, C-1′), 108.7, 109.4 (2×s, 2× *C*$(CH_3)_2$), 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.3, 128.4 (8×d, 15×Ar*C*H), 137.8, 138.2, 137.8 (3×s, Ar*C*); *m/*z (APCI+) 715.6 (M+Na^+, 15%). (Found: C, 67.10; H, 7.35. $C_{39}H_{48}O_{11}$ requires: C, 67.61; H, 7.35%). (HRMS Calcd. For $C_{39}H_{52}NO_{11}$ (M+NH_4^+) 710.3540. Found 710.3552).

4.15. Cyclohexyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside 12d

The *manno* enol ether **3** (100 mg, 0.17 mmol) and cyclohexanol (0.1 ml, 0.85 mmol) gave the β-cyclohexyl mannoside **12d** as a colourless oil; $[\alpha]_D^{24}$−19 (*c*, 1.6 in $CHCl_3$); ν_{max} (thin film) 3470 (br, OH) cm^{-1}; δ_H (400 MHz+COSY, $CDCl_3$) 1.22–2.08 (10H, m, OCH(CH_2)$_5$), 2.56 (1H, s, O*H*), 3.48 (1H, ddd, $J_{4,5}$=9.7 Hz, $J_{5,6}$=5.6 Hz, $J_{5,6'}$=1.9 Hz, H-5), 3.63 (1H, dd, $J_{2,3}$=3.1 Hz, $J_{3,4}$=9.1 Hz, H-3), 3.74 (1H, dd, $J_{6,6'}$= 10.8 Hz, H-6), 3.78–3.82 (1H, m, OC*H*$(CH_2)_5$), 3.85 (1H, dd, H-6′), 3.90 (1H, a-t, H-4), 4.12 (1H, d, H-2), 4.13–4.98 (6H, 6×d, 3×PhCH_2), 4.61 (1H, s, H-1), 7.28–7.46 (15H, m, Ar*H*); δ_C (100.6 MHz + DEPT, $CDCl_3$) 24.0, 24.1, 25.5, 31.6, 33.4 (5×t, 5×OCH(*C*H_2)$_5$), 68.8, 74.3, 75.2, 76.6, 81.7 (5×d, C-2, C-3, C-4, C-5,OCH$(CH_2)_5$), 69.4, 71.2, 73.4, 75.1 (4×t, C-6, 3×Ph*C*H_2), 97.3 (d, $J_{C\text{-}1,H\text{-}1}$=156.6 Hz, C-1), 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4 (8×d, Ar*C*H), 137.9, 138.2, 138.3 (3×s, Ar*C*); *m/z* (APCI +ve) 555 (M+Na^+, 50%). (HRMS Calcd. For $C_{33}H_{44}NO_6$ (M+NH_4^+) 550.3169. Found 550.3160).

4.16. One-pot reactions

The following were prepared in one-pot reactions.

4.17. 3,4,6-Tri-O-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 9c

The *gluco* enol ether **4** (278 mg, 0.48 mmol), diacetone galactose (373 mg, 1.43 mmol) and 4Å molecular sieves (200 mg, powdered) were stirred in dry DCE (3 ml) at −40°C under argon. *N*-Iodosuccinimide (322 mg, 1.43 mmol) in dry DCE (1 ml) was then added. After 40 min. all the starting material had reacted, and further *N*-iodosuccinimide (215 mg, 0.95 mmol), together with 2,6-di-*tert*-butyl-4-methyl pyridine (294 mg, 1.43 mmol) were added in DCE (5 ml). The mixture was then allowed to warm to room temperature. After approximately 22 h glycosylation was complete (as monitored by TLC in hexane:ethyl acetate, 2:1). Dichloromethane (50 ml) was added, the resulting mixture filtered through Celite®, washed with 10% aqueous sodium thiosulfate (25 ml), the organic phase dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was then dissolved in methanol (5 ml), acidic ion exchange resin (200 mg) added, and the mixture stirred at room temperature overnight. Subsequent filtration and concentration in vacuo yielded a crude product which was purified by flash column chromatography (DCM:ether, 3:1) to yield the α-disaccharide **9c** (226 mg, 68%) as a colourless oil, identical to the material described previously.

4.18. 3,4,6-Tri-O-benzyl-β-D-mannopyranosyl-(1→6)-1,2,3,4-di-O-isopropylidene-D-galactopyranose 12c

The *manno* enol ether **3** (138 mg, 0.24 mmol), diacetone galactose (186 mg, 0.72 mmol) and 4Å molecular sieves (200 mg, powdered) were stirred in dry DCE (1 ml) at −40°C under argon. *N*-Iodosuccinimide (161 mg, 0.72 mmol) in dry DCE (1 ml) was then added. After 15 min. all the starting material had reacted, and further *N*-iodosuccinimide (107 mg, 0.48 mmol), together with 2,6-di-*tert*-butyl-4-methyl pyridine (147 mg, 0.72 mmol) were added in DCE (4 ml). The mixture was then allowed to warm to room temperature. After 48 h glycosylation was complete (as monitored by TLC in hexane:ethyl acetate, 2:1). Dichloromethane (50 ml) was added, the resulting mixture filtered through Celite®, washed with 10% aqueous sodium

thiosulfate (25 ml), the organic phase dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was then dissolved in methanol (5 ml), acidic ion exchange resin (200 mg) added, and the mixture stirred at room temperature overnight. Subsequent filtration and concentration in vacuo yielded a crude product which was purified by flash column chromatography (DCM:ether, 2:1) to yield the β-disaccharide **12c** (138 mg, 84%) as a colourless oil, identical to the material described previously.

4.19. Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 9a

N-Iodosuccinimide (98 mg, 0.44 mmol) was added to a stirred solution of enol ether **7** (98 mg, 0.15 mmol), powdered molecular sieves (4 Å, 100 mg) and anhydrous methanol (0.018 ml, 0.44 mmol), in anhydrous DCM (2.5 ml), at 78°C under argon. After 15 min, a solution of *N*-iodosuccinimide (64 mg, 0.28 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (88 mg, 0.43 mmol) in anhydrous DCM (1.5 ml) was added. The reaction mixture was allowed to warm to room temperature. After 18 h the reaction mixture was diluted with DCM (200 ml), filtered through Celite®, washed with aqueous sodium thiosulfate solution (10% w/v, 2×70 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was taken up in 1,4-dioxan (5 ml) and stirred with acidic ion exchange resin (Dowex® 50WX8-100, 200 mg) at room temperature. After 4 h, TLC (petrol:ethyl acetate, 2:1) showed complete conversion of starting material (R_f 0.4) to a major product (R_f 0.1). The reaction mixture was filtered, concentrated in vacuo and purified by flash column chromatography (petrol:ethyl acetate, 4:1) and recrystallised (ethanol) to give the α-methyl glycoside **9a** (34 mg, 55%) as a white crystalline solid, identical to the material described previously.

4.20. 3,4,6-Tri-O-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 9c

A solution of enol ether **7** (64 mg, 0.09 mmol) in anhydrous DCM (1 ml), was added to a stirred solution of diacetone galactose (80 mg, 0.31 mmol), *N*-iodosuccinimide (63 mg, 0.28 mmol) and powdered molecular sieves (4Å, 100 mg), in anhydrous DCM (1 ml) at −78°C under argon. After 20 min, TLC (petrol:ethyl acetate, 2:1) indicated complete conversion of starting material (R_f 0.5) to a major product (R_f 0.4). A solution of *N*-iodosuccinimide (43 mg, 0.19 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (60 mg, 0.29 mmol) in anhydrous DCM (1.5 ml) was then added, at −78°C under argon. The resulting reaction mixture was allowed to warm to room temperature. After 18 h the reaction mixture was diluted with DCM (100 ml), filtered through Celite®, washed with aqueous sodium thiosulphate solution (10% w/v, 2×50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting brown residue was taken up in methanol (5 ml) and stirred with acidified ion exchange resin (Dowex® 50WX8-100, 100 mg) at room temperature. After 4 h, TLC (petrol:ethyl acetate, 2:1) showed complete conversion of the starting material (R_f 0.8) to a major product (R_f 0.4). The reaction mixture was filtered, concentrated in vacuo and purified by flash column chromatography (petrol:ethyl acetate, 4:1) to yield the α-disaccharide **9c** (32 mg, 49%), as a colourless oil identical to the material described previously.

4.21. Cyclohexyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 9d and cyclohexyl 3,4,6-tri-O-benzyl-β-D-glucopyranoside 15[18]

A solution of enol ether **7** (191 mg, 0.28 mmol) in anhydrous 1,2-dichloroethane (1.5 ml), was added to a stirred solution of cyclohexanol (90 μl, 0.85 mmol), *N*-iodosuccinimide (192 mg, 0.85 mmol) and powdered molecular sieves (4Å, 200 mg) in anhydrous dichloroethane (2 ml) at −40°C under argon. After 30 min, TLC (DCM:ether, 20:1) indicated complete consumption of starting material (R_f 0.6). A solution of *N*-iodosuccinimide (127 mg, 0.56 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (174 mg, 0.85 mmol) in anhydrous 1,2-dichloroethane (1 ml) was added under argon, and the reaction mixture was allowed to warm to room temperature. After 18 h, TLC (DCM:ether, 20:1) indicated formation of a major product (R_f 0.2) and a minor product (R_f 0.5). The reaction mixture was diluted with DCM (150 ml), filtered through Celite®, washed with aqueous sodium thiosulfate (10% w/v, 50 ml), and aqueous hydrochloric acid (1.0 M, 50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was stirred in a mixture of trifluoroacetic acid (1 ml), distilled water (1 ml) and methanol (8 ml) at room temperature. After 1 h, TLC (DCM:ether, 20:1) showed conversion of the minor product (R_f 0.5) to a product (R_f 0.3). Ether (150 ml) was added and the mixture was washed with saturated sodium bicarbonate solution (4×150 ml). The organic phase was dried (magnesium sulfate), filtered and concentrated in vacuo. The resulting residue was purified by flash column chromatography (DCM:diethyl ether, 50:1) to give firstly the β-glucoside **15** (18 mg, 12%) as a clear oil; $[\alpha]_D^{22}=-4.4$ (*c*, 0.25 in $CHCl_3$); ν_{max} (thin film) 3584 (br, OH) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.21–1.77 and 2.00–2.02 (10H, 2×m, 10×$(CH_2)_5$), 1.93 (1H, d, $J_{2,OH}$=11.0 Hz, O*H*), 3.54–3.75 (7H, m, H2, H3, H4, H5, H6, H6′, $(CH_2)_2CHO$), 4.37 (1H, d, $J_{1,2}$=7.6 Hz, H1), 4.56, 4.85 (2H, ABq, *J*=10.7 Hz, PhCH_2), 4.57, 4.62 (2H, ABq, *J*=12.3 Hz, PhCH_2), 4.84, 4.96 (2H, ABq, *J*=11.3 Hz, PhCH_2), 7.20–7.39 (15H, m, 15×Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 24.5, 24.7, 26.0, 32.5, 34.1 (5×t, $(CH_2)_5$) 69.5, 72.7, 75.5 (3×t, C6, 3×PhCH_2), 75.2, 75.5, 78.1, 85.0 (4×d, C2, C3, C4, C5, $OCH(CH_2)_5$), 101.5 (d, C1), 124.7, 128.0, 128.1, 128.2, 128.4, 128.4, 128.6, 128.8, 128.8, 128.9, 128.9, 129.0, 129.0, 131.4 (14×d, 15×Ar*C*H), 138.5, 138.6, 139.1 (3×s, 3×Ar*C*); *m/z* (APCI$^+$) 555 ($M+Na^+$). Further elution and recrystallisation (ethanol), gave the α-glucoside **9d**, as a white crystalline solid (59 mg, 39%), identical to the material described previously.

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