Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 231–243

TETRAHEDRON:
ASYMMETRY

Peptide templated glycosylation reactions

Richard J. Tennant-Eyles,[a] Benjamin G. Davis [b] and Antony J. Fairbanks [a,*]

[a] *Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, UK*

[b] *Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham DH1 3LE, UK*

Received 28 October 1999; accepted 5 November 1999

Abstract

Glycosyl donors and acceptors may be covalently linked to aspartic acid residues via OH-6 esters. Peptide elaboration allows glycosylation reactions to be performed between donors and acceptors linked to this peptide template. These reactions display increased regio- and stereoselectivities, which are dependent on the nature of the peptide. Simple molecular modelling is used to rationalise the differing product distributions obtained by variation of the linking amino acid sequence. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The ultimate goal for chemists interested in oligosaccharide synthesis is the development of a reliable, automatable, and generally applicable solid phase process, a feat which completely revolutionalised the synthesis of oligonucleotides and oligopeptides some 30 years ago. The importance of oligosaccharides in a plethora of biological processes is now extremely well documented[1] and it is universally acknowledged that the further unravelling of the biological roles that many oligosaccharide structures play would be greatly facilitated by more efficient synthetic approaches to these materials. However, the extra complications inherent in the construction of glycosidic bonds, namely those of control of regio- and stereochemistry, have been continually hampering this development. Although regiochemical control can be achieved via selective protecting group manipulations, such sequences are often protracted and time consuming. A much more difficult task is the ability to completely control the stereochemistry of the newly created interglycosidic linkage. Despite extremely significant advances in this area, there is still no completely general method for the stereospecific formation of glycosidic linkages. Considering the vast amount of time and effort that has gone into this avenue of research,[2] perhaps a single solution to such a complex problem simply does not exist.

As a potential solution to the problem of generality we recently disclosed[3] some preliminary investigations into a new approach to the construction of glycosidic linkages. Therein, the strategy is to

* Corresponding author. E-mail: antony.fairbanks@chem.ox.ac.uk

0957-4166/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(99)00494-2

abandon the classical philosophy of the search for a 'general glycosylation reaction', and to attempt to use combinatorial techniques to search for separate synthetic solutions to the construction of each individual glycosidic bond.

The idea was inspired by the technique of molecular tethering, so elegantly developed for the synthesis of β-mannosides by Stork,[4] Hindsgaul[5] and Ogawa.[6] Subsequent to these investigations several other groups have disclosed the use of more extended tethers for the stereo- and even regioselective construction of glycosidic linkages.[7] As a solution to the problems of glycosidic bond formation an approach was envisaged which combines the use of tethering and combinatorial chemistry. In theory this will facilitate rapid searches through libraries of tethers, screening their potential to promote the formation of particular glycosidic linkages in stereo- and regioselective fashions.

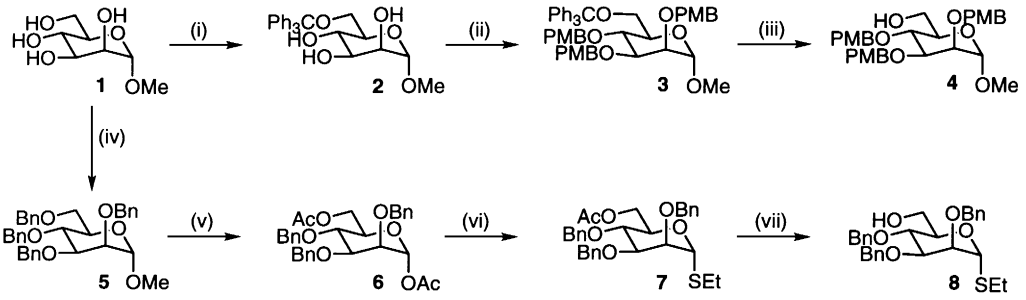
Since tethers were required in which structural diversity can be readily introduced by solid phase synthesis, initial investigations have focused on peptides. One particularly attractive feature of this approach is that it may allow the indirect use of existing automated methodology for solid phase peptide synthesis for oligosaccharide construction. However, before the development of such a technology can be contemplated, two questions must be answered. Firstly, can glycosylation reactions be performed between donors and acceptors that are linked to a peptide template? Secondly, can variation of the peptide amino acid sequence influence the stereo- and regiochemical outcome of this glycosylation reaction? Both of these two preliminary issues are addressed herein.

2. Results and discussion

2.1. Synthesis of glycosyl amino acid building blocks

For the initial studies mannose was chosen as both glycosyl donor and acceptor, since it was thought that any particular influence of the peptide template on the glycosylation reaction would be well demonstrated if large amounts of β-mannoside formation were observed. Initial investigations focused on a thioethylglycoside as the glycosyl donor, and it was decided to link both acceptor and donor to the peptide template via the OH-6 hydroxyl. Firstly, the differentially protected glycosyl acceptor **4** was synthesised in three steps from methyl mannopyranoside **1**. Tritylation of the primary hydroxyl yielded the triol **2**, which was then completely protected by treatment with excess *para*-methoxybenzyl (PMB) chloride and sodium hydride in DMF to yield **3**. Acid catalysed removal of the trityl group then yielded the glycosyl acceptor **4** in an overall yield of 41% (Scheme 1). Subsequently, the thioglycoside donor **8** was synthesised in four steps, again from methyl mannopyranoside **1** (Scheme 1). Thus, reaction of **1** with benzyl bromide and sodium hydride produced the tetrabenzyl methylpyranoside **5**. Acetolysis[8] of **5** then yielded the diacetate **6**. Reaction with ethanethiol and $BF_3 \cdot$etherate produced the thioglycoside **7**, which was simply deacetylated with sodium methoxide to yield the glycosyl donor **8** (44% yield over four steps).

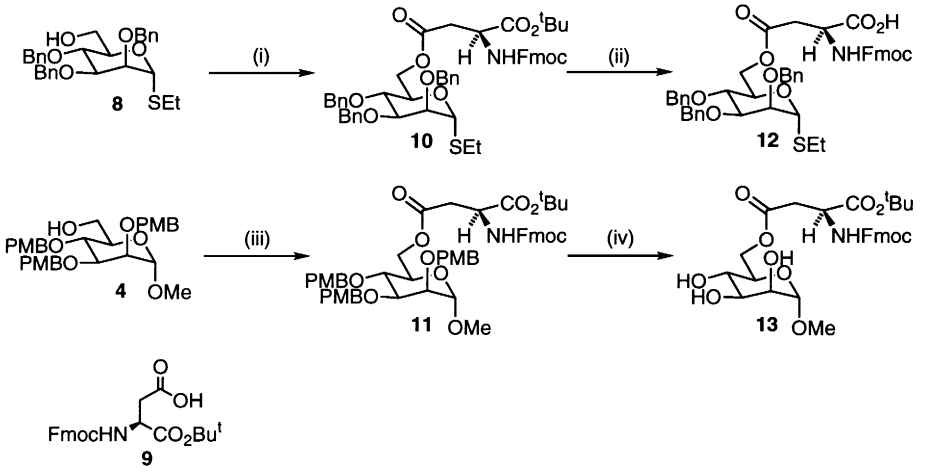
Both donor **8** and acceptor **4** were then coupled to the aspartic acid derivative **9** to yield the glycosyl amino acids **10** and **11**, in acceptable 72% and 75% yields, respectively, following existing protocol.[9] Subsequent protecting group manipulations, namely cleavage of the *tert*-butyl ester of **10** to yield the acid **12**, and removal of the PMB protecting groups from the glycosyl acceptor **12** yielding the deprotected donor **13**, were again performed as previously described[9] (Scheme 2).



Scheme 1. Reagents: (i) Ph_3CCl, DMAP, pyridine, 80°C, 75%; (ii) PMBBr, NaH, DMF, 76%; (iii) EtOH, AcOH, 80°C, 71%; (iv) BnBr, NaH, DMF, 83%; (v) Ac_2O, AcOH, H_2SO_4, 0°C, 90%; (vi) EtSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C, 65%; (vii) Na, MeOH, 0°C, 90%

2.2. Peptide elaboration

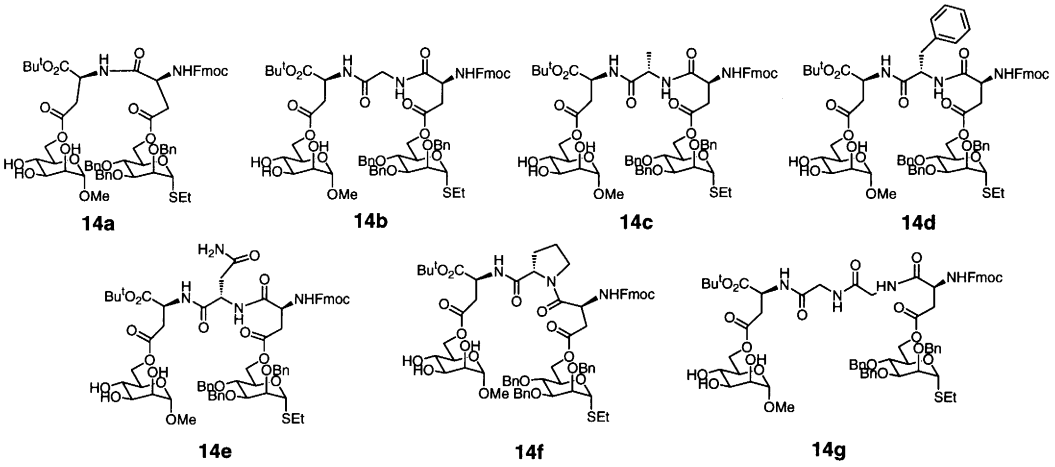
The aspartate linked glycosyl acceptor **13** was coupled to a series of amino acids. Peptide formation was achieved via a two-step coupling of **13**, involving initial piperidine-induced Fmoc removal and subsequent EEDQ mediated coupling with the required Fmoc-protected amino acid (Scheme 3). Once the desired intermediate amino acids had been added, the peptide sequence was completed by Fmoc deprotection and EEDQ mediated coupling to the aspartate-linked donor **12**. In this way the series of peptides **14a**–**g** was constructed for use in subsequent glycosylation reactions.



Scheme 2. Reagents: (i) **9**, DCC, DMAP, CH_2Cl_2, 75%; (ii) CF_3CO_2H, CH_2Cl_2, quantitative; (iii) **9**, DCC, DMAP, CH_2Cl_2, 72%; (iv) ceric ammonium nitrate, CH_3CN:H_2O, 9:1, 80%

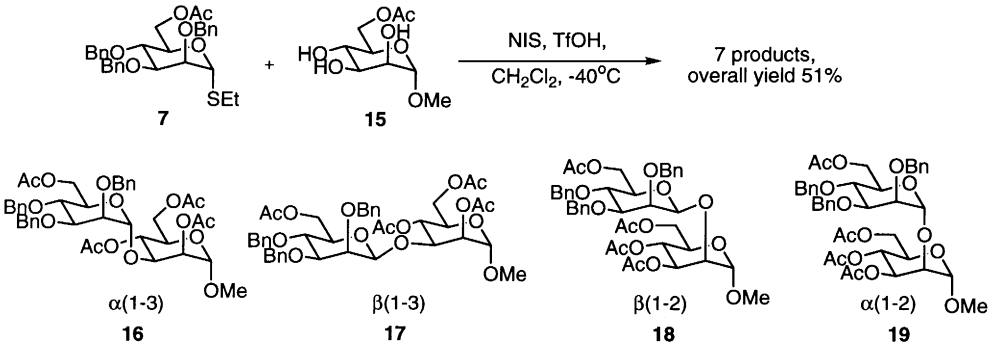
2.3. Glycosylation reactions

As a control reaction, the protected thioglycosyl donor **7** was glycosylated with the known triol **15**,[10] under standard activation conditions (*N*-iodosuccinimide and triflic acid in dichloromethane). This proceeded in moderate yield but with extremely poor selectivity (Scheme 4); of the seven products only two were found to be disaccharides, which were identified as the α(1–3)- and β(1–3)-linked materials **16** and **17**, respectively. Four of the other products were found to be undesired trisaccharides, and the final material was simply the product of hydrolysis.



Scheme 3.

Intramolecular glycosylation of the peptides **14a**–**f** was then undertaken, again mediated by *N*-iodosuccinimide and triflic acid in dichloromethane. The resulting disaccharides were separated by chromatography and cleaved from the peptide template by treatment with potassium carbonate in methanol, before complete acetylation and characterisation. Structural assignment was achieved by detailed NMR analysis.[11] Table 1 details the outcome of the glycosylation reactions of peptides **14a**–**f**.



Scheme 4.

The first positive result was that glycosylation did, indeed, occur between the templated donor and acceptor and that the template was compatible with the NIS/triflic acid activation conditions. In fact, in all cases the overall yields for these reactions were similar to that observed for the control reaction. Secondly, the absence of any trisaccharide products, in contrast to the control, was a clear indicator that glycosylation was effected intramolecularly. Thirdly, it was encouraging to find that moderate levels of regio- and stereoselectivity were achieved, and that the product distribution varied with the peptide sequence. Considering the results taken as a whole it is clear that the α(1–3) **16** and β(1–3) **17** products predominate throughout, although the relative amount of these two isomers is variable. In the case of no intermediate amino acid (AspAsp, **14a**) some of the β(1–2) product **18** (13%) was observed along with the α(1–3) (**16**, 11%) and β(1–3) (**17**, 23%) products. Insertion of an intermediate glycine (AspGlyAsp, **14b**) lead to the exclusion of the β(1–2) product **18**, and the formation of the α(1–3) (**16**, 21%) and β(1–3) (**17**, 20%) materials. Subsequent variation of the intermediate amino acid in the tripeptides from glycine to alanine (Ala) **14c**, to phenylalanine (Phe) **14d** actually influenced the outcome of the glycosylation reaction only slightly, the same α(1–3) and β(1–3) products being the major products in all cases. The

Table 1
Results of peptide templated glycosylation reactions

Peptide[a]	Total yield of Glycosylation reactions[b]	Distribution and Yields of Major Products of Glycosylation[b]	Yields of Acetylated Disaccharides[c]
Bu^{t}AspAspFmoc **14a**	59%	α (1-3) **16** 11%	α(1-3) **16** 60%
		β (1-3)**17** 23%	β (1-3) **17** 78%
		β (1-2)**18** 13%	β (1-2) **18** 54%
Bu^{t}AspGlyAspFmoc **14b**	41%	α (1-3) **16** 21%	α (1-3) **16** 58%
		β (1-3) **17** 20%	β (1-3) **17** 77%
Bu^{t}AspAlaAspFmoc **14c**	43%	α (1-3) **16** 20%	α (1-3) **16** 56%
		β (1-3) **17** 23%	β (1-3) **17** 59%
Bu^{t}AspPheAspFmoc **14d**	44%	α (1-3) **16** 13%	α (1-3) **16** 58%
		β (1-3) **17** 18%	β (1-3) **17** 71%
Bu^{t}AspAsnAspFmoc **14e**	43%	β (1-3) **17** 20%	β (1-3) **17** 63%
Bu^{t}AspProAspFmoc **14f**	49%	β (1-2) **18** 16%	β (1-2) **18** 73%
		β (1-3) **17** 19%	β (1-3) **17** 62%
		α (1-2) **19** 14%	α (1-2)**19** 79%
Bu^{t}AspGlyGlyAspFmoc **14g**	56%	α (1-3) + β (1-3)	α (1-3) **16** 30%
		16 + **17** 56%	β (1-3) **17** 42%

a) Glycosyl donor linked *via* β ester to N-terminal aspartate, glycosyl acceptor linked *via* β ester to C-terminal aspartate
b) Minor or inseparable reaction products not identified
c) Overall yield for cleavage from peptide backbone and subsequent acetylation

case of asparagine (Asn) **14e** was slightly more complicated. Here the β(1–3) product **17** was isolated in 20% yield, whilst the remaining 23% was an inseparable mixture of materials. Most notably the use of proline (Pro) as the linking residue **14f** resulted in a much higher degree of β selectivity; the β(1–2) **18**-linked disaccharide was now a major product, together with the β(1–3) **17** disaccharide, and now none of the previously predominant α(1–3)-linked product **16** was observed. Increasing the length of the peptide by the addition of another Gly residue **14g** did not greatly alter the outcome of the glycosylation reaction; again the α(1–3) **16** and β(1–3) **17** products were the sole products isolated as a mixture in a combined yield of 56%.

3. Molecular modelling

Some simple molecular modelling was undertaken to investigate the relationship between relative proportions of each disaccharide formed and the amino acid sequence of the peptide template. Potential energy minima locations for a selection of glycopeptides were probed by variation of the starting point, this being achieved by variation of the torsional angles in the linker. This process allowed a number of representative points at different relative orientations of the glycosyl acceptor ranging from the β-face to the α-face of the glycosyl donor to be probed. The glycosyl donor was itself approximated by a tetrahydropyran in which the thioethyl leaving group was replaced by a hydrogen atom. This was done in order to avoid any strong conformational influences of the anomeric leaving group and, therefore, provide a more applicable model for the glycosyl cation iself.

It was found that all of the modelled peptides AspGlyAsp **14b**, AspAlaAsp **14c** and AspPheAsp **14d** have energy minima in positions above both the α- and β-faces, i.e. there is little facial distinction, although the α-face minima are typically slightly lower in energy. For example, Fig. 1(a) shows (hydrogen atoms omitted for clarity) the AspGlyAsp peptide system **14b** in which the glycosyl acceptor occupies a minimum above the α-face of the glycosyl acceptor. In contrast, the half chair conformation of the proline residue shown in Fig. 1(b) biases the AspProAsp model towards a β-face energy minimum. This, therefore, suggests that the increased β selectivity observed for the AspProAsp peptide **14f** is a consequence of the conformation of this tether. In addition, changing identity of the intermediate amino acid from Gly to Ala or Phe changed the conformations of these minima only very slightly. This is consistent with the similar product distributions that were observed for these three peptide linkers. Finally, these simple models also provided a plausible explanation for the preponderance of (1–3)-linked disaccharide products; in all of the minimised models the 3-hydroxyl of the acceptor is readily disposed to react with the anomeric centre of the donor.

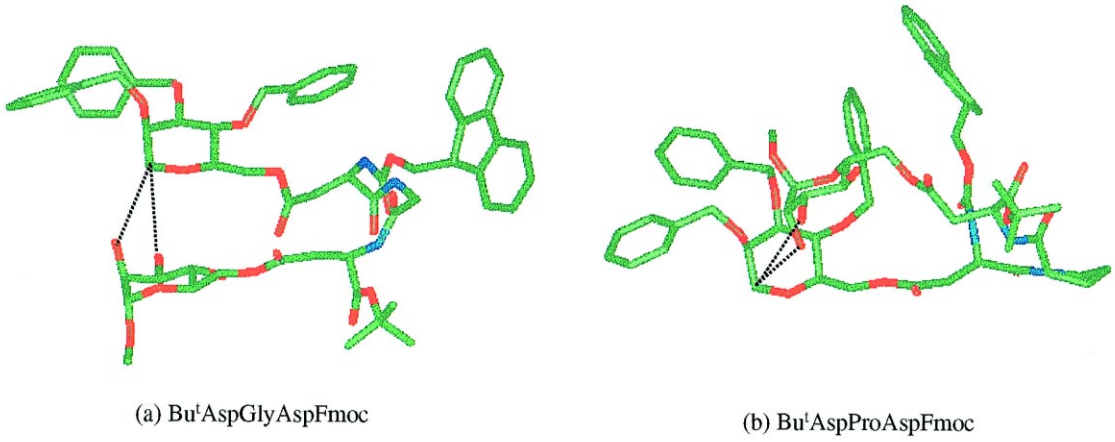


Fig. 1. Minimised structures of tripeptide-tethered systems illustrating the positions of O-2 and O-3 of the glycosyl acceptor relative to the anomeric centre of the glycosyl donor (hydrogens omitted for clarity)

4. Conclusions

In summary, we have successfully demonstrated for the first time that glycosylation reactions may be achieved between glycosyl donors and acceptors that are bound to a peptide template. In addition, these reactions show enhanced, although at present modest, regio- and stereoselectivities, the product distribution of which can be rationalised by simple molecular modelling. Since the current study has so far only examined an extremely limited number of peptide templates these moderate selectivities were not wholly unexpected. It is now necessary to screen rapidly large numbers of combinatorially assembled tethers in order to search for particular peptide sequences that promote completely regio- and stereoselective reactions, via a solid-phase approach. However, although the conformational preferences of this type of very short oligopeptide may not be great enough to effect really high levels of regio- and stereocontrol. For this reason it may well be that either peptides built from β amino acids, or other foldamers,[12] will be better choices as templates. Further investigations in these areas are currently in progress and the results will be published in due course.

5. Experimental

5.1. General experimental

Melting points were recorded on a Kofler hot block. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (200 MHz), Bruker AC 200 (200 MHz), Bruker DPX 400 (400 MHz) or Bruker AMX 500 (500 MHz) spectrometers. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50.3 MHz). Multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale. Infrared spectra were recorded on a Perkin–Elmer 150 Fourier Transform spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20-250, Micromass Platform 1 APCI, or Trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionisation (NH_3 DCI), electron impact (EI), chemical ionisation (NH_3 CI), atmospheric pressure chemical ionisation (APCI), and fast atom bombardment (FAB) techniques as stated. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Hydrogenations were run under an atmosphere of hydrogen gas maintained by an inflated balloon. 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 with $60F_{254}$ silica. Plates were developed using 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulphuric 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; methanol was distilled from magnesium methoxide, dichloromethane 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. Hexane was distilled between 40 and 60°C before use to remove involatile fractions.

5.2. Molecular modelling

Structural set up was performed with Insight II, version 95.0 (Biosym/MSI Technologies, Inc. San Diego, CA, USA). Structures were generated using the Builder module of Insight; the glycosyl cation intermediate was approximated by a tetrahydropyran in which the thioalkyl leaving group was replaced by a hydrogen atom. Initial coordinates for the minimisation were adjusted through torsional angle increments of approx. 30° to provide a representative number of differently oriented positions of donor relative to acceptor such that the pyran rings of donor and acceptor were within approx. 10 Å. Energy simulations were performed with the DISCOVER program, Version 2.9.7 on a Silicon Graphics Indigo 2 computer, using the consistent valence force field (CVFF) function. A non-bonded cut-off distance of 18 Å with a switching distance of 2 Å was employed. The non-bonded pair list was updated every 20 cycles and a dielectric constant of 1 was used in all calculations. Each stage of energy minimisation was conducted by means of the method of steepest descents without Morse or cross terms, until the derivative of energy with respect to structural perturbation was less than 1.0 kcal/Å; then the method of conjugate gradients, without Morse or cross terms until the derivative of energy with respect to structural perturbation was less than 0.1 kcal/Å; and, finally, the method of conjugate gradients, *with* Morse and cross terms until the final derivative of energy with respect to structural perturbation was less than 0.1 kcal/Å.

5.3. *Methyl 6-O-triphenylmethyl-α-D-mannopyranoside* **2**

Triphenylmethylchloride (21.56 g, 77.3 mmol) and DMAP (250 mg) were added to a stirred solution of methyl α-D-mannopyranoside **1** (10 g, 51.5 mmol) in pyridine (150 ml) and the reaction mixture heated to 80°C. After 2.5 h, t.l.c. (ethyl acetate:methanol, 9:1) indicated complete conversion of the starting material (R_f 0.1) to a single product (R_f 0.6). The reaction mixture was diluted with distilled water (1 ml) and concentrated in vacuo. The resulting syrup was dissolved in DCM (500 ml) and washed with a saturated ammonium chloride solution (2×200 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:ethyl acetate, 1:1) to give the trityl ether **2** (16.89 g, 75%) as a white foam; $[\alpha]_D^{22}$ +20.8 (*c* 0.91 in $CHCl_3$) [lit.[13] $[\alpha]_D^{20}$ +24 (*c*, 1.1 in $CHCl_3$)]; δ_H (200 MHz, $CDCl_3$): 3.39 (3H, s, MeO), 3.44 (2H, m), 3.69–3.79 (3H, m), 3.91 (1H, s), 4.73 (1H, d, $J_{1,2}$=1.5 Hz, H-1), 7.21–7.49 (15H, m, Ph_3C).

5.4. *Methyl 2,3,4-tri-O-(4-methoxybenzyl)-6-O-triphenylmethyl-α-D-mannopyranoside* **3**

4-Methoxybenzyl chloride (3.74 ml, 27.5 mmol) was added to a stirred solution of the triol **2** (3.0 g, 6.8 mmol) in DMF (15 ml). The reaction mixture was cooled to 0°C and sodium hydride (826 mg, 34.4 mmol) added portionwise. The mixture was allowed to warm to room temperature. After 16 h, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete conversion of starting material (R_f 0.1) to a single product (R_f 0.3). The reaction mixture was quenched with methanol, diluted with DCM (200 ml) and washed with distilled water (3×100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:ethyl acetate, 3:1) to give **3** (4.136 g, 76%) as a white foam; (found: C, 75.24; H, 6.64. $C_{50}H_{52}O_9$ requires: C, 75.40; H, 6.58%); $[\alpha]_D^{26}$ +15.2 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr disk): no significant peaks; δ_H (400 MHz, $CDCl_3$): 3.23 (1H, dd, $J_{3,2}$=5.5 Hz, $J_{3,4}$=9.8 Hz, H-3), 3.38 (3H, s, MeO), 3.47 (1H, dd, $J_{4,5}$=1.5 Hz, H-4), 3.74–3.77 (2H, m, H-2, 1H), 3.78, 3.79, 3.81 (9H, 3×s, 3×*Me*OBn), 3.83 (1H, m), 3.91 (1H, a-t, *J*=9.5 Hz), 4.19 (1H, d, *J*=12.1 Hz, Ph*CH*$_2$), 4.56 (2H, s, Ph*CH*$_2$), 4.63, 4.66 (2H, 2×s, Ph*CH*$_2$), 4.76 (2H, m, H-1, Ph*CH*$_2$), 6.69–6.71, 6.78–6.87, 7.21–7.36, 7.49–7.52 (27H, 4×m, Ar); δ_C (50.3 MHz, $CDCl_3$): 54.5 (q, MeO), 55.3 (q, 3×*Me*OBn), 63.5, 71.9, 72.0, 74.7 (4×t, C-6, 3×*C*H_2Ph), 71.9, 74.7, 74.8, 80.1 (4×d, C-2, C-3, C-4, C-5), 86.6 (s, *C*Ph_3), 98.9 (d, C-1), 119.7, 119.9, 127.1, 127.5, 128.0, 128.2, 128.5, 128.5, 129.9, 129.2, 129.5, 130.1 (12×d, Ar), 144.5, 144.8 (2×s, Ar); *m/z* (electrospray): 814 ($M+NH_4^+$, 100%).

5.5. *Methyl 2,3,4-tri-O-(4-methoxybenzyl)-α-D-mannopyranoside* **4**

A solution of the trityl ether **3** (17.87 g, 22.4 mmol) was stirred in ethanol:acetic acid (1:1, 100 ml) at 80°C. After 4 h, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete conversion of the starting material (R_f 0.7) to a single product (R_f 0.3). The reaction mixture was concentrated in vacuo (co-evaporation with toluene) and the resulting residue purified by flash column chromatography (hexane:ethyl acetate, 1:1) to give the alcohol **4** (8.804 g, 71%) as a white foam; (found: C, 67.30; H, 6.96. $C_{31}H_{38}O_9$ requires: C, 67.14; H, 6.91%); $[\alpha]_D^{26}$ +30.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr disk): 3480 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.08 (1H, s, OH), 3.29 (3H, s, MeO), 3.59 (1H, m, H-5), 3.75 (2H, m), 3.80, 3.81, 3.82 (9H, 3×s, 3×*Me*OBn), 3.84 (1H, m), 3.87 (2H, m), 4.56 (2H, s, Ph*CH*$_2$), 4.60 (1H, d, *J*=11.1 Hz, Ph*CH*$_2$), 4.65 (2H, m, H-1, Ph*CH*$_2$), 4.71 (1H, d, *J*=11.9 Hz, Ph*CH*$_2$), 4.86 (1H, d, *J*=10.6 Hz, Ph*CH*$_2$), 6.85–6.89, 7.23–7.29 (12H, 2×m, Ar); δ_C (50.3 MHz, $CDCl_3$): 54.7 (q, MeO), 55.3 (q, 3×*Me*OBn), 62.4, 71.9, 72.6, 74.9 (4×t, C-6, 3×*CH*$_2$Ph), 72.1, 74.3, 74.7, 79.9 (4×d, C-2, C-3, C-4, C-5), 99.5 (d, C-1), 113.8, 129.4,

129.8, 129.9 (4×d, Ar), 130.5, 130.8 (2×s, Ar); *m/z* (electrospray): 577 ($M+Na^+$, 100), 593 ($M+K^+$, 11%).

5.6. *Methyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside* **5**

Benzyl bromide (9.19 ml, 77 mmol) was added to a stirred solution of methyl α-D-mannopyranoside **1** (3.0 g, 15 mmol) in DMF (15 ml). The reaction mixture was cooled to 0°C and sodium hydride (2.23 g, 93 mmol) was then added portionwise. The mixture was then allowed to warm to room temperature. After 17 h, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete conversion of starting material (R_f 0.1) to a major product (R_f 0.6). The reaction mixture was quenched with methanol, diluted with diethyl ether (200 ml) and washed with distilled water (150 ml). The aqueous phase was extracted with diethyl ether (200 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:ethyl acetate, 4:1) to give **5** (7.138 g, 83%) as a pale yellow oil; $[\alpha]_D^{22}$ +29.2 (*c* 1.59 in $CHCl_3$) [lit.[14] $[\alpha]_D$ +28.0 (*c* 1.0 in $CHCl_3$)]; δ_H (500 MHz, $CDCl_3$): 3.34 (3H, s, MeO), 3.75–3.81 (4H, m), 3.89 (1H, dd, *J*=3.1, 9.6 Hz), 3.99 (1H, a-t, *J*=9.0 Hz), 4.79 (1H, d, $J_{1,2}$=1.6 Hz, H-1), 4.52 (1H, d, *J*=10.8 Hz, *CH*$_2$Ph), 4.57 (1H, d, *J*=12.1 Hz, *CH*$_2$Ph), 4.62 (2H, s, *CH*$_2$Ph), 4.68 (1H, d, *J*=12.1 Hz, *CH*$_2$Ph), 4.75 (2H, d, 3.8 Hz, *CH*$_2$Ph), 4.89 (1H, d, *J*=10.8 Hz, C*H*$_2$Ph), 7.17–7.40 (20H, m, Ar).

5.7. *1,6-Di-O-acetyl-2,3,4-tri-O-benzyl-α-D-mannopyranoside* **6**

Concentrated sulphuric acid (2 ml) was added dropwise to a stirred solution of **5** (10.78 g, 19.5 mmol) in acetic acid:acetic anhydride (1:1, 100 ml) at 0°C. After 30 min, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete conversion of the starting material (R_f 0.5) to a major product (R_f 0.3). The reaction mixture was washed with saturated sodium bicarbonate solution (100 ml) and ice cold distilled water (50 ml). The aqueous phase was extracted with DCM (2×150 ml) and the combined organics dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:ethyl acetate, 2:1) to give the diacetate **6** (9.361 g, 90%) as a white solid; m.p. 92–96°C (hexane/ethyl acetate); (found: C, 69.53; H, 6.41. $C_{31}H_{34}O_8$ requires: C, 69.65; H, 6.41%); $[\alpha]_D^{22}$ +31.3 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$, thin-film): 1740 (2×C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 2.04, 2.07 (6H, 2×s, 2×MeCO), 3.75 (1H, dd, $J_{2,3}$=2.9 Hz, H-2), 3.88 (2H, m, H-3, H-5), 3.99 (1H, a-t, $J_{4,5}$=$J_{4,3}$=9.5 Hz, H-4), 4.33 (2H, m, H-6, H-6′), 4.60 (3H, m, C*H*$_2$Ph), 4.73 (1H, d, *J*=12.1 Hz, C*H*$_2$Ph), 4.78 (1H, d, *J*=12.1 Hz, C*H*$_2$Ph), 4.96 (1H, d, *J*=10.6 Hz, C*H*$_2$Ph), 6.19 (1H, d, $J_{1,2}$=2.0 Hz, H-1), 7.29–7.42 (15H, m, Ar); δ_C (50.3 MHz, $CDCl_3$): 20.9, 21.0 (2×q, 2×*Me*CO), 63.2, 72.0, 72.6, 75.4 (4×t, 3×*C*H_2Ph, C-6), 72.4, 73.2, 73.8, 79.1, 91.6 (5×d, C-1, C-2, C-3, C-4, C-5), 127.7–128.5 (15×d, Ar), 137.7, 137.9 (3×s, Ar), 168.9, 170.9 (2×s, 2×C=O); *m/z* (Cl, NH_3): 552 ($M+NH_4^+$, 35%).

5.8. *Ethyl 6-O-acetyl-2,3,4-tri-O-benzyl-1-thio-α-D-mannopyranoside* **7**

Ethanethiol (5.38 ml, 48.4 mmol) was added to a stirred solution of diacetate **6** (8.614 g, 16.1 mmol) in DCM (80 ml). The reaction mixture was cooled to 0°C and boron trifluoride etherate (3.07 ml, 24.2 mmol) added dropwise. After 3 h at 0°C, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete conversion of starting material (R_f 0.4) to a major product (R_f 0.6). The reaction mixture was diluted with DCM (100 ml) and washed with saturated sodium bicarbonate solution (200 ml) and brine (200 ml). The aqueous phase was extracted with DCM (2×200 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:ethyl

acetate, 5:1) to give the thioglycoside **7** (5.579 g, 65%) as a clear oil; (found: C, 69.51; H, 6.66. $C_{31}H_{36}O_6S$ requires C, 69.38; H, 6.76%); $[\alpha]_D^{22}$ +73.8 (*c* 0.91 in $CHCl_3$); ν_{max} ($CHCl_3$, thin-film): 1740 (C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.26 (3H, t, *Me*CH_2S), 2.06 (3H, s, MeCO), 2.59 (2H, m, Me*CH*$_2$S), 3.85 (2H, m, H-2, H-3), 3.95 (1H, dd, $J_{4,3}$=9.2 Hz, $J_{4,5}$=9.6 Hz, H-4), 4.18 (1H, ddd, $J_{5,6}$=2.2 Hz, $J_{5,6'}$=5.0 Hz, H-5), 4.31 (1H, dd, $J_{6,6'}$=11.8 Hz, H-6), 4.36 (1H, dd, H-6′), 4.58 (3H, m, *CH*$_2$Ph), 4.68 (2H, m, *CH*$_2$Ph), 4.94 (1H, d, *J*=10.8 Hz, *CH*$_2$Ph), 5.37 (1H, d, $J_{1,2}$=1.0 Hz, H-1), 7.27–7.41 (15H, m, Ar); δ_C (50.3 MHz, $CDCl_3$): 15.1, 21.7 (2×q, SCH_2*Me*, *Me*CO), 25.5 (t, S*C*H_2Me), 63.7, 72.0, 75.4 (3×t, 3×*C*H_2Ph, C-6), 70.3, 74.8, 76.3, 80.6, 82.2 (5×d, C-1, C-2, C-3, C-4, C-5), 128.0–129.1 (15×d, Ar); *m/z* ($APCI^+$): 558.9 ($M+H^+$, 100%).

5.9. *Ethyl 2,3,4-tri*-O-*benzyl-1-thio*-α-D-*mannopyranoside* ***8***

A solution of sodium (115 mg) in methanol (25 ml) was added to a stirred solution of the acetate **7** (4.218 g) in methanol (25 ml) at 0°C, under argon. After 10 min, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete conversion of the starting material (R_f 0.4) to a single product (R_f 0.2). 1 M HCl (5 ml) and brine (100 ml) were then added. The aqueous phase was extracted with DCM (2×150 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane:ethyl acetate, 2:1) to give the alcohol **8** (3.504 g, 90%) as a clear oil; $[\alpha]_D^{22}$ +88.4 (*c* 1.15 in $CHCl_3$) [lit.[15] $[\alpha]_D^{22}$ +88.0 (*c* 1.0 in $CHCl_3$)]; δ_H (500 MHz, $CDCl_3$): 1.29, (3H, t, SCH_2*Me*), 1.99 (1H, s, OH), 2.61 (2H, m, S*C*H_2Me), 3.87 (2H, m, H-4, H-6), 3.89 (2H, m, H-2, H-6′), 4.05, (2H, m, H-3, H-5), 4.66, 4.76 (4H, 2×m, 2×C*H*$_2$Ph), 4.71, (1H, d, *J*=10.9 Hz, C*H*$_2$Ph), 4.99 (1H, d, *J*=10.9 Hz, C*H*$_2$Ph), 5.36 (1H, s, H-1), 7.31–7.44 (15H, m, Ar).

5.10. *General procedure for peptide couplings*

Piperidine (0.5 ml) was added dropwise to a stirred solution of the Fmoc protected amino acid (0.1 mmol) in DMF (2.5 ml). After 30 min, t.l.c. (hexane:ethyl acetate, 1:9) typically indicated complete conversion of starting material (R_f 0.3) to a single product (R_f 0.1). The solvents were removed in vacuo (co-evaporation with toluene) and the residue dissolved in benzene:ethanol (1:1, 2 ml). EEDQ (31 mg, 0.13 mmol) and the other amino acid (free carboxylic acid) (0.15 mmol, 1.5 equiv.) were added and the solution stirred under argon. After 15 h, t.l.c. (hexane:ethyl acetate, 1:9) typically indicated conversion of starting material (R_f 0.1) to a major product (R_f 0.2). The solvents were removed in vacuo and the residue was purified by flash column chromatography (hexane:ethyl acetate, 1:9) to give the Fmoc protected oligopeptide, typically as a white foam (yields ~80%). Simple iteration of this sequence allowed construction of all glycopeptides **14a**–**f**.

5.11. *General procedure for glycosylation reactions*

The peptide (**14a**–**f**, 0.44 mmol) was stirred with molecular sieves in DCM (5 ml) for 1 h at room temperature. The reaction mixture was then cooled to –40°C and NIS (94 mg, 0.42 mmol) and triflic acid (2.4×10^{-3} ml, 0.03 mmol) were added. After 5 min, t.l.c. (hexane:ethyl acetate, 1:5) typically indicated conversion of starting material (R_f 0.1) to two or three major products (R_f 0.6, 0.8 and 0.9). A single drop of collidine was added and the mixture was filtered through Celite®, diluted with DCM (200 ml) and washed with 10% aqueous sodium thiosulphate solution (100 ml). The aqueous phase was extracted with DCM (200 ml) and the combined organic phases dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (DCM:diethyl ether, 4:1 to 2:1) to typically

give two or three products as clear oils which were used without characterisation. Each of the separated products were individually stirred in methanol (3 ml) in the presence of K_2CO_3 (5 mg) for 30 min. They were then concentrated in vacuo and dissolved in a mixture of pyridine:acetic anhydride (1:1, 2 ml). After 4 h, t.l.c. (hexane:ethyl acetate, 2:1) indicated the formation of a single product in each case. The solvents were removed in vacuo and the individual disaccharides purified by flash chromatography.

*5.12. Methyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-*D*-mannopyranoside* ***16***

A clear oil; $[\alpha]_D^{22}$ +35.5 (*c* 0.61 in $CHCl_3$); ν_{max} ($CHCl_3$, thin-film): 1745 (s, 4×C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.86, 2.06, 2.09, 2.11 (12H, 4×s, 4×MeCO), 3.38 (3H, s, MeO), 3.67 (1H, a-t, $J_{2b,3b}=J_{2b,1b}$=2.3 Hz, H-2b), 3.76–3.87 (4H, m, H-3b, H-4b, H-5b, H-5a), 4.08 (1H, dd, $J_{6a,6a'}$=12.2 Hz, $J_{6a,5a}$=2.4 Hz, H-6a), 4.13 (1H, dd, $J_{3a,2a}$=3.4 Hz, $J_{3a,4a}$=9.8 Hz, H-3a), 4.20–4.30 (3H, m, H-6a′, H-6b, H-6b′), 4.55 (1H, d, *J*=11.1 Hz, *CH*$_2$Ph), 4.61 (2H, m, *CH*$_2$Ph), 4.67 (2H, ABq, *J*=12.0 Hz, *CH*$_2$Ph), 4.74 (1H, d, $J_{1a,2a}$=1.5 Hz, H-1a), 4.84 (1H, d, *J*=11.1 Hz, *CH*$_2$Ph), 4.95 (1H, d, H-1b), 5.15 (1H, dd, H-2a), 5.21 (1H, dd, $J_{4a,5a}$=10.0 Hz, H-4a), 7.28–7.35 (15H, m, Ar); δ_C (50.3 MHz, $CDCl_3$): 20.6, 20.7, 20.7, 20.9 (4×q, *Me*CO), 55.2 (q, MeO), 62.1 (t, C-6a), 63.5 (t, C-6b), 67.9 (d, C-4a), 68.4 (d, C-5a), 70.9 (d, C-5b), 71.5 (d, C-2a), 72.3 (t, *C*H$_2$Ph), 72.7 (t, *C*H$_2$Ph), 74.2 (d, C-3a), 74.4 (d, C-4b), 74.6 (t, *C*H$_2$Ph), 74.8 (d, C-2b), 79.7 (d, C-3b), 98.3 (d, C-1a), 100.5 (d, C-1b), 127.6, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4 (7×d, Ar), 138.0 (s, Ar), 169.5, 170.1, 170.7, 170.9 (4×s, 4×Me*C*O); *m/z* (electrospray): 812.48 ($M+NH_4^+$, 100%). HRMS (electrospray) calcd. for $C_{42}H_{50}O_{15}Na$ ($M+Na^+$): 817.3047. Found: 817.3047.

*5.13. Methyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-*D*-mannopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-*D*-mannopyranoside* ***17***

A clear oil; $[\alpha]_D^{22}$ –20.7 (*c* 1.23 in $CHCl_3$); ν_{max} ($CHCl_3$, thin-film): 1744 (s, 4×C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.99, 2.02, 2.11, 2.12 (12H, 4×s, 4×MeCO), 3.41 (3H, s, MeO), 3.44 (1H, ddd, $J_{5b,4b}$=9.6 Hz, $J_{5b,6b}$=4.4 Hz, $J_{5b,6b'}$=2.8 Hz, H-5b), 3.52 (1H, dd, $J_{3b,4b}$=9.5 Hz, $J_{3b,2b}$=2.9 Hz, H-3b), 3.75 (1H, d, H-2b), 3.86 (1H, dd, H-4b), 3.94 (1H, ddd, $J_{5a,4a}$=10.0 Hz, $J_{5a,6a}$=2.4 Hz, $J_{5a,6a'}$=5.6 Hz, H-5a), 4.16–4.19 (2H, m, H-3a, H-6a), 4.28 (1H, dd, $J_{6a',6a}$=12.2 Hz, H-6a′), 4.34 (2H, m, H-6b, H-6b′), 4.46 (1H, s, H-1b), 4.53–4.62 (4H, m, *CH*$_2$Ph), 4.74 (1H, d, $J_{1a,2a}$=1.5 Hz, H-1a), 4.82 (1H, d, *J*=12.2 Hz, *CH*$_2$Ph), 4.93 (1H, d, *J*=10.9 Hz, *CH*$_2$Ph), 5.22–5.29 (2H, m, H-2a, H-4a), 7.25–7.43 (15H, m, Ar); δ_C (50.3 MHz, $CDCl_3$): 20.6, 20.7, 20.7, 20.9 (4×q, 4×*Me*CO), 55.1 (q, MeO), 62.8 (t, C-6a), 63.1 (t, C-6b), 66.2 (d, C-4a), 68.0 (d, C-2a), 68.5 (d, C-5a), 71.3 (t, *C*H$_2$Ph), 72.9 (d, C-3a), 73.6 (d, t, C-5b, *C*H$_2$Ph), 73.9 (d, C-2b), 74.1 (d, C-4b), 75.1 (t, *C*H$_2$Ph), 82.2 (d, C-3b), 98.5 (d, C-1b), 98.9 (d, C-1a), 127.3, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4 (8×d, Ar), 138.0, 138.1, 148.9 (3×s, Ar), 170.1, 170.3, 170.6, 170.7 (4×s, 4×Me*C*O); *m/z* (electrospray): 812.84 ($M+NH_4^+$, 100%). HRMS (electrospray) calcd for $C_{42}H_{50}O_{15}Na$ ($M+Na^+$): 817.3047. Found: 817.3044.

*5.14. Methyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-*D*-mannopyranosyl)-(1→2)-3,4,6-tri-*O*-acetyl-α-*D*-mannopyranoside* ***18***

A clear oil; $[\alpha]_D^{22}$ –30.1 (*c* 0.58 in $CHCl_3$); ν_{max} ($CHCl_3$, thin-film): 1744 (s, 4×C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.97, 1.99, 2.06, 2.07 (12H, 4×s, 4×MeCO), 3.43 (3H, s, MeO), 3.40–3.45 (1H, m, H-5b), 3.50 (1H, dd, $J_{3b,2b}$=3.0 Hz, $J_{3b,4b}$=9.2 Hz, H-3b), 3.81 (1H, dd, $J_{4b,5b}$=9.7 Hz, H-4b), 3.94 (1H,

ddd, $J_{5a,4a}$=10.1 Hz, $J_{5a,6a}$=2.1 Hz, $J_{5a,\ 6a'}$=4.3 Hz, H-5a), 3.99 (1H, d, H-2b), 4.10 (1H, dd, $J_{6a,6a'}$=12.2 Hz, H-6a), 4.26–4.34 (2H, m, H-6b, H-6b′), 4.40–4.43 (2H, m, H-2a, H-6a′), 4.44 (2H, s, H-1b, *CH*$_2$Ph), 4.54 (2H, m, *CH*$_2$Ph), 4.75 (1H, d, $J_{1a,2a}$=1.3 Hz, H-1a), 4.92 (2H, m, *CH*$_2$Ph), 5.09–5.14 (2H, m, H-3a, *CH*$_2$Ph), 5.48 (1H, dd, $J_{4a,3a}$=10.2 Hz, H-4a), 7.26–7.58 (15H, m, Ar); δ_C (50.3 MHz, $CDCl_3$): 20.7, 20.8, 20.8 (3×q, 4×*Me*CO), 55.2 (q, MeO), 62.4 (t, C-6a), 63.7 (t, C-6b), 65.5 (d, C-4a), 68.5 (d, C-5a), 70.0 (d, C-3a), 70.9 (t, *C*H$_2$Ph), 72.7 (d, C-2a), 73.2 (d, C-2b), 73.7 (d, t, C-5b, *C*H$_2$Ph), 74.5 (d, C-4b), 75.2 (t, *C*H$_2$Ph), 81.6 (d, C-3b), 98.6 (d, C-1a), 99.9 (d, C-1b), 127.5, 127.6, 127.7, 127.8, 127.8, 128.1, 128.2, 128.4, 128.4 (9×d, Ar), 137.8, 137.9, 138.7 (3×s, Ar), 169.4, 170.1, 170.2, 170.3 (4×s, 4×Me*C*O); *m/z* (electrospray): 812.42 (M+NH_4^+, 100%). HRMS (electrospray) calcd for $C_{42}H_{50}O_{15}Na$ (M+Na^+): 817.3047. Found: 817.3046.

*5.15. Methyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-mannopyranosyl)-(1→2)-3,4,6-tri-*O*-acetyl-α-*D*-mannopyranoside **19***

A clear oil; $[\alpha]_D^{24}$ +22.6 (*c* 0.24 in $CHCl_3$); ν_{max} (KBr disk): 1747 (s, 4×C=O) cm^{-1}; δ_H (400 MHz, C_6D_6): 1.63, 1.66, 1.68, 1.75 (12H, 4×s, 4×MeCO), 3.78 (1H, ddd, $J_{5a,4a}$=9.9 Hz, $J_{5a,6a}$=2.5 Hz, $J_{5a,6a'}$=4.4 Hz, H-5a), 3.93 (1H, a-t, $J_{2b,3b}$=$J_{2b,1b}$=2.5 Hz, H-2b), 4.03 (1H, a-t, $J_{4b,3b}$=$J_{4b,5b}$=9.2 Hz, H-4b), 4.08 (1H, a-t, $J_{2a,1a}$=$J_{2a,3a}$=2.4 Hz, H-2a), 4.11 (1H, dd, H-3b), 4.14 (1H, dd, $J_{6a,6a'}$=12.2 Hz, H-6a), 4.21 (1H, ddd, $J_{5b,6b}$=6.2 Hz, $J_{5b,6b'}$=1.8 Hz, H-5b), 4.26 (1H, dd, H-6a′), 4.31 (1H, dd, $J_{6b,6b'}$=11.8 Hz, H-6b), 4.40–4.47 (3H, m, *CH*$_2$Ph), 4.56 (2H, m, H-6b′, *CH*$_2$Ph), 4.67 (1H, d, *J*=12.2 Hz, *CH*$_2$Ph), 4.85 (1H, d, *J*=11.0 Hz, *CH*$_2$Ph), 5.02 (2H, m, H-1a, H-1b), 5.61 (1H, dd, $J_{3a,4a}$=9.9 Hz, H-3a), 5.67 (1H, d, H-4a), 6.98–7.37 (15H, m, Ar); δ_C (50.3 MHz, $CDCl_3$): 20.3, 20.4, 20.4 (3×q, 4×*Me*CO), 54.9 (q, MeO), 61.6 (t, C-6a), 61.9 (d, C-3b), 63.4 (t, C-6b), 66.3 (d, C-4a), 68.8 (d, C-5a), 70.9 (d, C-3a), 71.3 (d, C-5b), 72.3, 72.9, 75.0 (3×t, 3×*C*H$_2$Ph), 75.7 (d, C-2b), 76.6 (d, C-4b), 80.2 (d, C-2a), 99.3 (d, C-1a), 100.5 (d, C-1b), 127.8, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7 (7×d, Ar), 138.8, 138.9 (2×s,Ar), 169.4, 169.9, 170.2 (3×s, 4×CO); *m/z* (FAB$^+$): 817.4 (M+Na^+, 47%). HRMS (electrospray) calcd for $C_{42}H_{50}O_{15}Na$ (M+Na^+): 817.3047. Found: 817.3048.

Acknowledgements

We gratefully acknowledge the EPSRC (Quota award to RTE) and the University of Durham for financial support. We would also like to acknowledge the use of the EPSRC's Mass Spectrometry Service at Swansea, UK, and of the EPSRC's Chemical Database Service at Daresbury.

References

1. Varki, A. *Glycobiology* **1993**, *3*, 97.
2. For some recent reviews and books, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503; Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095; *Modern Methods in Carbohydrate Synthesis*; Khan, S. H.; O'Neill, R. A., Eds.; Harwood Academic: Amsterdam, 1996; *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.
3. For a preliminary communication of some of this work, see: Tennant-Eyles, R. J.; Davis, B. G.; Fairbanks, A. J. *Chem. Commun.* **1999**, 1037.
4. Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087.
5. Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447; Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759; Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376.
6. Ito, Y.; Ohnishi, Y.; Ogawa, T.; Nakahara, Y. *Synlett* **1998**, 1102; Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680; Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765.

7. Zeigler, T.; Lemanski, G.; Rakoczy, A. *Tetrahedron Lett.* **1995**, 36, 8973; Zeigler, T.; Lau, R. *Tetrahedron Lett.* **1995**, *36*, 1417; Lau, R.; Schülle, G.; Schwaneberg, U.; Zeigler, T. *Liebigs Ann.* **1995**, 1475; Yamada, H.; Imamura, K.; Takahashi, T. *Tetrahedron Lett.* **1997**, *36*, 391; Valverde, S.; Gómez, A. M.; Hernández, A.; Herradón, B.; López, J. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2005.
8. Ponpipom, M. M. *Carohydr. Res.* **1977**, *59*, 311.
9. Tennant-Eyles, R. J.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **1999**, *10*, 391.
10. Borén, H. B.; Garegg, P. J.; Kenne, L.; Pilotti, A.; Svenson, S.; Swahn, C.-G. *Acta. Chem. Scand.* **1973**, *27*, 2740; Bianco, A.; Brufani, M.; Melchioni, C.; Romagnoli, P. *Tetrahedron Lett.* **1997**, *38*, 651.
11. HMBC experiments indicated cross coupling between C-1b/H-1b and the corresponding H-a/C-a, respectively (a/b referring to the acceptor/donor, respectively). The chemical shift of the correspondingly non-acetylated H-a position was also diagnostic (shielded by approximately 1 ppm). The stereochemistry of the newly formed anomeric linkage was also confirmed by measurement of the $J_{C\text{-}1,H\text{-}1}$ coupling constants (J_{α}=165–175 Hz, J_{β}=154–157 Hz).
12. For a manifesto, see: Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.
13. Winkler, A. D.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084.
14. Fugedi, P.; Liptak, A.; Namasi, P.; Neszmelyi, A. *Carbohydr. Res*. **1982**, *107*, C5.
15. Ottoson, H. *Carbohydr. Res*. **1990**, *197*, 101.