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Rapid assembly of oligosaccharides: 1,2-diacetal-mediated reactivity tuning in the coupling of glycosyl fluorides

Daniel K. Baeschlin, Luke G. Green, Michael G. Hahn, Berthold Hinzen, Stuart J. Ince and Steven V. Ley *

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK

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Abstract

This paper describes the application of 1,2-diacetal protecting groups to control the reactivity tuning of glycosyl fluorides in oligosaccharide coupling reactions. The synthetic potential of this new methodology is demonstrated by the 'one-pot' synthesis of a linear pentasaccharide and the efficient assembly of the core oligosaccharide of the GPI anchor of yeast (*Saccharomyces cerevisiae*).

1. Introduction

Carbohydrates play a crucial role in the mediation of many biological recognition processes.[1] Consequently considerable research has been directed towards the synthesis of highly complex oligosaccharide structures to probe the interactions of carbohydrates at their respective acceptor sites.[2] While there are many approaches that one could employ to enable oligosaccharide synthesis, the most efficient strategy is one that limits protecting group manipulations to a minimum and does not require the additional conversion of the growing oligosaccharide to one that contains an activatable leaving group. The idea that protecting groups may affect the reactivity of glycosides in coupling reactions is well established.[3–5] Fraser-Reid and co-workers extended the concept of reactivity tuning to the construction of oligosaccharides, expediting their synthesis.[6,7]

In 1992 our laboratory introduced the use of bis(dihydropyran)s to selectively protect 1,2-diequatorial diols as dispiroketals[8] and subsequently demonstrated the synthetic potential of these systems as stereoselective protecting groups,[9] desymmetrising agents[10] and chiral auxiliaries[11] for natural product synthesis. Furthermore it was shown that 1,2-diacetal groups are convenient protecting groups for sugars and that these units modulate the reactivity of glycosides through torsional deactivation in oligosaccharide coupling reactions.[12–15]

* Corresponding author. Fax: +44 1223-336442; e-mail: svl1000@cam.ac.uk

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Diacetal-mediated reactivity tuning was used in the assembly of complex oligosaccharides such as the high-mannose nonasaccharide from HIV gp120[16] and, more recently, a glycosylphosphatidylinositol (GPI) anchor of *Trypanosoma brucei*.[17] Furthermore the use of 'one-pot' procedures allows quicker entry to many of the target molecules.[16,18–24] In order to introduce even greater flexibility a new level of reactivity tuning that allowed not only the coupling of seleno- and thioglycosides but also fluoroglycosides was investigated. The concept is illustrated in Fig. 1. The difference in reactivity between level 1 and level 2 is provided by torsional deactivation due to the appended diacetal protecting group. Anomeric deactivation, such as replacing selenium with sulfur, affords level 3. A further level of reactivity tuning is gained if the acceptor is inert such as with alkylglycosides. Set 1 sugars comprise glycosyl fluorides capable of activation with the hafnocene dichloride/silver triflate (Cp_2HfCl_2/AgOTf)[25] promoter system. Set 2 sugars form an orthogonal set in that (typical) activation may be achieved with iodonium sources.[26–30]

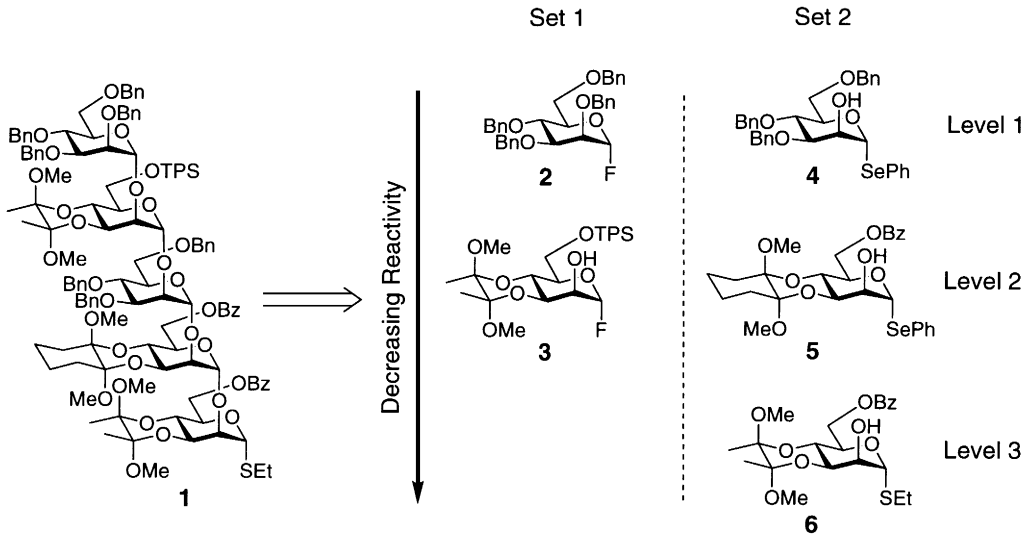


Fig. 1.

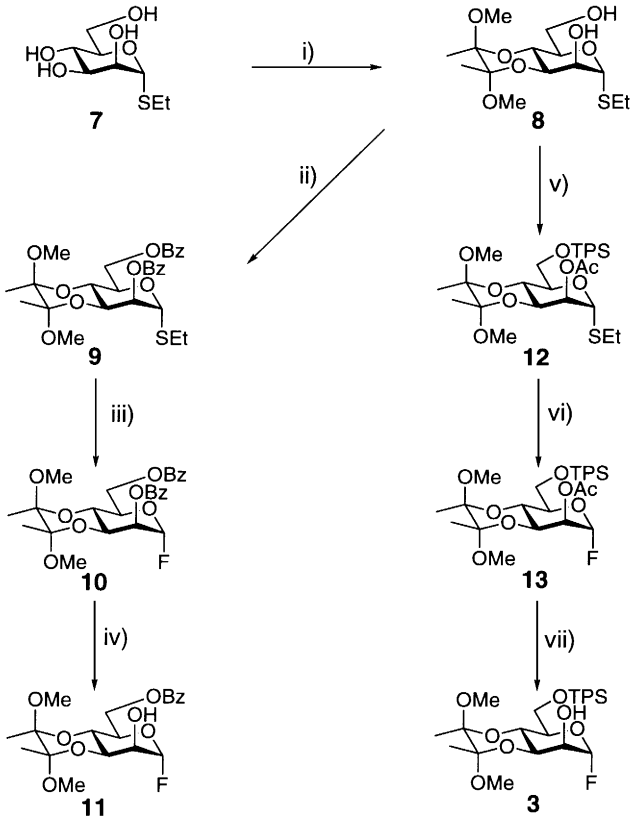
In this paper we report more details of our investigations into the reactivity tuning of glycosyl fluorides[31] and a further application of this methodology towards the synthesis of the GPI anchor of yeast (*Saccharomyces cerevisiae*).

2. Results and discussion

2.1. Reactivity tuning of glycosyl fluorides

Glycosyl fluorides have proved excellent donors in oligosaccharide synthesis[32,33] and, shortly after commencing this program, Castillon et al. communicated the first application of the reactivity tuning of glycosyl fluorides to disaccharide synthesis.[34] The first glycosyl fluoride we investigated contained a 6-*O*-benzoyl group as an additional tuning element to the BDA group, reasoning that the extra deactivation from an acyl substituent would enable a higher yielding glycosylation reaction. Preparation of the required monomer **11** was greatly simplified by the selective incorporation of the BDA motif at the 3,4-vicinal diol (Scheme 1). Conversion of the deactivated thioglycoside **9** with diethylaminosulfur trifluoride/*N*-bromosuccinimide (DAST/NBS)[35] was quantitative on a small scale but on scale-up the

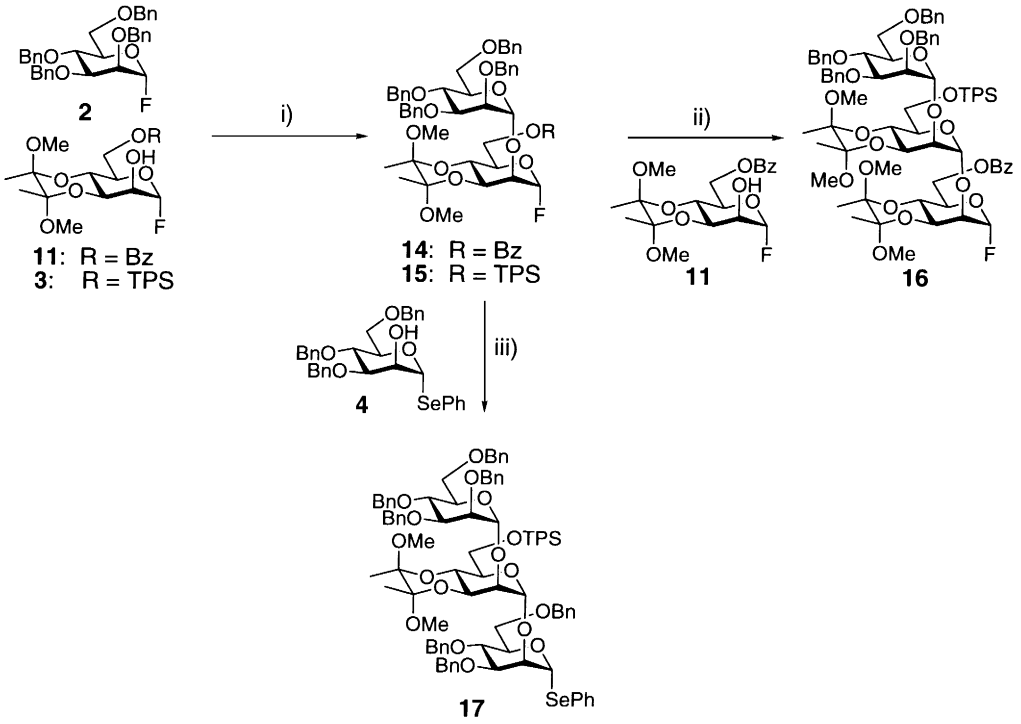
reaction times were excessive and the yield dropped noticeably. The simple modification involving replacement of NBS with *N*-iodosuccinimide (NIS) was found to improve matters satisfactorily and preparation of fluoride **10** with DAST/NIS proceeded in excellent yield. Debenzoylation of **10** gave **11** as the major product (53%); the mass balance was accounted for by the 2-*O*-benzoylated sugar (4%) and the 2,6-diol (33%).



Scheme 1. Reagents and conditions. (i) Butan-2,3-dione, $CH(OMe)_3$, CSA (cat.), MeOH, Δ, 81%; (ii) BzCl, py, 0°C–rt, 83%; (iii) DAST, NIS, CH_2Cl_2, −10°C–rt, 93%; (iv) K_2CO_3 (cat.), MeOH:CH_2Cl_2 (1:2), 53%; (v) TPS–Cl, im, THF, 0°C–rt; then Ac_2O, py, 0°C–rt, 76% over two steps; (vi) DAST, NIS, CH_2Cl_2, 0°C–rt, 88%; (vii) K_2CO_3 (cat.), MeOH, 94%

Perbenzylated fluoride **2**, first reported by Noyori,[36] was prepared in two steps from ethyl 1-thio-α-D-mannopyranoside.[37] The selective activation of fluoride **2** in the presence of acceptor **11**, using the Suzuki protocol,[25] furnished disaccharide **14** in near quantitative yield (Scheme 2). The 6-*O*-Bz group proved too deactivating, however, as attempts to activate disaccharide **14** with Cp_2HfCl_2/AgOTf were unsuccessful. To increase the reactivity, replacement of the benzoyl group with an ether protecting group was investigated. Preparation of acceptor **3**, containing a 6-*O*-*tert*-butyldiphenylsilyl (TPS) group, was rapid and high yielding (Scheme 1). It was pleasing to discover that, on cooling the reaction to −10°C, acceptor **3** proved sufficiently stable to allow selective activation of the more reactive donor **2**. In this way disaccharide **15** could be isolated in good yield (Scheme 2). If glycosylation was attempted with the analogous selenophenyl or thioethyl sugars reaction yields were poor due to homocoupling of the acceptor.[38] This result illustrates one advantage of glycosyl fluorides over the previous donors used; their lower reactivity enables greater influence of the appended protecting groups.[39]

Encouraged by this new result the applicability of donor **15** to trisaccharide synthesis was examined (Scheme 2). Activation of **15** in the presence of the known orthogonal selenosugar **4**,[40] prepared

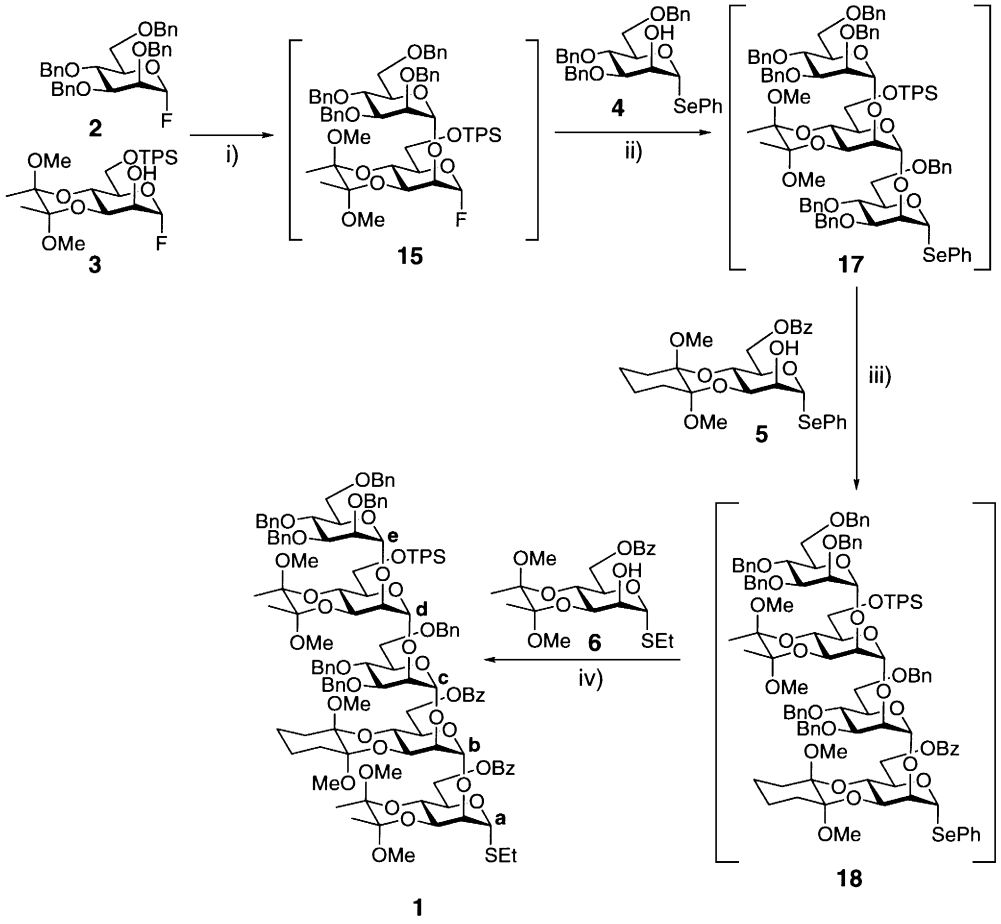


Scheme 2. Reagents and conditions. (i) R=Bz: Cp_2HfCl_2, AgOTf, 4 Å MS, CH_2Cl_2, 0°C–rt, >95%; R=TPS: Cp_2HfCl_2, AgOTf, 4 Å MS, CH_2Cl_2, –10°C, 78%; (ii) **11** then Cp_2HfCl_2, AgOTf, 4 Å MS, CH_2Cl_2, 38% (29% in one-pot from **2**); (iii) **4** then Cp_2HfCl_2, AgOTf, 4 Å MS, C_6H_5Me, 86% (65% in one-pot from **2**, using CH_2Cl_2 as solvent)

using known orthoester chemistry (vide infra),[41] was uneventful furnishing trisaccharide **17** in 86% yield. Unfortunately attempts to prepare fluorotrisaccharide **16** were low yielding. It appeared that homocoupling of **11** was occurring and in view of the deactivated nature of **11** this result was somewhat surprising. Comparable yields could be obtained for the one-pot preparation of **16** and **17**. Thus, if disaccharide **15** was not isolated but activated in situ with acceptor **11** or **4**, then trisaccharides **16** and **17** could be isolated in 29% (54% per step) and 65% (81% per step) yields, respectively. As envisaged, trisaccharide **16** was too unreactive for further elaboration. Cp_2HfCl_2/AgOTf returned only unreacted donor and treatment with $BF_3 \cdot OEt_2$, resulted in decomposition.

Trisaccharide **17** is fully armed and thus lends itself to further elaboration via reactivity tuning (Scheme 3). Intermediate trimannoside **17** was not isolated but selectively activated, with NIS/TfOH,[29] in the presence of known torsionally deactivated selenophenyl acceptor **5**,[13] to give the tetrasaccharide **18**. Activation of this intermediate, again using the NIS/TfOH conditions, effected the glycosylation of the thioglycoside **6** to afford pentasaccharide **1** in 8% yield (53% per glycosylation), which itself can potentially act as a glycosyl donor in following reactions. Further investigation identified that the final coupling proceeded in poor yield, presumably due to steric hindrance between donor **18** and acceptor **6**. Replacement of the CDA moiety with the more compact BDA group failed to alleviate the problem. It should be noted that the order of activation of the various glycosyl donors is important. Activation of fluorides followed by selenides or sulfides occurs smoothly. Conversely activation of a fluoride with Cp_2HfCl_2/AgOTf after NIS/TfOH activation of selenides or sulfides fails.[42] This may be due to decomposition of the hafnocene complex by by-products of the previous glycosylation, such as iodine. The use of alternative promoters such as methyl triflate[43] (MeOTf) remains to be investigated and it may

also be possible to sequester some of the side-products. Nevertheless, these results clearly demonstrate the applicability of the diacetal-mediated reactivity tuning of glycosyl fluorides, selenides and sulfides to one-pot oligosaccharide synthesis.



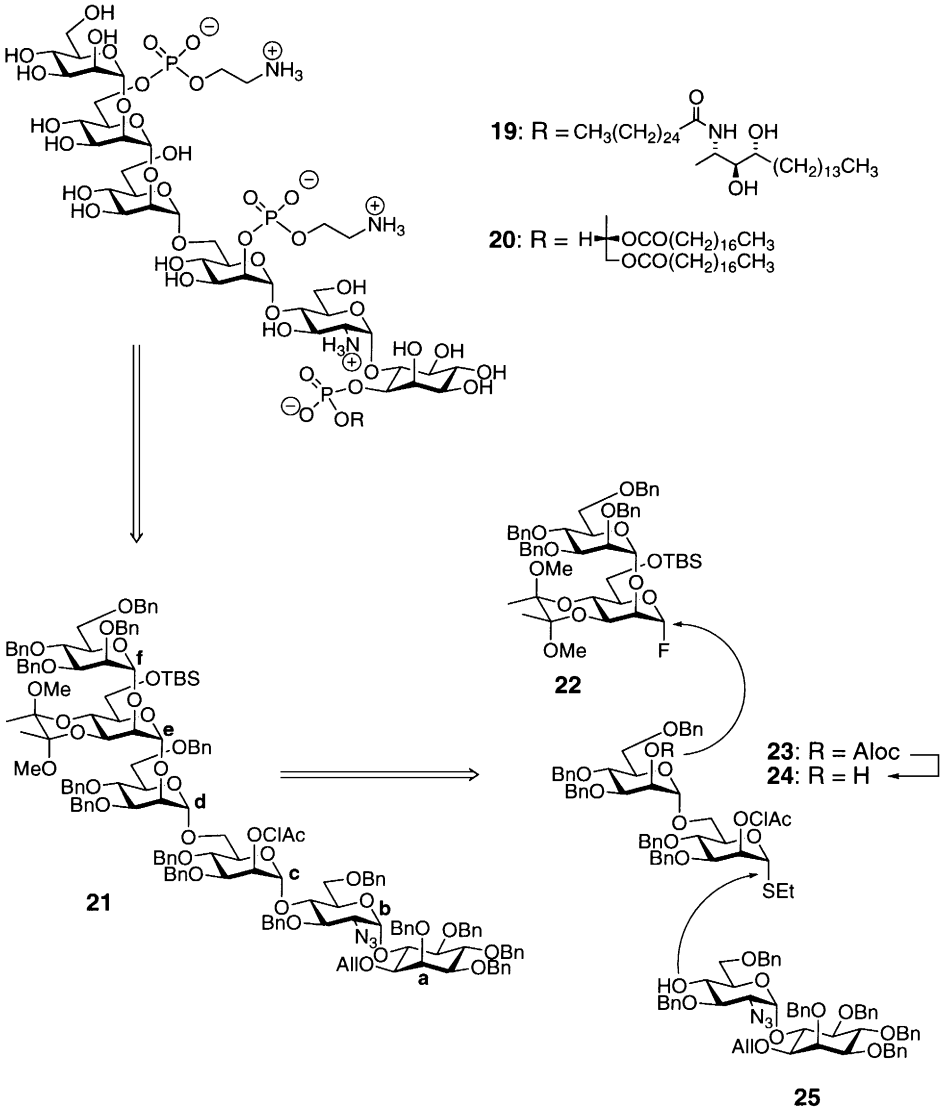
Scheme 3. Reagents and conditions. (i) Cp_2HfCl_2, AgOTf, 4 Å MS, CH_2Cl_2, −10°C; (ii) **4** then Cp_2HfCl_2, AgOTf, 4 Å MS, CH_2Cl_2, −10°C–rt; (iii) **5** then NIS, TfOH (cat.), 4 Å MS, CH_2Cl_2/Et_2O, –20°C; (iv) **6** then NIS, TfOH (cat.), 4 Å MS, CH_2Cl_2/Et_2O, −20°C–rt, 8% in one-pot from **2**

2.2. Application of diacetal-mediated fluoride tuning to GPI anchor synthesis

Parasitic protozoa and fungi often use GPI anchors as an efficient way of linking proteins to membranes.[44] There appears to be subtle species-specific differences between the biosynthesis of GPI anchors in the cells of fungi (e.g. yeast), parasitic protozoa (e.g. trypanosomes) and mammals,[45] which potentially could be exploited in the identification of drug targets against parasitic diseases. The chemical synthesis of GPI anchors and analogues is required if we are to fully understand GPI biosynthesis and research has culminated in five total syntheses[17,46–56] along with the syntheses of various part structures.[57–72] We have recently reported the total synthesis of a GPI anchor of the African parasitic protozoan *Trypanosoma brucei*.[17,48] As part of continuing investigations into the synthesis of GPIs, we have devised an efficient synthesis of a GPI anchor **20** of yeast (*Saccharomyces cerevisiae*).[73] Preparation

of the distearoylglyceride **20**, instead of the ceramide derivative **19**,[47,52] was chosen since there is interest in probing GPI biosynthesis before lipid remodelling.[74]

The recently developed methods (vide supra) suggest an efficient retrosynthetic simplification (Scheme 4). Thus, a reactivity-tuned coupling of two glycosyl fluorides yields fluorodisaccharide **22** and a further reactivity-tuned coupling of a selenoglycoside and a thioglycoside should furnish disaccharide **23**. Selective removal of the allyloxycarbonyl (Aloc) protecting group, which is hoped to play an important role in the α-selectivity via anchimeric assistance,[75] unmasks the required hydroxyl in acceptor **24**. Assembly of core **21** should be readily accomplished in two steps from the disaccharides **22**, **24** and **25**. Previous GPI total syntheses[17,48,49] have shown that elaboration of core **21** to an array of yeast GPI anchor analogues should be possible by the application of known phosphoramidite methodology.[76] Furthermore, global deprotection should furnish the GPI anchors in high yield.

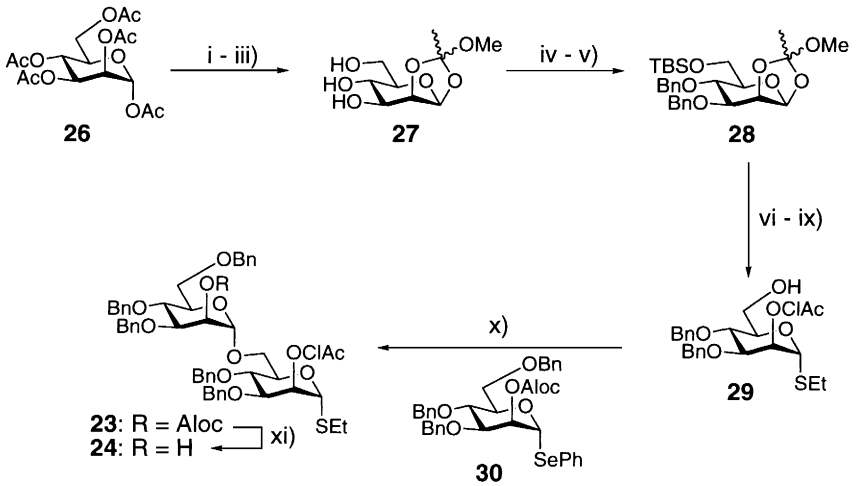


Scheme 4.

2.3. Synthesis of disaccharides **22** and **24**

The required disaccharide donor **22** was prepared in analogous fashion to **15** (Schemes 1 and 2). Replacement of the TPS group with TBS was necessary to avoid the requirement of a 'basic' fluoride deprotection step in the presence of labile phosphodiesters.[17]

Acceptor **24** was synthesised from penta-*O*-acetyl-α-D-mannopyranose **26**[77] via known orthoester **27**[41] (Scheme 5). Known selenide **30**[78] was also synthesised via orthoester **27**. The reactivity-tuned coupling of **29** and donor **30**, mediated by NIS/TMSOTf, proceeded smoothly to give the disaccharide **23** as a single anomer in 77% yield. Selective removal of the Aloc protecting group in **23** was accomplished with $Pd(PPh_3)_4$ and dimedone[79] to furnish alcohol **24** in good yield (75%).

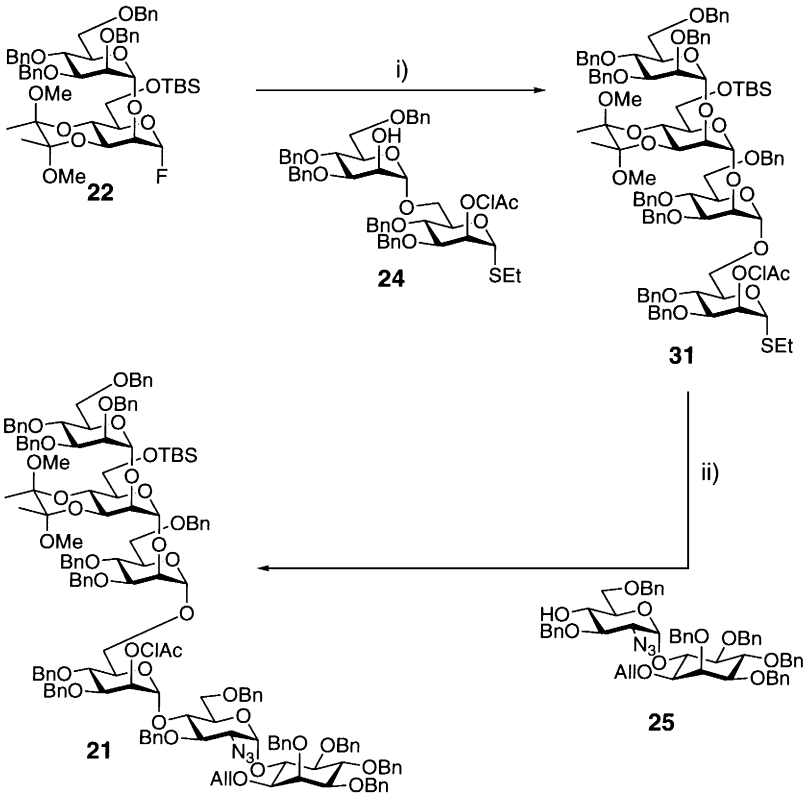


Scheme 5. Reagents and conditions. (i) HBr, AcOH; (ii) TBABr, $Me_2NCH(OMe)_2$, CH_2Cl_2, Δ; (iii) K_2CO_3 (cat.), MeOH; (iv) TBS–Cl, im, THF; (v) BnBr, TBAI, NaH, DMF, 0°C–rt, 70% over five steps; (vi) EtSH, $HgBr_2$ (cat.), 4 Å:5 Å MS (1:2), MeCN, 60°C, 72%; (vii) K_2CO_3 (cat.), MeOH; (viii) $(ClAc)_2O$, py, CH_2Cl_2, 0°C–rt, >95% over two steps; (ix) $HF_{(aq)}$, MeCN, 87%; (x) **30**, NIS, TMSOTf (cat.), 4 Å MS, CH_2Cl_2:Et_2O (1:1), 77%; (xi) $Pd(PPh_3)_4$ (cat.), dimedone, THF, 75%

2.4. Assembly of core pseudohexasaccharide **21**

With all the coupling components in hand the assembly of the core oligosaccharide **21** was investigated. Coupling of fluoride **22** and thioglycoside **24**, using the Suzuki activation system, proceeded under carefully optimised conditions in 73% yield (Scheme 6). Careful control of the concentration and mass of molecular sieves used was crucial to avoid decomposition of the donor **22**. Attention was turned to the pivotal coupling of tetrasaccharide **31** and pseudodisaccharide **25**. In the previous GPI anchor synthesis[17] an NIS/TfOH coupling allowed access to the required heptasaccharide core. Trial reactions with the NIS/TMSOTf promoter system showed the coupling of **31** and **25** to be much more sensitive to the reaction conditions. Activation of **31** occurred immediately, but as the hydroxyl moiety in **25** is hindered, degradation pathways rather than glycosylation predominated. In this way, hexasaccharide core **21** was isolated in an unoptimised 35% yield, 57% based on recovered acceptor **25**. Hydrolysed donor accounted for the majority of the remaining mass balance. A slower activation system that would allow glycosylation to occur but at the same time would limit acid concentration was required. Experiments with MeOTf were encouraging; no decomposition of the donor was observed but the glycosylation could not be forced to completion. Experiments are currently in progress to again examine NIS as promoter but

AgOTf as the source of the catalytic acid required.[26] Furthermore, the versatility of thioglycosides is such that if this or other promoter systems fail, conversion to the bromide and subsequent AgOTf activation remains a viable alternative.[30]



Scheme 6. Reagents and conditions. (i) **24**, Cp_2HfCl_2, AgOTf, 4 Å MS, CH_2Cl_2:C_6H_5Me (1:1), 73%; (ii) **25**, NIS, TMSOTf (cat.), 4 Å MS, CH_2Cl_2:Et_2O (3:1), 35%

3. Conclusion

In this paper the one-pot synthesis of linear pentasaccharide **1**, from five monomeric building blocks, serves to illustrate the capabilities of this methodology. During the synthesis it was shown that the diacetal method is readily applicable to the reactivity tuning of glycosyl fluorides introducing more flexibility to retrosynthetic analyses of complex oligosaccharide targets. The preparation of **21**, the core oligosaccharide of the GPI anchor of *Saccharomyces cerevisiae*, further reinforces the utility of the method for oligosaccharide assembly. The ability to construct and manipulate GPI anchor derivatives via efficient glycoside formation should allow the opportunity to ask important questions about GPI biosynthesis using these synthetic oligosaccharides to probe the biochemical pathways. Intensive effort is underway to complete the total synthesis of the yeast GPI anchor and results will be disclosed in due course.

4. Experimental

Dry toluene, acetonitrile, dichloroethane and dichloromethane were distilled from calcium hydride, methanol was distilled from magnesium, dry ether and tetrahydrofuran were distilled from sodium–benzophenone ketyl. Reactions were carried out at room temperature under argon in predried glassware unless otherwise stated. NaH was a 60% dispersion in mineral oil. AgOTf was dried azeotropically with toluene and in vacuo before use in glycosidations. Molecular sieves (powdered unless stated otherwise) were predried in the oven and activated for 10 min under vacuum at 300°C. Water was distilled. All aqueous (aq.) solutions were saturated unless otherwise stated. Solvents for chromatography and reaction work up were distilled. Petrol is 40–60°C petroleum ether, ether is diethyl ether. Column chromatography was carried out under pressure using Merck silica gel (230–400 mesh) or BDH Florosil® (200 US mesh, 0.075 mm). Medium performance liquid chromatography (MPLC) was performed on a Biotage Flash 75 Radial Compression Module (solvent pressure 30 psi; radial pressure 60 psi) using prepacked silica gel cartridges. Size exclusion chromatography was performed under reduced pressure (flow rates of ca 0.25 ml min^{-1}) using Sephadex® LH-20 purchased from Pharmacia. Analytical and preparative TLC was performed using precoated, glass backed plates (Merck silica gel 60 F 254) and visualised by ultra-violet radiation (254 nm) or acidic ammonium molybdate (IV).

^{1}H and ^{13}C NMR spectra were recorded at 27°C on Bruker AM400, Bruker DRX200, DRX400, DRX500 and DRX600 spectrometers using $CHCl_3$ (δ=7.26 ppm) and $CDCl_3$ (δ=77.0 ppm) as internal reference signals unless otherwise stated. *J* values are given in Hz. Signals were assigned by means of 2D spectra (COSY, HMQC, HMBC), APT, DEPT and 1D TOCSY. The assignment of ^{1}H and ^{13}C signals of the saccharide units correlates with the lettering in the schemes; i.e. lettering begins at the reducing end. Optical rotations were measured with an Optical Activity AA-1000 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Infra-red spectra were recorded on a Perkin Elmer FTIR 1620 spectrometer. Mass spectra were obtained on Micromass Platform LC-MS, Micromass Q-Tof, Kratos MS890MS and Bruker Daltonics Bio-Apex II (FTICR) spectrometers by the mass spectrometry service of the Department of Chemistry, University of Cambridge and on a Kratos Kompact 4. Microanalyses were determined in the microanalytical laboratories of the Department of Chemistry, University of Cambridge.

4.1. Synthesis of (2′S,3′S) ethyl 3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-1-thio-α-D-mannopyranoside ***8***

To a stirred solution of ethyl 1-thio-α-D-mannopyranoside **7**[37] (12.0 g, 53.5 mmol) and (±)-camphorsulfonic acid (1.44 g, 6.20 mmol) in methanol (150 ml) were sequentially added trimethylorthoformate (25.0 ml, 229 mmol) and butane-2,3-dione (7.50 ml, 85.6 mmol). The reaction vessel was fitted with a condenser and the mixture heated under reflux for 19 h. On cooling to room temperature, the reaction mixture was quenched by the addition of triethylamine (1 ml) and then concentrated in vacuo to give a red oil. Purification by flash chromatography on silica gel (eluent: 1:1 petrol:ether→ether) yielded the BDA-protected mannopyranoside **8** (14.7 g, 81%) as a foam; $[\alpha]_D^{27}$=+299 (*c* 1.05, $CHCl_3$); ν_{max} (film) 3442, 2950, 1455, 1132; δ_H (200 MHz, $CDCl_3$) 5.31 (1H, s, H-1), 4.14–4.11 (2H, m, H-4, H-5), 4.01–3.93 (2H, m, H-2, H-3), 3.85–3.79 (2H, m, H-6a, H-6b), 3.26 (3H, s, OCH_3 BDA), 3.25 (3H, s, OCH_3 BDA), 2.97 (1H, d, *J* 1.9, 2-OH), 2.75–2.51 (2H, m, SCH_2CH_3), 2.20 (1H, t, *J* 6.5, 6-OH), 1.31–1.24 (9H, m, CH_3 BDA, SCH_2CH_3); δ_C (50 MHz, $CDCl_3$) [100.3, 99.8 (acetal C BDA)], 84.4 (C-1), 71.1 (C-2), 70.7 (C-5), 68.7 (C-3), 63.2 (C-4), 61.2 (C-6), [48.0, 47.8 (OCH_3 BDA)], 25.1 (SCH_2CH_3), [17.7, 17.6 (CH_3 BDA)], 14.8 (SCH_2CH_3); *m/z* (+FAB): 337.0 (68%, M^+-H), 323.1 (58), 307.0 (84, M^+-OMe), 274.9 (24), 245.0 (20), 189.0 (30), 171.0 (59), 145.0 (22), 127.0 (60), 116.0 (100);

(found (+FAB): $M^+ - OMe$, 307.1191. $C_{13}H_{23}O_6S$ requires: *M*, 307.1215) (found: C, 46.0%; H, 7.05%. $C_{14}H_{26}O_7S$ requires C, 49.69%; H, 7.74%).

4.2. Synthesis of (2′S,3′S) ethyl 2-O-benzoyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-6-O-benzoyl-1-thio-α-D-mannopyranoside **9**

To a stirred solution of **8** (14.4 g, 42.5 mmol) in anhydrous pyridine (28 ml), at 0°C, was added benzoyl chloride (11.8 ml, 102 mmol), dropwise, via syringe. The mixture was warmed to room temperature and stirring was maintained for 17 h, before the reaction mixture was partitioned between ice-cold water (100 ml) and dichloromethane (100 ml). The separated aqueous portion was extracted with dichloromethane (100 ml) and the combined organic extracts concentrated in vacuo. This material was subsequently dissolved in ether (70 ml), washed with aqueous copper (II) sulfate solution (3×40 ml), then water (2×40 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give an orange oil. Purification by flash chromatography on silica gel (eluent: petrol→3:1 petrol:ether), followed by recrystallisation (ether:hexane), gave the benzoylated mannopyranoside **9** (19.3 g, 83%) as fine needles; mp 109–111°C; $[\alpha]_D^{26}$=+189 (*c* 0.98, $CHCl_3$); ν_{max} (solution in $CHCl_3$) 3017, 2966, 1719, 1602, 1518, 1451; δ_H (500 MHz, $CDCl_3$) 8.10–7.37 (10H, m, Ar-H), 5.44 (1H, s, H-1), 5.41 (1H, d, *J* 1.5, H-2), 4.64–4.57 (2H, m, H-6a, H-6b), 4.51–4.44 (2H, m, H-4, H-5), 4.23 (1H, dd, *J* 9.2, 2.7, H-3), 3.29 (3H, s, OCH_3 BDA), 3.19 (3H, s, OCH_3 BDA), 2.73–2.63 (2H, m, SCH_2CH_3), 1.31–1.28 (6H, m, SCH_2CH_3, CH_3 BDA), 1.24 (3H, s, CH_3 BDA); δ_C (100 MHz, $CDCl_3$) [166.3, 165.0 (CO)], [133.1 (×2) (Ar-C)], [130.3, 130.0 (Ar-C *ipso*)], [129.9, 129.6, 128.4 (×2) (Ar-C)], [100.3, 100.0 (acetal *C* BDA)], 83.2 (C-1), 72.9 (C-2), 69.2 (C-4/5), 67.0 (C-3), 63.8 (C-4/5), 62.8 (C-6), [48.1, 48.0 (OCH_3 BDA)], 25.9 (SCH_2CH_3), [17.7, 17.6 (CH_3 BDA)], 15.1 (SCH_2CH_3); (found (+ESI): M^++Na, 569.1806. $C_{28}H_{34}O_9NaS$ requires: *M*, 569.1821) (found: C, 61.5%; H, 6.25%. $C_{28}H_{34}O_9S$ requires: C, 61.52%; H, 6.27%).

4.3. Synthesis of (2′S,3′S) 2-O-Benzoyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-6-O-benzoyl-α-D-mannopyranosyl fluoride **10**

To a stirred solution of **9** (2.40 g, 4.40 mmol) in dichloromethane (35 ml) at –10 °C was added DAST (0.87 ml, 6.59 mmol), dropwise, via syringe. The pale yellow solution was warmed to room temperature over 10 minutes before NIS (1.35 g, 5.71 mmol) was added in one portion. Stirring was maintained for 1 hour before NMR analysis of an aliquot indicated the reaction was complete. The now dark purple reaction mixture was diluted with dichloromethane (100 ml) and washed with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution (1:1 v/v, 100 ml). The separated aqueous portion was re-extracted with dichloromethane (100 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow-orange oil. Purification by flash chromatography on silica gel (eluent: 19:1 petrol:ether → 3:1) gave the mannopyranosyl fluoride **10** (2.07 g, 93%) as a foam; $[\alpha]_D^{26}$=+122 (*c* 1.27, $CHCl_3$); ν_{max} (film) 3062, 2943, 1714, 1603, 1585, 1491, 1451, 1280, 1110; δ_H (400 MHz, $CDCl_3$) 8.08–8.06 (4H, m, Ar-H), 7.63–7.55 (2H, m, Ar-H), 7.45–7.37 (4H, m, Ar-H), 5.73 (1H, d, *J* 48.7, H-1), 5.47 (1H, s, H-2), 4.66 (1H, dd, *J* 12.2, 1.9, H-6a), 4.61 (1H, dd, *J* 12.2, 3, H-6b), 4.51 (1H, t, *J* 10.3, H-4), 4.33–4.29 (2H, m, H-3, H-5), 3.31 (3H, s, OCH_3 BDA), 3.19 (3H, s, OCH_3 BDA), 1.30 (3H, s, CH_3 BDA), 1.25 (3H, s, CH_3 BDA); δ_C (100 MHz, $CDCl_3$) [166.1, 165.5 (CO)], [133.3, 133.1, 129.9 (Ar-C)], 129.7 (Ar-C *ipso*), [129.6, 128.5, 128.4 (Ar-C)], 105.4 (d, *J* 224, C-1), [100.4, 100.1 (acetal C BDA)], 71.4 (C-3/5), 69.1 (d, *J* 37.9, C-2), 65.5 (C-3/5), 62.5 (C-4), 62.0 (C-6), [48.2, 48.0 (OCH_3 BDA)], [17.6, 17.5 (CH_3 BDA)]; (found (+ESI): M^++Na, 527.1676.

$C_{26}H_{29}FO_9Na$ requires: *M*, 527.1693) (found: C, 61.8%; H, 5.80%. $C_{26}H_{29}FO_9$ requires: C, 61.88%; H, 5.80%).

4.4. Synthesis of (2′S,3′S) 6-O-benzoyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-α-D-mannopyranosyl fluoride **11**

To a stirred solution of **10** (0.94 g, 1.87 mmol) in dichloromethane (10 ml) and methanol (5 ml) was added anhydrous potassium carbonate (50 mg, cat.) in one portion. Stirring was maintained for a further 32 h, before the reaction mixture was diluted with dichloromethane (35 ml) and filtered through Celite®. The filter-cake was washed with dichloromethane (2×40 ml) and the combined filtrates concentrated in vacuo to give an oil. Purification was accomplished by flash chromatography on silica gel (eluent: petrol→1:3 petrol:ether) to furnish the 6-*O*-benzoylated mannopyranoside **11** (0.40 g, 53%) as a foam; $[\alpha]_D^{26}$=+174 (*c* 1.02, $CHCl_3$); ν_{max} (film) 3466, 2944, 2951, 2835, 1723, 1602, 1585, 1452, 1276, 1113; δ_H (600 MHz, $CDCl_3$) 8.08–7.42 (5H, m, Ar-H), 5.64 (1H, d, *J* 48.9, H-1), 4.61 (1H, dd, *J* 12.1, 1.9, H-6a), 4.52 (1H, dd, *J* 12.2, 4.3, H-6b), 4.27 (1H, t, *J* 10.0, H-4), 4.22 (1H, dd, *J* 10.3, 2.3, H-5), 4.10 (1H, s, H-2), 4.09–4.06 (1H, m, H-3), 3.30 (3H, s, OCH_3 BDA), 3.15 (3H, s, OCH_3 BDA), 2.57 (1H, d, *J* 1.9, 2-OH), 1.34 (3H, s, CH_3 BDA), 1.29 (3H, s, CH_3 BDA); δ_C (150 MHz, $CDCl_3$) 166.3 (CO), 133.1 (Ar-C), 129.8 (Ar-C *ipso*), [129.7, 128.4 (Ar-C)], 107.6 (d, *J* 220, C-1), [100.5, 100.2 (acetal C BDA)], 71.2 (C-5), 68.2 (d, *J* 37.9, C-2), 67.5 (C-3), 62.4 (C-6), 62.2 (C-4), [48.2, 48.0 (OCH_3 BDA)], [17.7, 17.6 (CH_3 BDA)]; (found (+ESI): M^++Na, 423.1443. $C_{19}H_{25}FO_8Na$ requires: *M*, 423.1431) (found: C, 57.0%; H, 6.25%. $C_{19}H_{25}FO_8$ requires: C, 57.0%; H, 6.29%).

4.5. Synthesis of ethyl 2,3,4,6-tetra-O-benzyl-1-thio-α-D-mannopyranoside **32**

To a stirred suspension of NaH (6.2 g, 155 mmol) in DMF (20 ml), at 0°C, was added a solution of ethyl 1-thio-α-D-mannopyranoside[37] (5.90 g, 26.3 mmol) in DMF (80 ml) slowly via cannula. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The suspension was then cooled to 0°C before the dropwise addition of benzyl bromide (18.3 ml, 153 mmol) via syringe. The reaction mixture was warmed to room temperature, stirred for a further 19 h and then quenched by pouring onto ice (100 g). The mixture was extracted with ether (3×100 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 9:1→1:1) gave the perbenzylated mannopyranoside[80] **32** (13.4 g, 87%) as an oil; ν_{max} (neat) 3039, 2867, 1604, 1566, 1453, 1098; δ_H (600 MHz, $CDCl_3$) 7.40–7.18 (20H, m, Ar-H), 5.41 (1H, s, H-1), 4.89 (1H, d, *J* 10.8, PhCH_aH$_b$-A), 4.73 (1H, d, *J* 12.4, PhCH_aH$_b$-B), 4.68 (1H, d, *J* 12.4, PhCH$_a$$H_b$-B), 4.67 (1H, d, *J* 12.1, PhCH_aH$_b$-C), 4.60–4.56 (2H, m, $PhCH_2$-D), 4.53–4.51 (2H, m, PhCH$_a$$H_b$-A, PhCH$_a$$H_b$-C), 4.13 (1H, dd, *J* 9.7, 4.7, H-3), 4.03 (1H, t, *J* 9.9, H-4), 3.85 (1H, m, H-5), 3.84 (1H, s, H-2), 3.82 (1H, dd, *J* 11.0, 4.9, H-6a), 3.72 (1H, dd, *J* 10.8, 1.4, H-6b), 2.67–2.53 (2H, m, S$CH_2$$CH_3$), 1.25 (3H, t, *J* 7.4, SCH_2CH_3); δ_C (150 MHz, $CDCl_3$) [138.6, 138.4, 138.3, 138.2 (Ar-C *ipso*)], [128.4, 128.3 (×2), 128.2, 128.0, 27.9, 127.8 (×2), 127.7, 127.6, 127.5, 127.0 (Ar-C)], 81.9 (C-1), 80.4 (C-5), 76.4 (C-2), 75.2 ($PhCH_2$-A), 75.1 (C-4), 73.5 ($PhCH_2$-C), 72.1 ($PhCH_2$-D), 72.0 ($PhCH_2$-B), 72.0 (C-3), 69.6 (C-6), 25.3 (SCH_2CH_3), 15.0 (SCH_2CH_3) (found (+ESI): M^++Na, 607.2486. $C_{36}H_{40}O_5NaS$ requires: *M*, 607.2494).

4.6. Synthesis of 2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl fluoride **2**

To a stirred solution of **32** (2.00 g, 3.35 mmol) in dichloromethane (100 ml) at −5°C was added DAST (0.67 ml, 5.03 mmol), dropwise, via syringe. The reaction mixture was stirred for 10 min, at −5°C, before NIS (1.00 g, 4.36 mmol) was added in one portion. Stirring was maintained for 1 h at −5°C and at room temperature for 30 min. The now dark purple reaction mixture was washed with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution (1:1 v/v, 100 ml). The aqueous portion was extracted with dichloromethane (50 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 6:1→4:1) gave the mannopyranosyl fluoride[36] **2** (1.44 g, 79%) as a pale yellow oil; ν_{max} (neat) 3030, 2866, 1605, 1586, 1496, 1454, 1099; δ_H (500 MHz, $CDCl_3$) 7.35–7.18 (20H, m, Ar-H), 5.60 (1H, d, *J* 50.6, H-1), 4.88 (1H, d, *J* 10.8, PhCH_aH$_b$-A), 4.81 (1H, d, *J* 12.3, PhCH_aH$_b$-B), 4.70–4.63 (4H, m, PhCH$_a$$H_b$-B, PhCH$_2$-C, PhC$H_aH_b$-D), 4.56–4.53 (2H, m, PhCH$_a$$H_b$-A, PhCH$_a$$H_b$-D), 4.08 (1H, t, *J* 9.7, H-4), 3.93–3.88 (3H, m, H-2, H-3, H-5), 3.79 (1H, dd, *J* 11.0, 4.5, H-6a), 3.72 (1H, d, *J* 10.9, H-6b); δ_C (100 MHz, $CDCl_3$) [138.2 (×2), 137.9 (Ar-C *ipso*)], [128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6 (Ar-C)], 106.5 (d, *J* 222, C-1), 79.2 (C-3/4/5), 75.2 (PhCH$_2$-A), 74.2 (C-3/4/5), 74.1 (C-3/4/5), 73.6 (d, *J* 30.2, C-2), 73.5 (PhCH$_2$-D), 73.3 (PhCH$_2$-B), 72.6 (PhCH$_2$-C), 68.7 (C-6); (found (+ESI): M^++Na, 565.2381. $C_{34}H_{35}FO_5Na$ requires: *M*, 565.2366) (found: C, 75.1%; H, 6.55%. $C_{34}H_{35}FO_5$ requires: C, 75.26%; H, 6.50%).

4.7. Synthesis of (2′S,3′S) 6-O-benzoyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-2-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-α-D-mannopyranosyl fluoride **14**

A mixture of AgOTf (51 mg, 0.19 mmol), 4 Å MS (0.19 g) and Cp_2HfCl_2 (38 mg, 0.10 mmol) was suspended in dichloromethane (1 ml). The resulting suspension was cooled to 0°C and stirred for 2 min before a solution of **2** (50 mg, 90 μmol) and **11** (46 mg, 90 μmol) in dichloromethane (1 ml) was added, via syringe. Stirring was maintained at 0°C for 5 min and at room temperature for 1 h, before the reaction mixture was filtered through Celite®. The filter-cake was washed with dichloromethane (20 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (20 ml). The separated aqueous portion was extracted with dichloromethane (20 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo to give an oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 1:1) gave the dimannopyranoside **14** (88 mg, >95%) as a foam; ν_{max} (film) 3011, 2948, 2835, 1723, 1602, 1585, 1496, 1453, 1278, 1112; δ_H (600 MHz, $CDCl_3$) 8.03–7.13 (25H, m, Ar-H), 5.64 (1H, d, *J* 49.4, H-1^a), 5.45 (1H, d, *J* 1.3, H-1^b), 4.81–4.79 (2H, m, PhCH_aH$_b$-A, PhCH_aH$_b$-B), 4.66 (1H, d, *J* 12.1, PhCH_aH$_b$-C), 4.63 (1H, d, *J* 12.4, PhCH$_a$$H_b$-A), 4.59 (1H, d, *J* 12.3, H-6a^a), 4.54–4.52 (2H, m, H-6b^a, PhCH$_a$$H_b$-C), 4.47–4.45 (3H, m, PhCH_aH$_b$-B, PhCH$_2$-D), 4.25–4.21 (2H, m, H-4^a, H-5^a), 4.18 (1H, s, H-2^a), 4.12 (1H, d, *J* 9.3, H-3^a), 3.98 (1H, s, H-2^b), 3.96 (1H, t, *J* 9.2, H-4^b), 3.88 (1H, dd, *J* 8.7, 3.0, H-3^b), 3.82–3.80 (1H, m, H-5^b), 3.77 (1H, dd, *J* 10.6, 5.1, H-6a^b), 3.72 (1H, d, *J* 10.5, H-6b^b), 3.30 (3H, s, OCH$_3$ BDA), 3.14 (3H, s, OCH$_3$ BDA), 1.31 (3H, s, CH$_3$ BDA), 1.29 (3H, s, CH$_3$ BDA); δ_C (150 MHz, $CDCl_3$) 166.2 (CO), [138.4 (×2), 138.2, 133.0, 129.8, 129.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5 (×3) (Ar-C, Ar-C *ipso*)], 107.1 (d, *J* 223, C-1^a), [100.0, 99.9 (acetal C BDA)], 99.2 (C-1^b), 79.6 (C-3^b), 74.9 (C-4^b), 74.8 (PhCH$_2$-A), 74.7 (C-2^b), 73.3 (PhCH$_2$-C), 72.6 (d, *J* 34.7, C-2^a), 72.3 (C-5^b), 72.1 (PhCH$_2$-B), 71.9 (PhCH$_2$-D), 71.5 (C-5^a), 69.3 (C-6^b), 67.8 (C-3^a), 62.6 (C-4^a), 62.3 (C-6^a), [48.1, 48.0 (OCH$_3$ BDA)], [17.9, 17.7 (CH$_3$ BDA)]; (found (+ESI): M^++Na, 945.3833. $C_{53}H_{59}FO_{13}Na$ requires: *M*, 945.3837).

4.8. Synthesis of (2′S,3′S) ethyl 2-O-acetyl-6-O-tert-butyldiphenylsilyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-1-thio-α-D-mannopyranoside **12**

To a stirred solution of **8** (4.00 g, 11.8 mmol) and imidazole (1.77 g, 26.0 mmol) in THF (150 ml), at 0 °C, was added chlorodiphenyl-*tert*-butylsilane (3.70 ml, 14.2 mmol), dropwise, via syringe. The mixture was warmed to room temperature and stirring maintained for a further 5 h before filtering through Florisil®. The filter-cake was washed copiously with ether and the combined filtrates concentrated in vacuo to give the crude silylated mannopyranoside **33** as a pale yellow oil. The oil was used without further purification in the next step.

To a stirred solution of the crude **33** in pyridine (85 ml), at 0°C, was added acetic anhydride (6.0 ml, 59.0 mmol), dropwise, via syringe. The reaction was warmed to room temperature and stirring maintained for 16 h before the volatiles were removed in vacuo. This material was dissolved in ether (200 ml), sequentially washed with aqueous hydrochloric acid (100 ml of a 3N solution) and aqueous sodium bicarbonate solution (100 ml), then dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 3:1→1:1) gave the acetylated mannopyranoside **12** (5.50 g, 76% over two steps) as a foam; δ_H (600 MHz, $CDCl_3$) 7.72–7.33 (10H, m, Ar-H), 5.29 (1H, s, H-1), 5.12 (1H, d, *J* 2.1, H-2), 4.26 (1H, t, *J* 10.1, H-4), 4.11 (1H, dd, *J* 10.2, 3.1, H-3), 4.08 (1H, s, H-5), 4.00 (1H, dd, *J* 11.4, 3.8, H-6a), 3.84 (1H, dd, *J* 11.4, 1.6, H-6b), 3.26 (3H, s, OCH_3 BDA), 3.24 (3H, s, OCH_3 BDA), 2.65–2.52 (2H, m, SCH_2CH_3), 2.15 (3H, s, $COCH_3$), 1.28 (6H, s, CH_3 BDA), 1.25 (3H, t, *J* 7.4, SCH_2CH_3), 1.06 (9H, s, $SiC(CH_3)_3$); δ_C (50 MHz, $CDCl_3$) 170.6 (CO), [136.0, 135.4 (Ar-C)], [134.1, 133.1 (Ar-C *ipso*)], [129.5, 129.4, 127.5, 127.3 (Ar-C)], [100.2, 99.6 (acetal C BDA)], 82.5 (C-1), 72.4 (C-2), 71.8 (C-5), 66.9 (C-3), 63.1 (C-4), 61.8 (C-6), [47.9 (OCH_3 BDA)], 26.7 ($SiC(CH_3)_3$), 25.4 (SCH_2CH_3), 21.2 ($COCH_3$), 19.3 ($SiC(CH_3)_3$), [17.7, 17.6 (CH_3 BDA)], 14.8 (SCH_2CH_3); (found (+ESI): M^++Na, 641.2598. $C_{32}H_{46}O_8SiNaS$ requires: *M*, 641.2580) (found: C, 61.9%; H, 7.5%. $C_{32}H_{46}O_8SiS$ requires: C, 62.11%; H, 7.50%).

4.9. Synthesis of (2′S,3′S) 2-O-acetyl-6-O-tert-butyldiphenylsilyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-α-D-mannopyranosyl fluoride **13**

To a stirred solution of **12** (7.12 g, 11.5 mmol) in dichloromethane (125 ml) at 0°C was added DAST (3.00 ml, 23.1 mmol), dropwise, via syringe. The pale yellow solution was stirred for 20 minutes at 0°C before NIS (3.38 g, 15.0 mmol) was added in one portion. The rapid formation of a deep purple colour was observed as the reaction mixture was warmed to room temperature. Stirring was maintained for a further 2.5 h before the mixture was quenched by washing with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution (1:1 v/v, 150 ml). The separated organic extract was dried ($MgSO_4$), filtered and concentrated in vacuo to give an orange oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 9:1→2:1) gave the mannopyranosyl fluoride **13** (5.81 g, 88%) as a foam; ν_{max} (film) 2995, 2932, 2857, 1755, 1589, 1233, 1112; δ_H (600 MHz, $CDCl_3$) 7.71–7.35 (10H, m, Ar-H), 5.60 (1H, d, *J* 49.1, H-1), 5.19 (1H, s, H-2), 4.41 (1H, t, *J* 10.3, H-4), 4.18 (1H, dd, *J* 10.5, 2.8, H-3), 4.03 (1H, dd, *J* 11.6, 2.6, H-6a), 3.90–3.87 (2H, m, H-5, H-6b), 3.28 (3H, s, OCH_3 BDA), 3.26 (3H, s, OCH_3 BDA), 2.16 (3H, s, $COCH_3$), 1.31 (3H, s, CH_3 BDA), 1.30 (3H, s, CH_3 BDA), 1.07 (9H, s, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 170.4 (CO), [136.0, 135.4 (Ar-C)], [134.1, 132.9 (Ar-C *ipso*)], [129.7, 129.6, 127.6 (×2) (Ar-C)], 105.4 (d, *J* 223, C-1), [100.3, 99.8 (acetal C BDA)], 73.9 (C-5), 69.0 (d, *J* 37.8, C-2), 65.3 (C-3), 61.6 (C-4), 61.1 (C-6), [48.2, 48.1 (OCH_3 BDA)], 26.8 ($SiC(CH_3)_3$), 21.0 ($COCH_3$), 19.5 ($SiC(CH_3)_3$), [17.8, 17.7 (CH_3 BDA)]; (found (+ESI): M^++Na, 599.2439. $C_{30}H_{41}FO_8SiNa$ requires: *M*, 599.2452) (found: C, 62.3%; H, 7.2%. $C_{30}H_{41}FO_8Si$ requires C, 62.48%; H, 7.17%).

*4.10. Synthesis of (2′S,3′S) 6-*O*-tert-butyldiphenylsilyl-3-*O*,4-*O*-[2′,3′-dimethoxybutan-2′,3′-diyl]-α-*D*-mannopyranosyl fluoride **3***

To a stirred solution of **13** (3.14 g, 5.44 mmol) in anhydrous methanol (30 ml) was added anhydrous potassium carbonate (50 mg, cat.), via spatula. Stirring was maintained for a further 1 h before neutralisation with Amberlite IR-120 (plus) and immediate filtration. The residue was washed with methanol (30 ml) and the combined filtrates concentrated in vacuo to give an off-white gum. Purification was accomplished by flash chromatography on silica gel (eluent: petrol:ether 4:1→1:1) to furnish the deacylated mannopyranoside **3** (2.75 g, 94%) as a foam; $[\alpha]_D^{26}$=+121 (*c* 1.45, $CHCl_3$); ν_{max} (film) 3448, 3019, 2996, 2931, 2835, 1589, 1462, 1112; δ_H (600 MHz, $CDCl_3$) 7.73–7.35 (10H, m, Ar-H), 5.63 (1H, d, *J* 49.4, H-1), 4.30 (1H, t, *J* 10.2, H-4), 4.07 (1H, s, H-2), 4.06–4.03 (1H, m, H-3), 3.99 (1H, dd, *J* 11.7, 3.6, H-6a), 3.92 (1H, br s, H-5), 3.90 (1H, d, *J* 11.2, H-6b), 3.29 (3H, s, OCH_3 BDA), 3.22 (3H, s, OCH_3 BDA), 2.53 (1H, s, 2-OH), 1.34 (3H, s, CH_3 BDA), 1.29 (3H, s, CH_3 BDA), 1.06 (9H, s, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) [136.0, 135.6 (Ar-C)], [134.0, 133.2 (Ar-C *ipso*)], [129.6, 129.5, 127.6, 127.5 (Ar-C)], 107.8 (d, *J* 219, C-1), [100.4, 99.9 (acetal C BDA)], 74.0 (C-5), 68.4 (d, *J* 38.2, C-2), 67.7 (C-3), 61.6 (C-6), [48.2, 48.1 (OCH_3 BDA)], 26.9 ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$), [17.8, 17.7 (CH_3 BDA)]; (found (+ESI): M^++Na, 557.2325. $C_{28}H_{39}FO_7SiNa$ requires: *M*, 557.2347) (found: C, 63.1%; H, 7.5%. $C_{28}H_{39}FO_7Si$ requires: C, 62.90%; H, 7.35%).

*4.11. Synthesis of (2′S,3′S) 6-*O*-tert-butyldiphenylsilyl-3-*O*,4-*O*-[2′,3′-dimethoxybutan-2′,3′-diyl]-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl fluoride **15***

A mixture of AgOTf (135 mg, 0.51 mmol), 4 Å MS (1.0 g) and Cp_2HfCl_2 (78 mg, 0.21 mmol) was suspended in dichloromethane (2 ml). The resulting suspension was cooled to −10°C and stirred for 5 min, before a solution of **2** (112 mg, 0.21 mmol) and **3** (100 mg, 0.19 mmol) in dichloromethane (3 ml) was added, via syringe. The reaction mixture was stirred for a further 20 min at −10°C and then filtered through Celite®. The filter-cake was washed with dichloromethane (40 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (25 ml). The separated aqueous portion was extracted with dichloromethane (20 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo to give an oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 7:3) gave the dimannopyranoside **15** (169 mg, 78%) as a foam; ν_{max} (film) 3010, 2930, 2858, 1606, 1588, 1496, 1454, 1112; δ_H (600 MHz, $CDCl_3$) 7.72–7.13 (30H, m, Ar-H), 5.62 (1H, d, *J* 47.3, H-1^a), 5.58 (1H, s, H-1^b), 4.84 (1H, d, *J* 10.6, PhCH_aH$_b$-A), 4.82 (1H, d, *J* 12.2, PhCH_aH$_b$-B), 4.70 (1H, d, *J* 12.1, PhCH_aH$_b$-C), 4.59 (1H, d, *J* 12.5, PhCH$_a$$H_b$-B), 4.56 (1H, d, *J* 12.1, PhCH$_a$$H_b$-C), 4.47–4.43 (2H, m, PhCH$_a$$H_b$-A, PhC$H_aH_b$-D), 4.37 (1H, d, *J* 11.4, PhCH$_a$$H_b$-D), 4.35 (1H, t, *J* 10.0, H-4^a), 4.22 (1H, s, H-2^a), 4.11 (1H, d, *J* 10.5, H-3^a), 3.99–3.96 (3H, m, H-2^b, H-4^b, H-6a^a), 3.91–3.87 (2H, m, H-3^b, H-5^a), 3.85–3.80 (3H, m, H-5^b, H-6a^b, H-6b^a), 3.75 (1H, d, *J* 8.8, H-6b^b), 3.29 (3H, s, OCH_3 BDA), 3.24 (3H, s, OCH_3 BDA), 1.32 (3H, s, CH_3 BDA), 1.31 (3H, s, CH_3 BDA); 0.99 (9H, s, $SiC(CH_3)_3$); δ_C (150 MHz, $CDCl_3$) [138.6, 138.4, (Ar-C *ipso*)], [135.9, 135.6 (Ar-C)], [134.0, 132.9 (Ar-C *ipso*)], [129.7, 129.6, 128.3, 128.2 (×2), 128.0, 127.9, 127.8, 127.4 (×2) (Ar-C)], (107.5 d, *J* 222, C-1^a), [99.9, 99.7 (acetal C BDA)], 98.6 (C-1^b), 79.7 (C-3^b), 74.9 ($PhCH_2$-A), [74.2 (C-2^b, C-4^b, C-5^a)], 73.5 ($PhCH_2$-C), 72.1 (C-2^a/5^b), [71.9, 71.8 ($PhCH_2$-B, Ph*C*H$_2$-D)], 71.6 (C-2^a/5^b), 69.3 (C-6^b), 68.4 (C-3^a), 61.9 (C-4^a), 61.4 (C-6^a), [48.3, 48.2 (OCH_3 BDA)], 26.9 ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$), [18.0, 17.8 (CH_3 BDA)]; (found (+ESI): M^++Na, 1079.4716. $C_{62}H_{73}FO_{12}SiNa$ requires: *M*, 1079.4753) (found: C, 70.1%; H, 6.85%. $C_{62}H_{73}FO_{12}Si$ requires: C, 70.43%; H, 6.96%).

*4.12. Synthesis of (2′*S*,3′*S*, 2′′*S*,3′′*S*) 6*-O*-benzoyl-3*-O*,4*-O*-[2′,3′-dimethoxybutan-2′,3′-diyl]-2*-O*-(6*-O*-tert-butyldiphenylsilyl-3*-O*,4*-O*-[2′′,3′′-dimethoxybutan-2′′,3′′-diyl]-2*-O*-(2,3,4,6-tetra*-O*-benzyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl fluoride **16***

*4.12.1. From **15***

A mixture of AgOTf (114 mg, 0.44 mmol), 4 Å MS (1 g) and Cp_2HfCl_2 (56 mg, 0.15 mmol) was suspended in dichloromethane (2 ml). The resulting suspension was cooled to −10°C and stirred for 10 min, before a solution of **15** (120 mg, 0.11 mmol) and **11** (68 mg, 0.17 mmol) in dichloromethane (2 ml) was added, via syringe. The reaction mixture was stirred for a further 1.3 h at −10°C and then filtered through Celite®. The filter-cake was washed with ether (50 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (30 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 3:1→2:1) gave the trimannopyranoside **16** (61 mg, 38%) as a foam.

*4.12.2. From **2** in one-pot*

A mixture of AgOTf (57 mg, 0.22 mmol), 4 Å MS (0.60 g) and Cp_2HfCl_2 (43 mg, 0.11 mmol) was added to a Schlenk flask fitted with a solid addition tube (containing a second portion of activators). This mixture was suspended in dichloromethane (1 ml) and stirred, at −10°C, for 15 min before a solution of **2** (50 mg, 92 μmol) and **3** (59 mg, 0.11 mmol) in dichloromethane (1 ml) was added, via syringe. Stirring was maintained for a further 30 min, at −10°C, before a solution of **11** (64 mg, 0.17 mmol) in dichloromethane (1 ml) was added, via syringe. A mixture of AgOTf (85 mg, 0.33 mmol), 4 Å MS (0.40 g) and Cp_2HfCl_2 (64 mg, 0.11 mmol) was then added, from the addition tube, before the mixture was warmed to room temperature over 1 h. The reaction mixture was filtered through Celite®, the filter-cake washed with ether (40 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (20 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give an off-white foam. Purification by flash chromatography on silica gel (eluent: petrol:ether 3:1→2:1) gave the trisaccharide **16** (38 mg, 29% based on **2**) as a foam; ν_{max} (film) 3011, 2932, 2858, 1725, 1602, 1587, 1496, 1453, 1276, 1111; δ_H (600 MHz, $CDCl_3$) 8.06–7.12 (35H, m, Ar-H), 5.64 (1H, s, H-1^c), 5.59 (1H, d, *J* 49.4, H-1^a), 5.15 (1H, s, H-1^b), 4.89 (1H, d, *J* 10.7, PhC*H*$_a$H$_b$-A), 4.79 (1H, d, *J* 12.6, PhC*H*$_a$H$_b$-B), 4.75 (1H, d, *J* 12.1, PhC*H*$_a$H$_b$-C), 4.69 (1H, d, *J* 12.1, H-6a^a), 4.59 (1H, d, *J* 12.6, PhCH$_a$*H*$_b$-B), 4.50 (1H, d, *J* 10.7, PhCH$_a$*H*$_b$-A), 4.47 (1H, d, *J* 12.1, PhCH$_a$*H*$_b$-C), 4.46 (1H, d, *J* 11.5, PhC*H*$_a$H$_b$-D), 4.42 (1H, dd, *J* 12.2, 4.4, H-6b^a), 4.38 (1H, d, *J* 11.5, PhCH$_a$*H*$_b$-D), 4.22–4.16 (4H, m, H-2^b, H-4^c, H-4^a, H-5^a), 4.11 (1H, s, H-2^a), 4.05 (1H, d, *J* 10.0, H-3^a), 3.99–3.96 (2H, m, H-3^b, H-4^b), 3.94–3.90 (2H, m, H-2^c, H-3^c/5^c), 3.89–3.85 (2H, m, H-6a^b, H-6a^c), 3.81–3.75 (3H, m, H-3^c/5^c, H-5^b, H-6b^b), 3.69 (1H, d, *J* 10.6, H-6b^c), 3.23 (3H, s, OCH_3 BDA), 3.15 (3H, s, OCH_3 BDA), 3.10 (3H, s, OCH_3 BDA), 3.02 (3H, s, OCH_3 BDA), 1.27 (3H, s, CH_3 BDA), 1.25 (3H, s, CH_3 BDA), 1.22 (3H, s, CH_3 BDA), 1.21 (3H, s, CH_3 BDA), 0.99 (9H, s, SiC(CH_3)$_3$); δ_C (150 MHz, $CDCl_3$) 166.2 (CO), [138.8, 138.7, 138.5, 138.3 (Ar-C *ipso*)], [135.8, 135.5 (Ar-C)], [133.8, 133.2 (Ar-C *ipso*)], 133.0 (Ar-C), 130.0 (Ar-C *ipso*), [129.6 (×2), 129.5, 128.4, 128.2 (×3), 128.1 (×2), 128.0 (×2), 127.9 (×2), 127.8 (×2), 127.6 (×2), 127.5 (×2), 127.4, 127.3 (×2) (Ar-C)], 106.9 (d, *J* 222, C-1^a), 100.4 (C-1^b), [100.0, 99.9, 99.6, 99.5 (acetal C BDA)], 98.0 (C-1^c), 79.7 (C-3^c/5^c), 74.9 (PhCH$_2$-A), 74.4 (C-5^a/4^c/4^a), 74.3 (C-2^c), 73.6 (PhCH$_2$-C), 72.9 (C-3^c/5^c), 72.6 (C-2^b), 72.0 (C-5^b), [71.8 (PhCH$_2$-B, PhCH$_2$-D)], [71.4 (C-2^a, C-5^a/4^c/4^a)], 69.1 (C-3^b/4^b), 68.8 (C-6^c), 67.7 (C-3^a), 63.3 (C-3^b/4^b), 62.6 (C-5^a/4^c/4^a), [62.5, 62.4 (C-6^a, C-6^b)], [48.1, 48.0, 47.9, 47.7 (OCH_3 BDA)], 26.7 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$), [17.9, 17.7, 17.7, 17.6 (CH_3 BDA)]; (found (+ESI): M$^+$+Na, 1459.6102. $C_{81}H_{97}FO_{20}SiNa$ requires: *M*, 1459.6224).

*4.13. Synthesis of (2′*S*,3′*S*) phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(6-*O*-tert-butyldiphenylsilyl-3-*O*,4-*O*-[2′,3′-dimethoxybutan-2′,3′-diyl]-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl)-1-seleno-α-*D*-mannopyranoside **17***

*4.13.1. From **15***

A mixture of AgOTf (237 mg, 0.92 mmol), 4 Å MS (3 g) and Cp_2HfCl_2 (117 mg, 0.31 mmol) was suspended in toluene (4 ml). The resulting suspension was stirred for 10 minutes before a solution of **15** (250 mg, 0.24 mmol) and **4**[40] (181 mg, 0.31 mmol) in toluene (3 ml) was added, via syringe. The reaction mixture was stirred for a further 2 h and then filtered through Celite®. The filter-cake was washed with ether (50 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (25 ml). The aqueous portion was extracted with ether (50 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 4:1→1:1) gave the trimannopyranoside **17** (331 mg, 86%) as a foam.

*4.13.2. From **2** in one-pot*

A mixture of AgOTf (57 mg, 0.22 mmol), 4 Å MS (0.60 g) and Cp_2HfCl_2 (43 mg, 0.11 mmol) was added to a Schlenk flask fitted with a solid addition tube (containing a second portion of activators). This mixture was suspended in dichloromethane (0.75 ml) and stirred for 10 min before cooling to −10°C. A solution of **2** (50 mg, 92 μmol) and **3** (59 mg, 0.11 mmol) in dichloromethane (1 ml) was then added, via syringe. Stirring was maintained for a further 30 min, at −10°C, before a solution of **4**[40] (70 mg, 0.11 mmol) in dichloromethane (0.75 ml) was added, via syringe. The second mixture of AgOTf (85 mg, 0.33 mmol), 4 Å MS (0.40 g) and Cp_2HfCl_2 (64 mg, 0.11 mmol) was then added, from the addition tube, before the mixture was warmed to room temperature over 1.5 h. The reaction mixture was filtered through Celite®, the filter-cake washed with ether (40 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (20 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give an off-white foam. Purification by flash chromatography on silica gel (eluent: petrol:ether 7:3) gave the trisaccharide **17** (97 mg, 65% based on **2**) as a foam; ν_{max} (film) 3010, 2930, 2858, 1579, 1496, 1454, 1111; δ_H (600 MHz, $CDCl_3$) 7.72–7.03 (50H, m, Ar-H), 5.69 (1H, d, *J* 1.1, H-1^a), 5.57 (1H, s, H-1^c), 5.25 (1H, s, H-1^b), 4.88 (1H, d, *J* 10.8, PhC*H*$_a$H$_b$-A), 4.84 (1H, d, *J* 10.6, PhC*H*$_a$H$_b$-B), 4.79 (1H, d, *J* 12.5, PhC*H*$_a$H$_b$-C), 4.71 (1H, d, *J* 11.4, PhC*H*$_a$H$_b$-D), 4.65 (1H, d, *J* 12.2, PhC*H*$_a$H$_b$-E), 4.62 (1H, d, *J* 12.1, PhC*H*$_a$H$_b$-F), 4.59 (1H, d, *J* 12.6, PhCH$_a$*H*$_b$-C), 4.55–4.53 (2H, m, PhCH$_a$*H*$_b$-B, PhCH$_a$*H*$_b$-D), 4.49–4.43 (3H, m, PhCH$_a$*H*$_b$-A, PhCH$_a$*H*$_b$-F, PhC*H*$_a$H$_b$-G), 4.39–4.37 (2H, m, H-2^a, PhCH$_a$*H*$_b$-G), 4.35 (1H, d, *J* 12.2, PhCH$_a$*H*$_b$-E), 4.22–4.19 (2H, m, H-2^b, H-4^b), 4.12–4.10 (1H, m, H-5^a), 4.08–4.04 (2H, m, H-3^b, H-4^c), 4.01 (1H, br s, H-2^c), 3.95–3.92 (2H, m, H-3^c, H-4^a), 3.88–3.84 (2H, m, H-3^a, H-6a^b), 3.80–3.73 (3H, m, H-5^c, H-6a^a, H-5^b), 3.69–3.65 (3H, m, H-6a^c, H-6b^b, H-6b^a), 3.54 (1H, dd, *J* 10.6, 1.5, H-6b^c), 3.18 (3H, s, OCH_3 BDA), 3.10 (3H, s, OCH_3 BDA), 1.26 (3H, s, CH_3 BDA), 1.25 (3H, s, CH_3 BDA), 0.99 (9H, s, SiC(C*H*$_3$)$_3$); δ_C (150 MHz, $CDCl_3$) [138.9, 138.7, 138.5, 138.4, 138.3, 137.7 (Ar-C *ipso*)], [135.9, 135.5 (Ar-C)], 134.0 (Ar-C *ipso*), 133.9 (Ar-C), 133.2 (Ar-C *ipso*), 129.5 (Ar-C), 129.4 (Ar-C *ipso*), [129.4, 129.0, 128.6, 128.3, 128.2 (×3), 128.1, 128.0 (×2), 127.9, 127.8, 127.7, 127.6 (×2), 127.5 (×2), 127.4 (×3), 127.3, 127.2 (Ar-C)], 100.7 (C-1^b), [99.6, 99.5 (acetal C BDA)], 98.5 (C-1^c), 85.3 (C-1^a), 80.9 (C-3^a), 80.0 (C-3^c), 75.2 ($PhCH_2$-B), 74.9 ($PhCH_2$-A), [74.7 (×3), 74.6, 74.5 (C-2^a, C-2^c, C-4^a, C-4^c, C-5^a)], 73.6 (C-2^b), [73.2, 73.1 ($PhCH_2$-E, $PhCH_2$-F)], 72.5 (C-5^b), 72.3 ($PhCH_2$-D), 72.0 (C-5^c), 71.9 ($PhCH_2$-C), 71.6 ($PhCH_2$-G), [68.9 (×2) (C-6^a, C-6^c)], 68.9 (C-3^b), 62.8 (C-4^b), 62.0 (C-6^b), [48.1, 48.0 (OCH_3 BDA)], 26.8 (SiC(*C*H$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$), [18.0, 17.8 (CH_3 BDA)]; (found (+ESI): M^++Na, 1649.6406. $C_{95}H_{106}O_{17}SeSiNa$ requires: *M*, 1649.6261); (found: C, 70.0%; H, 6.5%. $C_{95}H_{106}O_{17}SeSi$ requires: C, 70.14%; H, 6.57%).

4.14. Synthesis of (2′S,3′S) ethyl 6-O-benzoyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-1-thio-α-D-mannopyranoside ***6***

To a stirred solution of **8** (0.50 g, 1.48 mmol) in toluene (20 ml) was added bis-(tri-*n*-butyl tin) oxide (0.83 ml, 1.63 mmol), via syringe. The reaction vessel was fitted with a Dean–Stark separator and the mixture heated under reflux for 21 h. The solution was concentrated by the removal of ca. 12 ml of distillate and the reaction mixture cooled to room temperature before 4 Å MS (1 g) were added. The resulting suspension was cooled to 0°C before benzoyl chloride (0.19 ml, 1.63 mmol) was added dropwise via syringe. The reaction was warmed to room temperature and stirring continued for 18 h before filtration through Celite®. The filter-cake was washed with ethyl acetate (30 ml) and the combined filtrates concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (eluent: petrol→1:2 petrol:ether) gave the 6-*O*-benzoylated mannopyranoside **6** (0.50 g, 76%) as a foam; $[\alpha]_D^{26}$=+270 (*c* 1.05, $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 8.05 (2H, d, *J* 7.1, Ar-H), 7.56–7.53 (1H, m, Ar-H), 7.44–7.41 (2H, m, Ar-H), 5.36 (1H, s, H-1), 4.57 (1H, dd, *J* 11.9, 2.1, H-6a), 4.51 (1H, dd, *J* 11.9, 5.4, H-6b), 4.46–4.43 (1H, m, H-5), 4.21 (1H, t, *J* 9.9, H-4), 4.04 (1H, d, *J* 1.6, H-2), 4.02 (1H, dd, *J* 9.9, 3.0, H-3), 3.27 (3H, s, OCH_3 BDA), 3.15 (3H, s, OCH_3 BDA), 2.65 (1H, d, *J* 1.9, 2-OH), 2.71–2.57 (2H, m, S*CH*$_2$CH$_3$), 1.32 (3H, s, CH_3 BDA), 1.29–1.26 (6H, m, CH_3 BDA, SCH_2CH_3); δ_C (150 MHz, $CDCl_3$) 166.3 (CO), 133.0 (Ar-C), 130.0 (Ar-C *ipso*), [129.6, 128.3 (Ar-C)], [100.4, 100.0 (acetal C BDA)], 84.3 (C-1), 71.1 (C-2), [68.9, 68.8 (C-3, C-5)], 63.6 (C-4), 63.1 (C-6), [48.0, 47.9 (OCH_3 BDA)], 25.0 (S*CH*$_2$CH$_3$), [17.7, 17.6 (CH_3 BDA)], 14.8 (SCH_2CH_3); (found (+ESI): M^++Na, 465.1565. $C_{21}H_{30}O_8NaS$ requires: *M*, 465.1559).

4.15. Synthesis of (2′S,3′S, 1′′S,2′′S, 2′′′S,3′′′S) ethyl 6-O-benzoyl-3-O,4-O-[2′,3′-dimethoxybutan-2′,3′-diyl]-2-O-(6-O-benzoyl-3-O,4-O-[1′′,2′′-dimethoxycyclohexan-1′′,2′′-diyl]-2-O-(3,4,6-tri-O-benzyl-2-O-(6-O-tert-butyldiphenylsilyl-3-O,4-O-[2′′′,3′′′-dimethoxybutan-2′′′,3′′′-diyl]-2-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-1-thio-α-D-mannopyranoside ***1***

4.15.1. From ***2*** *in one-pot*

A mixture of AgOTf (57 mg, 0.22 mmol), 4 Å MS (0.60 g) and Cp_2HfCl_2 (43 mg, 0.11 mmol) was added to a Schlenk flask fitted with a solid addition tube (containing a second portion of activators). This mixture was suspended in dichloromethane (0.60 ml) and stirred for 10 min before cooling to −10°C. A solution of **2** (50 mg, 92 μmol) and **3** (59 mg, 0.11 mmol) in dichloromethane (0.60 ml) was then added, via syringe. Stirring was maintained for a further 30 min, at −10°C, before a solution of **4**[40] (64 mg, 0.11 mmol) in dichloromethane (0.60 ml) was added, via syringe. The second mixture of AgOTf (85 mg, 0.33 mmol), 4 Å MS (0.40 g) and Cp_2HfCl_2 (64 mg, 0.11 mmol) was then added, from the addition tube, before the mixture was warmed to room temperature over 1.5 h. A solution of **5**[13] (68 mg, 0.12 mmol) in ether (0.60 ml) was added, via syringe, before the mixture was cooled to −20°C. NIS (26 mg, 0.11 mmol) was added in one portion followed, immediately, by TfOH (50 μl of a stock solution of 30 μl TfOH in 1 ml 1:1 dichloromethane:ether), via syringe. Stirring was maintained for a further 30 min, at −20°C, before the addition of a solution of **6** (57 mg, 0.13 mmol), via syringe. NIS (28 mg, 0.12 mmol) was added in one portion followed, immediately, by TfOH (50 μl of a stock solution of 30 μl TfOH in 1 ml 1:1 dichloromethane:ether), via syringe. The reaction mixture was then warmed to room temperature over 1 h before filtration through Celite®. The filter-cake was washed with ether (50 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (20 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography

on silica gel (eluent: petrol:ether 4:1 →1:1), followed by size exclusion chromatography on Sephadex® LH-20 (eluent: 1:1 dichloromethane:methanol) and preparative TLC (eluent: 3:2 petrol:ether) gave the pentamannopyranoside **1** (17 mg, 8%) as a foam; δ_H (600 MHz, $CDCl_3$) 8.04–7.12 (55H, m, Ar-H), 5.69 (1H, s, H-1^e), 5.51 (1H, s, H-1^d), 5.33 (1H, s, H-1^a), 5.24 (1H, s, H-1^c), 5.20 (1H, s, H-1^b), 4.87 (1H, d, *J* 10.8, PhC*H*$_a$H$_b$-A), 4.83 (1H, d, *J* 12.6, PhC*H*$_a$H$_b$-B), 4.80 (1H, d, *J* 10.8, PhC*H*$_a$H$_b$-C), 4.71–4.67 (2H, m, PhC*H*$_a$H$_b$-D, PhC*H*$_a$H$_b$-E), 4.63 (1H, d, *J* 10.3, PhCH$_a$*H*$_b$-E), 4.62–4.36 (11H, m, PhCH$_a$*H*$_b$-A, PhCH$_a$*H*$_b$-B, PhCH$_a$*H*$_b$-C, PhCH$_a$*H*$_b$-D, PhC*H*$_a$H$_b$-F, H-6a^a, H-4^d, H-6a^b, H-5^a, H-6b^a, H-6b^b), 4.34 (1H, d, *J* 11.9, PhC*H*$_a$H$_b$-G), 4.31 (1H, s, H-2^d), 4.29 (1H, d, *J* 11.6, PhCH$_a$*H*$_b$-G), 4.27–4.25 (2H, m, PhCH$_a$*H*$_b$-F, H-2^c), 4.20 (1H, dd, *J* 10.5, 2.6, H-3^d), 4.18–4.07 (9H, m, H-3^b, H-4^a, H-4^b, H-2^a, H-4^e, H-6a^d, H-4^c, H-5^b, H-2^e), 4.06 (1H, s, H-2^b), 4.01–3.98 (2H, m, H-3^a, H-3^c), 3.93 (1H, dd, *J* 9.4, 3.3, H-3^e), 3.88 (1H, d, *J* 10.8, H-6b^d), 3.78–3.71 (4H, m, H-6a^c, H-5^d, H-5^e, H-5^c), 3.60–3.55 (2H, m, H-6b^c, H-6a^e), 3.46 (1H, d, *J* 9.3, H-6b^e), 3.29 (3H, s, OCH_3), 3.16 (3H, s, OCH_3), 3.08 (3H, s, OCH_3), 3.05 (3H, s, OCH_3), 2.96 (3H, s, OCH_3), 2.65 (3H, s, OCH_3), 2.61–2.51 (2H, m, S*C*H_2CH$_3$), 1.54–1.11 (23H, m, $(CH_2)_4$ CDA, CH_3 BDA, CH_3 BDA, CH_3 BDA, CH_3 BDA, SCH_2CH_3), 1.00 (9H, s, $SiC(CH_3)_3$); δ_C (150 MHz, $CDCl_3$) [166.4, 166.3 (CO)], [139.1, 138.8, 138.7, 138.5 (×2), 138.3, 138.0 (Ar-C *ipso*)], [135.9, 135.3 (Ar-C)], [134.3, 133.3 (Ar-C *ipso*)], [133.0, 132.9 (Ar-C)], [130.1, 129.8 (Ar-C *ipso*)], [129.6, 129.5 (×2), 128.5, 128.4, 128.3 (×2), 128.2 (×2), 128.1, 128.0 (×2), 127.9, 127.8, 127.7 (×2), 27.6, 127.5 (×2), 127.4 (×2), 127.3, 127.2 (×2), 127.0 (Ar-C)], 100.0 (C-1^b), [99.9, 99.8, 99.7 (BDA/CDA acetal C)], [99.7 (C-1^c, C-1^d)], [99.5, 98.5, 98.4 (BDA/CDA acetal C)], 98.2 (C-1^e), 84.1 (C-1^a), 81.1 (C-3^c), 80.3 (C-3^e), 75.1 ($PhCH_2$-C), 74.9 ($PhCH_2$-A), 74.7 (C-2^a), 74.6 (C-4^e/4^c/5^b), 74.5 (C-4^e/4^c/5^b), 74.3 (C-2^e), 73.6 (C-2^b), [73.3 ($PhCH_2$-E, $PhCH_2$-F)], 73.1 (C-2^d), 72.7 (C-5^e/5^d/5^c), 72.4 ($PhCH_2$-D), 72.1 (C-5^e/5^d/5^c), 71.9 (C-5^e/5^d/5^c), 71.6 ($PhCH_2$-B), 71.5 ($PhCH_2$-G), 70.8 (C-2^c), 69.8 (C-4^e/4^c/5^b), 69.2 (C-3^a), 69.1 (C-5^a), [68.9 (C-4^b, C-3^d)], 68.5 (C-6^e), 68.4 (C-6^c), [64.3, 63.8 (C-3^b, C-4^a)], 63.4 (C-6^b), 63.0 (C-6^a), 62.2 (C-4^d), 62.0 (C-6^d), [48.4, 48.0, 47.8, 47.7, 46.4 (OCH_3 BDA/CDA)], 26.9 (CH_2 CDA), 26.8 ($SiC(CH_3)_3$), 26.7 (CH_2 CDA), 25.4 (SCH_2CH_3), [21.2, 20.9 (CH_2 CDA)], 19.5 ($SiC(CH_3)_3$), [18.1, 17.8, 17.6, 17.5 (CH_3 BDA)], 14.9 (SCH_2CH_3); (found (+ESI): M^++Na, 2340.0101. $C_{131}H_{156}O_{33}SiSNa$ requires: *M*, 2339.9911).

*4.16. Synthesis of 3,4-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-(methoxyethylidene)-β-*D*-manno-pyranose **28***

To a stirred solution of **26**[77] (15.0 g, 38.0 mmol) in glacial acetic acid (80 ml) was added a solution of HBr in glacial acetic acid (100 ml of a 45% w/v solution), dropwise over 1 h. Stirring was maintained for 14 h before the reaction was quenched by pouring into ice-cold water (500 ml). The mixture was extracted with dichloromethane (2×400 ml) and the combined organic extracts washed with aqueous sodium bicarbonate solution (2×300 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude mannopyranosyl bromide **34**[41] as a yellow oil. This material was used directly in the next step without further purification.

To a stirred solution of the crude **34** and tetrabutylammonium bromide (13.2 g, 35.0 mmol) in refluxing dichloromethane (100 ml) was added *N*,*N*-dimethylformamide dimethyl acetal (10.5 ml, 79 mmol), via syringe. Stirring was maintained, at reflux, for 21 h. On cooling, the reaction was washed with water (2×125 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude orthoester **35**[41] as a brown oil. This material was used directly in the next step without further purification.

To a stirred solution of the crude **35** in methanol (100 ml) was added anhydrous potassium carbonate (200 mg, cat.) in two portions. Stirring was maintained for 7 h before the volatiles were removed in vacuo

to give the crude deacylated orthoester **27**[41] as a brown oil. This material was used directly in the next step without further purification.

To a stirred solution of the crude **27** and imidazole (5.75 g, 84.0 mmol) in THF (200 ml) was added *tert*-butyldimethylsilyl chloride (6.49 g, 42.0 mmol), in one portion. Stirring was maintained for a further 2 h before filtering through Florisil®. The filter-cake was washed copiously with ether and the combined filtrates concentrated in vacuo to give the crude silylated orthoester **36** as an orange oil. This material was used directly in the next step without further purification.

To a stirred solution of the crude **36** and tetrabutylammonium iodide (0.50 g, 1.33 mmol) in DMF (200 ml) was added benzyl bromide (14.3 ml, 114 mmol), via syringe. The solution was cooled to 0°C and NaH (3.83 g, 114 mmol) was added portionwise. The solution was warmed to room temperature and stirring maintained for a further 14 h, before the reaction was quenched by pouring into ice-cold water (200 ml). The mixture was extracted with ether (2×200 ml) and the organic extract washed successively with water (3×200 ml) and brine (200 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give a brown oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 9:1→1:5) gave the benzylated orthoester **28** (14.2 g, 70% over five steps) as an oil; δ_H (600 MHz, $CDCl_3$) 7.41–7.29 (10H, m, Ar-H), 5.31 (1H, d, *J* 2.3, H-1), 4.93 (1H, d, *J* 10.7, PhCH_aH$_b$-A), 4.81 (1H, d, *J* 12.2, PhCH_aH$_b$-B), 4.78 (1H, d, *J* 12.2, PhCH$_a$$H_b$-B), 4.74 (1H, d, *J* 10.8, PhCH$_a$$H_b$-A), 4.37–4.36 (1H, m, H-2), 3.99 (1H, t, *J* 9.3, H-4), 3.94 (1H, dd, *J* 11.1, 3.3, H-6a), 3.82 (1H, dd, *J* 11.1, 1.7, H-6b), 3.73 (1H, dd, *J* 9.3, 4.0, H-3), 3.29 (3H, s, OCH_3 orthoester), 3.24–3.22 (1H, m, H-5), 1.75 (3H, s, CH_3 orthoester), 0.91 (9H, s, SiC$(CH_3)_3$), 0.07 (6H, s, Si$(CH_3)_2$)]; δ_C (150 MHz, $CDCl_3$) [138.6, 138.0 (Ar-C *ipso*)], [128.5, 128.4 (×2), 128.0, 127.9 (×2), 127.7 (Ar-C)], 124.0 (orthoester), 97.6 (C-1), 79.2 (C-3), 77.3 (C-2), 75.2 (PhCH$_2$-A), 74.8 (C-5), 73.8 (C-4), 72.5 (PhCH$_2$-B), 62.0 (C-6), 49.6 (OCH_3 orthoester), 25.9 (SiC(CH_3)$_3$), 24.5 (CH_3 orthoester), 18.2 (Si$C$$(CH_3)_3$), [−5.3, −5.4 (Si$(CH_3)_2$)]; (found (+ESI): M^++Na, 553.2584. $C_{29}H_{47}O_7SiNa$ requires: *M*, 553.2598); (found: C, 65.9%; H, 8.05%. $C_{29}H_{42}O_7Si$ requires: C, 65.63%; H, 7.98%).

*4.17. Synthesis of ethyl 2-acetyl-3,4-di-*O*-benzyl-6-*O*-tert-butyldimethylsilyl-1-thio-α-*D*-mannopyranoside **37***

To a stirred suspension of **28** (6.65 g, 12.5 mmol), $HgBr_2$ (0.45 g, 1.25 mmol) and MS (6 g of a 1:2 mixture of 4 Å and 5 Å) in acetonitrile (40 ml) was added ethanethiol (6.0 ml, 78.9 mmol), via syringe. The reaction vessel was fitted with a condenser and the mixture heated at 60°C for 4.5 h. On cooling to room temperature, the reaction mixture was filtered through Celite®. The filter-cake was washed with ether (60 ml) and the combined filtrates washed with aqueous sodium hydroxide (2×100 ml of a 0.1 M solution), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification was accomplished by flash chromatography (eluent: petrol:ether 12:1→3:1) to furnish the thiomannopyranoside **37** (5.05 g, 72%) as an oil; δ_H (600 MHz, $CDCl_3$) 7.36–7.28 (10H, m, Ar-H), 5.40–5.39 (1H, m, H-2), 5.26 (1H, s, H-1), 4.90 (1H, d, *J* 10.9, PhCH_aH$_b$-A), 4.69 (1H, d, *J* 11.3, PhCH_aH$_b$-B), 4.64 (1H, d, *J* 10.9, PhCH$_a$$H_b$-B), 4.54 (1H, d, *J* 11.3, PhCH$_a$$H_b$-B), 3.99 (1H, dd, *J* 9.0, 3.4, H-5), 3.94–3.88 (3H, m, H-6a, H-3, H-4), 3.82 (1H, dd, *J* 11.4, 1.2, H-6b), 2.66–2.56 (2H, m, SCH_2CH$_3$), 2.13 (3H, s, COCH$_3$), 1.27 (3H, t, *J* 7.4, SCH$_2$CH_3), 0.92 (9H, s, SiC$(CH_3)_3$), 0.09 (3H, s, Si$(CH_3)_2$), 0.06 (3H, s, Si$(CH_3)_2$); δ_C (150 MHz, $CDCl_3$) 170.3 (CO), [138.6, 137.8 (Ar-C *ipso*)], [128.4, 128.3, 128.1, 127.8 (×2), 127.6 (Ar-C)], 82.1 (C-1), 78.5 (C-3), 75.2 (PhCH$_2$-A), 74.5 (C-4), 73.2 (C-5), 71.9 (PhCH$_2$-B), 70.7 (C-2), 62.2 (C-6), 25.8 (SiC(CH$_3$)$_3$), 25.3 (SCH$_2$CH$_3$), 21.0 (COCH$_3$), 18.2 (Si$C$$(CH_3)_3$), 14.8 (SCH$_2$$CH_3$), [−5.2, −5.4 (Si$(CH_3)_2$)]; (found (+ESI): M^++Na,

583.2516. $C_{30}H_{44}O_6SiNaS$ requires: *M*, 583.2520) (found: C, 64.5%; H, 7.9%. $C_{30}H_{44}O_6SiS$ requires C, 64.48%; H, 7.58%).

*4.18. Synthesis of (2′S,3′S) ethyl 6-*O-tert-*butyldimethylsilyl-2-*O-*chloroacetyl-3-*O,*4-*O-*[2′,3′-dimethoxybutan-2′,3′-diyl]-1-thio-α-*D-*mannopyranoside **38** and (2′S,3′S) ethyl 2-*O-*chloroacetyl-3-*O,*4-*O-*[2′,3′-dimethoxybutan-2′,3′-diyl]-1-thio-α-*D-*mannopyranoside **29***

To a stirred solution of **37** (5.05 g, 9.04 mmol) in methanol (100 ml) was added anhydrous potassium carbonate (50 mg, cat.) in one portion. Stirring was maintained for a further 14 h before neutralisation with Amberlite IR-120 (plus) and immediate filtration through Celite®. The filter-cake was washed with methanol (30 ml) and the combined filtrates concentrated in vacuo to give the crude hydroxymannopyranoside **39** as an oil. The oil was used without further purification in the next step.

To a stirred solution of the crude **39** in dichloromethane (100 ml) was added pyridine (2.9 ml, 36.1 mmol), via syringe. The reaction mixture was cooled to 0°C before a solution of chloroacetic anhydride (3.18 g, 18.1 mmol) in dichloromethane (20 ml) was added, dropwise, via syringe. Stirring was maintained for a further 1 h at 0°C before further quantities of pyridine and chloroacetic anhydride (as above) were added. Stirring was maintained for a further 15 min, at 0°C, before the reaction was quenched by washing successively with dilute aqueous hydrochloric acid (1.5N, 60 ml) and aqueous sodium bicarbonate solution (100 ml). The organic extract was dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. The crude material was filtered through a short pad of silica to give the chloroacetyl mannopyranoside **38** (0.88 g); ν_{max} (neat) 3064, 3030, 2952, 2928, 2856, 1767, 1606, 1454, 1100; δ_H (600 MHz, $CDCl_3$) 7.35–7.28 (10H, m, Ar-H), 5.47 (1H, s, H-2), 5.27 (1H, s, H-1), 4.87 (1H, d, *J* 10.8, PhC*H*$_a$H$_b$-A), 4.68 (1H, d, *J* 11.2, PhC*H*$_a$H$_b$-B), 4.63 (1H, d, *J* 10.9, PhCH$_a$*H*$_b$-A), 4.55 (1H, d, *J* 11.2, PhCH$_a$*H*$_b$-B), 4.16 (1H, d, *J* 15.2, $COCH_2Cl$), 4.12 (1H, d, *J* 15.2, $COCH_2Cl$), 3.99 (1H, dd, *J* 9.6, 3.0, H-5), 3.94 (1H, dd, *J* 9.4, 3.2, H-3), 3.91 (1H, dd, *J* 11.5, 4.3, H-6a), 3.86 (1H, t, *J* 9.5, H-4), 3.81 (1H, dd, *J* 11.4, 1.3, H-6b), 2.69–2.56 (2H, m, S*CH*$_2$CH$_3$), 1.28 (3H, t, *J* 7.4, SCH$_2$*CH*$_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.08, (3H, s, $Si(CH_3)_2$), 0.06 (3H, s, $Si(CH_3)_2$); δ_C (150 MHz, $CDCl_3$) 166.8 (CO), [138.5, 137.5 (Ar-C *ipso*)], [128.4, 128.3, 128.2, 127.9 (× 2), 127.7 (Ar-C)], 81.7 (C-1), 78.4 (C-3), 75.2 ($PhCH_2$-A), 74.3 (C-4), 73.2 (C-5), 72.7 (C-2), 72.1 ($PhCH_2$-B), 62.1 (C-6), 40.8 ($COCH_2Cl$), 25.8 ($SiC(CH_3)_3$), 25.4 (S*CH*$_2$CH$_3$), 18.2 ($SiC(CH_3)_3$), 14.8 (SCH$_2$*CH*$_3$), [−5.2, −5.4 ($Si(CH_3)_2$)]; (found (+FAB): M^+, 594.2201. $C_{30}H_{43}ClO_6SSi$ requires: *M*, 594.2238); (found: C, 60.8%; H, 7.35%. $C_{30}H_{43}ClO_6SSi$ requires: C, 60.53%; H, 7.28%) and slightly impure material (4.7 g, combined yield >95% over two steps) which was carried forward to the next step without further purification.

To a stirred solution of the crude **38** (4.7 g, 7.9 mmol) in acetonitrile (10 ml) was added aqueous hydrofluoric acid (48% w/v, 0.36 ml, 8.7 mmol), via syringe. Stirring was maintained for 1 h before the reaction was quenched by the addition of aqueous sodium bicarbonate solution (100 ml). The reaction was extracted with dichloromethane (2×150 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo to give a syrup. Purification by flash chromatography on silica gel (eluent: petrol:ether 4:1→1:2) gave the desilylated mannopyranoside **29** (3.29 g, 87%) as an oil, which solidified on storage at −20°C. Subsequent precipitation (ether:hexane) gave an amorphous solid; $[\alpha]_D^{26}$=+80.3 (*c* 0.98, $CHCl_3$); ν_{max} (KBr) 3432, 3064, 3030, 2962, 2923, 2869, 1757, 1496, 1454, 1183, 1097; δ_H (600 MHz, $CDCl_3$) 7.36–7.28 (10H, m, Ar-H), 5.50 (1H, s, H-2), 5.28 (1H, s, H-1), 4.89 (1H, d, *J* 11.0, PhC*H*$_a$H$_b$-A), 4.69 (1H, d, *J* 11.2, PhC*H*$_a$H$_b$-B), 4.63 (1H, d, *J* 11.0, PhCH$_a$*H*$_b$-A), 4.55 (1H, d, *J* 11.2, PhCH$_a$*H*$_b$-B), 4.14 (2H, s, $COCH_2Cl$), 4.05 (1H, dt, *J* 9.7, 3.3, H-5), 3.95 (1H, dd, *J* 9.3, 3.1, H-3), 3.85 (1H, t, *J* 9.6, H-4), 3.82–3.80 (2H, m, H-6a, H-6b), 2.67–2.58 (2H, m, S*CH*$_2$CH$_3$), 1.81 (1H, dd, *J* 7.1, 5.8, 6-OH), 1.28 (3H, t, *J* 7.4, SCH$_2$*CH*$_3$); δ_C (150 MHz, $CDCl_3$) 166.7 (CO), [138.1, 137.4

(Ar-C *ipso*)], [128.5, 128.4, 128.2, 128.0, 127.9, 127.8 (Ar-C)], 82.1 (C-1), 78.3 (C-3), 75.2 ($PhCH_2$-A), 74.0 (C-4), 72.5 (C-2), 72.4 (C-5), 72.1 ($PhCH_2$-B), 62.0 (C-6), 40.8 ($COCH_2Cl$), 25.6 (SCH_2CH_3), 14.8 (SCH_2CH_3); (found (+ESI): M^++Na, 503.1258. $C_{24}H_{29}ClO_6SNa$ requires: *M*, 503.1271); (found: C, 59.7%; H, 6.15%. $C_{24}H_{29}ClO_6S$ requires: C, 59.93%; H, 6.08%).

*4.19. Synthesis of ethyl 3,4-di-*O*-benzyl-2-*O*-chloroacetyl-6-*O*-(2-*O*-allyloxycarbonyl-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-1-thio-α-*D*-mannopyranoside **23***

To a stirred suspension of **30**[78] (0.92 g, 1.56 mmol), **29** (0.50 g, 1.04 mmol) and 4 Å MS (3.0 g) in dichloromethane/ether (1:1, 20 ml) was added NIS (0.37 g, 1.56 mmol) in one portion, followed immediately by TMSOTf (100 μl of a stock solution of 100 μl TMSOTf in 1 ml dichloromethane) via syringe. The reaction mixture was stirred for a further 15 min and then filtered through Celite®. The filter-cake was washed with ether (80 ml) and the combined filtrates washed with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution (1:1 v/v, 80 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by iterative flash chromatography on silica gel (eluent: 3:1→1:1 petrol:ether) gave the dimannopyranoside **23** (0.80 g, 77%) as a pale yellow oil; ν_{max} (film) 3063, 3029, 2927, 2870, 1746, 1649, 1605, 1586, 1497, 1454, 1368, 1260, 1215, 1095; δ_H (600 MHz, $CDCl_3$) 7.34–7.14 (25H, m, Ar-H), 5.97–5.91 (1H, m, $H_2C{=}CHCH_2O$), 5.48 (1H, s, H-2^a), 5.38 (1H, d, *J* 17.2, *trans* *H*HC=CHCH$_2$O), 5.28–5.26 (2H, m, *cis* *H*HC=CHCH$_2$O, H-1^a), 5.22 (1H, s, H-2^b), 5.12 (1H, s, H-1^b), 4.87 (1H, d, *J* 10.9, PhCH_aH_b-A), 4.86 (1H, d, *J* 10.8, PhCH_aH_b-B), 4.74 (1H, d, *J*, 11.5, PhCH_aH_b-C), 4.70 (1H, d, *J* 11.1, PhCH_aH_b-D), 4.65–4.63 (3H, m, $H_2C{=}CHCH_2O$, PhCH_aH_b-E), 4.58 (1H, d, *J* 11.5, $PhCH_aH_b$-C), 4.54 (1H, d, *J* 11.1, $PhCH_aH_b$-D), 4.51 (1H, d, *J* 11.0, $PhCH_aH_b$-A), 4.49–4.47 (2H, m, $PhCH_aH_b$-B, $PhCH_aH_b$-E), 4.23–4.14 (3H, m, H-5^a, $COCH_2Cl$), 3.97–3.87 (4H, m, H-3^a, H-$6a^a$, H-3^b, H-4^b), 3.82–3.76 (3H, m, H-4^a, H-$6b^a$, H-5^b), 3.72 (1H, dd, 10.8, 4.5, H-$6a^b$), 3.64 (1H, d, 10.7, H-$6b^b$), 2.65–2.52 (2H, m, SCH_2CH_3), 1.25 (3H, t, *J* 7.4, SCH_2CH_3); δ_C (150 MHz, $CDCl_3$) 166.9, ($COCH_2Cl$), 154.6 ($CO_2CH_2CH{=}CH_2$), [138.4, 138.2, 138.1, 137.9, 137.4 (Ar-C *ipso*)], 131.5 ($H_2C{=}CHCH_2O$), [128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 127.8, 127.8, 127.7, 127.5 (Ar-C)], 119.0 ($H_2C{=}CHCH_2O$), 97.5 (C-1^b), 81.8 (C-1^a), [78.4, 77.7 (C-3^a,C-3^b)], [75.2 ($PhCH_2$-A, $PhCH_2$-B)], 74.3 (C-4^b), 74.1 (C-4^a/C-5^b), 73.4 ($PhCH_2$-E), [72.4, 72.3 (C-2^a, C-2^b)], 72.0 ($PhCH_2$-D), 71.8 (C-5^a), 71.7 ($PhCH_2$-C), 71.6 (C-4^a/C-5^b), 68.9 (C-6^b), 68.8 ($H_2C{=}CHCH_2O$), 65.4 (C-6^a), 40.9 ($COCH_2Cl$), 25.5 (SCH_2CH_3), 14.9 (SCH_2CH_3); (found (+ESI): M^++Na, 1019.3425. $C_{55}H_{61}ClO_{13}SNa$ requires: *M*, 1019.3414); (found: C, 66.4%; H, 6.3%. $C_{55}H_{61}ClO_{13}S$ requires: C, 66.22%; H, 6.16%).

*4.20. Synthesis of ethyl 3,4-di-*O*-benzyl-2-*O*-chloroacetyl-6-*O*-(3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-1-thio-α-*D*-mannopyranoside **24***

To a stirred solution of **23** (1.05 g, 1.05 mmol) and dimedone (0.78 g, 5.26 mmol) in THF (30 ml) was added $Pd(PPh_3)_4$ (15 mg, cat.) in one portion. The solution was degassed once and stirring maintained for a further 14 h before adsorption onto silica. Purification by MPLC on silica gel (eluent: 3:2 petrol:ethyl acetate) gave the hydroxydimannopyranoside **24** (0.72 g, 75%) as a yellow oil; ν_{max} (neat) 3442, 3087, 3062, 3029, 2926, 1738, 1604, 1495, 1453, 1367, 1284, 1243, 1100; δ_H (600 MHz, $CDCl_3$) 7.36–7.16 (25H, m, Ar-H), 5.50 (1H, m, H-2^a), 5.27 (1H, s, H-1^a), 5.06 (1H, s, H-1^b), 4.89 (1H, d, *J* 11.0, PhCH_aH_b-A), 4.83 (1H, d, *J* 10.9, PhCH_aH_b-B), 4.71–4.66 (3H, m, $PhCH_2$-C, PhCH_aH_b-D), 4.63 (1H, d, *J* 12.1, PhCH_aH_b-E), 4.54–4.47 (4H, m, $PhCH_aH_b$-A, $PhCH_aH_b$-B, $PhCH_aH_b$-D, $PhCH_aH_b$-E), 4.16 (1H, dd, *J*

9.8, 3.4, H-5[a]), 4.14–4.10 (3H, m, $COCH_2Cl$, H-2[b]), 3.96–3.91 (2H, m, H-3[a], H-6a[a]), 3.89–3.84 (2H, m, H-3[b], H-4[b]), 3.79–3.74 (3H, m, H-4[a], H-5[b], H-6b[a]), 3.67 (1H, dd, 10.8, 4.3, H-6a[b]), 3.61 (1H, dd, 10.7, 1.5, H-6b[b]), 2.66–2.53 (2H, m, SCH_2CH_3), 2.44 (1H, d, 2.4, 2-OH[b]), 1.26 (3H, t, *J* 7.4, SCH_2CH_3); δ_C (150 MHz, $CDCl_3$) 166.6 (*C*OCH_2Cl), [138.4, 138.3, 138.2, 137.8, 137.4 (Ar-C *ipso*)], [128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (Ar-C)], 99.2 (C-1[b]), 81.7 (C-1[a]), 79.9 (C-3[b]), 78.5 (C-3[a]), 75.1 ($PhCH_2$-A), 75.0 ($PhCH_2$-B), 74.3 (C-4[a]), 74.2 (C-4[b]), 73.4 ($PhCH_2$-E), 72.3 (C-2[a]), 72.0 ($PhCH_2$-C), 71.8 ($PhCH_2$-D), 71.6 (C-5[a]), 71.1 (C-5[b]), 68.8 (C-6[b]), 68.2 (C-2[b]), 65.7 (C-6[a]), 40.8 (CO*C*H_2Cl), 25.5 (SCH_2CH_3), 14.9 (SCH_2CH_3); (found (+ESI): M^++Na, 935.3152. $C_{51}H_{57}ClO_{11}SNa$ requires: *M*, 935.3208); (found: C, 66.9%; H, 6.4%. $C_{51}H_{57}ClO_{11}S$ requires: C, 67.06%; H, 6.29%).

*4.21. Synthesis of (2′*S*,3′*S*) ethyl 3,4-di-*O*-benzyl-2-*O*-chloroacetyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-(6-*O*-tert-butyldimethylsilyl-3-*O*,4-*O*-[2′,3′-dimethoxybutan-2′,3′-diyl]-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl)-1-thio-α-*D*-mannopyranoside **31***

To a mixture of AgOTf (74 mg, 0.28 mmol), 4 Å MS (0.50 g) and Cp_2HfCl_2 (55 mg, 0.14 mmol) was added a solution of **24** (50 mg, 55 μmol) in toluene (0.6 ml) via syringe. The resulting suspension was stirred for 10 min before a solution of **22** (67 mg, 72 μmol) in dichloromethane (0.6 ml) was added via syringe. Stirring was maintained for a further 45 min before the reaction mixture was sonicated briefly. Stirring was maintained for a further 1.25 h and then filtered through Celite®. The filter-cake was washed with chloroform (50 ml) and the combined filtrates washed with aqueous sodium bicarbonate solution (50 ml). The aqueous portion was extracted with chloroform (50 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica gel (eluent: petrol:ether 2:1→1:1) gave the tetramannopyranoside **31** (73 mg, 73%) as a foam; δ_H (600 MHz, $CDCl_3$) 7.45–7.44 (2H, m, Ar-H), 7.32–7.12 (42H, m, Ar-H), 7.03 (1H, t, *J* 7.4, Ar-H), 5.55 (1H, s, H-1[d]), 5.49 (1H, s, H-2[a]), 5.25 (1H, s, H-1[a]), 5.21 (1H, s, H-1[c]), 4.88–4.86 (3H, m, H-1[b], $PhCH_2$-A), 4.82 (1H, d, *J* 10.9, $PhCH_aH_b$-B), 4.78 (1H, d, *J* 12.4, $PhCH_aH_b$-C), 4.69–4.59 (5H, m, $PhCH_aH_b$-D, $PhCH_aH_b$-C, $PhCH_aH_b$-E, $PhCH_aH_b$-F, $PhCH_aH_b$-G), 4.55–4.46 (8H, m, $PhCH_aH_b$-B, $PhCH_aH_b$-D, $PhCH_aH_b$-E, $PhCH_aH_b$-G, $PhCH_2$-H, $PhCH_2$-I), 4.32 (1H, d, *J* 12.2, $PhCH_aH_b$-F), 4.20 (1H, s, H-2[c]), 4.19–4.16 (1H, m, H-5[a]), 4.15 (1H, s, H-2[b]), 4.12–4.06 (5H, m, H-4[c], H-4[d], H-3[c], $COCH_2Cl$), 4.01 (1H, s, H-2[d]), 3.95–3.78 (7H, m, H-6a[c], H-6b[c], H-6a[a], H-3[a], H-3[d], H-4[b], H-3[b]), 3.76–3.59 (7H, m, H-5[c], H-6b[a], H-4[a], H-5[d], H-6a[d], H-6a[b], H-5[b]), 3.55–3.50 (2H, m, H-6b[b], H-6b[d]), 3.27 (3H, s, OCH_3 BDA), 3.11 (3H, s, OCH_3 BDA), 2.61–2.48 (2H, m, SCH_2CH_3), 1.28 (3H, s, CH_3 BDA), 1.27 (3H, s, CH_3 BDA), 1.21 (3H, t, *J* 7.4, SCH_2CH_3), 0.86 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 166.7 (*C*OCH_2Cl), [138.9, 138.8, 138.5, 138.3, 138.2, 138.0, 137.3 (Ar-C *ipso*)], [128.5, 128.4, 128.3 (×3), 128.2 (×2), 128.1, 128.0 (×2), 127.9, 127.8, 127.7 (×2), 127.5, 127.4 (×3), 127.3 (×2) (Ar-C)], 100.7 (C-1[c]), [99.6, 99.4 (BDA acetal C)], 98.9 (C-1[b]), 98.4 (C-1[d]), 81.5 (C-1[a]), 80.1 (C-3[d]), 79.9 (C-3[b]), 78.7 (C-3[a]), 74.9 ($PhCH_2$-A, $PhCH_2$-B), 74.6 (C-4[b], C-4[d]), 74.5 (C-2[d]), 74.4 (C-4[a]), 73.6 (C-2[c]), 73.3 ($PhCH_2$-F), [72.5, 72.4 (C-2[b], C-5[c])], 72.2 (C-2[a]), 72.0 (C-5[d]/5[b]), 72.0 ($PhCH_2$-C), 71.9 (C-5[d]/5[b]), [71.9, 71.8, 71.6 ($PhCH_2$-D, $PhCH_2$-E, $PhCH_2$-H, $PhCH_2$-I)], 71.1 (C-5[a]), 69.0 (C-6[b]), 68.9 (C-3[c]), 68.8 (C-6[d]), 66.1 (C-6[a]), 62.8 (C-4[c]), 61.6 (C-6[c]), [48.0, 47.7 (OCH_3 BDA)], 40.8 (CO*C*H_2Cl), 25.9 ($SiC(CH_3)_3$), 25.2 (SCH_2CH_3), 18.3 ($SiC(CH_3)_3$), [18.0, 17.8 (CH_3 BDA)], 14.8 (SCH_2CH_3), [–4.7, –5.4 ($Si(CH_3)_2$]; (found (+ESI): M^++Na, 1847.7812. $C_{103}H_{125}ClO_{23}SSiNa$ requires: *M*, 1847.7682).

*4.22. Synthesis of (2′S,3′S) 1-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-6-*O*-(2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-(6-O-tert-butyldimethylsilyl-3-*O*,4-*O*-[2′,3′-dimethoxybutan-2′,3′-diyl]-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl)-α-*D*-mannopyranosyl)-α-*D*-glucopyranosyl)-*D*-myo-inositol **21***

To a stirred suspension of **31** (50 mg, 27 μmol), **25**[17] (14 mg, 14 μmol) and 4 Å MS (0.14 g) in dichloromethane:ether (3:1, 0.36 ml) was added NIS (13 mg, 55 μmol) in one portion, followed immediately by the addition of TMSOTf (50 μl of a stock solution of 80 μl TMSOTf in 1 ml dichloromethane), via syringe. The reaction mixture was stirred for a further 20 min before the resulting purple suspension was filtered through Celite®. The filter-cake was washed with ether (40 ml) and the combined filtrates washed with a mixture of aqueous sodium bicarbonate and aqueous sodium thiosulfate solution (1:1 v/v, 20 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil. Purification by preparative TLC (eluent: dichloromethane:ether 97:3) gave the pseudohexasaccharide **21** (13 mg, 35%) as a pale yellow oil; δ_H (600 MHz, $CDCl_3$) 7.43–6.91 (75H, m, Ar-H), 5.94–5.91 (1H, m, $H_2C{=}CHCH_2O$), 5.72 (1H, d, *J* 3.3, H-1^b), 5.55 (1H, s, H-1^f), 5.44 (1H, s, H-2^c), 5.36 (1H, s, H-1^c), 5.28 (1H, d, *J* 17.0, *trans* *H*HC=CHCH$_2$O), 5.20–5.18 (2H, m, H-1^e, *cis* *H*HC=CHCH$_2$O), 5.03 (1H, d, *J* 11.4, PhCH_aH_b), 4.96–4.92 (2H, m, PhCH_aH_b, PhCH_aH_b), 4.85–4.83 (4H, m, PhCH_aH_b, PhCH_aH_b, PhCH$_2$), 4.78–4.57 (11H, m, PhCH_aH_b, PhCH_aH_b, PhCH_aH_b, PhCH_aH_b, PhCH_aH_b, PhCH$_a$*H*$_b$, PhCH$_a$*H*$_b$, PhCH$_a$*H*$_b$, PhCH$_a$*H*$_b$, PhCH$_a$*H*$_b$, H-1^d), 4.52–4.24 (13H, m, PhCH$_a$*H*$_b$, PhCH$_a$*H*$_b$, PhCH$_a$*H*$_b$, PhCH$_a$*H*$_b$, PhCH$_2$, PhCH$_2$, PhCH$_2$, PhCH$_2$, H-6^a), 4.17–4.00 (9H, m, H-2^e, H-4^e, H-2^d, H-4^a, H-5^b, H-3^e, H-4^f, H-2^a, H-2^f), 3.95–3.63 (17H, m, H-3^b, H-3^f, H-4^b, H-6a^e, COCH$_2$Cl, $H_2C{=}CHCH_2O$, H-6a^c, H-3^c, H-3^d, H-4^d, H-5^f, H-4^c, H-6a^f, H-5^e, H-6b^e), 3.55–3.48 (3H, m, H-5^c, H-5^d, H-6b^f), 3.45–3.38 (4H, m, H-1^a, H-3^a, H-5^a, H-6a^d), 3.33 (1H, d, *J* 11.2, H-6b^d), 3.30–3.25 (4H, m, H-6a^b, OCH_3 BDA), 3.22–3.20 (2H, m, H-2^b, H-6b^c), 3.13 (1H, d, *J* 9.9, H-6b^b), 3.07 (3H, s, OCH_3 BDA), 1.27 (6H, s, CH_3 BDA), 0.82 (9H, $SiC(CH_3)_3$), 0.01 (3H, s, $SiCH_3$), 0.00 (3H, $SiCH_3$); δ_C (150 MHz, $CDCl_3$) 166.3 (*C*OCH$_2$Cl), [138.9–137.5 (Ar-C *ipso*)], 134.2 ($H_2C{=}CHCH_2O$), [128.5–126.9 (Ar-C, Ar-C *ipso*)], 117.1 ($H_2C{=}CHCH_2O$), 100.5 (C-1^e), [99.6, 99.4 (BDA acetal C)], 99.0 (C-1^d), 98.5 (C-1^c), 98.2 (C-1^f), 97.6 (C-1^b), 82.0 (C-4^a), 81.8 (C-1/3^a), 81.3 (C-5^a), 80.9 (C-1/3^a), 80.4 (C-3^b), 80.1 (C-3^f/4^b), 79.7 (C-3^d), 78.6 (C-3^c), 75.8 (PhCH$_2$), 75.4 (C-6^a), [75.2, 75.0, 74.9 (PhCH$_2$)], 74.6 (C-4^d), [74.5 (C-3^f/4^b, C-4^f)], 74.3 (C-2^f), [74.1, 74.0 (PhCH$_2$)], 73.4 (C-2^e), [73.4, 73.3 (PhCH$_2$)], 73.2 (C-4^c/5^e), [73.1, 72.8 (PhCH$_2$)], 72.8 (C-2^a), 72.2 (C-4^c/5^e), [71.9 (C-2^d, C-5^f, C-5^d)], [71.9 (PhCH$_2$)], [71.8, 71.6, 71.5 (PhCH$_2$)], 71.0 (C-5^c), 70.8 ($H_2C{=}CHCH_2O$), 70.4 (C-2^c), 69.5 (C-5^b), 68.9 (C-3^e), 68.7 (C-6^d, C-6^f), 68.4 (C-6^b), 65.8 (C-6^c), 63.4 (C-2^b), 62.5 (C-4^e), 61.4 (C-6^e), [48.0, 47.7 (OCH_3 BDA)], 40.7 (CO*C*H$_2$Cl), 25.9 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), [18.0, 17.8 (CH_3 BDA)], [−4.6, −5.5 (Si(CH$_3$)$_2$)]; (found (+ESI): M$^+$+Na, 2733.1664. $C_{158}H_{180}ClN_3O_{33}SiNa$ requires: *M*, 2733.1849).

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