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# The synthesis of phosphorylated disaccharide components of the extracellular phosphomannan of *Pichia* (*Hansenula*) *holstii* NRRL Y-2448

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**Abstract**—Methods for the stereoselective synthesis of α-(1→2)- and α-(1→3)-linked $6^{II}$-*O*-phosphomannobiosides were developed. Two strategies were successfully employed: a D-mannosyl acceptor was coupled with a phosphorylated D-mannosyl trichloroacetimidate donor, or alternatively with a differentially 6-*O*-protected D-mannosyl trichloroacetimidate donor which, after glycosylation, was selectively deprotected and phosphorylated. Two target phosphomannobiosides intended for use in SAR studies of the antiangiogenic drug candidate PI-88, 2-*O*-(6-*O*-phospho-α-D-mannopyranosyl)-D-mannopyranose and methyl 3-*O*-(6-*O*-phospho-α-D-mannopyranosyl)-α-D-mannopyranoside, were synthesized. The former is a minor component of the side-chain repeating unit of the extracellular phosphomannan of *Pichia* (*Hansenula*) *holstii* NRRL Y-2448, whilst the latter represents a nonreducing end fragment of the phosphomannan.


## 1. Introduction

The phosphosulfomannan agent PI-88 (**1**)[1] has been identified as a promising inhibitor of tumour growth and metastasis and is currently undergoing Phase II clinical trials in patients with advanced malignancies.[2] PI-88 inhibits angiogenesis by antagonizing the interactions of angiogenic growth factors (principally FGF-1, FGF-2 and VEGF) and their receptors with heparan sulfate.[1,3] PI-88 is also a potent inhibitor of heparanase, an endoglucuronidase that cleaves heparan sulfate and plays a key role in metastasis and angiogenesis.[4,5] In addition to its anticancer effects, PI-88 inhibits the blood coagulation cascade,[6–8] blocks vascular smooth muscle cell proliferation and intimal thickening[9] and inhibits herpes simplex virus (HSV) infection of cells and cell-to-cell spread of HSV-1 and HSV-2.[10]

PI-88 is prepared by exhaustive sulfonation[11] of the oligosaccharide phosphate fraction (**2**) obtained by mild, acid-catalyzed hydrolysis of the extracellular phosphomannan of the yeast *Pichia* (*Hansenula*) *holstii* NRRL Y-2448.[12,13] The major components of **2** are the penta- and tetrasaccharide phosphates **3** (~60%) and **4** (~30%), respectively, whilst the remaining 10% comprises di-, tri- and hexasaccharide phosphates (**5**–**7**) and a tetrasaccharylamine (not shown).[13,14] These oligosaccharides represent the repeating units of the side chains attached to the core of the phosphomannan. The individual components of **2** have not previously been isolated primarily due to an inability to effectively fractionate the mixture.† Consequently, structure–activity relationship (SAR) studies of PI-88 have been restricted to sulfonating the more readily available nonphosphorylated derivatives of oligosaccharides **3**–**6**,[3,10] or using partially purified fractions obtained by size exclusion chromatography of PI-88 itself (Fig. 1).[11]

To address the need for quantities of pure, phosphorylated PI-88 oligosaccharides for SAR studies, the synthesis of the individual phosphomannans present in **2** (and their subsequent sulfonation) is required. We therefore sought to develop methods for the synthesis of phosphomannans containing α-(1→2) and α-(1→3) linkages. The initial synthetic targets were the phosphomannobiosides **5** and **8**. The α-(1→2)-linked phosphomannobioside **5** is the smallest component present in **2** and is thus the first target, whilst the α-(1→3)-linked **8** is a nonreducing end

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† This has been attributed to the presence of the phophate group.[13]

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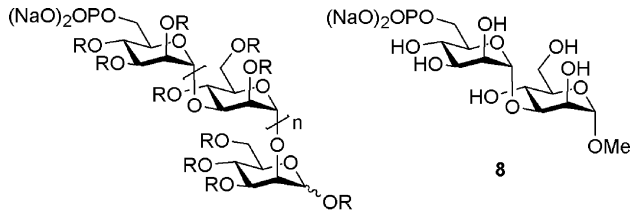


| | n | R |
|---|---|---|
| **1** | 0-4 | $SO_3Na$ or H |
| **2** | 0-4 | H |
| **3** | 3 | H |
| **4** | 2 | H |
| **5** | 0 | H |
| **6** | 1 | H |
| **7** | 4 | H |

**Figure 1.**

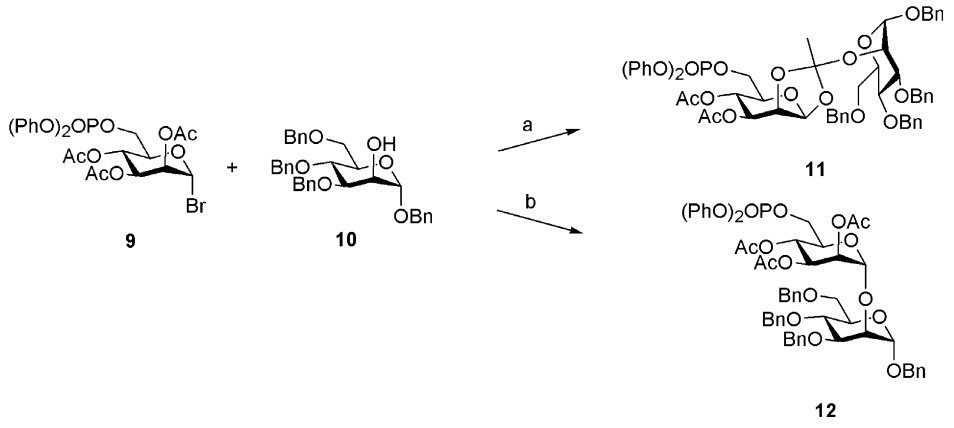
fragment of these phosphomannans, with the methyl glycoside representing the fixed α-linkage to succeeding sugars. Two strategies were explored for the synthesis of these disaccharides. Firstly, the glycosylation of a suitable acceptor with a 6-*O*-phosphorylated D-mannopyranosyl donor, or alternatively, glycosylation with a differentially 6-*O*-protected D-mannopyranosyl donor, followed by removal of the protecting group and subsequent phosphorylation.

## 2. Results and discussion

### 2.1. Synthesis via phosphorylated D-mannopyranosyl donors

Many of the known procedures for synthesising 6-*O*-phosphomannobiosides rely on the condensation of a phosphorylated D-mannopyranosyl donor with a suitably protected alcohol acceptor[15–19] with good yields being reported for both primary (6-OH) and secondary (2-OH or 3-OH) glycosyl acceptors, though not with universally successful outcomes. With precedent,[18] the bromide **9** was condensed with the alcohol **10**[20] in a silver triflate (AgOTf)-promoted reaction incorporating 1,1,3,3-tetramethylurea (TMU) as a free-acid scavenger. However,[18] in our hands this procedure resulted in exclusive formation of the orthoester **11** (65%) (Scheme 1). While the potential for rearrangement[21] to the α-glycoside under acidic conditions exists, it was subsequently found that omission of TMU from the reaction gave the desired (1→2)-linked disaccharide **12** in good yield (70%) (Scheme 1).

The alcohol **13**[22] was then targeted for glycosylation for the preparation of a (1→3)-linked disaccharide, but under these same conditions the reaction was not successful. Similar observations were noted by Matta et al. in attempts to glycosylate some secondary alcohol acceptors.[15] An alternative, more reactive glycosyl donor was thus sought to effect the desired glycosylation (Fig. 2).



**Scheme 1.** (a) Literature[18] conditions, 65%; (b) modified conditions, 70%.

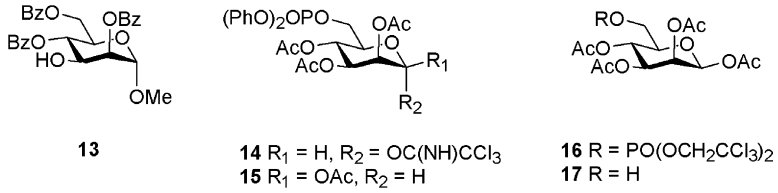
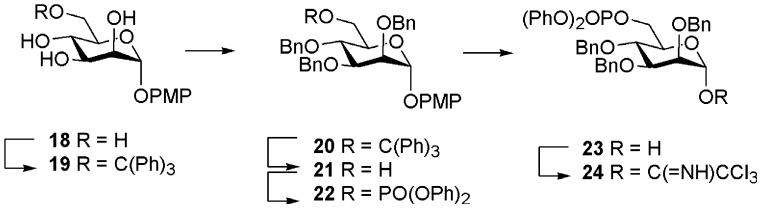


**Figure 2.**

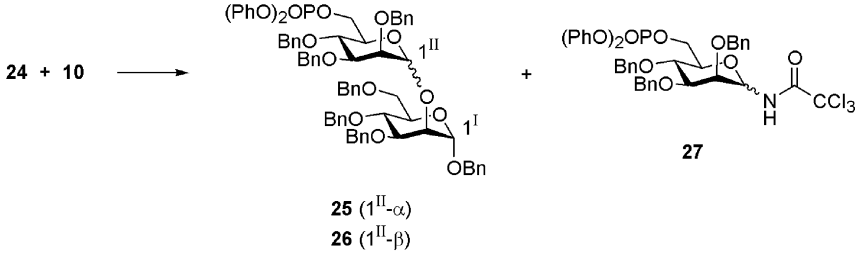
From the multitude of available methods for activating monosaccharides for glycosylation, trichloroacetimidates were selected for further investigation. A classical route to preparing an imidate such as **14** from the readily available[23] tetraacetate **15** necessitates selective (anomeric) deacylation prior to condensation with trichloroacetonitrile. Treatment of **15** with benzylamine or hydrazine acetate, however, led to unwanted reactions at the phosphate ester. The documented versatility of the bis(trichloroethyl) phosphate protecting group in disaccharide synthesis[17] lead us to prepare compound **16** from the alcohol **17**[24] as an alternative synthon. Disappointingly, this group proved equally prone to nucleophilic attack during manipulation of the anomeric centre. A new strategy for preparing a suitable glycosyl donor was therefore required.

The *p*-methoxyphenyl α-D-mannoside **18**[25] was converted by way of the trityl ether **19** to the tribenzyl ether **20**. Acid-catalyzed hydrolysis of the trityl ether was rapid, yielding the alcohol **21** as the sole product. This in turn was treated with diphenyl phosphorochloridate and triethylamine to yield the diphenyl phosphate **22** in good yield (72%) (Scheme 2). Oxidative cleavage of the *p*-methoxyphenyl protecting group with cerium(IV) ammonium nitrate (CAN) at low temperature (0 °C)[26] afforded a product, presumably the hemiacetal **23**, which upon treatment with trichloroacetonitrile and DBU was successfully converted into the trichloroacetimidate **24**. A trimethylsilyl triflate (TMSOTf) promoted glycosylation of the alcohol **10** with the imidate **24** resulted in an unexpected outcome. In addition to a chromatographically indistinguishable mixture (9:1) of the phosphomannobiosides **25** and **26** (55%), the amide **27**, presumably resulting from an acid catalyzed rearrangement of the imidate,[27] was obtained (31%) (Scheme 3). Imidate rearrangements of this type have been previously noted in attempted glycosylations of poor nucleophiles.[28–30]

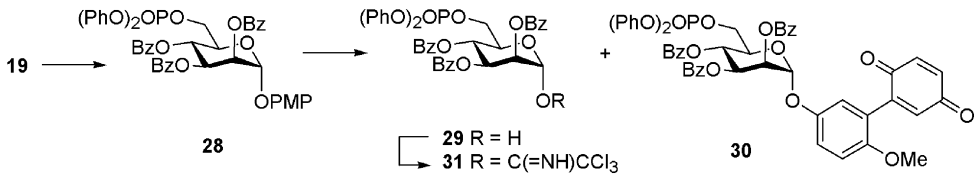
In order to improve selectivity in glycosylation, a 2-*O*-acyl (participating) protecting group was desired. The tribenzoylated mannoside **28** was prepared from the trityl ether **19** in a similar procedure to the one previously outlined (Scheme 2). In contrast to the tribenzylether **22**, treatment of the tribenzoate **28** with CAN under similar conditions yielded an equal mixture of the hemiacetal **29** and an oxidatively-coupled by-product (**30**) (Scheme 4). The occurrence of this by-product was effectively diminished, however, when the reaction was performed at slightly elevated temperatures (30 °C).[22] Upon treatment with trichloroacetonitrile and potassium carbonate, the hemiacetal **29** gave the imidate **31** in good yield (85%).



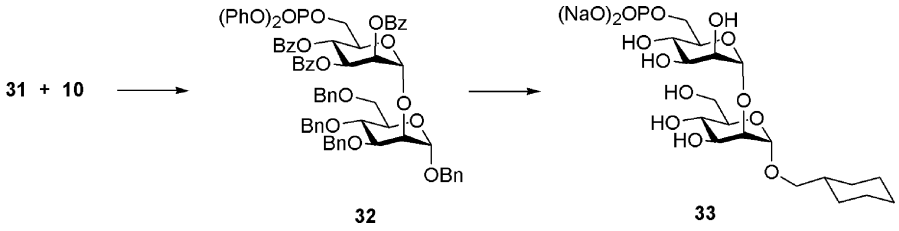

**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

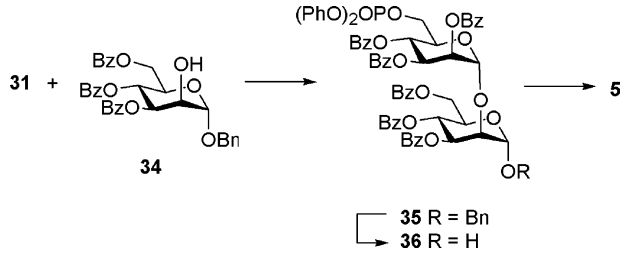



**Scheme 5.**

TMSOTf was once again employed for glycosylation of the alcohol **10** with the imidate **31** and resulted in the exclusive formation of the α-(1→2)-phosphomannobioside **32** (79%) (Scheme 5). The identity of the phosphomannobioside was confirmed through a variety of spectroscopic techniques including $^{1}H$, $^{31}P$ and $^{13}C$ NMR with characteristic $^{13}C$–$^{31}P$ coupling constants[19] observed ($^{2}J_{C6,P}$ = 5.7 Hz and $^{3}J_{C5,P}$ = 7.3 Hz).

A published protocol[16] for deprotection of the newly synthesized $6^{II}$-*O*-phosphomannobioside **32** was then followed. This involved Pd/C-catalyzed hydrogenolysis of the benzyl ethers, $PtO_2$-catalyzed hydrogenation of the phosphate phenyl groups (100 psi) and transesterification of the benzoate esters. Thus, phosphomannobioside **32** was submitted to the reaction sequence but gave irreproducible results—the reaction was generally plagued by an incomplete and indiscriminate hydrogenolysis of the benzyl ether protecting groups even over extended periods of time. In one outcome, following an exhaustive hydrogenolysis with Pd/C and then Pearlman's catalyst [$Pd(OH)_2$/C], the crude reaction mixture was successively hydrogenated with $PtO_2$ and transesterified but yielded only the 1-*O*-methylcyclohexyl mannobioside **33** in 23% yield (Scheme 5).

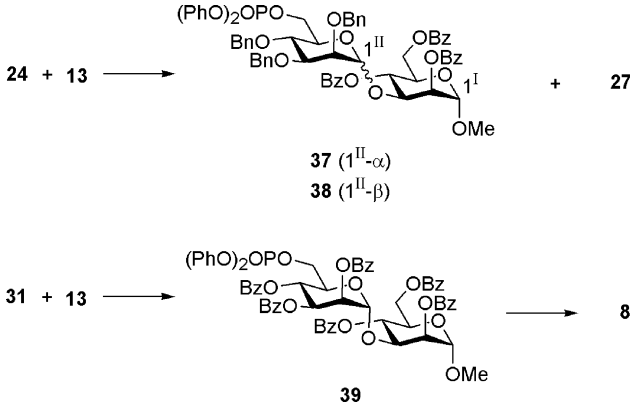
In an effort to monitor the removal of the benzyl ether protecting group more closely, the alcohol **34** [derived from 3,4,6-tri-*O*-acetyl-1,2-*O*-(benzyloxyethylidene)-β-D-mannopyranose[20] through the processes of transesterification, benzoylation, orthoester rearrangement and acid-catalyzed deacetylation] was glycosylated with the imidate **31** to form the hexabenzoate **35** in good yield (84%). Hydrogenolysis of the $1^{I}$-*O*-benzyl ether of **35** over Pearlman's catalyst was slow (72 h at 100 psi) although the hemiacetal product **36** was confirmed by an absence of benzylic-$CH_2$ protons in the $^{1}H$ NMR spectrum ($\delta$ 4.61, 4.79 AB quartet) (Scheme 6).



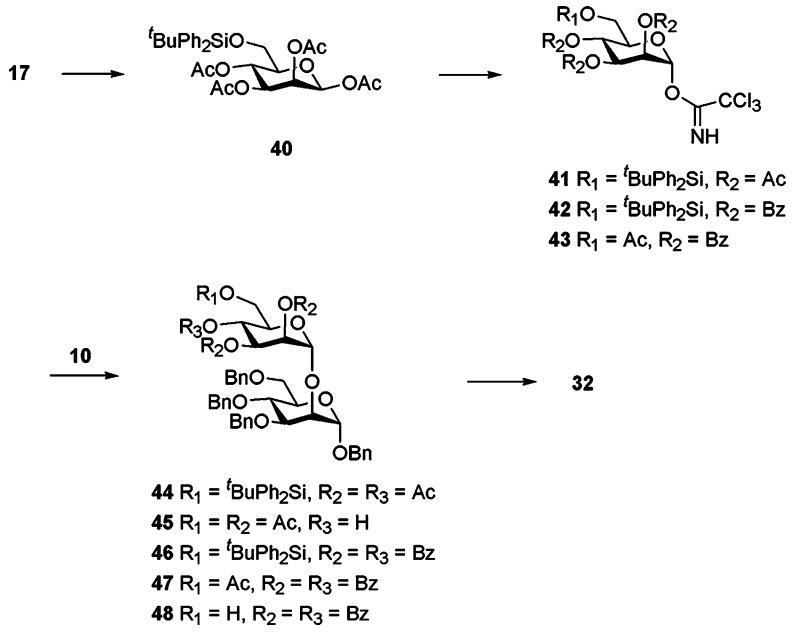

**Scheme 6.**

Though necessarily lengthy, these conditions did not lead to either complete or partial hydrolysis of the $6^{II}$-*O*-diphenylphosphate group. Sabesan and Neira[31] have observed that conversion of benzoyl to cyclohexylcarbonyl esters may occur under the forcing conditions required for hydrogenation of sugar diphenylphosphates ($PtO_2/H_2$/100 psi). While such groups may well have been formed during the hydrogenation of **36**, all esters were susceptible to methoxide-induced transesterification and the target α-(1→2)-phosphomannobioside **5** was obtained as the sole product over the three steps (30%). This sample was isolated as the disodium salt following purification by size exclusion chromatography (Bio-Gel P-2) and characterized both spectroscopically ($^{1}H$ and $^{31}P$ NMR) and by capillary electrophoresis (CE, $t_m$ = 18.8 min). In an improved protocol, the hexabenzoate **35** was first subjected to base-catalyzed hydrolysis (2 M KOH/THF/18-crown-6), during which the diphenyl phosphate was partially deprotected, and then rapid (<1 h each) hydrogenolyses of the benzyl ether and remaining phenyl phosphate. The product of these reactions was acidified (AG® 50W-X8, $H^+$) and then neutralized with $Na_2CO_3$ (1 M) prior to size exclusion chromatography (Bio-Gel P-2) to yield the phosphomannobioside **5** (49%), identical in all respects to the sample previously prepared.

Attention was then turned to investigating the outcomes of glycosylation of the alcohol **13** with the two imidates at hand for the preparation of a (1→3)-linked disaccharide. Firstly, when the tribenzyl ether **24** was used as glycosyl donor, a mixture (2:1) of the disaccharides **37** and **38** (72%) was obtained and once again the amide




**Scheme 7.**




**Scheme 8.**

by-product **27** was formed (31% on **24**). In contrast, complete selectivity in glycosylation was observed when the tribenzoylated imidate **31** was used as glycosyl donor and the α-(1→3)-phosphomannobioside **39** was isolated as the sole product (78%). The deprotection of the phosphomannobioside **39** was less challenging than for **35** as a consequence of having only two types of protecting groups in place. Slight modifications to the two previously established protocols were investigated: hydrogenation of the diphenyl phosphate ($PtO_2/H_2$/100 psi) and then transesterification (NaOMe) of the benzoyl esters, or base catalyzed ester hydrolysis (2 M KOH/THF/18-crown-6) followed by hydrogenation of the partially deprotected diphenyl phosphate. In both cases, the reaction mixtures were acidified upon completion (AG® 50W-X8, $H^+$) and then neutralized with $Na_2CO_3$ (1 M) before passage through a size exclusion column (Bio-Gel P-2). An identical product, confirmed ($^1H$ and $^{31}P$ NMR spectroscopy) to be the α-1,3-phosphomannobioside disodium salt **8**, was obtained from both strategies (Scheme 7).

## 2.2. Synthesis via differentially protected D-mannopyranosyl imidates

An alternative approach to the target phosphomannobiosides was also investigated. The strategy was to glycosylate the acceptor alcohols (such as **10** and **13**) with a glycosyl donor lacking a 6-*O*-phosphodiester and then to introduce the phospho group after assembly of the disaccharide. This necessitated the use of a differentially protected D-mannopyranosyl donor to provide access to an alcohol at C-$6^{II}$, the site of phosphorylation, after assembly of the disaccharide. Such an approach would also allow for the synthesis of C-$6^{II}$-analogues of the disaccharides, if required. The initial glycosyl donor chosen was the imidate **41**, which was readily obtained from the alcohol **17** via silylation, anomeric de-*O*-acetylation and base catalyzed condensation with trichloroacetonitrile (Scheme 8).

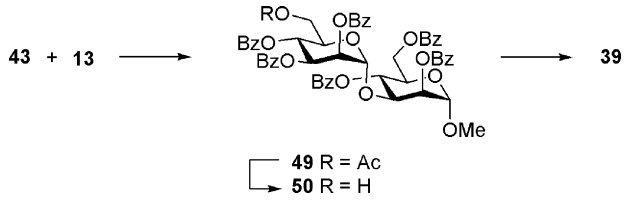
While a TMSOTf-catalyzed glycosylation of the alcohol **10** with **41** proceeded in near quantitative yield to give the disaccharide **44**, the attempted desilylation of **44** with tetrabutylammonium fluoride (TBAF), even when buffered with acetic acid, resulted in quantitative acyl migration to give **45**. The tribenzoyl disaccharide **46**, prepared via glycosylation with the corresponding benzoylated donor **42**, was more amenable to deprotection with TBAF but still susceptible to some acyl migration. Kong and co-workers[32] have demonstrated the utility of the 6-*O*-acetyl imidate **43** in generating branched oligomannans since this D-mannopyranosyl moiety may be deacetylated without benzoyl ester migration. Following these procedures, the imidate **43** was used in the glycosylation of the alcohol **10** furnishing the disaccharide **47** in good yield (80%, Scheme 8). The acetyl protecting group was easily removed thereby liberating the alcohol **48**.

Reaction of the alcohol **48** with diphenyl phosphorochloridate at ambient temperature resulted in the slow formation of diphenyl phosphate **32**.[‡] The reaction was greatly accelerated upon heating, as described for the preparation of inositol phosphates,[33] with the desired product **32** obtained in a relatively short period (3 h).[§] The phosphomannobioside **32** was identical in all respects to that prepared by the previous method (Scheme 9).

In accordance with the above procedure, the imidate **43** was condensed with the alcohol **13** to yield the

[‡] The phosphorylation reaction was also very difficult to follow by TLC because the alcohol **48** and product **32** co-migrate under many solvent systems.

[§] In repeated syntheses, this reaction was conveniently run over a longer period of time (o/n).




**Scheme 9.**

disaccharide **49** in good yield (73%). Deacetylation furnished the alcohol **50** which was, in turn, phosphorylated, thereby affording the α-(1→3)-phosphomannobioside **39**. Once again, the product was identical in all respects to that prepared by the previous method.

The successful synthesis of these disaccharides demonstrates the utility of the imidates **31** and **43** as useful glycosyl donors for the stereoselective assembly of α-linked $6^{II}$-*O*-phosphomannobiosides such as **35** and **39**. In addition, we have employed reproducible protocols for the deprotection of such phosphomannobiosides to yield the target compounds **5** and **8**, respectively. Efforts are now directed towards employing these strategies for the synthesis of the higher phosphorylated oligosaccharides from the *Pichia* (*Hansenula*) *holstii* extracellular phosphomannan.

## 3. Experimental

### 3.1. General

Nuclear magnetic resonance (NMR) spectra were recorded at 400 or 200 MHz for $^1$H, 100 MHz for $^{13}$C or 162 MHz for $^{31}$P, either in deuteriochloroform ($CDCl_3$) with residual $CHCl_3$ ($^1$H, $\delta$ 7.26) or deuterium oxide ($D_2O$), employing residual HOD ($^1$H, $\delta$ 4.78) as internal standard, at ambient temperatures (298 K), unless specified otherwise. Where appropriate, analysis of $^1$H NMR spectra was aided by gCOSY experiments. Flash chromatography (FC) or rapid silica filtration (RSF) was performed on silica gel (40–63 μm) under a positive pressure with the specified eluants. Size exclusion chromatography was performed on Bio-Gel P-2; 50 × 1000 mm; 0.1 M $NH_4HCO_3$; flow rate 2.8 mL min$^{-1}$; collecting fractions each 2.8 min. All solvents used were of analytical grade. The progress of the reactions was monitored by thin layer chromatography (TLC) using commercially prepared silica gel 60 $F_{254}$ aluminium-backed plates. Compounds were visualized by charring with 5% sulfuric acid in methanol and/or by visualization under ultraviolet light. The term 'workup' refers to dilution with water, extraction into an organic solvent, sequential washing of the organic extract with aqueous hydrochloric acid (1 M, where appropriate), saturated aqueous sodium bicarbonate and brine, followed by drying over anhydrous magnesium sulfate, filtration and evaporation of the solvent by means of a rotary evaporator at reduced pressure and where appropriate, extensive drying of the residue at <1 mmHg. Capillary electrophoresis was performed as previously described[14] with the use of 6 mM potassium sorbate (pH 10.3) as the background electrolyte and detection by indirect UV absorbance at 214 nm. Compound homogeneity was determined by $^1$H and/or $^{13}$C NMR spectroscopy and, where appropriate, by capillary electrophoresis.

### 3.2. 3,4-Di-*O*-acetyl-6-*O*-diphenylphosphoryl-α-D-mannopyranose-1,2-(benzyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranosid-2-yl)orthoacetate (11)

A combined mixture of the freshly prepared bromide **9**[18] (38 mg, 63 μmol), the alcohol **10**[20] (35 mg, 64 μmol) and TMU (15 μL, 133 μmol) in $CH_2Cl_2$ (2 mL) was stirred in the presence of mol sieves (200 mg of 3 Å powder) (−40 °C, 20 min). AgOTf (17 mg, 66 μmol) was added and stirring was continued (45 min). The mixture was neutralized with $Et_3N$ (50 μL), filtered and concentrated and the residue was subjected to FC (25–40% EtOAc/hexanes) to yield the orthoester **11** as a colourless oil (45 mg, 65%, a 93:7 mixture of diastereomers). $^1$H NMR (major diastereoisomer: 400 MHz, $CDCl_3$) $\delta$ 1.67 (s, 3H, *ortho*-Me),[34] 1.98, 1.99 (2s, 2 × 3H, 2 × Ac), 3.66–3.83 (m, 5H, $H4^I$,$5^I$,$6a^I$,$6b^I$,$5^{II}$), 3.88 (dd, 1H, $J_{2,3}$ 3.3, $J_{3,4}$ 8.8 Hz, $H3^I$), 4.06 (dd, 1H, $J_{1,2}$ 1.7 Hz, $H2^I$), 4.28–4.55, 4.62–4.81 (2m, 11H, $H2^{II}$, $6a^{II}$, $6b^{II}$, 4 × C$H_2$Ph), 4.56 (dd, 1H, $J_{1,2}$ 2.9, $J_{2,3}$ 4.0 Hz, $H2^{II}$), 4.95 (d, 1H, $H1^I$), 5.07 (dd, 1H, $J_{3,4}$ 9.7 Hz, $H3^{II}$), 5.18 (dd, 1H, $J_{3,4\sim4,5}$ 9.4 Hz, $H4^{II}$), 5.37 (d, 1H, $H1^{II}$), 7.09–7.35 (m, 30H, Ph); ESMS: *m*/*z* 1061.3 $[M+H]^+$.

### 3.3. Benzyl 2-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (12)

AgOTf (17 mg, 66 μmol) was added to the bromide **9** (38 mg, 63 μmol) and alcohol **10** (35 mg, 64 μmol) as described for **11** except for the omission of TMU, to yield the mannobioside **12** as a colourless oil (48 mg, 70%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.96, 2.00, 2.04 (3s, 3 × 3H, 3 × Ac), 3.76–3.86 (*AB*X, 2H, $H6a^I$,$6b^I$), 3.80–3.95, 4.20–4.40 (2m, 6H, $H3^I$,$4^I$,$5^I$,$6a^I$,$6b^I$,$5^{II}$), 3.98 (dd, 1H, $J_{1,2\sim2,3}$ 2.2 Hz, $H2^I$), 4.38–4.83 (m, 8H, PhC$H_2$), 4.96 (d, 1H, $J_{1,2}$ 1.8 Hz, $H1^I$), 5.01 (d, 1H, $J_{1,2}$ 1.8 Hz, $H1^{II}$), 5.28 (dd, 1H, $J_{3,4\sim4,5}$ 9.7 Hz, $H4^{II}$), 5.43 (dd, 1H, $J_{2,3}$ 3.5, $J_{3,4}$ 9.7 Hz, $H3^{II}$), 5.54 (dd, 1H, $H2^{II}$), 7.10–7.40 (m, 30H, Ph); HRMS calcd for $C_{58}H_{62}O_{17}P$ $[M+H]^+$ 1061.3719, found 1061.3794.

### 3.4. 1,2,3,4-Tetra-*O*-acetyl-6-*O*-bis(trichloroethyl)phosphoryl-β-D-mannopyranose (16)

A mixture of the alcohol **17**[24] (377 mg, 1.08 mmol), bis(2,2,2-trichloroethyl)phosphorochloridate (1.23 g, 3.24 mmol) and $Et_3N$ (820 μL, 11.1 mmol) in 1,2-DCE (25 mL) was stirred (rt, 3 h). The mixture was concentrated, filtered and the filtrate washed ($H_2O$ and then satd NaCl). The solvent was evaporated and the residue subjected to FC (35–50% EtOAc/hexanes) to yield the tetraacetate **16** as a pale yellow oil (550 mg, 87%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.01, 2.08, 2.10, 2.21 (4s, 4 × 3H), 3.82–3.88 (m, 1H), 4.27–4.37 (m, 2H), 4.64 (s, 2H), 4.67 (s, 2H), 5.14 (dd, 1H, *J* 3.2, 9.9 Hz), 5.32 (t, 1H, *J* 9.9 Hz), 5.49 (dd, 1H, *J* 1.1, 3.2 Hz), 5.87 (d, 1H, *J* 1.1 Hz); ESMS: *m*/*z* 688.9 $[M+H]^+$.

### 3.5. *p*-Methoxyphenyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (21)

(A) Trityl chloride (3.06 g, 11.0 mmol) was added to a solution of the mannoside **18**[25] (2.82 g, 9.86 mmol) in pyridine (20 mL) and the combined mixture stirred (0 °C → rt, o/n). The mixture was subjected to workup ($CH_2Cl_2$) and FC (10–35% EtOAc/$CH_2Cl_2$) to yield, presumably, the trityl ether **19** as a colourless foam (4.39 g). This sample was further dried under high vacuum (18 h) and used in the following reaction without further purification or characterization. (B) The trityl ether **19** (2.22 g, 4.20 mmol, max.) in DMF (10 mL) was added dropwise to a cooled (0 °C), stirred suspension of pre-washed (hexane) NaH (1.21 g of 50% oil suspension, 25.2 mmol) in DMF (30 mL). Once the addition was complete, stirring was maintained (0 °C → rt, 20 min). The mixture was cooled (0 °C, 5 min) and BnBr (1.94 mL, 16.4 mmol) was introduced dropwise with continued stirring (0 °C → rt, 2 h). The mixture was cooled once again (0 °C) and MeOH (5 mL) was introduced with continued stirring (5 min). The solvent was evaporated and the residue was subjected to workup ($CH_2Cl_2$) and evaporation to yield, presumably, the tribenzylether **20** as a pale yellow oil. This residue was co-evaporated (2 × 100 mL MeCN) and used in the next reaction without further purification or characterization. (C) *p*-TsOH·$H_2O$ (150 mg) was added to the crude mixture from (B) in MeOH (30 mL) and MeCN (30 mL) and the combined mixture stirred (rt, o/n). The mixture was treated with $Et_3N$ (1 mL), the solvents were evaporated and the residue subjected to workup (EtOAc) and FC (0–35% EtOAc/hexane) to yield the alcohol **21** as a pale yellow oil (2.06 g, 88%, three steps). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.73–3.78 (m, 6H, H5,6a,6b,OMe), 3.94 (dd, 1H, $J_{1,2\sim2,3}$ 2.3 Hz, H2), 4.03–4.11 (m, 2H, H3,4), 4.66, 4.94 (AB quartet, $J_{A,B}$ 10.9 Hz, PhC$H_2$a), 4.68, 4.74 (AB quartet, $J_{A,B}$ 11.6 Hz, PhC$H_2$b), 4.71, 4.81 (AB quartet, $J_{A,B}$ 12.4 Hz, PhC$H_2$c), 5.39 (d, 1H, H1), 6.75–6.88, 7.23–7.39 (2m, 19H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 55.8, 62.3, 73.1, 74.8, 75.0, 72.7, 73.3, 75.5, 80.1, 97.6, 114.8, 117.9, 127.8(7), 127.8(8), 128.0, 128.1, 128.3, 128.6(2), 128.6(3), 128.6(4), 128.7, 138.3, 138.5, 138.6, 150.2, 155.2.

### 3.6. *p*-Methoxyphenyl 3,4,6-tri-*O*-benzyl-6-*O*-diphenylphosphoryl-α-D-mannopyranoside (22)

Diphenyl phosphorochloridate (1.9 mL, 9.0 mmol) was added to a solution of the alcohol **21** (2.0 g, 3.6 mmol) and $Et_3N$ (2.5 mL, 18 mmol) in 1,2-DCE (20 mL) and the combined mixture stirred (0 °C → rt, 4 h). The mixture was subjected to workup ($CHCl_3$) and FC (10–40% EtOAc/hexane) to yield the phosphate **22** as a colourless oil (2.0 g, 72%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.71 (s, 3H, OMe), 3.88–3.93 (m, 1H, H5), 3.94 (dd, 1H, $J_{1,2}$ 2.0, $J_{2,3}$ 3.0 Hz, H2), 4.02 (dd, 1H, $J_{3,4\sim4,5}$ 9.6 Hz, H4), 4.09 (dd, 1H, $J_{3,4}$ 9.2 Hz, H3), 4.43–4.46 (m, 2H, H6a,6b), 4.48, 4.83 (AB quartet, $J_{A,B}$ 10.4 Hz, PhC$H_2$a), 4.68 (s, 2H, PhC$H_2$b), 4.73, 4.77 (AB quartet, $J_{A,B}$ 12.6 Hz, PhC$H_2$c), 5.40 (d, 1H, H1), 6.76–6.84, 7.26–7.39 (2m, 29H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 55.8, 67.9 (d, $J_{C,P}$ 5.7 Hz), 71.6 (d, $J_{C,P}$ 8.2 Hz), 72.5, 73.2, 75.4, 74.2, 74.9, 80.0, 97.4, 114.8, 117.8, 120.4(0), 120.4(3), 120.4(6), 120.4(8), 125.4(3), 125.4(4), 125.4(6), 125.4(8), 127.8(9), 127.9(2), 127.9(6), 128.0(0), 128.0(3), 128.2, 128.6(1), 128.6(4), 128.7, 138.2(8), 138.2(9), 138.5, 150.4, 155.2; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.4 ($PO(OPh)_2$); ESMS: *m/z* 789.2 $[M+H]^+$.

### 3.7. 3,4,6-Tri-*O*-benzyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl trichloroacetimidate (24)

(A) CAN (3.35 g, 6.09 mmol) was added portionwise to a solution of the mannoside **22** (1.60 g, 2.03 mmol) in 4:1 MeCN–$H_2O$ (60 mL) and the combined mixture stirred (0 °C, 10 min). The mixture was then diluted ($H_2O$), and extracted (EtOAc). The organic extracts were successively washed (satd aq $NaHCO_3$, $Na_2S_2O_3$, NaCl), dried ($MgSO_4$), filtered and evaporated. The residue was subjected to FC (20–50% EtOAc/hexane) to yield an orange oil. This residue was co-evaporated (2 × 30 mL MeCN) and used in the next reaction without further purification or characterization. (B) DBU (50 μL) was added to a solution of the product from (A) and trichloroacetonitrile (355 μL, 3.55 mmol) in 1,2-DCE (10 mL) and the combined mixture stirred (0 °C, 10 min). The mixture was concentrated and the residue subjected to FC (10–20% EtOAc/hexane) to yield the imidate **24** as a pale yellow oil (728 mg, 43%, two steps). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.83 (dd, 1H, $J_{1,2}$ 2.0, $J_{2,3}$ 3.0 Hz, H2), 3.90 (dd, 1H, $J_{3,4}$ 9.4 Hz, H3), 3.94–3.98 (m, 1H, H5), 4.05 (dd, 1H, $J_{3,4\sim4,5}$ 9.6 Hz, H4), 4.45, 4.84 (AB quartet, $J_{A,B}$ 10.6 Hz, PhC$H_2$a), 4.46–4.48 (m, 2H, H6a,6b), 4.56, 4.69 (AB quartet, $J_{A,B}$ 11.8 Hz, PhC$H_2$b), 4.72 (s, 2H, PhC$H_2$c), 6.31 (d, 1H, H1), 7.08–7.39 (m, 25H, Ph), 8.51 (br s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 67.5 (d, $J_{C,P}$ 5.4 Hz), 72.4, 73.0, 73.5, 73.7(0), 73.7(1) (d, $J_{C,P}$ 8.0 Hz), 75.6, 79.0, 96.0, 120.4(1), 120.4(4), 120.4(6), 120.4(9), 125.4(6), 125.4(7), 125.4(9), 125.5(0), 128.0, 128.0(8), 128.0(9), 128.1(4), 128.4, 128.6(1), 128.6(3), 128.7, 129.8(9), 129.9(0), 129.9(1), 129.9(2), 138.0, 138.0(8), 138.0(9), 160.5; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.4 ($PO(OPh)_2$); HRMS calcd for $C_{39}H_{38}O_8P$ $[M+H-CCl_3CONH_2]^+$ 665.2304, found 665.2143.

### 3.8. Benzyl 2-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-diphenylphosphoryl-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (25/26)

A mixture of the imidate **24** (430 mg, 0.52 mmol) and the alcohol **10** (192 mg, 0.36 mmol) in 1,2-DCE (8 mL) was stirred in the presence of mol sieves (400 mg of 3 Å powder) under an atmosphere of argon (30 min). The mixture was cooled (0 °C) with continued stirring (10 min) prior to the addition of TMSOTf (94 μL, 0.52 mmol). After 10 min, $Et_3N$ (100 μL) was introduced and the mixture was filtered. The solvent was evaporated and the residue subjected to FC (10–30% EtOAc/hexane) to yield two fractions. Firstly, an anomeric mixture (9:1)

of the disaccharides **25/26** was produced as a colourless oil (242 mg, 55%). Partial $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.88 (d, 1H, $J_{1,2}$ 1.9 Hz, H1$^I$-major), 4.89 (d, 1H, $J_{1,2}$ 2.0 Hz, H1$^I$-minor), 5.01 (d, 1H, $J_{1,2}$ 1.8 Hz, H1$^{II}$-major); $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.4 ($PO(OPh)_2$-minor), −11.3 ($PO(OPh)_2$-major). ESMS: *m/z* 1205.4 $[M+H]^+$. Next, the amide **27** was obtained as a colourless oil (136 mg, 31%). $^1$H NMR (major anomer: 400 MHz, $CDCl_3$) $\delta$ 3.55–3.59 (m, 1H, H5), 3.71 (dd, 1H, $J_{2,3}$ 2.4, $J_{4,5}$ 9.2 Hz, H3), 3.93 (dd, 1H, $J_{1,2}$ 1.6 Hz, H2), 3.96 (dd, 1H, $J_{4,5}$ 9.6 Hz, H4), 4.37–4.60 (m, 3H, H6a,6b,PhC$H_2$a), 4.65, 5.04 (AB quartet, $J_{A,B}$ 11.6 Hz, PhC$H_2$b), 4.78 (s, 2H, PhC$H_2$c), 4.80 (B of AB quartet, $J_{A,B}$ 10.8 Hz, PhC$H_2$a), 5.17 (dd, 1H, $J_{1,NH}$ 8.8 Hz, H1), 7.10–7.36 (m, 25H, Ph), 7.52 (d, 1H, NH); $^{13}$C NMR (major anomer: 100 MHz, $CDCl_3$) $\delta$ 67.5 (d, $J_{C,P}$ 4.2 Hz), 73.4, 73.6, 75.1, 75.2, 75.3, 75.9 (d, $J_{C,P}$ 8.0 Hz), 78.7, 83.1, 120.3(8), 120.4(2), 125.5, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.9, 137.7, 137.8, 137.9, 150.6, 150.7, 161.3; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.7(5) ($PO(OPh)_2$-minor), −11.6(6) ($PO(OPh)_2$-major). ESMS: *m/z* 826.3 (100%), 828.3 (97%) $[M+H]^+$.

### 3.9. *p*-Methoxyphenyl 2,3,4-tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranoside (28)

(A) Benzoyl chloride (1.19 mL, 10.3 mmol) was added dropwise to a cooled (0 °C) solution of the trityl ether **19** (1.21 g, 2.30 mmol) in 1,2-DCE (10 mL) and the combined mixture was stirred (0 °C → rt, o/n). After this time, the mixture was cooled (0 °C) and MeOH (5 mL) was introduced with continued stirring (5 min). The solvent was evaporated and the residue was subjected to workup (EtOAc) and evaporation, and the residual oil subjected to RSF (10–35% EtOAc/hexanes) to yield a yellow oil. This residue was co-evaporated (2 × 50 mL MeCN) and used in the next reaction without further purification or characterization. (B) *p*-TsOH·$H_2O$ (100 mg) was added to the crude product from (A) in MeOH (10 mL) and MeCN (10 mL) and the combined mixture heated (70 °C, 10 min). $Et_3N$ (1 mL), was added, the solvents were evaporated and the residue subjected to FC (10–40% EtOAc/hexane) to yield *p*-methoxyphenyl 2,3,4-tri-*O*-benzoyl-α-D-mannopyranoside (**51**) as a colourless oil (710 mg, 83%, two steps). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.72 (dd, 1H, $J_{5,6a}$ 3.4, $J_{6a,6b}$ 13.0 Hz, H6a), 3.76 (s, 3H, OMe), 3.79 (dd, 1H, $J_{5,6b}$ 2.2 Hz, H6b), 4.16–4.20 (m, 1H, H5), 5.69 (d, 1H, $J_{1,2}$ 1.8 Hz, H1), 5.84 (dd, 1H, $J_{2,3}$ 3.4 Hz, H2), 5.91 (dd, 1H, $J_{3,4\sim4,5}$ 10.1 Hz, H4), 6.16 (dd, 1H, H3), 6.82–8.11 (m, 19H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 55.9, 61.3, 67.3, 69.7, 70.7, 71.7, 97.0, 115.0, 118.0, 128.6, 128.7, 128.9, 129.3, 129.4, 129.9, 130.1, 130.2, 133.5, 133.8(6), 133.9(4), 150.1, 155.6, 165.7, 166.8. (C) $Et_3N$ (767 μL, 5.50 mmol) was added to a solution of the alcohol **51** (658 mg, 1.10 mmol) and diphenyl phosphorochloridate (570 μL, 2.75 mmol) in 1,2-DCE (10 mL) and the combined mixture stirred (0 °C → rt, o/n). The mixture was subjected to workup ($CHCl_3$) and FC (10–40% EtOAc/hexane) to yield the diphenyl phosphate **28** as a colourless oil (851 mg, 93%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.73 (s, 3H, OMe), 4.42–4.48 (m, 3H, H5,6a,6b), 5.59 (d, 1H, $J_{1,2}$ 1.9 Hz, H1), 5.82 (dd, 1H, $J_{2,3}$ 3.2 Hz, H2), 5.98 (dd, 1H, $J_{3,4}$ 10.0, $J_{4,5}$ 9.5 Hz, H4), 6.05 (dd, 1H, H3), 6.77–7.58, 7.82–8.09 (m, 24H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 55.8, 66.7, 67.4 (d, $J_{C,P}$ 5.5 Hz), 70.0, 70.2 (d, $J_{C,P}$ 8.5 Hz), 70.6, 97.1, 114.9, 118.2, 120.1(8), 120.2(3), 120.2(6), 120.3(1), 125.4, 125.4(6), 125.5(1), 125.5(2), 128.5, 128.7, 128.9, 129.0, 129.2, 129.3, 129.8(2), 129.8(3), 129.8(8), 129.8(9), 129.9(6), 130.0(4), 130.1, 150.3, 155.7, 165.6, 165.6(7), 165.6(9); $^{31}$P NMR ($CDCl_3$) $\delta$ −11.5 ($PO(OPh)_2$). ESMS: *m/z* 831.2 $[M+H]^+$.

### 3.10. 2,3,4-Tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranose (29)

(A) CAN (1.66 g, 3.03 mmol) was added to the mannoside **28** (841 mg, 1.01 mmol) as described for the preparation of **24** to yield two fractions. Firstly, 4-methoxy-3-[1,4]benzoquinonyl-1-phenyl 2,3,4-tri-*O*-benzoyl-6-*O*-diphenylphopshoryl-α-D-mannopyranoside (**30**) was obtained as an orange oil (183 mg, 19%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.69 (s, 3H, OMe), 4.43–4.49 (m, 3H, H5,6a,6b), 5.63 (d, 1 H, $J_{1,2}$ 1.9 Hz, H1), 5.82 (dd, 1H, $J_{2,3}$ 3.0 Hz, H2), 5.99 (dd, 1H, $J_{3,4}$ 10.0, $J_{4,5}$ 9.3 Hz, H4), 6.05 (dd, 1H, H3), 6.72–6.82, 7.03–7.58, 7.81–8.09 (3m, 31H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 56.4, 66.6, 67.4 (d, $J_{C,P}$ 5.5 Hz), 69.9, 70.3(9) (d, $J_{C,P}$ 8.8 Hz), 70.4(3), 97.2, 112.5, 119.3, 119.8, 120.2(2), 120.2(4), 120.2(6), 120.3(1), 123.6, 125.4(8), 125.4(9), 125.5(3), 125.5(4), 128.6, 128.7, 128.9(0), 128.9(4), 129.1, 129.2, 129.8, 129.9, 130.0, 130.1, 130.2, 133.5, 133.8, 133.9, 134.8, 136.3, 137.2, 145.1, 149.9, 153.3, 165.5(6), 165.6(4), 165.7, 185.6, 187.5; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.4 ($PO(OPh)_2$); ESMS: *m/z* 937.2 $[M+H]^+$. Next, the hemiacetal **29** was obtained as a colourless oil (353 mg, 48%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.42 (dd, 1H, $J_{5,6a}$ 1.5, $J_{6a,6b}$ 9.0 Hz, H6a), 4.44 (d, 1H, $J_{5,6b}$ 0.0 Hz, H6b), 4.52–4.56 (m, 1H, H5), 5.31 (d, 1H, $J_{1,2}$ 1.8 Hz, H1), 5.62 (dd, 1H, $J_{2,3}$ 3.3 Hz, H2), 5.83 (dd, 1H, $J_{3,4\sim4,5}$ 10.0 Hz, H4), 5.92 (dd, 1H, H3), 7.06–7.55, 7.71–8.04 (2m, 25H, Ph). (B) CAN (58 mg, 105 μmol) was added to the mannoside **28** (25 mg, 30 μmol) as described in (A), except for performing the reaction at 30 °C, to yield the hemiacetal **29** as a colourless oil (14 mg, 64%). This sample was spectroscopically identical to that produced in (A).

### 3.11. 2,3,4-Tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl trichloroacetimidate (31)

$K_2CO_3$ (374 mg, 2.70 mmol) was added to a stirred solution of the hemiacetal **29** (353 mg, 0.490 mmol) and trichloroacetonitrile (1.00 mL, 10.0 mmol) in 1,2-DCE (5 mL) and the combined mixture stirred (0 °C, 10 min). After this time, the mixture was concentrated and the residue subjected to FC (10–20% EtOAc/hexane) to yield the imidate **31** as a pale yellow oil (382 mg, 90%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.41–4.55 (m, 3H, H5,6a,6b), 5.86 (dd, 1H, $J_{1,2}$ 2.0, $J_{2,3}$ 3.3 Hz, H2), 5.91 (dd, 1H, $J_{3,4}$ 10.1 Hz, H3), 6.02 (dd, 1H, $J_{4,5}$ 10.1 Hz, H4), 6.53 (d, 1H, H1), 7.08–8.06 (m,

25H, Ph), 8.81 (br s, 1H, NH); $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.5 ($PO(OPh)_2$). HRMS calcd for $C_{39}H_{32}O_{11}P$ $[M+H-CCl_3CONH_2]^+$ 707.1682, found 707.1348.

### 3.12. Benzyl 2-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (32)

TMSOTf (24 μL, 0.13 mmol) was added to the imidate **31** (116 mg, 0.13 mmol) and alcohol **10** (60 mg, 0.11 mmol) as described for the preparation of **25/26** to yield the mannobioside **32** as a colourless oil (110 mg, 79%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.74 (dd, 1H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 10.6 Hz, H6a$^I$), 3.79 (dd, 1H, $J_{5,6b}$ 5.1 Hz, H6b$^I$), 3.86 (ddd, 1H, $J_{4,5}$ 9.2 Hz, H5$^I$), 3.97 (dd, 1H, $J_{2,3}$ 2.8, $J_{3,4}$ 9.1 Hz, H3$^I$), 4.02 (dd, 1H, H4$^I$), 4.05–4.06 (m, 1H, H2$^I$), 4.37–4.50 (m, 7H, H5$^I$, 5$^{II}$, PhC$H_2$a-c), 4.56, 4.86 (AB quartet, $J_{A,B}$ 11.6 Hz, PhC$H_2$d), 4.61 (dd, 1H, $J_{5,6a}$ 2.9, $J_{6a,6b}$ 11.8 Hz, H6a$^{II}$), 4.69 (dd, 1H, $J_{5,6b}$ 5.4 Hz, H6b$^{II}$), 4.71 (B of AB quartet, $J_{A,B}$ 10.9 Hz, PhC$H_2$c), 5.13 (d, 1H, $J_{1,2}$ 1.8 Hz, H1$^I$), 5.20 (d, 1H, $J_{1,2}$ 1.6 Hz, H1$^{II}$), 5.86–5.94 (m, 3H, H2$^{II}$, 3$^{II}$, 4$^{II}$), 7.14–8.05 (m, 45H, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 66.8, 67.6 (d, $J_{C,P}$ 4.6 Hz), 69.3, 69.6, 70.0 (d, $J_{C,P}$ 7.3 Hz), 70.2, 70.4, 72.2, 72.8, 73.5, 75.1, 75.5, 76.6, 79.9, 98.4, 99.6, 120.2, 120.2(8), 120.3(2), 125.4(6), 125.5(0), 127.7, 127.7(7), 127.8(3), 127.9, 128.0, 128.1, 128.4, 128.4(7), 128.5(4), 128.5(8), 128.6(2), 128.7, 128.8, 129.0, 129.4, 129.6, 129.8(7), 129.9(2), 130.0(9), 130.1(3), 133.3, 133.5(9), 133.6(3), 137.4, 138.4, 138.5, 138.6, 150.5(9), 150.6(2), 150.6(6), 150.6(9), 165.3, 165.4, 165.6; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.3 ($PO(OPh)_2$); HRMS calcd for $C_{73}H_{67}O_{17}P$ $[M+H]^+$ 1247.4189, found 1247.4105.

### 3.13. Attempted deprotection of the tetrabenzyl ether (32): Methylcyclohexyl 2-*O*-(6-*O*-phospho-α-D-mannopyranosyl)-α-D-mannopyranoside, disodium salt (33)

Pd (20 mg of 10% on C) was added to a solution of the tetrabenzyl ether **32** (100 mg, 83.5 mmol) in MeOH (2 mL) and EtOAc (2 mL) containing AcOH (50 μL) and the combined mixture was vigorously stirred under hydrogen (100 psi, 48 h). The mixture was filtered and $Pd(OH)_2$ (20 mg of 10% on C) was introduced and stirring continued under hydrogen (100 psi, 48 h). The mixture was filtered and $PtO_2$ (10 mg) was introduced and stirring continued under hydrogen (100 psi, 48 h). The mixture was filtered and the solvent evaporated. The residue was dissolved in MeOH (2 mL) and NaOH (1 mL of 1 M, 1.0 mmol) and the combined mixture was stirred (rt, o/n). The mixture was acidified to pH 2.0 by the addition of AG® 50W-X8 ($H^+$ form) and filtered. The filtrate was neutralized with $Na_2CO_3$ (1 M) and the solvent evaporated. The residue was subjected to gel filtration chromatography (Bio-Gel P-2; 0.1 M $NH_4HCO_3$; 170 mL/h) to yield, after lyophilization, the methylcyclohexyl mannobioside **33** as a colourless powder (9.6 mg, 23%). $^1$H NMR (400 MHz, $D_2O$) $\delta$ 0.75–0.85, 0.99–1.11, 1.45–1.62 (3m, 11H, cHex), 3.23 (dd, 1H, $J_{H,cHex(CH)}$ 5.8, $J_{H,H}$ 9.6 Hz, cHexC$H_2$), 3.35 (dd, 1H, $J_{H,cHex(CH)}$ 7.6 Hz, cHexC$H_2$), 3.46 (ddd, 1H, $J_{4,5}$ 9.7, $J_{5,6a}$ 2.0, $J_{5,6b}$ 5.7 Hz, H5$^I$), 3.51 (dd, 1H, $J_{3,4}$ 9.8 Hz, H4$^I$), 3.58 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H6b$^I$), 3.61–3.66 (m, 1H, H5$^{II}$), 3.68–3.72 (m, 3H, H6a$^I$,3$^{II}$,4$^{II}$), 3.74 (dd, 1H, $J_{2,3}$ 3.3 Hz, H3$^I$), 3.78–3.83, 3.89–3.96 (2m, 4H, H2$^I$,2$^{II}$,6a$^{II}$,6b$^{II}$), 4.84 (d, 1H, $J_{1,2}$ 1.4 Hz, H1$^I$), 4.88 (d, 1H, $J_{1,2}$ 1.6 Hz, H1$^{II}$); $^{31}$P NMR (162 MHz, $D_2O$) $\delta$ 2.7 ($PO(ONa)_2$); HRMS calcd for $C_{19}H_{35}O_{14}P$ $[M+H]^+$ 519.1837, found 519.1789; CE: $t_m$ = 21.28 min.

### 3.14. Benzyl 3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (34)

(A) A small piece of sodium metal (50 mg) was added to a suspension of 3,4,6-tri-*O*-acetyl-1,2-*O*-(benzyloxyethylidene)-β-D-mannopyranose[20] (5.21 g, 11.8 mmol) and the combined mixture was stirred (1 h). The solid slowly dissolved and after 1 h, the mixture was neutralized by the addition of AG® 50W-X8 resin ($H^+$ form) and filtered. The solvent was evaporated and co-evaporated (2 × 100 mL MeCN) and the residual oil used in the following reaction without further purification. (B) Benzoyl chloride (4.83 mL, 41.6 mmol) was added dropwise to a cooled (0 °C) solution of the crude product from (A) in pyridine (30 mL) and the combined mixture was stirred (0 °C → rt, o/n). After this time, the mixture was cooled (0 °C) and MeOH (5 mL) was introduced with continued stirring (5 min). The solvent was evaporated and the residue was subjected to workup (EtOAc), FC (10–40% EtOAc/hexanes) and recrystallization to yield 3,4,6-tri-*O*-benzoyl-1,2-*O*-(benzyloxyethylidene)-β-D-mannopyranose (**52**) as colourless needles (3.26 g, 57%, two steps), mp 140–141 °C (EtOAc/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.84 (s, 3H, *ortho*-$CH_3$), 4.07 (ddd, 1H, $J_{4,5}$ 9.4, $J_{5,6a}$ 3.3, $J_{5,6b}$ 4.7 Hz, H5), 4.46 (dd, 1H, $J_{6a,6b}$ 12.1 Hz, H6b), 4.53, 4.57 (AB quartet, $J_{A,B}$ 11.3 Hz, PhC$H_2$), 4.62 (dd, 1H, H6a), 4.85 (dd, 1H, $J_{1,2}$ 2.7, $J_{2,3}$ 3.8 Hz, H2), 5.56 (dd, 1H, $J_{3,4}$ 9.8 Hz, H3), 5.67 (d, 1H, H1), 5.91 (dd, 1H, $J_{4,5}$ 9.7 Hz, H4), 7.16–8.02 (m, 20H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.0, 63.5, 65.1, 66.6, 71.6, 72.0, 76.8, 97.9, 124.6, 127.8, 128.0, 128.5, 128.6, 129.1, 129.2, 129.9, 130.2, 133.3, 133.6, 133.7, 137.6, 165.4, 166.2, 166.4. (C) TMSOTf (424 μL, 2.34 mmol) was added to the orthoester **52** (972 mg, 1.56 mmol) and benzyl alcohol (180 μL, 1.71 mmol) as described for the preparation of **25** to yield a colourless oil. This residue was co-evaporated (2 × 10 mL MeCN) and used in the next reaction without further purification or characterization. A small sample was purified by FC (10–40% EtOAc/hexanes), yielding benzyl 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (**53**) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.10 (s, 3H, Ac), 4.39 (ddd, 1H, $J_{4,5}$ 9.7, $J_{5,6a}$ 2.8, $J_{5,6b}$ 5.3 Hz, H5), 4.47 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H6b), 4.57 (dd, 1H, H6a), 4.63, 4.80 (AB quartet, $J_{A,B}$ 11.8 Hz, PhC$H_2$), 5.00 (d, 1H, $J_{1,2}$ 1.8 Hz, H1), 5.52 (dd, 1H, $J_{2,3}$ 3.3 Hz, H2), 5.82 (dd, 1H, $J_{3,4}$ 10.0 Hz, H3), 5.91 (dd, 1H, H4), 7.30–7.54, 7.86–8.06 (2m, 20H, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.0, 63.5, 65.5, 67.4, 69.3, 69.9, 70.1, 96.8, 127.2, 127.8, 128.3, 128.4, 128.5(9), 128.6(3), 128.7, 128.8, 129.1, 129.4, 129.8(6), 129.8(9), 130.0(1), 130.0(3), 133.3, 133.5, 133.6, 136.5,

165.6, 165.8, 166.3, 170.0. (D) AcCl (0.5 mL) was added to a solution of the crude product from (C) in 1,2-DCE (10 mL) and MeOH (20 mL) and the combined mixture was stirred (rt, o/n). The mixture was cooled (0 °C) and $Et_3N$ (1 mL) was introduced with continued stirring (5 min) prior to evaporation of the solvent. The residue was subjected to workup (EtOAc) and FC (10–40% EtOAc/hexanes) to yield the alcohol **34** as a colourless oil (418 mg, 40%, two steps). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.33 (dd, 1H, $J_{1,2}$ 1.8, $J_{2,3}$ 3.0 Hz, H2), 4.38 (ddd, 1H, $J_{4,5}$ 9.9, $J_{5,6a}$ 3.0, $J_{5,6b}$ 5.4 Hz, H5), 4.47 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H6b), 4.55 (dd, 1H, H6a), 4.62, 4.81 (AB quartet, $J_{A,B}$ 11.9 Hz, PhC$H_2$), 5.03 (d, 1H, H1), 5.70 (dd, 1H, $J_{3,4}$ 9.9 Hz, H3), 5.94 (dd, 1H, H4), 7.29–7.52, 7.90–8.03 (2m, 20H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 63.7, 67.3, 69.2, 69.6(7), 69.7(0), 72.9, 98.8, 128.4, 128.6, 128.8, 129.3, 129.40, 129.9, 129.9(7), 129.9(9), 133.3, 133.5(2), 133.5(4), 136.8, 165.7(9), 165.8(3), 166.4; HRMS calcd for $C_{34}H_{30}O_9$ $[M+H]^+$ 583.1963, found 583.1939.

### 3.15. Benzyl 2-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (35)

TMSOTf (22.5 μL, 123 μmol) was added to the imidate **31** (107 mg, 123 μmol) and alcohol **34** (60 mg, 103 μmol) as described for the preparation of **25/26** to yield the mannobioside **35** as a colourless oil (112 mg, 84%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.29–4.66 (m, 7H, H2$^I$,5$^I$,6a$^I$,6b$^I$,5$^{II}$,6a$^{II}$,6b$^{II}$), 4.61, 4.79 (AB quartet, $J_{A,B}$ 11.7 Hz, PhC$H_2$), 5.13 (d, 1H, $J_{1,2}$ 1.6 Hz, H1$^{II}$), 5.26 (d, 1H, $J_{1,2}$ 1.7 Hz, H1$^I$), 5.86–5.91, 5.95–6.02 (2m, 5H, H3$^I$,4$^I$,2$^{II}$,3$^{II}$,4$^{II}$), 7.00–7.54, 7.81–8.09 (2m, 45H, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 63.8, 66.7, 67.5 (d, $J_{C,P}$ 5.3 Hz), 67.8, 69.3, 69.8, 70.2, 70.4 (d, $J_{C,P}$ 7.7 Hz), 71.1, 98.3, 99.9, 120.2, 125.5, 125.5(6), 125.5(7), 128.3(0), 128.3(4), 128.5, 128.6(7), 128.7(0), 128.7(3), 128.8, 128.9, 129.1, 129.2(9), 129.3(3), 129.8(7), 129.9(1), 129.9(3), 129.9(6), 129.9(8), 130.0(4), 130.0(8), 130.1(2), 130.2, 133.3(2), 133.3(4), 133.4, 133.5, 133.6, 133.7, 136.8, 165.1, 165.2, 165.4, 165.6, 165.8, 166.6; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.5 ($PO(OPh)_2$); HRMS calcd for $C_{73}H_{62}O_{20}P$ $[M+H]^+$ 1289.3572, found 1289.3599.

### 3.16. 2-*O*-(6-*O*-Phospho-α-D-mannopyranosyl)-D-mannopyranose, disodium salt (5)

*Method A*: (A) $Pd(OH)_2$ (2 mg of 10% on C) was added to a solution of the benzyl ether **35** (10 mg, 7.8 μmol) in THF (1 mL) and AcOH (2.5 μL) and the combined mixture was vigorously stirred under hydrogen (100 psi, 72 h). The mixture was filtered and the solvent evaporated and co-evaporated (2 × 1 mL $H_2O$) to yield a colourless oil. Partial $^1$H NMR (400 MHz, $D_2O$) $\delta$ 5.13 (d, 1H, $J_{1,2}$ 1.7 Hz, H1$^{II}$), 5.58 (d, 1H, $J_{1,2}$ 1.8 Hz, H1$^I$). (B) The product from (A) was dissolved in THF (1 mL) and treated with $PtO_2$ (5 mg) and the combined mixture was vigorously stirred under hydrogen (100 psi, o/n). After this time, the filtrate was neutralized with $Na_2CO_3$ (1 M) and the solvent evaporated. (C) KOH (1 mL of 2.0 M) was added to the product from (B) in THF (1.2 mL) and the combined mixture was stirred (rt, o/n). After this time the mixture was acidified with AG® 50W-X8 resin ($H^+$ form) and filtered. The filtrate was neutralized with $Na_2CO_3$ (1 M) and the solvent evaporated. The residue was subjected to gel filtration chromatography (Biogel P2; 0.1 M $NH_4HCO_3$; 170 mL/h) to yield, after lyophilization, an anomeric mixture (17:3) of the α-1,2-mannobioside (**5**) as a colourless powder (1.0 mg, 30%, three steps). $^1$H NMR (400 MHz, $D_2O$) $\delta$ 3.45–3.80 (m, 11H, H3$^I$,4$^I$,5$^I$,6a$^I$, 6b$^I$,2$^{II}$,3$^{II}$,4$^{II}$,5$^{II}$,6a$^{II}$,6b$^{II}$), 3.92 (d, 1H, $J_{1,2}$ 1.8, $J_{2,3}$ 3.4 Hz, H2$^I$-major), 3.96 (d, 1H, $J_{1,2}$ 1.8, $J_{2,3}$ 3.4 Hz, H2$^I$-minor), 4.76 (d, 1H, H1$^I$-minor), 4.89 (d, 1H, H1$^I$-major), 4.99 (d, 1H, H1$^{II}$-minor), 5.23 (d, 1H, H1$^{II}$-major); $^{13}$C NMR (major anomer; 400 MHz, $D_2O$) $\delta$ 61.1, 61.2, 67.0, 67.2, 70.1, 70.5, 72.6, 73.0, 73.4, 79.3, 92.6, 102.3; $^{31}$P NMR (162 MHz, $D_2O$) $\delta$ −1.5(7) ($PO(ONa)_2$-minor), −1.6(4) ($PO(ONa)_2$-major); HRMS calcd for $C_{12}H_{22}O_{14}P$ $[M+H]^+$ 422.0820, found 422.0812; CE: $t_m$ = 22.13 min.

*Method B*: The hexabenzoate **35** (15 mg, 11.6 μmol) in THF was first treated with KOH with the inclusion of 18-crown-6 (13.1 mg, 49.6 μmol), and then $Pd(OH)_2$/C and $PtO_2$ as described in the previous method [steps (C), (A) and then (B), except that the reaction was performed over a short period (1 h)] to yield, after lyophilization, the phosphomannobioside **5** as a colourless powder (2.4 mg, 49%, three steps). This sample was identical in all respects to that produced in the previous method.

### 3.17. Methyl 3-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-diphenylphosphoryl-D-mannopyranosyl)-2,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (37/38)

TMSOTf (56 μL, 310 μmol) was added to the imidate **24** (256 mg, 310 μmol) and alcohol **13** (150 mg, 266 μmol) as described for the preparation of **25/26** to yield two fractions. Firstly, the amide **27** was produced as a pale yellow coloured oil (53 mg, 21% on **24**). This sample was spectroscopically identical to that produced during the synthesis of **25/26**. Next, an anomeric mixture (2:1) of the disaccharides **37/38** was produced as a colourless oil (226 mg, 72%). Partial $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.40 (s, 3H, OMe-major), 3.44 (s, 3H, OMe-minor), 4.85 (d, 1H, $J_{1,2}$ 1.7 Hz, H1$^I$-major), 4.92 (d, 1H, $J_{1,2}$ 1.6 Hz, H1$^I$-minor), 5.01 (d, 1H, $J_{1,2}$ 1.7 Hz, H1$^{II}$-major); $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.5 ($PO(OPh)_2$-minor), −11.4 ($PO(OPh)_2$-major). ESMS: *m/z* 1171.4 $[M+H]^+$.

### 3.18. Methyl 3-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl)-2,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (39)

TMSOTf (15 μL, 82 μmol) was added to the imidate **31** (42 mg, 48 μmol) and alcohol **13** (25 mg, 44 μmol) as described for the preparation of **25/26** to yield the hexabenzoate **39** as a colourless oil (44 mg, 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.42 (s, 3H, OMe), 4.24–4.30 (m, 2H, H5$^I$,6a$^{II}$), 4.41–4.45 (m, 3H, H6b$^I$,5$^{II}$,6b$^{II}$), 4.58 (dd, 1H, $J_{2,3}$ 3.4, $J_{3,4}$ 9.9 Hz, H3$^I$), 4.69 (dd, 1H,

$J_{5,6}$ 2.7, $J_{6,6}$ 12.2 Hz, H6a$^{I}$), 4.92 (d, 1H, $J_{1,2}$ 1.6 Hz, H1$^{I}$), 5.16 (d, 1H, $J_{1,2}$ 1.8 Hz, H1$^{II}$), 5.26 (dd, 1H, $J_{2,3}$ 3.3 Hz, H2$^{II}$), 5.60–5.64 (m, 2H, H2$^{I}$,3$^{II}$), 5.86 (dd, 1H, $J_{3,4}$ 10.0, $J_{4,5}$ 10.0 Hz, H4$^{II}$), 5.96 (dd, 1H, $J_{4,5}$ 10.1 Hz, H4$^{I}$), 7.05–8.18 (m, 40H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 55.6, 63.2, 66.2, 67.0 (d, $J_{C,P}$ 5.4 Hz), 68.8, 69.0, 69.5, 70.2 (d, $J_{C5,P}$ 8.7 Hz), 70.3, 71.8, 75.8, 98.8, 99.5, 120.2(8), 120.3(3), 120.3(6), 120.4(0), 125.3(0), 125.3(2), 125.3(7), 125.3(9), 128.3, 128.5, 128.5(7), 128.6(0), 128.6(4), 128.9, 129.1, 129.2, 129.2(8), 129.3(4), 129.5, 129.7(8), 129.8(2), 129.8(3), 129.9, 129.9(6), 130.0(2), 130.1, 130.2, 130.4, 133.1, 133.2, 133.4(7), 133.4(9), 133.8, 164.9, 165.2, 165.5, 166.1, 166.4; $^{31}$P NMR (162 MHz, $CDCl_3$) $\delta$ −11.4 ($PO(OPh)_2$); HRMS calcd for $C_{67}H_{57}O_{20}P$ $[M+H]^+$ 1213.3254, found 1213.3208.

### 3.19. Methyl 3-*O*-(6-*O*-phospho-α-D-mannopyranosyl)-α-D-mannopyranose (8)

*Method A*: The hexabenzoate **39** (82 mg, 64 μmol) was treated first with $PtO_2$ and then KOH in THF as described for the preparation of **5** [steps (B) and (C)] to yield, after lyophilization, the phosphomannobioside **8** as a colourless powder (14 mg, 48%, two steps). $^1$H NMR (400 MHz, $D_2O$) $\delta$ 3.25 (s, 3H, OMe), 3.49 (ddd, 1H, $J_{4,5}$ 10.0, $J_{5,6a}$ 2.1, $J_{5,6b}$ 5.8 Hz, H5$^{I}$), 3.55–3.63 (m, 3H, H4$^{I}$,6$^{I}$,4$^{II}$), 3.68 (dd, 1H, $J_{2,3}$ 3.4, $J_{3,4}$ 9.5 Hz, H3$^{I}$), 3.72–3.76 (m, 3H, H6$^{I}$,3$^{II}$,5$^{II}$), 3.85–3.87 (m, 3H, H2$^{II}$,6a$^{II}$,6b$^{II}$), 3.98 (dd, 1H, $J_{1,2}$ 1.8 Hz, H2$^{I}$), 4.58 (d, 1H, H1$^{I}$), 4.92 (d, 1H, $J_{1,2}$ 1.6 Hz, H1$^{II}$); $^{13}$C NMR (100 MHz, $D_2O$) $\delta$ 54.9, 61.0, 63.8 (d, $J_{C,P}$ 5.3 Hz), 66.1, 66.5, 69.5, 70.2, 70.3, 72.6 (d, $J_{5,P}$ 6.9 Hz), 72.7, 79.3, 101.1, 102.8; $^{31}$P NMR (162 MHz, $D_2O$) $\delta$ 2.7 ($PO(ONa)_2$); HRMS calcd for $C_{13}H_{25}O_{14}P$ $[M+H]^+$ 437.1055, found 437.1040; CE: $t_m$ = 21.46 min.

*Method B*: The hexabenzoate **39** (10 mg, 7.8 μmol) was treated first with KOH in THF and then $PtO_2$ as described for the preparation of **5** [steps (C) and (B)] to yield the phosphomannobioside **8** as a colourless powder (2.1 mg, 49%, two steps). This sample was identical in all respects to that produced in the previous method.

### 3.20. 2,3,4-Tri-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl trichloroacetimidate (41)

(A) Imidazole (167 mg, 2.45 mmol) and *tert*-butyldiphenylsilyl chloride (640 μL, 5.61 mmol) were added to a solution of the alcohol **17** (785 mg, 2.25 mmol)[25] in 1,2-DCE (10 mL) and the combined mixture was stirred (1 h). The mixture was filtered and the filtrate subjected to FC (25% EtOAc/hexanes) to yield, presumably the silyl ether **40**, as a colourless oil (1.19 g). (B) Benzylamine (856 μL, 7.83 mmol) was added to a solution of the tetraacetate **40** (1.15 g, 1.96 mmol, max.) and in $Et_2O$ (20 mL) and the combined mixture was stirred (rt, o/n). The mixture was subjected to workup ($Et_2O$). The solution was used in the following reaction without further purification or characterization. (C) Cesium carbonate (1.3 g, 3.7 mmol) was added to the product from (B), trichloroacetonitrile (1 mL, 10 mmol) and mol sieves (500 mg of 3 Å powder) and the combined mixture was stirred (rt, o/n). The mixture was filtered and evaporated and the residue subjected to FC (15% EtOAc/hexanes) to yield the imidate **41** as a colourless oil (647 mg, 48%, two steps). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.06 (s, 9H), 1.92, 2.01, 2.17 (3s, 3 × 3H), 3.70–3.80 (*AB*X, 2H), 4.05 (dt, 1H, *J* 3.3, 9.9 Hz), 5.41 (dd, 1H, *J* 3.3, 9.9 Hz), 5.45 (dd, 1H, *J* 1.5, 3.3 Hz), 5.57 (t, 1H, *J* 9.9 Hz), 6.33 (d, 1H, *J* 1.8 Hz), 7.30–7.80 (m, 10H), 8.75 (s, 1H).

### 3.21. Benzyl 2-*O*-(2,3,4-tri-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (44)

TMSOTf (15 μL, 82 μmol) was added to the imidate **41** (100 mg, 145 μmol) and alcohol **10** (60 mg, 111 μmol) as described for the preparation of **25/26** to yield the mannobioside **44** as a colourless oil (117 mg, 99%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.09 (s, 9H), 1.91, 2.03, 2.12 (3s, 3 × 3H), 3.60–4.05 (m, 8H), 4.12 (t, 1H, *J* 2.0 Hz), 4.36–4.88 (m, 8H), 4.99 (d, 1H, *J* 1.8 Hz), 5.14 (d, 1H, *J* 1.5 Hz), 5.40–5.50 (m, 3H), 7.10–7.80 (m, 35H).

### 3.22. Benzyl 2-*O*-(2,3,6-tri-*O*-acetyl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (45)

A combined mixture of TBAF (170 μL of 1 M in THF, 170 μmol), acetic acid (20 μL) and the silyl ether **44** (37 mg, 35 μmol) in THF (1 mL) was stirred (rt, 2 d). EtOAc (10 mL) was added and the solution was successively washed (satd aq NaCl), dried ($Na_2SO_4$), filtered and evaporated. The residue was subjected to FC (25–50% EtOAc/hexanes) to yield the alcohol **45** as a colourless oil (18 mg, 63%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.03–2.05 (m, 9H), 3.60–4.20 (m, 11H), 4.37 (dd, 1H, *J* 4.4, 12.4 Hz), 4.39–4.65 (m, 8H), 4.76 (t, 1H, *J* 9.9 Hz), 4.92 (br s, 2H), 5.20 (dd, 1H, *J* 3.3, 9.9 Hz), 5.38 (dd, 1H, *J* 1.5, 3.3 Hz), 7.10–7.40 (m, 20H).

### 3.23. Benzyl 2-*O*-(2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (48)

(A) TMSOTf (123 μL, 0.68 mmol) was added to the imidate **43**[32] (464 mg, 0.68 mmol)[32] and alcohol **10** (308 mg, 0.57 mmol) as described for the preparation of **25/26** to yield a colourless oil. This residue was co-evaporated (2 × 10 mL MeCN) and used in the next reaction without further purification or characterization. (B) Acetyl chloride (1.0 mL) was added to a solution of the product from (A) and MeOH (10 mL) in 1,2-DCE (5 mL) and the combined mixture was stirred (rt, o/n). The mixture was cooled and neutralized ($Et_3N$) and the solvents were evaporated. The residue was subjected to workup (EtOAc) and FC (10–40% EtOAc/hexane) to yield the alcohol **48** as a colourless oil (422 mg, 73%, two steps). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.60–3.61 (m, 2H, H6a$^{II}$,6b$^{II}$), 3.72 (dd, 1H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 10.4 Hz, H6a$^{I}$), 3.77 (dd, 1H, $J_{5,6b}$ 5.2 Hz, H6b$^{I}$), 3.82–3.88 (m, 1H, H5$^{II}$), 3.99–4.02 (m, 3H, H2$^{I}$,3$^{I}$,4$^{I}$), 4.11–4.16 (m, 1H, H5$^{II}$), 4.46–4.74 (m, 7H, PhC$H_2$), 4.85 (B of AB quartet, $J_{A,B}$ 11.0 Hz, PhC$H_2$), 5.03 (d, 1H, $J_{1,2}$ 1.6 Hz, H1$^{I}$), 5.21 (d, 1H, $J_{1,2}$ 1.2 Hz, H1$^{II}$), 5.73 (dd, 1H,

$J_{3,4\sim4,5}$ 10.4 Hz, H4$^{II}$), 5.85 (dd, 1H, $J_{2,3}$ 3.2 Hz, H2$^{II}$), 5.99 (dd, 1H, $J_{3,4}$ 10.0 Hz, H3$^{II}$), 7.10–7.60, 7.78–8.06 (2m, 35H, Ph); ESMS: *m/z* 1015.5 $[M+H]^+$.

### 3.24. Alternative synthesis of benzyl 2-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (32)

$Et_3N$ (96 μL, 0.69 mmol) was added to a solution of the alcohol **48** (140 mg, 0.14 mmol) and diphenyl phosphorochloridate (86 μL, 0.42 mmol) in 1,2-DCE (5 mL) and the combined mixture was heated (80 °C, 3 h). The mixture was diluted ($CHCl_3$) and subjected to workup and FC (10–40% EtOAc/hexane) to yield the diphenyl phosphate **32** as a colourless oil (157 mg, 91%). This sample was identical in all respects to that prepared by the previous method.

### 3.25. Methyl 3-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-2,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (49)

TMSOTf (38.6 μL, 0.213 mmol) was added to the imidate **43** (145 mg, 0.213 mmol) and alcohol **13** (94 mg, 0.164 mmol) as described for the preparation of **25/26** to yield the acetate **49** as a colourless oil (142 mg, 79%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.06 (s, 3H, Ac), 3.45 (s, 3H, OMe), 4.13 (dd, 1H, $J_{5,6a}$ 2.4, $J_{6a,6b}$ 12.1 Hz, H6a$^{II}$), 4.18 (dd, 1H, $J_{5,6b}$ 5.2 Hz, H6b$^{II}$), 4.25 (ddd, 1H, $J_{4,5}$ 10.1, $J_{5,6a}$ 2.7, $J_{5,6b}$ 4.5 Hz, H5$^{I}$), 4.36 (ddd, 1H, $J_{4,5}$ 9.8 Hz, H5$^{II}$), 4.43 (dd, 1H, $J_{6a,6b}$ 12.1 Hz, H6b$^{I}$), 4.59 (dd, 1H, $J_{2,3}$ 3.4, $J_{3,4}$ 9.8 Hz, H3$^{I}$), 4.68 (dd, 1H, H6a$^{I}$), 4.98 (d, 1H, $J_{1,2}$ 1.5 Hz, H1$^{I}$), 5.25–5.28 (m, 2H, H1$^{II}$,2$^{II}$), 5.59 (dd, 1H, H2$^{I}$), 5.62 (dd, 1H, $J_{2,3}$ 3.2, $J_{3,4}$ 9.8 Hz, H3$^{II}$), 5.74 (dd, 1H, H4$^{II}$), 5.97 (dd, 1H, H4$^{I}$), 7.14–7.82, 8.02–8.18 (2m, 30H, Ph); HRMS calcd for $C_{57}H_{51}O_{18}$ $[M+H]^+$ 1023.3075, found 1023.3091.

### 3.26. Methyl 3-*O*-(2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl)-2,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (50)

Acetyl chloride (1.0 mL) was added to the acetate **49** (120 mg, 0.110 mmol) as described for the preparation of **48** to yield the alcohol **50** as a colourless glass (95 mg, 82%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.46 (s, 3H, OMe), 3.53 (dd, 1H, $J_{5,6a}$ 3.5, $J_{6a,6b}$ 13.0 Hz, H6a$^{II}$), 3.72 (dd, 1H, $J_{5,6b}$ 2.1 Hz, H6b$^{II}$), 4.02–4.06 (m, 1H, H5$^{II}$), 4.26 (ddd, 1H, $J_{4,5}$ 10.0, $J_{5,6a}$ 2.6, $J_{5,6b}$ 4.5 Hz, H5$^{I}$), 4.44 (dd, 1H, $J_{6a,6b}$ 12.2 Hz, H6b$^{I}$), 4.57 (dd, 1H, $J_{2,3}$ 3.4, $J_{3,4}$ 9.4 Hz, H3$^{I}$), 4.68 (dd, 1H, H6a$^{I}$), 4.93 (d, 1H, $J_{1,2}$ 1.7 Hz, H1$^{I}$), 5.27–5.29 (m, 2H, H1$^{II}$,2$^{II}$), 5.57 (dd, 1H, H2$^{I}$), 5.67 (dd, 1H, $J_{3,4-4,5}$ 9.9 Hz, H4$^{II}$), 5.71 (dd, 1H, $J_{2,3}$ 3.2 Hz, H3$^{II}$), 5.98 (dd, 1H, H4$^{I}$), 7.13–7.82, 8.12–8.15 (2m, 30H, Ph); ESMS: *m/z* 981.4 $[M+H]^+$.

### 3.27. Alternative synthesis of methyl 3-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-diphenylphosphoryl-α-D-mannopyranosyl)-2,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (39)

The alcohol **50** (76 mg, 0.73 mmol) was treated with $Et_3N$ (75 μL, 0.73 mmol) and diphenyl phosphorochloridate (80 μL, 0.390 mmol) as described for the preparation of **32** to yield the diphenyl phosphate **39** as a colourless oil (94 mg, 90%). This sample was identical in all respects to that prepared by the previous method.

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