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### Synthesis of mono- and disaccharide analogs of moenomycin and lipid II for inhibition of transglycosylase activity of penicillin-binding protein 1b

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Abstract—Three types of mono- and disaccharides 3a, b, 4a-c, 5, and some chaetomellic acid A analogs 6 and 42-44 were synthesized as potential inhibitors of the transglycosylase activity of penicillin-binding protein 1b (PBP1b), a key bacterial enzyme responsible for the formation of the polysaccharide backbone of peptidoglycan as well as for cross-linking of its peptide portions. The target compounds combine structural features of both the active portion of moenomycin and the natural PBP1b substrate, lipid II. The desired skeletons were obtained in a convergent fashion involving attachment of the lipid-alkylated glyceric acid moieties 11a, b to the corresponding carbohydrate-containing phosphonic acids 23, 24a, and 24b. Compounds 3a, b were prepared to verify the distance requirements between the sugar and the noncleavable *C*-phosphonate moieties. Compounds 4a-c were synthesized to examine the importance of the first sugar unit of moenomycin, a known inhibitor of transglycosylase catalysis by PBP1b, with respect to antibiotic activity. These were prepared by condensation of 11a, b with 28a and 28c, which were made by glycosylation of 3-bromopropanol with oxazolines 25a, b, and Arbuzov reaction with triethyl or trimethyl phosphite, followed by dealkylation with bromotrimethylsilane. Compound 5 was generated to verify the possibility of using a dicarboxylate group to mimic the diphosphate of lipid II. It was synthesized by coupling of alcohol 31 with  $\alpha$ -trichloroacetimidate 34. Chaetomellic acid A analogs were found to inhibit PBP1b, albeit with modest potency. © 2004 Elsevier Ltd. All rights reserved.

### 1. Introduction

The biosynthesis of the bacterial peptidoglycan cell wall layer provides numerous targets for the design and development of new antimicrobial agents as it has no counterpart in eukaryotic cells.<sup>1–6</sup> Among these is penicillin-binding protein 1b (PBP1b), a transpeptidase with glycosyltransferase (transglycosylase) activity, that catalyzes both the polymerization of the lipid-bearing monomer units **1** of peptidoglycan to make long polysaccharide chains as well as the cross-linking of these at the D-Ala unit (Fig. 1).<sup>7–9</sup> Although many antibiotics are known to interfere with processing of the

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peptide portion of the polysaccharide chain, only a few compounds are believed to selectively inhibit transglycosylase activity. In the past few years, among the transglycosylase inhibitors that have been identified are ramoplanin,<sup>10–12</sup> coleophomone A and B,<sup>13</sup> the mannopeptimycins,<sup>14</sup> glycopeptide antibiotics based on the parent structures of erenomycin, chloroerenomycin,<sup>15,16</sup> vancomycin,<sup>17</sup> and chlorobiphenyl vancomycin,<sup>18</sup> as well as the moenomycin-type compounds.

Moenomycin A (2) is one of the most potent transglycosylase inhibitors known but its absorption upon oral delivery is relatively poor. Extensive structure–activity relationship studies of moenomycin analogs have been done.<sup>19–22</sup> Systematic degradation studies on these phosphoglycolipids have revealed that moenomycin analogs with at least three carbohydrate units (C, E, and F) are active in vivo against Gram-positive bacteria. Moenomycin disaccharide derivatives (lacking units A, B, C, and D) are also active transglycosylase inhibitors,<sup>23</sup> but they lack antibacterial activity.<sup>24</sup> Studies by Welzel and

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Figure 1. Structure of the peptidoglycan precursor, lipid II, with schematic representation of transglycosylation reaction wherein the 4-hydroxy of the Glc-NAc moiety (blue) displaces the undecaprenyl diphosphate attached to the peptide-bearing Mur-NAc residue (green). Moenomycin A (2) is a powerful inhibitor of the transglycosylation reaction catalyzed by PBP1b.

co-workers demonstrated that the equatorial hydroxyl function at C4 plays an important role in the interaction of the transglycosylase inhibitors with the enzyme.<sup>25</sup> It has been postulated that the interaction with the ring oxygen of the phosphorylated unit of the growing peptidoglycan chain could be replaced by the binding interaction with the equatorial hydroxyl group at C4.26 It has also been shown that the methyl group at C4 is not necessary for antibiotic activity.<sup>27</sup> The contribution to the binding of moenomycin A to the enzyme furnished by the acetamido group of unit C and E has been highlighted.<sup>28,29</sup> Interestingly, moenomycin-type transglycosylase inhibitors bearing a terminal hydroxyl function in the lipid part are biologically inactive.<sup>30</sup> Since many phosphoglycolipids are nontoxic to mammals, synthetically accessible analogs that are transglycosylase inhibitors with better solubility than moenomycin A may be effective against organisms resistant to current therapy.

In connection with our early report on the synthesis of a *C*-phosphonate disaccharide as a possible inhibitor of transglycosylase,<sup>31</sup> we now report the preparation of disaccharides **3a** and **3b** that combine features of lipid II (1) and moenomycin A (2) (Fig. 2). We also describe the synthesis of a series of extended monosaccharide analogs **4a–c** of the active portion of moenomycin. Although they lack the physiologically active peptide chain of lipid

II that contributes to immune response and/or toxicity in mammals,<sup>32</sup> all these analogs contain features likely to be needed for recognition by transglycosylase. Key structural characteristics in these molecules include a phosphoglycerate anionic group mimicking a diphosphate, a terminal N-acetylglucosamine unit and a lipid tail. Furthermore, in these compounds, the noncleavable C-glycoside and phosphonate moieties can serve as stable surrogates of O-glycosides and phosphate esters, respectively. In addition to potentially inhibiting transglycosylase, they could also 'end-cap' the growing polysaccharide chain if they are incorporated into peptidoglycan. We also describe the synthesis of derivative 5 of the peptidoglycan monomer unit which possesses a dicarboxylate moiety as a mimic of the diphosphate of lipid II (1), as well as the synthesis of analogs (42-44) of chaetomellic acid A (6) as possible inhibitors of transglycosylase. Results from inhibition studies with PBP1b for all of these compounds are presented.

### 2. Results and discussion

### 2.1. Preparation of glyceric acid derivatives

The lipid-bearing glyceric acid moieties **11a** and **11b** are key intermediates for synthesis of the target compounds



Figure 2. Target compounds for inhibition studies with PBP1b.

**3a**, **3b**, and **4a–c**. These can be prepared using a slightly improved procedure to that first devised by Schubert and Welzel<sup>33</sup> and subsequently modified by Hecker et al.<sup>34</sup> (Scheme 1). Thus, alkylation of dibenzylidenemannitol **7** with octyl or (*R*)-citronellyl bromide affords **8a** and **8b**, which are converted by hydrolysis to **9a** and hydrogenolysis to **9b**, respectively. Oxidative cleavage with sodium periodate, silver(I) oxide, and sodium



Scheme 1. Synthesis of lipid-bearing glyceric acid derivatives.

hydroxide gives **10a** and **10b**, which can be esterified to generate **11a** and **11b**.

### 2.2. Synthesis of disaccharides 3a and 3b

These compounds are designed to probe the distance requirements between the sugar and the noncleavable C-phosphonate groups. Their synthesis proceeds via a convergent approach involving attachment of 11a or **11b** to the initially coupled protected D-glucose C-phosphonate and protected D-glucosamine, followed by complete deprotection. The known derivative  $14^{35,36}$  can be prepared from D-glucose by an improved four-step route in 50% overall yield (Scheme 2). Thus, Fischer glycosylation of D-glucose with allyl alcohol using pre-dried AG50W-X8 (H<sup>+</sup>) ion exchange resin as catalyst, followed by treatment with benzaldehyde and zinc chloride affords 12 as a 1.1:1 mixture of  $\alpha$ - and  $\beta$ -anomers. Benzylation of the two remaining hydroxyl groups produces 13. Finally, isomerization of the allyl moiety with potassium tert-butoxide in DMSO followed by hydrolysis with mercuric chloride and mercuric oxide gives 14. It should also be noted that the use of the Wilkinson's catalyst followed by hydrolysis, a well-established sequence for the removal of an allyl group in carbohydrate chemistry, also removes the benzylidene group present in 13. Wittig reaction of 14 with methyltriphenylphosphonium bromide and *n*-butyllithium generates 15, which cyclizes upon treatment with mercury trifluoroacetate to produce 16. Iodomercuration affords 17 as a 4.3:1 mixture of  $\alpha$ - and  $\beta$ -isomers that is readily separated by flash chromatography. The configuration at the anomeric center of 17 can be unequivocally assigned on the basis of NMR studies ( $J_{1,2} = 4.5$  Hz, NOE<sub>1,2</sub> = 14% for the  $\alpha$ isomer). Reductive ring opening of the benzylidene acetal of 17 using sodium cyanoborohydride in acidic ether-THF gives the required 4-hydroxy C-glycoside 18.37 Finally, Arbuzov reaction<sup>38</sup> produces phosphonate 19 in preparation for the next glycosylation reaction.



Scheme 2. Synthesis of C-glycoside phosphonate 19.

Condensation of **19** with the known protected 1-chloroglucosamine derivative  $20^{39,40}$  using silver triflate gives **21**, which is easily transformed into **22** by the well-established hydrazinolysis and acetylation sequence (Scheme 3). Dealkylation of **22** with bromotrimethylsilane provides **23**, which can be coupled with the available glycerate lipids **11a** and **11b** using trichloroacetonitrile in pyridine<sup>41</sup> to form **24a** and **24b**. Finally, hydrogenolysis of the benzyl groups with 10% Pd/C as catalyst followed by de-*O*-acetylation using methanolic sodium methoxide affords the desired target compounds **3a** and **3b** in high yield.

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### 2.3. Synthesis of analogs 4a-c

These molecules were designed so that the distance between the N-glucosamine unit and the phosphorus atom is similar to that in moenomycin. They were expected to

highlight the importance of the first sugar unit in moenomycin with respect to antibiotic activity. Earlier investigations on the synthesis of monosaccharide analogs of moenomycin A reported no biological activity.<sup>34,42</sup> Nevertheless, as a monosaccharide degradation product of moenomycin A retains some biological activity in enzyme assays and antibacterial testing,43 compound 4a was synthesized. The synthetic approach for targets 4a-c involves coupling of the independently prepared sugar and glycerate lipid 11a and 11b moieties. Reaction of 3-bromopropanol with the known oxazoline derivatives  $25a^{44}$  and  $25b^{45}$  in the presence of 10-(R)camphorsulfonic acid<sup>46</sup> provides the corresponding acetamido-β-glycosides **26a.b** (Scheme 4). Arbuzov reaction of **26a** with triethyl phosphite, and of **26b** with trimethyl phosphite, affords the corresponding ethyl and methyl phosphonates 27a and 27c, respectively. Removal of the ethyl and methyl groups using bromotrimethylsilane and subsequent hydrolysis generates the corresponding phosphonic acids 28a and 28c. The ethyl phosphonate 27b is also available via Arbuzov reaction, however attempted deprotection with bromotrimethylsilane is unsuccessful and gives 28b. Difficulties in deprotection





of ethyl phosphonates have previously been reported.<sup>47</sup> Trichloroacetonitrile mediated coupling of the monosaccharide **28a** with **11b** and of the disaccharide **28c** with **11a,b** produces **29a** and **27b,c**, respectively. Finally, hydrogenation of **29a** with 10% Pd/C catalyst followed by removal of the acetate groups affords the desired monosaccharide target **4a**. In contrast, compounds **30b,c**, resulting from the hydrogenolysis of disaccharides **29b,c**, can be isolated and characterized before saponification of the esters to give the expected amphiphilic target analogs **4b,c**.

### 2.4. Synthesis of monosaccharide 5

This compound was designed to examine the possibility of using a dicarboxylate group as a mimic of the diphosphate of lipid II. The ability of a variety of chaetomellic acid analogs (see below) to inhibit protein prenvl transferases<sup>48</sup> illustrates the ability of a maleic acid moiety bearing an appropriate lipid to mimic a prenyl diphosphate. The preparation of 5 could be realized via coupling of an  $\alpha$ -O-glycosyl trichloroacetimidate and the aglycone 31, followed by complete deprotection. Compound 31 is available by the method previously developed in our group by Ratemi et al.<sup>48</sup> (Scheme 5). Reaction of CuBr·Me<sub>2</sub>S, tetradecylmagnesium chloride, and DMAD in the presence of HMPA, followed by alkylation of the conjugate adduct with a trimethylsilylethoxymethyl chloride (SEMCl) gives a separable mixture of Z and E protected compounds 32 (28%) and 33 (54%). The stereochemical assignment for these tetrasubstituted alkenes is based on NOE experiments. Even though the desired Z isomer 32 is the minor product formed during this reaction, enough material is generated to continue the synthesis of hydroxymethyl derivative 31. The use of the Lewis acid boron trifluoride etherate is an efficient method for the deprotection of (2-trimethylsilylethoxy)methyl compounds.<sup>49</sup> Removal of the trimethylsilylethyl group of 32 is achieved using BF<sub>3</sub>·Et<sub>2</sub>O in acetonitrile to afford the desired alcohol 31 in 95% yield.

The utility of *O*-glycosyl trichloroacetimidates for the formation of  $\alpha$ -*O*-glycosides from 2-azido sugars has been widely investigated. It is known that upon treatment with acid they produce the desired  $\alpha$ -linkages. The key intermediate  $\alpha$ -trichloroacetimidate  $34^{50}$  for the synthesis of the targeted  $\alpha$ -*O*-monosaccharide 5 can be prepared from D-glucosamine hydrochloride according to the usual methods.<sup>51,52</sup> Compound 34 is not very stable and must be immediately used after purification for the glycosylation reaction with alcohol 31 in



Scheme 6. Synthesis of monosaccharide 5.

the presence of trimethylsilyl triflate and 4A molecular sieves in diethyl ether to produce the desired  $\alpha$ -*O*-glycosides **35** (Scheme 6). Reaction of azide **35** with tin chloride, thiophenol, and triethylamine in acetonitrile affords the corresponding amino compound, which is immediately treated with pyridine and acetic anhydride to give acetamide **36**. Deprotection of the hydroxyl functionality of **36** using methanolic sodium methoxide generates diester **37**. Finally, hydrolysis of the methyl esters of **37** with lithium hydroxide gives the desired monosaccharide **5**.

### 2.5. Synthesis of chaetomellic acid A analogs

The long lipid chain of moenomycin has been shown to be essential for good antimicrobial activity.<sup>53</sup> Analogs of



Table 1. Preparation of chaetomellic acid A analogs by conjugate addition to DMAD

	RCu(M	e₂S)∙MgBrCl	1. MeO <sub>2</sub> CC=CCO <sub>2</sub> Me 2. EX, HMPA:THF/1:1 3. NH <sub>4</sub> Cl/H <sub>2</sub> O		LiOH THF:H <sub>2</sub> O/1:1	E − C <sup>-</sup> Li <sup>+</sup> O <sup>-</sup> Li <sup>+</sup>	
R	EX	Е		Product	Yield (%) <sup>a</sup>	Hydrolysis product	Yield (%)
<i>n</i> -C <sub>14</sub> H <sub>29</sub>	MeI	Me		38	76	6	99
Me	Geranyl-Br	$\gamma$	CH2-	39	84	42	90
Me	Farnesyl-Br	$\rightarrow$	CH2-	40	82	43	99
Me	Nerolyl-Br <sup>b</sup>		CH2-	41	73	44	99

<sup>a</sup> Isolated yields.

<sup>b</sup> Freshly prepared from nerol.

chaetomellic acid A (6) were tested to verify if such molecules, which resemble the undecaprenyl diphosphate moiety of lipid II, could inhibit the bacterial cell wall transglycosylase. Such studies have not yet been reported. Compounds 6 and 38–44 could be prepared according to the method previously developed in our group by Ratemi et al.<sup>48</sup> (Table 1). Michael addition of various organocopper reagents to DMAD in the presence of HMPA, followed by capture of the resulting enolates with a variety of electrophiles affords chaetomellic acid analogs 38–41 as methyl esters. Ester hydrolysis with lithium hydroxide furnishes derivatives 6 and 42–44. In addition to studies with the PBP1b transglycosylase (see below), these compounds were also investigated for their ability to inhibit rubber transferase.<sup>54</sup>

### 2.6. Inhibition studies

All of the synthesized target compounds were tested in vitro for inhibitory effects on the major E. coli transglycosylase, PBP1b (Table 2), and most show some inhibition. Incubating PBP1b with a [<sup>14</sup>C]-GlcNAc-labeled lipid II analog containing a heptaprenyl lipid chain and 100 µM of disaccharides 3a,b demonstrates that 3a inhibits PBP1b transglycosylase by 17%, whereas **3b** does not. Compounds 4a-c were also tested. When present at 100 and 200 µM, monosaccharide 4a inhibits PBP1b at 25% and 37%, respectively. Disaccharide 4b is weakly inhibitory (10%) when included in the assay at  $100 \,\mu$ M. Compound 4c, when present at 100 and  $200\,\mu\text{M}$ , inhibits activity of PBP1b by 25% and 61%, respectively. Compound 5 ( $100 \,\mu$ M) is also an inhibitor of PBP1b (28%). Finally, chaetomellic acid A analogs 6 and 42-44  $(100\,\mu\text{M})$  were also found to inhibit the *E. coli* transglycosylase at 11%, 12%, 24%, and 17%, respectively.

### 3. Conclusion

Using convergent synthetic approaches, the synthesis of three types of mono- and disaccharides **3a**,**b**, **4a**–**c**, and **5** 

Table 2. % Inhibition of GTase module of E. coli PBP1b

Compds tested <sup>a</sup>	Inhibition (%) <sup>b</sup>		
3a	17		
3b	_		
4a	25		
4a <sup>c</sup>	37		
4b	10		
4c	25		
4c <sup>c</sup>	61		
5	28		
6	11 <sup>d</sup>		
42	12		
43	24 <sup>d</sup>		
44	17		

 $^a$  The final concentration of each compound is  $100\,\mu\text{M}$  except for the two noted.

<sup>b</sup>% Inhibition was calculated by comparing the reaction rate in the presence of the compound to the rate in the absence of any inhibitory compound.

<sup>c</sup> Final concentration of 200 µM.

<sup>d</sup> Not accurate because these two compounds were not completely dissolved.

has been achieved. The required glycerate-alkyl ethers **11a,b** were readily prepared from **D**-mannitol by modification of literature procedures. Compounds 3a,b, which had been designed to determine the importance of the distance between the sugar and the noncleavable Cphosphonate groups, were synthesized in 13 steps in 5-6% overall yield. As part of their synthesis, a procedure was also developed to offer improved access to 14. Compounds 4a-c, which had been designed to determine the relative contribution to antibiotic activity of the first sugar unit in moenomycin, were prepared from the known oxazoline derivatives 25a,b in six steps in 52-72% overall yield. Compound 5, designed to verify the possibility of using a dicarboxylate moiety in place of the diphosphate of lipid II, was synthesized from known  $\alpha$ -trichloroacetimidate 34 in four steps in 39% overall yield. The methodologies developed can be used not only to synthesize these molecules, but also other more complicated systems useful for inhibition studies. Finally,

chaetomellic acid analogs **6** and **42–44** were prepared in two steps in 72–81% overall yield. All of the compounds described above were tested for inhibitory activity against the *E. coli* transglycosylase PBP1b. Compound **3b** was found to not inhibit PBP1b. All the other compounds, when present in 100–200  $\mu$ M inhibited activity of the bacterial transglycosylase at 10–61%. These results confirm that simple analogs of moenomycin and lipid II analogs can inhibit the PBP1b transglycosylase. However, additional recognition elements on substrate analogs are clearly required to achieve potent binding and inhibition comparable to that of moenomycin A.

### 4. Experimental

#### 4.1. General procedures

Most common experimental procedures and instrumentation have been previously described.<sup>55</sup> All reactions involving air sensitive reagents were conducted under argon using oven-dried glassware. All reagents employed were of American Chemical Society (ACS) grade or finer and were used without further purification unless otherwise stated. Copper(I) bromide-dimethyl sulfide complex (CuBr·Me<sub>2</sub>S) was either used fresh from commercial sources or recrystallized from old bottles.<sup>56</sup> Dimethyl acetylenedicarboxylate (DMAD) was distilled at reduced pressure before use (95-98°C/19mmHg). Hexamethylphosphoramide (HMPA) was dried by stirring with calcium hydride under argon for 36h, followed by distillation at reduced pressure and was stored over molecular sieves. Solvents were dried and distilled prior to use according to standard procedures.<sup>57,58</sup> Melting points are uncorrected.

## 4.2. (*R*)-3-((2-Acetamido-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)- $\alpha$ -D-glucopyranosyl)methylphosphinato)-2-octyl-oxypropanoic acid (3a)

A solution of 24a (96mg, 0.1 mmol) in acetic acid-95% EtOH (1:1 v/v) (4mL) was stirred under H<sub>2</sub> in the presence of 10% Pd/C (90 mg) for 28 h. The mixture was diluted with MeOH, filtered through Celite<sup>®</sup>, and then concentrated in vacuo. The resulting residue was dissolved in anhydrous MeOH (2mL) and was cooled to 0°C. Sodium methoxide (2mL of a 0.2M solution in MeOH, 0.4mmol) was then added dropwise over a period of 20min. The resulting solution was stirred at 0°C for 20min and then at rt for 1h. An excess amount of AG50W-X8 (H<sup>+</sup>) ion exchange resin was added. Filtration followed by concentration in vacuo afforded a residue, which was precipitated from acetone-MeOH to give **3a** (52 mg, 96%) as a glassy solid: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3333, 2924, 2854, 1736, 1462, 1378, 1212, 1202, 1086, 1067, 1055 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz)  $\delta$  4.90 (br s, 9H), 4.50–4.00 (m, 5H), 4.00–3.35 (m, 14H), 2.35-2.20 (m, 2H), 2.00 (s, 3H), 1.65-1.55 (m, 2H), 1.45–1.20 (m, 10H), 0.90 (t, 3H, J = 8.0 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 75MHz) δ 174.0, 173.3, 103.0, 81.1, 79.4 (d, J = 5.5 Hz), 78.1, 75.8, 73.6, 73.2, 72.3, 72.2, 72.0, 66.4 (d, J = 5.5 Hz), 62.6, 61.6, 57.3, 48.5 (obscured by CD<sub>3</sub>OD peaks, but can be detected in DMSO- $d_6$ ),

33.0, 30.7, 30.5, 30.4, 27.1, 25.0, 23.7, 23.1, 14.4; <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  29.8; LRMS (FAB, glycerol) *m*/*z* (relative intensity) 662.3 (MH<sup>+</sup>, 0.6%).

### 4.3. (2R,3'R)-3- $((2-Acetamido-2-deoxy-\beta-D-glucopyrano$ $syl-<math>(1\rightarrow 4)$ - $\alpha$ -D-glucopyranosyl)methylphosphinato)-2-(3',7'-dimethyloctyloxy)propanoic acid (3b)

The procedure used for the preparation of **3a** was utilized to prepare **3b**. Reaction of **24b** (117 mg, 0.1 mmol) with 10% Pd/C (80 mg) in acetic acid–95% EtOH (1:3 v/v) (10 mL) and sodium methoxide (1.94 mL of a 0.2 M solution in MeOH, 0.4 mmol) gave **3b** (51 mg, 95%) as a glassy solid: IR (CH<sub>2</sub>Cl<sub>2</sub>–MeOH cast) 3363, 2926, 1736, 1652, 1561, 1384, 1071 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>–CD<sub>3</sub>OD–D<sub>2</sub>O/3:3:1, 400 MHz)  $\delta$  4.25 (d, 1H, J = 8.5 Hz), 4.15 (br s, 10H), 4.10–4.00 (m, 2H), 3.89–3.86 (m, 1H), 3.72–3.68 (br m, 1H), 3.50–3.15 (m, 13H), 2.10–1.95 (m, 2H), 1.82 (s, 3H), 1.50–0.90 (m, 10H), 0.68 (2d, 6H and 3H, J = 7.0 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>–CD<sub>3</sub>OD–D<sub>2</sub>O/3:3:1, 162 MHz)  $\delta$  29.6; LRMS (FAB, Cleland) m/z (relative intensity) 712 (MNa<sup>+</sup>, 2%).

### 4.4. (2*R*,3'*R*)-3-(3-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)propylphosphinato)-2-(3',7'-dimethyloctyloxy)propanoic acid (4a)

The procedure utilized to prepare 3a from 24a was followed. Reaction of 29a (27mg, 0.03mmol) with 10% Pd/C (15mg) in 95% EtOH (2mL) (4h) and sodium methoxide (0.7mL of a 0.2M solution in MeOH, 0.14 mmol) provided 4a (19 mg, 96%) as a white powder: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3425, 2925, 2853, 1717, <sup>1</sup>H NMR ( $CDCl_3$ - $CD_3OD/4:1$ , 1384,  $1050 \,\mathrm{cm}^{-1}$ ; 400 MHz)  $\delta$  4.30–4.15 (m, 7H), 4.12–4.08 (br m, 2H), 3.88-3.84 (br m, 1H), 3.75-3.65 (m, 2H), 3.65-3.45 (m, 3H), 3.50-3.10 (m, 5H), 1.90 (br s, 3H), 1.75-1.55 (br m, 2H), 1.50-0.90 (m, 10H), 0.70 (t, 9H, J = 6.5 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>-CD<sub>3</sub>OD/4:1, 100 MHz)  $\delta$  173.3, 172.1, 100.5, 77.7 (d,  $J = 7.0 \,\mathrm{Hz}$ ), 75.7, 74.4, 70.6, 69.5, 68.5 (d, J = 14.0 Hz), 64.6 (d, J = 5.3 Hz), 61.4, 56.2, 38.9, 37.0, 36.2, 29.5, 27.6, 24.3, 22.2, 22.1, 21.8, 19.1; <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>-CD<sub>3</sub>OD/4:1, 162 MHz)  $\delta$  32.2; LRMS (FAB, Cleland) m/z (relative intensity) 595 (MNa<sup>+</sup>, 2%), 103 (100%).

### 4.5. (*R*)-3-[3-*O*-(2-Acetamido-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- $\beta$ -D-glucopyranosyl)propylphosphinato]-2-octyloxypropanoic acid (4b)

To a solution of **30b** (19 mg, 0.02 mmol) in dry MeOH (1.5 mL) at 0 °C was added sodium methoxide (3.65 mL of a 43.5 mM solution in MeOH, 0.2 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at rt for 3.25 h. An excess amount of AG50W-X8 (H<sup>+</sup>) ion exchange resin was added. Filtration followed by concentration in vacuo afforded **4b** (15 mg, quant.) as a colorless solid: IR (microscope) 3297, 2853, 1735, 1653, 1559 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 360 MHz)  $\delta$  4.49 (d, 1H, J = 8.4 Hz), 4.39 (d, 1H, J = 8.3 Hz), 4.23 (m, 2H), 4.11 (t, 1H, J = 3.8 Hz), 3.90 (dd, 1H, J = 11.8, 1.6 Hz), 3.87–3.31 (m, 15H), 2.02 and 2.01 (2s, 6H), 1.81 (m, 4H), 1.61 (m, 2H), 1.30 (m, 10H), 0.89 (t, 3H, 3.87–3.31)

J = 6.8 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz)  $\delta$  175.5, 174.9, 173.7, 104.0, 103.2, 82.0, 79.6 (d, J = 5.4 Hz), 78.6, 76.8, 76.2, 74.6, 72.5, 72.3, 70.3 (d, J = 12.4 Hz), 66.5 (d, J = 4.5 Hz), 62.7, 61.9, 57.5, 56.7, 32.8, 30.5, 30.3, 30.2, 26.8, 23.6 (br), 23.4, 22.9 (d, J = 113.7 Hz), 22.7, 14.0; <sup>31</sup>P NMR (CD<sub>3</sub>OD, 162 MHz)  $\delta$  32.2; LRMS (FAB, glycerol/HCl) m/z (relative intensity) 769.4 (MNa<sup>+</sup>, 2.9%), 747.2 (MH<sup>+</sup>, 0.8%).

### 4.6. (2*R*,3'*R*)-3-[3-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-2-deoxy-β-D-glucopyranosyl)propylphosphinato]-2-(3',7'-dimethyloctyloxy)propanoic acid (4c)

Compound 4c was prepared from 30c (25mg, 0.03 mmol) by the same procedure as that used for the synthesis of 4b, employing sodium methoxide (4.7 mL of a 43.5mM solution in MeOH, 0.2mmol) in dry MeOH (1.5mL) to give the title compound (20mg, quant.) as a colorless solid: IR (MeOH cast) 3311, 2870, 1726, 1650, 1562 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 360 MHz)  $\delta$  4.49 (d, 1H, J = 8.4 Hz), 4.38 (d, 1H, J = 8.3 Hz, 4.23 (m, 2H), 4.11 (t, 1H, J = 3.9 Hz), 3.89 (dd, 1H, J = 11.9, 1.9 Hz), 3.86–3.31 (m, 15H), 2.01 and 1.99 (2s, 2×3H), 1.81 (m, 4H), 1.70–1.11 (m, 10H), 0.89 (t, 9H, J = 6.5 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) δ 173.8, 173.7, 173.2, 103.3, 102.6, 81.6, 79.3 (d, J = 7.6 Hz), 78.2, 76.4, 75.9, 74.3, 72.0, 70.5, 70.0 (d, J = 16.9 Hz), 66.2 (d, J = 6.2 Hz), 62.6, 61.8, 57.3, 56.5, 40.5, 38.5, 37.8, 30.9, 29.1, 25.8, 24.0 (br), 23.2 (d, J = 142.7 Hz), 23.2, 23.1, 23.0, 22.9, 20.0; <sup>31</sup>P NMR (CD<sub>3</sub>OD, 162MHz)  $\delta$  32.2; LRMS (FAB, Cleland) m/z(relative intensity) 813.1 (MK<sup>+</sup>, 3.9%), 797.1 (MNa<sup>+</sup>, 3.8%).

### 4.7. (Z)-2-(2-Acetamido-2-deoxy-α-D-glucopyranosyl)oxymethyl-3-tetradecylbutenedioic acid dilithium salt (5)

1 N LiOH (38  $\mu$ L, 2.3 equiv) was added to compound 37 (9.5 mg, 17  $\mu$ mol) in a THF-H<sub>2</sub>O/1:1 solution (1 mL). The reaction mixture was stirred at rt for 21 h. The solvent was removed under reduced pressure and the remaining solid was dissolved in H<sub>2</sub>O. Nonpolar impurities including unreacted starting material were removed by extraction with CH<sub>2</sub>Cl<sub>2</sub>. Freeze drying of the aqueous layer followed by reversed-phase HPLC (C<sub>18</sub> Bondpak, flow rate: 15 mL/min, gradient elution: 30% MeCN in H<sub>2</sub>O) gave 5 ( $t_R$  6.6 min, 8.5 mg, 90%) as a white solid. HRMS (ES+) calcd for C<sub>27</sub>H<sub>47</sub>NO<sub>10</sub>Li 552.3360, found 552.3357 (MH<sub>2</sub>+Li)<sup>+</sup>.

### 4.8. Chaetomellic acid A dilithium salt (6)

A solution of 1 N LiOH (0.3 mL, 2.1 equiv) was added to diester **38** (50 mg, 0.14 mmol) in a THF-H<sub>2</sub>O/1:1 solution (2 mL). The reaction mixture was stirred at rt for 3 days. The solvent was removed under reduced pressure and the remaining solid was dissolved in H<sub>2</sub>O. Nonpolar impurities including unreacted starting material were removed by extraction with Et<sub>2</sub>O. Freeze drying of the aqueous layer gave **6** (47 mg, 99%) as a white solid: IR (KBr) 3440, 2921, 2851, 1555, 1438 cm<sup>-1</sup>; <sup>1</sup>H NMR

(CD<sub>3</sub>OD, 400 MHz)  $\delta$  2.24 (t, 2H, J = 7.8 Hz), 1.83 (s, 3H), 1.47 (m, 2H), 1.28 (br m, 22H), 0.89 (t, 3H, J = 6.8 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 75 MHz)  $\delta$  180.2, 179.9, 139.6, 132.8, 33.1, 31.6, 31.1, 30.5, 30.4, 30.3, 29.5, 23.7, 16.3, 16.2; MS (FAB Cleland) m/z (relative intensity) 339 (MH<sup>+</sup>, 9%).

### 4.9. 1,3:4,6-Di-O-benzylidene-D-mannitol (7)

To a stirred suspension of *D*-mannitol (5.0g, 27.4 mmol) and freshly distilled benzaldehyde (6.0 mL, 59.0 mmol) in DMF (15mL) was added concd  $H_2SO_4$  (98%, 1mL) dropwise. The resulting mixture was stirred at rt for 3 days. A solution of  $K_2CO_3$  (2g) in  $H_2O$  (150 mL) was added portionwise to the reaction mixture, followed by petroleum ether (50 mL). The resulting mixture was stirred at rt for 30 min, and the precipitate which formed was collected by filtration. Purification by flash chromatography (SiO<sub>2</sub>, petroleum ether-EtOAc, gradient elution, 4:1 to 3:1) afforded 7 (3.52g, 26%) as white crystals: mp 173–174 °C (lit.<sup>59</sup> mp 192–193 °C);  $[\alpha]_{D}^{26}$ -9.82 (c 1.10, acetone); IR (CHCl<sub>3</sub> cast) 3439, 1456, 1219, 1105, 1065, 1028 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>-D<sub>2</sub>O, 300 MHz)  $\delta$  7.50–7.30 (m, 10H), 5.51 (s, 2H), 4.29 (dd, 2H, J = 10.0, 5.0 Hz), 4.05–3.90 (m, 4H), 3.61 (dd, 2H, J = 10.0, 10.0 Hz; <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>-D<sub>2</sub>O, 75 MHz)  $\delta$  138.4, 129.2, 128.5, 126.6, 101.5, 79.5, 71.6, 60.3; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 359 (MH<sup>+</sup>, 100%); Anal. Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>6</sub>: C, 67.03; H, 6.19. Found: C, 66.91; H, 6.28.

## 4.10. 1,3:4,6-Di-O-benzylidene-2,5-di-O-octyl-D-mannitol (8a)

To a solution of 7 (760mg, 2.1mmol) in dry DMF (5mL) was added NaH (0.3g of a 60% suspension in oil, 7.5 mmol) in small portions. The resulting mixture was heated at 70 °C for 20 min, and then 1-bromooctane (1.2g, 6.2mmol) was added. After stirring at 70°C for 24h, the mixture was cooled to rt, poured into brine, and extracted with Et<sub>2</sub>O. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by flash chromatography ( $SiO_2$ , petroleum ether-EtOAc/13:1) to give 8a (870 mg, 71%) as a clear oil: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3035, 2953, 2925, 2854, 1456,  $1030 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.50–7.30 (m, 10H), 5.49 (s, 1H), 4.45 (dd, 2H, J = 10.0, 5.0 Hz), 3.97 (d, 2H, J = 8.5 Hz), 3.70 (ddd, 2H, J = 10.0, 8.5, 5.0 Hz), 3.62 (dd, 2H, J = 10.0, 10.0 Hz), 3.61 (dt, 2H, J = 9.5, 3.0 Hz), 3.51 (dt, 2H, J = 9.5, 6.5 Hz), 1.60– 1.50 (m, 4H), 1.40–1.20 (m, 20H), 0.85 (t, 6H, J = 8.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  138.4, 129.1, 128.5, 126.5, 101.4, 78.0, 71.2, 70.1, 67.6, 32.3, 30.5, 29.8, 29.7, 26.5, 23.0, 14.2; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 600 (MNH<sub>4</sub><sup>+</sup>, 4%), 583 (MH<sup>+</sup>, 50%), 57 (100%); Anal. Calcd for C<sub>36</sub>H<sub>54</sub>O<sub>6</sub>: C, 74.19; H, 9.34. Found: C, 74.32; H, 9.39.

## 4.11. (3'*R*)-1,3:4,6-Di-*O*-benzylidene-2,5-di-*O*-(3',7'-dimethyl-6'-octenyl)-D-mannitol (8b)

This was prepared using the same procedure to that described for **8a**. Reaction of 7 (1.0 g, 2.8 mmol) with NaH

(0.5 g of a 60% suspension in oil, 12.5 mmol) and (*R*)citronellyl bromide (1.41 g, 6.4 mmol) in DMF (10 mL) gave compound **8b** (93 mg, 52%) as a colorless oil:  $[\alpha]_{26}^{26}$  -35.2 (*c* 1.15, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 2962, 2924, 1454, 1029 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$ 7.50-7.40 (m, 10H), 5.50 (s, 2H), 5.12-5.04 (m, 2H), 4.42 (dd, 2H, *J* = 10.5, 5.0 Hz), 3.95 (d, 2H, *J* = 9.0 Hz), 3.78 (ddd, 2H, *J* = 10.0, 9.0, 5.0 Hz), 3.70-3.52 (m, 6H), 2.05-1.90 (m, 4H), 1.70 and 1.60 (2s, 12H), 1.65-1.50 (m, 4H), 1.45-1.30 (m, 4H), 1.20-1.10 (m, 2H), 0.90 (d, 6H, *J* = 6.5 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 75 MHz)  $\delta$  138.4, 131.5, 129.1, 128.5, 126.5, 125.1, 101.4, 78.0, 70.1, 69.4, 67.6, 37.5, 37.4, 29.8, 25.8, 19.7, 17.7; LRMS (FAB, Cleland) *m/z* (relative intensity) 635.4 (MH<sup>+</sup>, 1.2%), 105 (100); Anal. Calcd for C<sub>40</sub>H<sub>58</sub>O<sub>6</sub>: C, 75.67; H, 9.21. Found: C, 75.82; H, 9.44.

### 4.12. 2,5-Di-O-octyl-D-mannitol (9a)

A solution of 8a (655mg, 1.1mmol) and 12N HCl (1.1 mL) in 80% EtOH (18 mL) was heated at 70 °C for 20h. The mixture was cooled to rt and a saturated solution of Na<sub>2</sub>CO<sub>3</sub> (20mL) was added dropwise. The resulting mixture was concentrated in vacuo, and the residue was dissolved in brine and extracted with Et<sub>2</sub>O. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Purification by flash chromatography (SiO2, CH2Cl2-MeOH/24:1) afforded 9a (402mg, 88%) as a colorless oil: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3363, 3349, 2921, 2871, 2853, 1467, 1093, 1045 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  3.87 (dd, 2H, J = 6.0, 6.0 Hz, 3.82–3.68 (m, 4H), 3.62 (dt, 2H, J = 9.0, 7.0 Hz), 3.50 (dt, 2H, J = 9.0, 6.5 Hz), 3.61 (ddd, 2H, J = 6.0, 5.0, 3.5 Hz), 3.10 (d, 2H,J = 6.0 Hz, 2.50 (br s, 2H), 1.60–1.50 (m, 4H), 1.40– 1.20 (m, 20H), 0.90 (t, 6H, J = 8.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz) & 80.9, 71.2, 70.2, 61.5, 32.2, 30.5, 29.8, 29.6, 26.5, 23.0, 14.2; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 424 (MNH<sub>4</sub><sup>+</sup>, 5%), 407 (MH<sup>+</sup>, 37%), 57 (100%); Anal. Calcd for C<sub>22</sub>H<sub>46</sub>O<sub>6</sub>: C, 64.99; H, 11.40. Found: C, 65.04; H, 11.41.

## 4.13. (3'*R*)-2,5-Di-*O*-(3',7'-dimethyloctyl)-D-mannitol (9b)

A suspension of 5% Pd/C (0.1g) in acetic acid (5mL) was stirred under H<sub>2</sub> for 20min. A solution of 8b (850mg, 1.3mmol) in acetic acid (15mL) was added and the resulting mixture was stirred under H<sub>2</sub> for 12h. 10% Pd/C (50mg) was added and the mixture was stirred for an additional 24h before filtration and removal of the solvent in vacuo. Purification by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH/60:1) gave 9b (247 mg, 40%) as a waxy solid:  $[\alpha]_{\rm D}^{26}$  -20.7 (c 0.98, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 3374, 2953, 2926, 1464, 1093, 1031 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>-D<sub>2</sub>O, 400 MHz)  $\delta$  3.86 (d, 2H, J = 6.5 Hz), 3.78 (dd, 2H, J = 11.5, 5.0 Hz), 3.72 (dd, 2H, J = 11.5, 3.5 Hz), 3.64 (ddd, 2H, J = 9.0, 7.0, 6.5 Hz), 3.55 (ddd, 2H, J = 9.0, 7.5, 5.5 Hz), 3.45 (ddd, 2H, J = 6.5, 5.0, 3.5 Hz), 1.65-1.10 (m, 20H),0.95–0.85 (m, 18H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$ 80.9, 70.0, 69.5, 61.3, 39.7, 37.7, 37.5, 30.3, 28.4, 25.0, 22.8, 22.7, 19.8; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 463 (MH<sup>+</sup>, 100%); Anal. Calcd for  $C_{26}H_{54}O_6$ : C, 67.49; H, 11.76. Found: C, 67.45; H, 12.13.

### 4.14. (R)-3-Hydroxy-2-octyloxypropanoic acid (10a)

To a solution of 9a (225mg, 0.6mmol) in THF (3mL) was added a solution of sodium periodate (127mg, 0.7 mmol) in H<sub>2</sub>O (1 mL). The resulting mixture was stirred at 60 °C for 1 h. The white precipitate was filtered and washed with THF (4mL). Silver(I) oxide (257mg, 1.1 mmol) and NaOH (44 mg, 1.1 mmol) were added to the filtrate and the resulting mixture was stirred at rt for 6h. The mixture was filtered, and the filtrate was concentrated in vacuo. A solution of NaOH (10mg) in  $H_2O$  (2mL) was added to the remaining aqueous solution and the resulting mixture was extracted with  $CH_2Cl_2$ . The aqueous layer was then acidified to pH1 with concd HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated in vacuo to give 10a (206 mg, 85%) as an oil: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3429–3024, 2955, 2926, 2856, 1733, 1466, 1458, 1125, 1052 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.20–6.20 (br s, 2H), 4.00 (dd, 1H, J = 5.0, 4.0 Hz), 3.91 (dd, 1H, J = 12.0, 3.5 Hz), 3.85 (dd, 1H, J = 12.0, 3.5 Hz), 3.68 (dt, 1H, J = 9.5, 6.5 Hz), 3.51 (dt, 1H, J = 9.5, 9.5 Hz), 1.70–1.50 (m, 2H), 1.40–1.10 (m, 10H), 0.85 (t, 3H, J = 8.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  174.6, 79.7, 71.9, 63.2, 32.2, 30.0, 29.7, 29.6, 26.3, 23.0, 14.2; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 236 (MNH<sub>4</sub><sup>+</sup>, 100%), 218 (MH<sup>+</sup>, 1%).

## **4.15.** (2*R*,3'*R*)-3-Hydroxy-2-(3',7'-dimethyloctyloxy)-propanoic acid (10b)

Compound 9b (230mg, 0.5mmol) was treated with sodium periodate (116mg, 0.6mmol) in THF-H<sub>2</sub>O (9:1 v/v, 5 mL) at 50 °C for 1 h. The reaction mixture was filtered and the solvent was removed in vacuo. The remaining oil was treated with silver(I) oxide (246 mg, 0.9 mmol) and NaOH (42 mg, 1.1 mmol) in THF-H<sub>2</sub>O (5:1 v/v, 6mL) for 18h. A further portion of NaOH (42 mg, 1.1 mmol) in H<sub>2</sub>O (1 mL) was then added, and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the remaining aqueous solution was extracted with petroleum ether. The aqueous layer was acidified to pH1 with concd HCl and extracted with petroleum ether. The organic extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated to give 10b (215mg, 94%) as a pale yellow oil: IR (CHCl<sub>3</sub> cast) 3400, 2954, 2927, 2869, 1728, 1126 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 200 MHz)  $\delta$  7.50–7.20 (br s, 2H), 4.00-3.60 (m, 4H), 3.55-3.45 (m, 1H, J = 9.5, 9.5 Hz), 1.85–1.00 (m, 10H), 1.00–0.70 (s, 9H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 75 MHz) & 174.2, 79.9, 70.2, 63.1, 39.6, 37.7, 37.0, 30.2, 28.4, 25.0, 22.8, 22.7, 19.7; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 264 (MNH<sub>4</sub><sup>+</sup>, 100%).

### 4.16. Benzyl (R)-3-hydroxy-2-octyloxypropanoate (11a)

To a stirred solution of **10a** (78 mg, 0.4 mmol) in dry DMF (2.5 mL) was added NaHCO<sub>3</sub> (92 mg, 1.1 mmol) and the mixture was heated at 50 °C for 10 min. Benzyl bromide (186 mg, 1.1 mmol) was added and the resulting

mixture was heated at 70 °C for 24h, then poured into brine and extracted with  $Et_2O$ . The combined extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. Purification by flash chromatography (SiO<sub>2</sub>, petroleum ether–EtOAc/7:1) gave **11a** (98 mg, 89%) as an oil:  $[\alpha]_D^{2c}$ +37.8 (c 0.60, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 3453, 2953, 2927, 1750, 1186, 1127, 1058 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz) 7.40–7.30 (m, 5H), 5.20 (AB<sub>q</sub>, 2H, J = 11.5 Hz, 4.00 (dd, 1H, J = 6.5, 3.6 Hz), 3.85 (ddd, 1H, J = 11.0, 6.5, 3.6Hz), 3.76 (ddd, 1H, J = 11.0, 6.5, 6.5 Hz), 3.68 (dt, 1H, J = 9.0, 6.5 Hz), 3.42 (dt, 1H, J = 9.0, 6.5 Hz), 2.15 (t, 1H, J = 6.5 Hz), 1.65–1.55 (m, 2H), 1.40–1.20 (m, 10H), 0.86 (t, 3H, J = 8.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz) δ 171.0, 136.2, 128.9, 128.7, 128.5, 80.1, 71.7, 66.9, 63.8, 32.2, 30.1, 29.8, 29.6, 26.4, 23.0, 14.2; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 326 (MNH<sub>4</sub><sup>+</sup>, 100%), 309 (MH<sup>+</sup>, 12%); Anal. Calcd for C<sub>18</sub>H<sub>28</sub>O<sub>4</sub>: C, 70.10; H, 9.15. Found: C, 70.24; H, 9.30.

### **4.17.** Benzyl (2*R*,3'*R*)-3-hydroxy-2-(3',7'-dimethyloctyl-oxy)propanoate (11b)

The procedure used to prepare **11a** was followed. Reaction of **10b** (192mg, 0.8 mmol) with NaHCO<sub>3</sub> (228 mg, 2.7 mmol) and benzyl bromide (466 mg, 2.7 mmol) in DMF (5 mL) provided **11b** (202 mg, 77%) as a colorless oil: IR (CHCl3 cast) 3400, 2954, 2927, 1751, 1183, 1127 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.40–7.36 (m, 5H), 5.20 (AB<sub>q</sub>, 2H, J = 11.5Hz), 4.00 (dd, 1H, J = 6.0, 4.0Hz), 3.85 (ddd, 1H, J = 11.0, 7.0, 4.0Hz), 3.80–3.70 (m, 2H), 3.45 (dt, 1H, J = 9.0, 7.0Hz), 2.10 (t, 1H, J = 7.0Hz), 1.70–1.10 (m, 10H), 0.88 and 0.84 (2s, 3H and 6H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  171.0, 136.2, 128.9, 128.7, 128.5, 80.2, 70.0, 66.9, 63.8, 39.6, 37.7, 37.1, 30.2, 28.4, 25.0, 22.8, 22.7, 19.7; LRMS (CI, NH<sub>3</sub>) *m/z* (relative intensity) 354 (MNH<sub>4</sub><sup>+</sup>, 72%), 91 (100%).

### 4.18. Allyl 4,6-O-benzylidene-D-glucopyranoside (12)

To a suspension of D-glucose (9g, 50.0 mmol) in anhydrous allyl alcohol (60 mL) was added AG50W-X8 (H<sup>+</sup>) ion exchange resin (5g, 50–100 mesh) (dried at 56 °C in vacuo for 1 day). After stirring at 100 °C for 3h, the mixture was filtered and concentrated in vacuo. ZnCl<sub>2</sub> (7g, 51.4 mmol) and freshly distilled benzaldehyde (50 mL, 492.0 mmol) were added to the residue, and the mixture was stirred at rt under argon for 2 days. After extraction with petroleum ether the mixture solidified. The solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, petroleum ether–EtOAc/1:1) gave **12** (11.2 g, 72%) as a mixture of  $\alpha$ - and  $\beta$ -anomers as well as some fractions containing pure  $\alpha$ - and  $\beta$ -anomers.

Data for the  $\alpha$ -anomer:  $[\alpha]_D^{26}$  +93.8 (*c* 1.26, CHCl<sub>3</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3543, 3280, 3065, 2009, 2866, 1451, 1385, 1372, 1150, 1075, 1044, 1015 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.50–7.35 (m, 5H), 5.95 (dddd, 1H, *J* = 17.0, 10.5, 5.0, 5.0 Hz), 5.51 (s, 1H), 5.32 (dddd, 1H, *J* = 17.0, 1.5, 1.5, 1.5 Hz), 5.23 (dddd, 1H, *J* = 10.5,

1.5, 1.5, 1.5Hz), 4.91 (d, 1H, J = 4.0 Hz), 4.25 (dd, 1H, J = 10.0, 4.5Hz), 4.24 (dddd, 1H, J = 13.0, 6.0, 1.5, 1.5Hz), 4.05 (dddd, 1H, J = 13.0, 6.0, 1.5, 1.5Hz), 3.89 (dd, 1H, J = 9.5, 9.5Hz), 3.82 (ddd, 1H, J = 10.0, 10.0, 5.0Hz), 3.70 (dd, 1H, J = 10.0, 10.0Hz), 3.57 (dd, 1H, J = 9.0, 4.0Hz), 3.46 (dd, 1H, J = 9.5, 9.5Hz), 3.20 (br, 1H), 2.60 (br, 1H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  137.8, 134.1, 129.4, 128.6, 126.6, 118.0, 102.1, 98.5, 81.3, 73.3, 72.0, 69.2, 69.1, 63.0; LRMS (CI, NH<sub>3</sub>) *m/z* (relative intensity) 326 (MNH<sub>4</sub><sup>+</sup>, 27.8%), 309 (MH<sup>+</sup>, 100%); Anal. Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>6</sub>: C, 62.33; H, 6.54. Found: C, 62.22; H, 6.70.

Data for the  $\beta$ -anomer: mp 144–145 °C;  $[\alpha]_D^{26}$  –47.3 (c 1.30, CHCl<sub>3</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3510, 3218, 3076, 2924, 2846, 1452, 1402, 1373, 1351, 1267, 1171, 1105, 1087, 1044, 1031,  $1003 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.50–7.35 (m, 5H), 5.95 (dddd, 1H, J = 17.5, 10.5, 5.5, 5.5 Hz, 5.53 (s, 1H), 5.32 (dddd, 1H, J = 17.5, 1.5, 1.5, 1.5Hz), 5.22 (dddd, 1H, J = 10.5, 1.5, 1.5, 1.5 Hz), 4.42 (d, 1H, J = 8.0 Hz), 4.35 (dddd, 1H, J = 12.5, 5.5, 1.5, 1.5 Hz), 4.31 (dd, 1H, 1)J = 10.5, 5.0 Hz), 4.12 (dddd, 1H, J = 12.5, 5.5, 1.5, 1.5 Hz), 3.76 (dd, 1H, J = 10.5, 10.5 Hz), 3.75 (ddd, 1H, J = 9.5, 9.5, 2.5 Hz), 3.51 (dd, 1H, J = 9.5, 9.5 Hz), 3.49–3.39 (m, 2H), 3.30 (d, 1H, J = 2.5 Hz), 2.94 (d, 1H, J = 3.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$ 137.8, 134.3, 129.5, 128.6, 126.7, 118.0, 102.6, 102.1, 80.9, 74.9, 73.5, 70.8, 69.0, 66.7; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 326 (MNH<sub>4</sub><sup>+</sup>, 12.9%), 309 (MH<sup>+</sup>, 100%); Anal. Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>6</sub>: C, 62.33; H, 6.54. Found: C, 62.07; H, 6.39.

### 4.19. Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside (13)

To a solution of **12** (219mg, 0.7mmol) in dry DMF (10mL) was added NaH (71mg of a 60% suspension in oil, 1.8mmol). The reaction mixture was stirred for 20min, and then benzyl chloride (537mg, 4.4mmol) was added dropwise. The resulting mixture was heated at 75 °C for 24h. It was then poured into iced-water and extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. Purification by flash chromatography (SiO<sub>2</sub>, petroleum ether–EtOAc/20:1) afforded **13** (278mg, 80%) as a mixture of  $\alpha$ - and  $\beta$ -anomers as well as some fractions containing pure  $\alpha$ - and  $\beta$ -anomers.

Data for  $\alpha$ -anomer: mp 78–79 °C;  $[\alpha]_D^{26} - 3.75$  (*c* 1.12, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 2913, 2866, 1452, 1367, 1153, 1109, 1089, 1051, 1028 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.50–7.25 (m, 15H), 5.98 (dddd, 1H, J = 17.5, 10.5, 5.0, 5.0Hz), 5.59 (s, 1H), 5.36 (dddd, 1H, J = 10.5, 1.5, 1.5, 1.5, 1.5Hz), 5.24 (dddd, 1H, J = 10.5, 1.5, 1.5, 1.5Hz), 4.90 (d, 1H, J = 11.5Hz), 4.89 (d, 1H, J = 3.4Hz), 4.82 (d, 1H, J = 11.5Hz), 4.79 (d, 1H, J = 10.0, 5.0Hz), 4.21 (dddd, 1H, J = 13.0, 5.0, 1.5, 1.5Hz), 4.01 (dddd, 1H, J = 13.0, 5.0, 1.5, 1.5Hz), 4.01 (dddd, 1H, J = 13.0, 5.0, 1.5, 1.5Hz), 4.01 (ddd, 1H, J = 10.0, 10.0, 5.0Hz), 3.71 (dd, 1H, J = 10.0, 10.0Hz), 3.62 (dd, 1H, J = 10.0, 9.5Hz), 3.59 (dd, 1H, J = 9.5, 9.5Hz), 9.5Hz)

3.4 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  139.5, 138.9, 138.2, 134.3, 129.2, 128.7, 128.5, 128.3, 128.2, 128.1, 127.8, 126.5, 118.0, 101.6, 97.3, 82.6, 80.0, 78.7, 75.3, 73.7, 69.4, 68.8, 62.9; LRMS (CI, NH<sub>3</sub>) *m/z* (relative intensity) 506 (MNH<sub>4</sub><sup>+</sup>, 13), 489 (MH<sup>+</sup>, 42%), 91 (100%); Anal. Calcd for C<sub>30</sub>H<sub>32</sub>O<sub>6</sub>: C, 73.75; H, 6.60. Found: C, 73.88; H, 6.69.

Data for  $\beta$ -anomer:  $[\alpha]_D^{26}$  -33.7 (*c* 1.12, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 2875, 1452, 1365, 1180, 1126, 1090, 1076, 1029, 1006 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.50–7.20 (m, 15H), 5.95 (dddd, 1H, J = 17.0, 11.0, 5.5, 5.5 Hz), 5.51 (s, 1H), 5.35 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.21 (dddd, 1H, J = 11.0, 1.5, 1.5, 1.5 Hz), 4.90 (d, 2H, J = 11.0 Hz), 4.80 (d, 1H, J = 11.0 Hz), 4.78 (d, 1H, J = 11.0 Hz), 4.55 (d, 1H, J = 7.5 Hz), 4.40 (dddd, 1H, J = 13.0, 5.5, 1.5, 1.5Hz), 4.35 (dd, 1H, J = 10.5, 5.0 Hz), 4.15 (dddd, 1H, J = 13.0, 5.5, 1.5, 1.5 Hz), 3.79(dd, 1H, J = 10.5, 10.5 Hz), 3.74 (dd, 1H, J = 8.5, 8.5 Hz), 3.69 (dd, 1H, J = 8.5, 8.5 Hz), 3.49 (dd, 1H,J = 8.5, 8.5 Hz, 3.40 (ddd, 1H, J = 10.5, 8.5, 5.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  139.3, 139.1, 138.1, 134.5, 129.2, 128.6, 128.6, 128.5, 128.3, 128.0, 127.9, 126.5, 117.4, 103.6, 101.5, 82.6, 81.9, 81.3, 75.5, 75.2, 70.8, 69.2, 66.4; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 506 (MNH<sub>4</sub><sup>+</sup>, 15%), 489 (MH<sup>+</sup>, 21%), 91 (100%); Anal. Calcd for C<sub>30</sub>H<sub>32</sub>O<sub>6</sub>: C, 73.75; H, 6.60. Found: C, 73.77; H, 6.69.

### 4.20. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (14)

A mixture of 13 (674mg, 1.4mmol) and potassium tertbutoxide (186mg, 1.7mmol) in dry DMSO (4mL) was heated at 100 °C for 2h. The resulting solution was cooled to rt and concentrated under high vacuum overnight. The remaining solution was poured into icedwater and extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give a white solid. This was dissolved in acetone-H<sub>2</sub>O (10:1; 44mL), and yellow mercuric oxide (357 mg, 1.7 mmol) was added followed by dropwise addition of a solution of mercuric chloride (448 mg, 1.7 mmol) in acetone-H<sub>2</sub>O (10:1, 8 mL). The resulting mixture was stirred at rt for an additional 20min, and was filtered through Celite<sup>®</sup>. The filtrate was concentrated in vacuo and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aqueous KI (100 mL) and 10% aqueous sodium sulfite. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, petroleum ether-EtOAc, gradient elution, 5:1 to 3:1) provided 14 (535 mg, 86%) as a 1.1:1 mixture of  $\alpha$ - and  $\beta$ -anomers: mp 168–169 °C (lit.<sup>35</sup> mp 160–162 °C);  $[\alpha]_D^{26}$  –26.3 (*c* 1.20, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 3402, 1451, 1386, 1366, 1090, 1071, 1028, 1007 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>– trace of D<sub>2</sub>O, 400 MHz, 1.1:1 mixture of α- and β-anomers) & 7.55-7.25 (m, 15H), 5.60 (s, 1H), 5.24 (d, 0.5H, J = 4.0 Hz, 4.95-4.68 (m, 4.5H), 4.35-4.25 (dd, 1H, J = 10.0, 5.0 Hz), 4.05–3.98 (m, 1H), 3.80–3.60 (m, 3H), 3.50–3.35 (m, 1H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz, 1.1:1 mixture of  $\alpha$ -,  $\beta$ -anomers)  $\delta$  139.3, 139.2, 139.0, 138.4, 138.1, 138.0, 129.2, 128.8, 128.6, 128.55, 128.53,

128.4, 128.3, 128.0, 127.9, 126.5, 126.45, 101.6, 101.5, 98.2, 92.4, 83.6, 82.4, 82.0, 81.3, 80.1, 78.5, 75.4, 75.24, 75.17, 74.0, 69.4, 69.1, 66.8, 66.6, 62.9; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 466 (MNH<sub>4</sub><sup>+</sup>, 64%), 449 (MH<sup>+</sup>, 65%), 35 (100%); Anal. Calcd for C<sub>27</sub>H<sub>28</sub>O<sub>6</sub>: C, 72.30; H, 6.29. Found: C, 72.50; H, 6.36.

## 4.21. 3,4-Di-*O*-benzyl-5,7-*O*-benzylidene-1,2-dideoxy-D-glucohept-1-enitol (15)

To a stirred suspension of methyltriphenylphosphonium bromide (6.93g, 19.4mmol) in dry DME (70mL) at -78°C under argon was added dropwise n-BuLi (12.1 mL of a 1.6 M solution in hexanes, 19.4 mmol). The mixture was warmed to rt and stirred for 30 min to give a bright yellow suspension of the ylide. In a separate flask, n-BuLi (4.18 mL of a 1.6 M solution in hexanes, 6.7 mmol) was added to a suspension of 14 (3 g. 6.7 mmol) in dry DME (90 mL) at  $-78 \,^{\circ}$ C over a period of 10min. The mixture was warmed to rt and stirred for 20 min to give a clear solution. The ylide prepared above was added to this solution rapidly through a cannula and the resulting suspension was heated at 45°C for 140 min. Acetone (40 mL) was added and the resulting solution was stirred for an additional 2h. The solvents were removed in vacuo and the residue was suspended in brine and extracted with Et<sub>2</sub>O. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, petroleum ether-EtOAc, gradient elution, 6:1 to 4:1) gave 13 (2.35 g, 79%) as a white crystalline solid: mp 94–95 °C;  $[\alpha]_D^{26}$  –10.7 (*c* 1.20, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 3430, 1453, 1398, 1154, 1074,  $1027 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz) & 7.45–7.25 (m, 15H), 5.90 (ddd, 1H, J = 18.0, 10.0, 7.0 Hz), 5.39 (dd, 1H, J = 18.0, 1.0 Hz), 5.35 (dd, 1H, J = 10.0, 1.0 Hz), 5.33 (s, 1H), 4.86 (d, 1H, J = 12.0 Hz), 4.79 (d, 1H, J = 12.0 Hz), 4.65 (d, 1H, J = 11.5 Hz), 4.47 (d, 1H, J = 11.5 Hz), 4.29 (dd, 1H, J = 7.0, 7.0 Hz), 4.21 (dd, 1H, J = 10.0, 5.0 Hz), 3.86 (ddd, 1H, J = 10.0, 10.0, 5.0 Hz), 3.76 (dd, 1H, J = 7.0, 3.5 Hz), 3.62 (dd, 1H, J = 10.0, 3.5 Hz), 3.49 (dd, 2H, J = 10.0, 10.0 Hz), 1.85 (br s, 1H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  139.0, 138.8, 138.4, 135.6, 129.1, 129.0, 128.8, 128.7, 128.5, 128.3, 128.2, 127.9, 126.4, 119.4, 101.3, 82.5, 81.8, 79.1, 74.9, 71.4, 71.3, 62.2; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 464 (MNH<sub>4</sub><sup>+</sup>, 8%), 91 (100%); Anal. Calcd for C<sub>28</sub>H<sub>30</sub>O<sub>5</sub>: C, 75.31; H, 6.77. Found: C, 75.22; H, 6.85.

### 4.22. (2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylmercuric chloride (16)

A solution of **15** (98 mg, 0.2 mmol) and mercuric trifluoroacetate (123 mg, 0.2 mmol) in dry THF (7 mL) was stirred at rt overnight. A solution of KCl (115 mg, 1.6 mmol) in H<sub>2</sub>O (2 mL) was added and the mixture was stirred for a further 5h. THF was removed in vacuo and the remaining aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. Flash chromatography (SiO<sub>2</sub>, petroleum ether–EtOAc/ 8:1) of the residue afforded a mixture of  $\alpha$ - and  $\beta$ -ano-

mers of 16 (145 mg, 96%) in a ratio of 4.3:1 (determined by <sup>1</sup>H NMR) as a white foam. The major  $\alpha$ -anomer could be separated from the  $\beta$ -anomer by further flash chromatography (SiO<sub>2</sub>, petroleum ether–EtOAc/12:1): For the  $\alpha$ -anomer:  $[\alpha]_D^{26}$  –19.7 (*c* 1.17, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 1453, 1368, 1086, 1075, 1027 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz) & 7.50-7.30 (m, 15H), 5.58 (s, 1H), 4.92 (d, 1H, J = 11.5 Hz), 4.90 (d, 1H, J = 11.5 Hz), 4.80 (d, 1H, J = 11.5 Hz), 4.70 (d, 1H, J = 11.5 Hz, 4.23 (m, 2H), 3.85 (dd, 1H, J = 8.5, 8.5Hz), 3.75 (m, 2H), 3.66 (m, 2H), 2.15 (dd, 1H, J = 12.0, 10.0 Hz), 1.90 (dd, 1H, J = 12.0, 6.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz) δ 139.1, 138.0, 137.8, 129.2, 129.07, 128.97, 128.6, 128.5, 128.4, 128.3, 128.0, 126.4, 101.6, 83.3, 78.7, 75.1, 74.9, 74.8, 70.0, 63.6, 26.9; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 700 (MNH<sub>4</sub><sup>+</sup>, 0.2), 683 (MH<sup>+</sup>, 0.5%), 35 (100%); Anal. Calcd for C<sub>28</sub>H<sub>29</sub>ClHgO<sub>5</sub>: C, 49.34; H, 4.29. Found: C, 49.39; H, 4.23.

## 4.23. (2,3-Di-*O*-benzyl-4,6-*O*-benzylidene- $\alpha$ -D-glucopy-ranosyl)methyl iodide (17)

A solution of 16 (1.81g, 2.7 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated with I<sub>2</sub> (2.16g, 8.5 mmol). After stirring for 4h, 10% aqueous sodium sulfite (50mL) was added and the mixture was stirred for 20min. The organic layer was separated, washed with 5% aqueous KI, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. Purification by flash chromatography ( $SiO_2$ , petroleum ether-EtOAc/15:1) gave a 4.3:1 mixture (determined by <sup>1</sup>H NMR) of  $\alpha$ - and  $\beta$ -anomers of 17 (1.22g, 80%) as a waxy solid. The  $\alpha$ -isomer 17 was separated from the  $\beta$ -anomer by further flash chromatography (SiO<sub>2</sub>, petroleum ether-EtOAc/20:1). Data for the  $\alpha$ -anomer: IR (CHCl<sub>3</sub> cast) 1453, 1367, 1141, 1097, 1063 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.50–7.25 (m, 15H), 5.58 (s, 1H), 4.90 (d, 1H, J = 11.5 Hz), 4.76 (d, 2H, J = 11.5 Hz, 4.65 (d, 1H, J = 11.5 Hz), 4.30 (dd, 1H, J = 10.0, 5.0 Hz), 4.16 (ddd, 1H, J = 11.5, 4.5, 4.5 Hz), 3.82 (dd, 1H, J = 9.0, 8.5 Hz), 3.79 (dd, 1H, J = 8.5, 4.5 Hz), 3.71 (dd, 1H, J = 10.0, 10.0 Hz), 3.68 (dd, 1H, J = 10.0, 9.0 Hz), 3.62 (dd, 1H, J = 11.5, 4.5 Hz), 3.54 (ddd, H, J = 10.0, 10.0, 5.0 Hz), 3.47 (dd, 1H,J = 11.5, 11.5 Hz; <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$ 139.1, 138.4, 138.0, 129.2, 128.8, 128.6, 128.5, 128.3, 127.9, 126.4, 101.6, 82.7, 79.6, 78.7, 75.8, 74.8, 74.2, 69.7, 64.0, 3.5; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 590 (MNH<sub>4</sub><sup>+</sup>, 30%), 573 (MH<sup>+</sup>, 52%), 35 (100%); Anal. Calcd for C<sub>28</sub>H<sub>29</sub>IO<sub>5</sub>: C, 58.75; H, 5.11. Found: C, 58.55; H, 5.12.

## 4.24. (2,3,6-Tri-*O*-benzyl-α-D-glucopyranosyl)methyl iodide (18)

Et<sub>2</sub>O saturated with HCl gas was added in small portions to a mixture of 17 (250 mg, 0.4 mmol), NaBH<sub>3</sub>CN (300 mg, 4.8 mmol), and powdered 3 Å molecular sieves (0.1 g) in dry THF (12 mL) at 0 °C until gas evolution ceased. The resulting mixture was stirred at 0 °C for 30 min and then at rt for 20 min. The reaction was quenched with brine, extracted with Et<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. Purification by flash chromatography (SiO<sub>2</sub>, petroleum ether–EtOAc, gradient elution, 10:1 to 7.5:1) provided 18 (161 mg, 64%) as a waxy solid: IR (CHCl<sub>3</sub> cast) 3340, 3030, 2905, 2869, 1496, 1453, 1365, 1096, 1048,  $1027 \,\mathrm{cm}^{-1}$ ; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.40–7.25 (m, 15H), 4.80 (d, 1H, J = 11.5 Hz), 4.70 (d, 1H, J = 11.5 Hz), 4.69 (d, 1H, J = 11.5 Hz), 4.60 (d, 1H, J = 11.5 Hz), 4.58 (d, 1H, J = 11.5 Hz), 4.52 (d, 1H, J =11.5 Hz), 4.12 (ddd, 1H, J = 10.5, 4.5, 4.5 Hz), 3.80-3.60 (m, 6H), 3.51 (dd, 1H, J = 10.0, 4.5 Hz), 3.41 (dd,1H, J = 10.5, 10.0 Hz), 2.87 (d, 1H, J = 4.0 Hz); NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz) δ 138.9, 138.7, 138.1, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 128.06, 127.97, 79.4, 78.4, 74.7, 73.8, 73.7, 73.67, 73.4, 70.8, 70.1, 3.2; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 592 (MNH<sub>4</sub><sup>+</sup>, 42%), 91 (100%); Anal. Calcd for C<sub>28</sub>H<sub>31</sub>IO<sub>5</sub>: C, 58.54; H, 5.44. Found: C, 58.35; H, 5.41.

### 4.25. Diethyl (2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)methylphosphonate (19)

A solution of 18 (152mg, 0.3mmol) in freshly distilled triethyl phosphite (10 mL) was heated at reflux under argon. After 7h, a further portion of triethyl phosphite (1 mL) was added, and the resulting solution was heated at reflux for an additional 2.5h. The solution was then cooled to rt and concentrated in vacuo. The residue was purified by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH/100:1) to give 19 (82mg, 53%) as a colorless oil: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3355, 3063, 3033, 2906, 1453, 1367, 1247, 1224, 1096, 1052,  $1027 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR  $(CD_2Cl_2, 400 \text{ MHz}) \delta$  7.40–7.25 (m, 15H), 4.82 (d, 1H, J = 12.5 Hz), 4.72 (d, 1H, J = 12.5 Hz), 4.68 (d, 1H, J = 12.5 Hz), 4.64 (d, 1H, J = 12.5 Hz), 4.57 (d, 1H, J = 12.5 Hz), 4.52 (d, 1H, J = 12.5 Hz), 4.48 (dddd, 1H, J = 11.0, 10.0, 5.0, 4.5 Hz), 4.05 (dq, 4H, J = 7.5, 7.5 Hz), 3.80-3.71 (m, 2H), 3.70-3.62 (m, 3H), 3.58 (dd, 1H, J = 9.0, 9.0 Hz), 2.23 (ddd, 1H, J = 17.5, 17.5, 17.5)10.0 Hz), 2.15 (ddd, 1H, J = 17.5, 17.5, 4.5 Hz), 1.29 (t, 3H, J = 7.5 Hz), 1.26 (t, 3H, J = 7.5 Hz); <sup>13</sup>C NMR  $(CD_2Cl_2, 100 \text{ MHz}) \delta$  139.2, 138.7, 138.4, 128.8, 128.75, 128.7, 128.4, 128.24, 128.20, 128.1, 128.02, 127.99, 79.8, 78.6 (d, J = 10.8 Hz), 74.7, 73.9, 73.3, 71.1, 70.3, 69.1 (d, J = 3.6 Hz), 62.02 (d, J = 7.2 Hz), 61.95 (d, J = 7.2 Hz), 23.9 (d, J = 153.6 Hz), 16.6 (d, J = 5.4 Hz; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 585 (MH<sup>+</sup>, 100%); Anal. Calcd for C<sub>32</sub>H<sub>41</sub>O<sub>8</sub>P: C, 65.74; H, 7.07. Found: C, 66.05; H, 7.20.

## 4.26. Diethyl (3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-*O*-benzyl- $\alpha$ -D-glucopyranosyl)methylphosphonate (21)

A mixture of **19** (0.84g, 1.5 mmol) and silver trifluoromethanesulfonate (0.57 mg, 2.2 mmol) was dried overnight in vacuo over  $P_2O_5$  in the dark. Collidine (300 µL, 2.2 mmol), powdered 4Å molecular sieves (0.1 g), and dry CH<sub>2</sub>Cl<sub>2</sub> (14 mL) were then added, and the resulting mixture was stirred at  $-78 \,^{\circ}$ C for 30 min. A solution of **20** (1.01 g, 2.2 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (6 mL) was then added. The reaction mixture was stirred at  $-30 \,^{\circ}$ C for 1 h, and was then allowed to warm to rt. After stirring for 24 h, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and filtered. The filtrate was washed with  $H_2O$ , 1N HCl, NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. Purification by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, gradient elution, 12.5:1 to 10:1) gave **21** (1.22 g, 83%) as a white foam: IR (CHCl<sub>3</sub> cast) 1750, 1718, 1386, 1366, 1240, 1227, 1077, 1029 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  7.85– 7.70 (m, 4H), 7.40–7.20 (m, 15H), 5.72 (dd, 1H, J = 10.5, 9.0 Hz), 5.60 (d, 1H, J = 8.0 Hz), 5.11 (dd, 1H, J = 10.0, 9.0Hz), 4.92 (d, 1H, J = 11.5Hz), 4.76 (d, 1H, J = 11.5 Hz), 4.61 (d, 1H, J = 11.5 Hz), 4.51 (d, 1H, J = 11.5Hz), 4.42–4.32 (m, 3H), 4.27 (dd, 1H, J = 10.5, 8.0 Hz, 4.12 (dd, 1H, J = 12.0, 4.5 Hz), 4.03 (dd, 1H, J = 9.0, 7.5 Hz), 3.99-3.89 (m, 5H), 3.69 (dd, 1H, J = 9.0, 7.5 Hz), 3.99-3.89 (m, 5H), 3.69 (dd, 1H, 1H, 1H))1H, J = 7.5, 7.5 Hz), 3.62 (ddd, 1H, J = 7.5, 5.0, 1.5 Hz), 3.54-3.48 (m, 2H), 3.45-3.30 (m, 2H), 2.09-1.93 (m, 2H), 1.99, 1.97, and 1.81 (3s,  $3 \times 3H$ ), 1.16  $^{13}$ C NMR (CD<sub>2</sub>Cl<sub>2</sub>, (dt, 6H, J = 18.0, 7.5 Hz); 100 MHz)  $\delta$  170.7, 170.3, 169.8, 139.6, 138.9, 138.6, 134.7, 131.9, 128.7, 128.6, 128.3, 128.1, 127.81, 127.79, 127.7, 123.9, 97.9, 79.5, 78.5 (d, J = 12.6 Hz), 75.9, 74.4, 73.3, 73.2, 72.2, 72.0, 71.0, 69.5 (d,  $J = 3.6 \,\text{Hz}$ ), 69.2, 68.7, 62.0, 61.98 (d, J = 5.0 Hz), 61.7 (d,  $J = 5.0 \,\mathrm{Hz}$ , 55.6, 23.7 (d,  $J = 143.6 \,\mathrm{Hz}$ ), 20.84, 20.80, 20.6, 16.5 (d, J = 4.0 Hz); <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  28.7; LRMS (FAB, Cleland) m/z (relative intensity) 1002.2 (MH<sup>+</sup>, 34%), 119 (100%); Anal. Calcd for C<sub>52</sub>H<sub>60</sub>NO<sub>17</sub>P: C, 62.33; H, 6.04; N, 1.40. Found: C, 62.39; H, 6.15; N, 1.38.

## 4.27. Diethyl (2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-O-benzyl- $\alpha$ -D-glucopyranosyl)methylphosphonate (22)

Hydrazine hydrate (58 µL of an 85% aqueous solution, 57.0 mmol) was added to a solution of 21 (43 mg, 0.04 mmol) in 95% EtOH (2mL), and the resulting mixture was heated at 80°C for 1.5h. The solvents were removed in vacuo and the residue was dried under high vacuum for 4h. The resulting solid was treated with pyridine (3mL) and Ac<sub>2</sub>O (3mL) for 12h. 95% EtOH was added and the mixture was concentrated in vacuo. Purification by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, gradient elution, 100:1 to 30:1) provided 22 (35 mg, 88%) as a white foam: IR (CHCl<sub>3</sub> cast) 1747, 1367, 1241, 1230, 1164, 1106, 1073, 1043 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz) δ 7.50–7.20 (m, 15H), 5.02– 4.98 (m, 2H), 4.96 (dd, 1H, J = 10.0, 10.0 Hz), 4.95 (d, 1H, J = 12.0 Hz), 4.71 (d, 1H, J = 11.5 Hz), 4.69 (d, 1H, J = 11.5 Hz), 4.63 (d, 1H, J = 8.5 Hz), 4.62 (d, 1H, J = 11.5 Hz, 4.54 (d, 1H, J = 11.5 Hz), 4.44 (d, 1H, J = 11.5 Hz, 4.44–4.40 (m, 1H), 4.11 (dd, 1H, J = 12.0, 4.5 Hz), 4.09–4.00 (m, 4H), 3.92–3.87 (m, 2H), 3.75 (ddd, 1H, J = 10.0, 10.0, 9.0 Hz), 3.70-3.60 (m, 4H),3.60-3.57 (m, 1H), 3.49 (ddd, 1H, J = 10.0, 4.0, 2.0 Hz), 2.21–2.05 (m, 2H), 2.00, 1.99, 1.90, and 1.71 (4s,  $4 \times 3$ H), 1.30 (dt, 6H, J = 13.0, 6.5 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz) 170.7, 170.1, 169.7, 139.7, 138.6, 138.5, 129.1, 129.0, 128.7, 128.6, 128.5, 128.3, 128.0, 127.7, 127.6, 112.8, 100.9, 79.7, 78.5 (d, J = 12.1 Hz), 77.6, 74.6, 73.9, 73.4, 73.0, 72.1, 71.9, 69.6 (d, J = 4.0 Hz), 68.9, 68.7, 62.3, 62.1 (d, J = 5.0 Hz), 61.8 (d, J = 6.0 Hz), 55.2, 23.6 (d, J = 132.8 Hz), 23.3, 20.8,

16.6 (d, J = 6.0 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 162 MHz)  $\delta$ 28.8; LRMS (FAB, Cleland) *m*/*z* (relative intensity) 936.4 (MNa<sup>+</sup>, 1.4%), 914.2 (MH<sup>+</sup>, 18%), 92 (100%); Anal. Calcd for C<sub>46</sub>H<sub>60</sub>NO<sub>16</sub>P: C, 60.45; H, 6.62; N, 1.53. Found: C, 60.74; H, 6.33; N, 1.60.

## 4.28. (2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glu-copyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-*O*-benzyl- $\alpha$ -D-glucopyranosyl)methylphosphonic acid (23)

Bromotrimethylsilane (50 µL, 0.4 mmol) was added dropwise to a solution of 22 (31 mg, 0.03 mmol) in dry  $CH_2Cl_2$  (0.4 mL). The resulting mixture was stirred for 2h and then concentrated in vacuo. The residue was redissolved in acetone (1.5 mL) and water (10 µL). After 20 min, the solvent was removed in vacuo to give an offwhite residue, which was precipitated from CH<sub>2</sub>Cl<sub>2</sub>-acetone-petroleum ether to afford 22 (26mg, 91%) as a white solid: IR (CH<sub>2</sub>Cl<sub>2</sub>-MeOH cast) 3290, 1745, 1661, 1549, 1375, 1251, 1228, 1117, 1050,  $1032 \,\mathrm{cm}^{-1}$ ; <sup>1</sup>H NMR (CDCl<sub>3</sub>–DMSO- $d_6$ , 400 MHz)  $\delta$  7.35–7.15 (m, 15H), 5.50 (br, 3H), 5.11 (dd, 1H, J = 10.0, 10.0 Hz), 4.86–4.78 (m, 3H), 4.68–4.45 (m, 5H), 4.42– 4.38 (m, 1H), 3.88–3.75 (m, 3H), 3.75–3.55 (m, 5H), 3.38 (m, 1H), 2.05-1.85 (m, 8H), 1.80 and 1.70 (2s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>–DMSO- $d_6$ , 100 MHz)  $\delta$  169.5, 169.4, 169.3, 168.7, 138.8, 138.3, 137.9, 127.8, 127.7, 127.6, 127.4, 127.0, 126.9, 126.7, 99.9, 77.4, 75.8, 72.9, 72.2, 71.6, 71.1, 70.6, 68.6, 68.38, 61.5, 54.1, 22.5, 20.1; <sup>31</sup>P NMR (CDCl<sub>3</sub>–DMSO-*d*<sub>6</sub>, 162 MHz) δ 23.6; LRMS (FAB, Cleland) m/z (relative intensity) 879.8 (MNa<sup>+</sup>, 5), 857.8 (MH<sup>+</sup>, 2%), 119 (100%).

# 4.29. Benzyl (*R*)-3-((2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-*O*-benzyl- $\alpha$ -D-glucopyranosyl)methylphosphinato)-2-octyloxypropano-ate (24a)

Trichloroacetonitrile (1.6mL, 15.96mmol) was added dropwise to a solution of 23 (94mg, 0.1 mmol) and 11a (55mg, 0.2mmol) in anhydrous pyridine (3mL). The resulting solution was heated at 70 °C for 42 h under argon. The solvent was removed in vacuo, and the residue was triturated with petroleum ether to remove unreacted compound 9a. The remaining residue was then extracted with toluene, the toluene extracts were evaporated under reduced pressure to give 24a (96mg, 78%) as a glassy solid: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3284, 2953, 2927, 2856, 1747, 1666, 1454, 1367, 1231, 1087, 1070,  $1045 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>-CD<sub>3</sub>OD, 400 MHz) 7.45-7.20 (m, 15H), 5.20-5.05 (m, 3H), 5.00-4.85 (m, 2H), 4.70-4.40 (m, 6H), 4.40-3.35 (m, 16H), 2.10-1.90 (m, 8H), 1.90 and 1.80 (2s, 2 × 3H), 1.55 (m, 2H), 1.60–1.45 (m, 2H), 1.40–1.15 (m, 10H), 0.80 (t, 3H, J = 8.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 75 MHz) δ 172.3, 171.5, 171.4, 171.3, 170.4, 139.5, 138.7, 138.6, 136.1, 129.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.6, 101.1, 79.4, 78.9, 78.5, 78.3, 77.2, 74.3, 73.9, 73.1, 72.9, 72.7, 72.0, 71.8, 70.1, 69.3, 69.2, 67.3, 64.7, 62.4, 55.4, 32.3, 30.0, 29.8, 29.7, 26.3, 23.1, 22.8, 20.69, 20.66, 20.6, 14.1; <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  30.2; LRMS (FAB, Cleland) m/z (relative intensity) 1171.5 (MHNa<sup>+</sup>, 23%), 1170.5 (MNa<sup>+</sup>, 35%).

4.30. Benzyl (2*R*,3'*R*)-3-((2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)methylphosphinato)-2-(3',7'-dimethyloctyloxy)propanoate (24b)

Compound 24b was prepared from 23 (94 mg, 0.1 mmol) and 11b (55mg, 0.2mmol) by the same method as that employed for the synthesis of 24a, using trichloroacetonitrile (1.6 mL, 16.0 mmol) in pyridine (4 mL) to give the title compound (126mg, 98%) as a glassy solid: IR (CHCl<sub>3</sub> cast) 3380, 2990, 2980, 1750, 1663, 1455, 1367, 1230, 1073, 1044 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 300 MHz)  $\delta$ 7.50–7.30 (m, 20H), 5.52 (d, 1H, J = 8.5 Hz), 5.18  $(AB_q, 2H, J = 11.5 \text{ Hz}), 5.06 \text{ (dd, 1H, } J = 10.0, 9.0 \text{ Hz}),$ 4.97 (dd, 1H, J = 9.0, 9.0 Hz), 4.94 (d, 1H, J = 11.5 Hz, 4.72–4.64 (m, 3H), 4.58 (AB<sub>q</sub>, 2H, J = 11.5 Hz, 4.52–4.42 (m, 2H), 4.32–4.23 (m, 2H), 4.15-4.05 (m, 2H), 3.94-3.87 (m, 2H), 3.80 (dd, 1H,  $J = 10.0, 10.0 \,\text{Hz}$ ,  $3.75 - 3.55 \,(\text{m}, 6 \,\text{H})$ ,  $3.50 - 3.40 \,(\text{m}, 6 \,\text{H})$ 2H), 2.40-1.00 (m, 10H), 2.00, 1.99, 1.90, and 1.75 (4s,  $4 \times 3H$ ), 0.90–0.80 (m, 9H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>). 100 MHz) 170.7, 170.6, 170.1, 169.8, 139.6, 138.4, 136.0, 130.0, 129.1, 128.9, 128.7, 128.6, 128.5, 128.3, 128.1, 127.63, 127.60, 101.0, 79.0, 78.7 (d, J = 6.9 Hz), 78.0 (d, J = 12.9 Hz), 77.3, 74.4, 73.8, 73.1, 72.9, 72.3, 71.9, 70.2, 69.1 (d, J = 3.4 Hz), 69.0, 68.8, 67.2, 65.3 (d, J = 2.8 Hz), 62.3, 55.3, 39.6, 37.6, 37.0, 30.2, 28.3, 25.0, 23.3, 22.8, 22.7, 20.8, 19.7; <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  30.9; LRMS (FAB, Cleland) m/z (relative intensity) 1198 (MNa<sup>+</sup>, 0.6%), 1176 (MH<sup>+</sup>, 1.0%).

### 4.31. 3-Bromopropyl 2-acetamido-3,4,6-tri-*O*-acetyl-2deoxy-β-D-glucopyranoside (26a)

To a mixture of 25a (1.05g, 3.19 mmol) and powdered 4A molecular sieves (0.5g) in CH<sub>2</sub>Cl<sub>2</sub> (35mL) was added 10-(R)-camphorsulfonic acid (0.3g, 1.3mmol), which had been azeotropically dried with benzene (10mL). Freshly distilled 3-bromopropanol (5mL, 55.3 mmol) was then added. The reaction vessel was sealed and heated at 42°C overnight and then at 60°C for 1h. The reaction mixture was cooled and washed with saturated aq NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo to remove 3-bromopropanol. Purification by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, gradient elution, 100:1 to 50:1) afforded 26a (1.36 g, 91%) as a white solid: mp 129–131 °C;  $[\alpha]_{D}^{2t}$ +0.137 (c 1.16, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 3283, 1748, 1659, 1551, 1369, 1229, 1044 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  5.68 (d, 1H, J = 9.0 Hz), 5.21 (dd, 1H, J = 10.6, 9.5 Hz), 5.01 (dd, 1H, J = 9.5, 9.5 Hz), 4.60 (d, 1H, J = 8.5 Hz), 4.24 (dd, 1H, J = 12.5, 5.0 Hz), 4.10 (dd, 1H, J = 12.5, 2.5Hz), 3.95 (ddd, 1H, J = 10.0, 5.0, 5.0 Hz, 3.85 (ddd, 1H, J = 10.5, 9.0,8.5 Hz), 3.71 (ddd, 1H, J = 9.5, 5.0, 2.5 Hz), 3.65 (ddd, J = 9.5, 5.0, 2.5 Hz)), 3.65 (ddd, J = 9.5, 5.0, 2.5 Hz))) 1H, J = 10.0, 8.5, 5.0 Hz), 3.52–3.48 (m, 2H), 2.20–1.90 (m, 14H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 75 MHz)  $\delta$  171.1, 170.8, 170.3, 169.7, 101.7, 72.7, 72.3, 69.1, 67.3, 62.5, 54.8, 32.8, 30.9, 23.5, 20.9; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 470 (M(<sup>81</sup>Br)H<sup>+</sup>, 90%), 468 (M(<sup>79</sup>Br)H<sup>+</sup>, 100%); Anal. Calcd for  $C_{17}H_{26}BrNO_9$ : C, 43.60; H, 5.60; N, 2.99. Found: C, 43.82; H, 5.30; N, 2.96.

### 4.32. 3-Bromopropyl 2-acetamido-3,4,6-tri-*O*-acetyl-2deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-3,6-di-*O*acetyl-2-deoxy-β-D-glucopyranoside (26b)

This was prepared using a similar procedure to that outlined for 26a employing 23b (481 mg, 0.8 mmol), 4Å molecular sieves (770 mg), 10-(R)-camphorsulfonic acid (72mg, 0.3mmol), and 3-bromopropanol (3.5mL, 38.7 mmol) in 1,2-dichloroethane (60 mL) to provide **26b** (550 mg, 93%) as a white solid: mp 231 °C (dec);  $[\alpha]_{D}^{26}$  -30.2 (c 0.51, CH<sub>2</sub>Cl<sub>2</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3083, 1746, 1662, 1547, 1434 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 360 MHz)  $\delta$  6.15 (d, 1H, J = 8.9 Hz), 5.92 (d, 1H, J = 9.4 Hz), 5.20 (t, 1H, J = 9.9 Hz), 5.10 (dd, 1H, J =10.0, 8.6 Hz), 5.01 (t, 1H, J = 9.7 Hz), 4.60 (d, 1H, J = 8.4 Hz), 4.47 (d, 1H, J = 8.1 Hz), 4.36 (m, 2H), 4.24 (dd, 1H, J = 12.0, 5.0 Hz), 4.00 (dd, 1H, J = 12.4, 2.1 Hz), 3.91 (m, 2H), 3.76 (m, 2H), 3.64 (m, 3H), 3.46 (dd, 2H, J = 7.1, 5.6 Hz), 1.99 (m, 2H), 2.10, 2.04, 2.03, 1.96, 1.91, and 1.89 (6s,  $6 \times 3H$ ); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz) δ 171.3, 171.1, 171.0, 170.8, 170.7, 170.4, 169.7, 101.8, 101.4, 76.5, 73.3, 72.8, 72.7, 72.2, 68.6, 67.6, 62.7, 62.1, 55.2, 54.2, 32.8, 30.9, 23.4, 23.3, 21.2, 21.0, 20.9, 20.8; HRMS (EI) calcd for  $C_{29}H_{44}^{79}BrN_2O_{16}$  755.1874, found 755.1884; Anal. Calcd for  $C_{29}H_{44}BrN_2O_{16}$ : C, 46.10; H, 5.74; N, 3.71. Found: C, 46.08; H, 5.94; N, 3.66.

### 4.33. Diethyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2deoxy-β-D-glucopyranosyl)propylphosphonate (27a)

Compound 27a was synthesized from 26a (800 mg, 1.7 mmol) by the same method as that utilized for the preparation of 19, using triethyl phosphite (11.5mL) over 16h to give the desired compound (803mg, 89%) as an oil: IR (CHCl<sub>3</sub> cast) 1749, 1369, 1231, 1041, 962 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 400 MHz)  $\delta$  6.42 (br d, 1H, J = 8.5Hz), 5.18 (dd, 1H, J = 10.5, 9.5 Hz), 5.01 (dd, 1H, J = 10.0, 9.5 Hz), 4.62 (d, 1H, J = 8.5 Hz), 4.25 (dd, 1H, J = 12.0, 5.0 Hz), 4.20–4.00 (m, 5H), 3.92-3.80 (m, 2H), 3.70 (ddd, 1H, J = 10.0, 5.0, 2.5 Hz), 3.64–3.55 (m, 1H), 2.05, 1.99, 1.98, and 1.89 (4s,  $4 \times 3$ H), 1.30 (dt, 6H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  170.9, 170.8, 170.4, 169.8, 101.2, 73.2, 72.2, 69.4 (d, J = 14.1 Hz), 63.0 (d, J = 8.0 Hz), 62.5, 61.9 (d, J = 6.0 Hz), 54.6, 23.3, 22.8 (d, J = 5.0 Hz), 21.8 (d, J = 141.9 Hz), 20.8, 16.6 (d, J = 4.0 Hz); <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  31.6; LRMS (CI, NH<sub>3</sub>) m/z (relative intensity) 526 (MH<sup>+</sup>, 100%); Anal. Calcd for C<sub>21</sub>H<sub>36</sub>NO<sub>12</sub>P: C, 48.00; H, 6.91; N, 2.67. Found: C, 47.81; H, 7.14; N, 2.63.

# 4.34. Diethyl 3-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2-acetamido-3,6-di-O-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)propylphosphonate (27b)

The procedure used for the conversion of **18** to **19** was utilized to prepare **27b** as a white solid (36 mg, 88%) from **26b** (38 mg, 0.05 mmol), employing triethyl phosphite (4.5 mL) over 21 h: mp 194–196 °C;  $[\alpha]_D^{26}$  –33.8 (*c* 0.99, CH<sub>2</sub>Cl<sub>2</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3469, 1747, 1664, 1550, 1441 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 360 MHz)  $\delta$  6.38 (d, 1H,

J = 9.1 Hz, 6.26 (d, 1H, J = 8.9 Hz), 5.21 (dd, 1H, J = 10.5, 9.5 Hz), 5.09 (dd, 1H, J = 10.0, 8.7 Hz), 5.01 (t, 1H, J = 9.7 Hz), 4.63 (d, 1H, J = 8.3 Hz), 4.51 (d, 1H, J = 8.2 Hz), 4.35 (m, 2H), 4.24 (dd, 1H, J = 12.0, 5.0 Hz), 4.04 (m, 5H), 3.86 (m, 3H), 3.75 (t, 1H, J = 8.7 Hz, 3.65 (m, 2H), 3.55 (m, 1H), 2.11, 2.04, 2.03, 1.98, 1.97, 1.90, and 1.89 (7s, 7 × 3H), 2.11-1.71 (m, 4H), 1.29 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz; <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 100 MHz)  $\delta$  171.1, 171.0, 170.9, 170.8, 170.7, 170.6, 169.7, 101.3, 101.1, 76.8, 73.4, 73.1, 72.7, 72.0, 69.4, 68.7, 62.9, 62.1, 62.0 (d, J = 7.1 Hz), 61.9 (d, J = 7.1 Hz), 55.2, 54.2, 23.2, 23.0 (d, J = 4.9 Hz), 22.0 (d, J = 142.8 Hz), 21.3, 21.0, 20.9, 20.8, 16.6 (d, J = 5.0 Hz); <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  31.6; LRMS (FAB, Cleland) m/z (relative intensity) 813.7 (MH<sup>+</sup>, 7.2%); Anal. Calcd for C<sub>33</sub>H<sub>53</sub>N<sub>2</sub>O<sub>19</sub>P: C, 48.77; H, 6.57; N, 3.45. Found: C, 48.63; H, 6.40; N, 3.43.

# 4.35. Dimethyl 3-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2-acetamido-3,6-di-O-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)propylphosphonate (27c)

The procedure utilized for the transformation of 18 into **19** was used to prepare **27c** as a white solid (263 mg, 94%) from 26b (269mg, 0.36mmol), employing trimethyl phosphite (18mL) over 42h: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3281, 2956, 1746, 1666, 1548, 1439 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>, 360 MHz)  $\delta$  6.67 (d, 1H, J = 8.9 Hz), 6.63 (d, 1H, J = 9.2 Hz), 5.25 (t, 1H, J = 9.9 Hz), 5.12 (dd, 1H, J =10.1, 8.7 Hz), 4.99 (t, 1H, J = 9.7 Hz), 4.71 (d, 1H, J = 8.3 Hz, 4.55 (d, 1H, J = 8.2 Hz), 4.38 (dd, 1H, J = 11.8, 2.1 Hz), 4.36 (dd, 1H, J = 12.4, 4.1 Hz), 4.20 (dd, 1H, J = 11.9, 5.4 Hz), 3.99 (dd, 1H, J = 12.4, 2.2 Hz), 3.81 (m, 2H), 3.76 (m, 2H), 3.70 (d, 3H, J = 2.2 Hz, 3.67 (d, 3H, J = 2.3 Hz), 3.66 (m, 2H), 3.54 (m, 1H), 2.09 (s, 3H), 2.03 (s, 6H), 1.97, 1.96, 1.90, and 1.88 (4s,  $4 \times 3$ H), 1.80 (m, 4H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 75 MHz)  $\delta$  171.2, 170.9, 170.8, 170.7, 170.5, 169.7, 101.3, 101.2, 76.7, 73.3, 73.2, 72.7, 72.1, 69.4 (d,  $J = 15.7 \,\mathrm{Hz}$ , 68.7, 62.9, 62.2, 55.2, 54.6, 52.6 (d, J = 6.0 Hz), 52.6 (d, J = 6.2 Hz), 23.3, 23.2, 22.9 (d, J = 4.8 Hz), 21.1, 21.0, 20.9 (d, J = 141.6 Hz), 20.8, 20.7; <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  34.2; LRMS (FAB, Cleland) m/z (relative intensity) 785.4 (MH<sup>+</sup>, 6.8%); Anal. Calcd for C<sub>31</sub>H<sub>49</sub>N<sub>2</sub>O<sub>19</sub>P: C, 47.45; H, 6.29; N, 3.57. Found: C, 47.07; H, 6.20; N, 3.47.

## 4.36. 3-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphonic acid (28a)

Compound **28a** was prepared from **27a** (119 mg, 0.2 mmol) by the same procedure as that used for the synthesis of **23**, employing bromotrimethylsilane (80 µL, 0.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) to give the title compound (106 mg, 99%) as a glassy solid: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3246, 3064, 2940, 2888, 1749, 1561, 1369, 1230, 1166, 1043 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>–CD<sub>3</sub>OD, 400 MHz)  $\delta$  5.15 (dd, 1H, J = 10.0, 10.0 Hz), 4.98 (dd, 1H, J = 10.0, 9.5 Hz), 4.58 (d, 1H, J = 8.5 Hz), 4.22 (dd, 1H, J = 12.0, 4.5 Hz), 4.09 (dd, 1H, J = 12.0, 2.5 Hz), 3.60–3.50 (m, 2H), 3.70 (ddd, 1H, J = 9.5, 4.5, 2.5 Hz), 3.60–3.50 (m,

1H), 2.04, 1.98, 1.97, and 1.91 (4s,  $4 \times 3$ H), 1.90–1.70 (m, 4H); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>–CD<sub>3</sub>OD, 100 MHz)  $\delta$  172.8, 171.5, 171.2, 170.3, 101.1, 73.1, 72.0, 69.7, 69.2, 62.6, 54.5, 23.5 (d, J = 139.5 Hz), 23.1 (d, J = 3.8 Hz), 22.6, 20.71, 20.68; <sup>31</sup>P NMR (CD<sub>2</sub>Cl<sub>2</sub>, 162 MHz)  $\delta$  32.6; LRMS (FAB, Cleland) *m*/*z* (relative intensity) 492.4 (MNa<sup>+</sup>, 3.3%), 470.5 (MH<sup>+</sup>, 11%), 103 (100%).

### 4.37. Ethyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxyβ-D-glucopyranosyl-(1→4)-2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphinate (28b)

Using a procedure analogous to the one used for the synthesis of 23, compound 28b was prepared from 27b (17 mg, 0.02 mmol) using bromotrimethylsilane  $(9 \mu \text{L}, 10 \mu \text{m})$ 0.07 mmol) in  $CH_2Cl_2$  (0.2 mL) to give the title compound (14mg, 85%) as a cream solid: IR (KBr disc) 3389, 1749, 1661, 1650, 1643, 1551 cm<sup>-1</sup>; <sup>1</sup>H NMR  $(D_2O, 360 \text{ MHz}) \delta 5.12 \text{ (d, 1H, } J = 9.9 \text{ Hz}), 5.00 \text{ (dd,}$ 1H, J = 10.3, 8.9 Hz), 4.88 (t, 1H, J = 9.6 Hz), 4.68 (d, 1H, J = 8.5 Hz), 4.55 (d, 1H, J = 8.7 Hz), 4.37 (d, 1H, J = 10.6 Hz, 4.32 (dd, 1H, J = 12.7, 3.3 Hz), 3.96–3.82 (m, 6H), 3.71 (m, 4H), 3.54 (m, 1H), 2.02, 1.99, 1.98, 1.93, 1.90, 1.84, and 1.83 (7s,  $7 \times 3H$ ), 1.65 (m, 4H), 1.14 (t, 3H, J = 7.0 Hz); <sup>13</sup>C NMR (D<sub>2</sub>O-CD<sub>3</sub>OD, 100 MHz)  $\delta$  174.2, 174.1, 174.0, 173.5, 173.4, 172.8, 172.5, 100.4, 100.1, 75.9, 73.7, 72.3, 71.8, 70.7, 69.9, 68.1, 62.3, 62.1 (d, J = 6.2 Hz), 61.6, 54.0, 53.7, 22.2 (d, J = 2.6 Hz), 21.8, 21.7, 21.3 (d, J = 139.1 Hz), 20.2, 20.1, 20.0, 19.9, 19.7, 15.5 (d, J = 5.9 Hz); <sup>31</sup>P NMR (D<sub>2</sub>O, 162 MHz)  $\delta$  30.9; LRMS (FAB, glycerol/HCl) m/z (relative intensity) 758.6 (MH<sup>+</sup>, 1.8%).

### 4.38. 3-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-Dglucopyranosyl-(1→4)-2-acetamido-3,6-di-O-acetyl-2deoxy-β-D-glucopyranosyl)propylphosphonic acid (28c)

Compound 28c was prepared from 27c (100 mg, 0.1 mmol) by the same method as that used for the synthesis of 23, employing bromotrimethylsilane  $(50 \mu L,$ 0.4 mmol) in  $CH_2Cl_2$  (1 mL) to give the title compound (97 mg, quant.) as a white solid: IR (MeOH cast) 3313, 2934, 1747, 1696, 1685, 1661, 1538, 1433 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O, 360 MHz)  $\delta$  5.12 (dd, 1H, J = 10.5, 9.5 Hz), 5.00 (dd, 1H, J = 10.4, 8.8Hz), 4.88 (t, 1H, J = 9.6Hz), 4.68 (d, 1H, J = 8.4Hz), 4.55 (d, 1H, J = 8.5Hz), 4.38 (dd, 1H, J = 10.2, 2.2Hz), 4.32 (dd, 1H, J = 12.7, 3.4 Hz), 3.93 (m, 2H), 3.85 (m, 2H), 3.72 (m, 4H), 3.54 (m, 1H), 2.02, 1.99, 1.98, 1.93, 1.90, 1.84, and 1.83 (7s, 7 × 3H), 1.65 (m, 4H);  $^{13}\text{C}$  NMR (D<sub>2</sub>O, 100 MHz)  $\delta$ 174.4, 174.2, 173.6, 173.5, 172.9, 172.6, 100.4, 100.1, 75.9, 73.7, 72.4, 71.9, 70.8, 70.1 (d, *J* = 17.8 Hz), 68.1, 62.3, 61.6, 54.0, 53.7, 22.7 (d,  $J = 137.0 \,\text{Hz}$ ), 22.3 (d,  $J = 4.6 \,\text{Hz}$ ), 21.8, 21.7, 20.2, 20.1, 20.0, 19.9, 19.8; <sup>31</sup>P NMR (D<sub>2</sub>O, 162MHz)  $\delta$  30.4; LRMS (FAB, Cleland) m/z (relative intensity) 757.2 (MH<sup>+</sup>, 2%).

### 4.39. Benzyl (2*R*,3'*R*)-3-(3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphinato)-2-(3',7'-dimethyloctyloxy)propanoate (29a)

Compound **29a** was prepared from **28a** (89 mg, 0.2 mmol) and **11a** (75 mg, 0.2 mmol) by the same proce-

dure as that employed for the synthesis of 24a, using trichloroacetonitrile (2mL, 20.0mmol) in pyridine (3mL) to give the desired compound (138 mg, 93%) as a glassy solid: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3279, 2954, 2929, 1747, 1665, 1368, 1231, 1044 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>-CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.40–7.30 (m, 5H), 5.20–5.12 (m, 3H), 5.00 (dd, 1H, J = 10.0, 9.5 Hz), 4.50 (d, 1H, J = 8.5 Hz), 4.28-4.20 (m, 3H), 4.15-4.06 (m, 2H), 3.80-3.65 (m, 4H), 3.53-3.40 (m, 2H), 2.04, 1.99, 1.98, and 1.90 (4s, 4×3H), 1.85-1.05 (m, 14H), 0.86 and 0.84 (2d, 9H, J = 7.0 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>-CD<sub>3</sub>OD, 100 MHz)  $\delta$ 172.1, 171.3, 171.1, 170.5, 170.1, 135.8, 129.0, 128.8, 128.6, 100.8, 78.6 (d, J = 7.1 Hz), 73.1, 72.0, 70.3, 69.9 (d, J = 14.6 Hz), 69.2, 67.4, 64.9 (d, J = 5.4 Hz), 62.6, 54.2, 39.6, 37.6, 36.9, 30.1, 28.3, 25.0, 22.8, 22.7, 22.6, 22.0 (d, J = 108.5 Hz), 20.8, 20.7, 19.6; <sup>31</sup>P NMR  $(CD_2Cl_2, 162 \text{ MHz}) \delta$  34.5; LRMS (FAB, Cleland) m/z(relative intensity) 811 (MNa<sup>+</sup>, 0.5%), 789 (MH<sup>+</sup>, 1.4%), 119 (100%).

### 4.40. Benzyl (*R*)-3-[3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphinato]-2-octyloxypropanoate (29b)

Compound 29b was prepared from 28c (55mg, 0.07 mmol) and 11a (68 mg, 0.2 mmol) by the same method as that employed for the synthesis of 24a, using trichloroacetonitrile (1.1 mL, 11.0 mmol) in pyridine (4mL). Purification by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>–MeOH, gradient elution, 20:1 to 1:1) gave **29b** (60 mg, 79%) as a tan solid: IR (CH<sub>2</sub>Cl<sub>2</sub> cast) 3304, 2953, 1747, 1659, 1499 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.36 (m, 5H), 5.29 (dd, 1H, J = 10.4, 9.4 Hz), 5.21 (AB<sub>q</sub>, 1H, J = 12.1 Hz), 5.19 (AB<sub>q</sub>, 1H, J = 12.1 Hz, 5.10 (dd, 1H, J = 10.3, 8.9 Hz), 4.94 (t, 1H, J = 9.6 Hz), 4.76 (d, 1H, J = 8.3 Hz), 4.49 (m, 2H), 4.41 (dd, 1H, J = 12.5, 3.9 Hz), 4.19 (m, 3H), 4.04 (m, 2H), 3.79 (m, 4H), 3.64 (m, 3H), 3.48 (m, 2H), 2.08, 2.04, 2.03, 1.97, 1.96, 1.90, and 1.89 (7s, 7 × 3H), 1.74 (m, 2H), 1.54 (m, 4H), 1.28 (m, 10H), 0.89 (t, 3H, J = 6.7 Hz; <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz)  $\delta$  173.6, 172.4, 172.2, 172.0, 171.8, 171.2, 137.2, 129.7, 129.4, 102.0, 101.6, 80.3 (d, J = 6.4 Hz), 77.7, 74.9, 74.1, 73.7, 72.8, 72.2, 70.9 (d, J = 16.5 Hz), 69.9, 67.9, 65.3 (br), 63.9, 63.0, 56.3, 55.6, 33.0, 30.8, 30.5, 30.4, 27.1, 24.7 (d, J = 4.8 Hz), 24.2 (d, J = 140.5 Hz), 23.7, 23.0, 22.9, 21.1, 20.9, 20.7, 20.6, 20.5, 14.5; <sup>31</sup>P NMR (CD<sub>3</sub>OD, 81 MHz)  $\delta$  26.1; LRMS (FAB, Cleland) m/z (relative intensity) 1047.1 (MH<sup>+</sup>, 1.9%).

### 4.41. Benzyl (2*R*,3'*R*)-3-[3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphinato]-2-(3',7'-dimethyloctyloxy)propanoate (29c)

Compound **29c** was synthesized in 4 days from **28c** (37 mg, 0.05 mmol) and **11b** (34 mg, 0.1 mmol) in the same manner as **24a** was prepared from **23** and **11a**, using trichloroacetonitrile (0.75 mL, 7.5 mmol) in pyridine (2 mL). Purification by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>–MeOH, gradient elution, 40:1 to 7:3) afforded **29c** (38 mg, 72%) as a tan solid: IR (MeOH cast)

3316, 2930, 1745, 1661, 1455 1499 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 360 MHz) & 7.37 (m, 5H), 5.29 (t, 1H, J = 9.7 Hz, 5.20 (AB<sub>q</sub>, 1H, J = 12.0 Hz), 5.18 (AB<sub>q</sub>, 1H, J = 12.0 Hz), 5.12 (t, 1H, J = 9.5 Hz), 4.95 (t, 1H, J = 9.7 Hz, 4.76 (d, 1H, J = 8.4 Hz), 4.52 (m, 2H), 4.41 (dd, 1H, J = 12.4, 3.7 Hz), 4.06 (m, 5H), 3.77 (m, 4H),3.65 (m, 3H), 3.49 (m, 2H), 2.07 (s, 3H), 2.04 (s, 6H), 1.97, 1.96, 1.91, and 1.89 (4s, 4 × 3H), 1.75–1.11 (m, 14H), 0.87 (m, 9H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz)  $\delta$ 173.6, 173.4, 172.4, 172.2, 172.0, 171.8, 171.6, 171.3, 137.2, 129.7, 129.4, 101.9, 101.8, 79.6 (d, J = 7.1 Hz), 77.7, 74.9, 74.0, 73.6, 72.8, 70.6, 70.3 (d, J = 16.6 Hz), 69.9, 68.0, 65.9 (d, J = 5.0 Hz), 63.8, 63.0, 56.3, 55.5,40.5, 38.4, 37.8, 30.9, 29.1, 25.8, 24.0 (br), 23.3 (d, J = 137.2 Hzz), 23.1, 23.0, 22.9, 21.1, 20.8, 20.7, 20.6, 20.5, 20.0; <sup>31</sup>P NMR (CD<sub>3</sub>OD, 81 MHz)  $\delta$  30.9; LRMS (FAB, Cleland) m/z (relative intensity) 1113.5 (MK<sup>+</sup>, 0.7%), 1097.5 (MNa<sup>+</sup>, 1.6%), 1075.5 (MH<sup>+</sup>, 0.6%).

### 4.42. (*R*)-3-[3-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-3,6-di-*O*acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphinato]-2octyloxypropanoic acid (30b)

A solution of 29b (35 mg, 0.03 mmol) in acetic acid-95% EtOH (1:1 v/v) (2mL) was stirred under  $H_2$  in the presence of 10% Pd/C (12mg) for 6h. The mixture was filtered through a Millex-HV µm filter and then concentrated in vacuo to give 30b (33mg, quant.) as a white solid: IR (MeOH cast) 3325, 2871, 1700, 1661, 1539, 1456, 1437 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 360 MHz)  $\delta$ 5.29 (t, 1H, J = 9.8 Hz), 5.12 (t, 1H, J = 9.5 Hz), 4.95 (t, 1H, J = 9.6 Hz), 4.76 (d, 1H, J = 8.3 Hz), 4.54 (m, 2H), 4.43 (dd, 1H, J = 12.4, 3.7 Hz), 4.04 (m, 5H), 3.80 (m, 4H), 3.67 (m, 3H), 3.52 (m, 2H), 2.09, 2.05, 2.04, 1.97, 1.96, 1.93, and 1.90 (7s, 7 × 3H), 1.79 (m, 2H), 1.61 (m, 4H), 1.29 (m, 10H), 0.89 (t, 3H, J = 6.6 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) & 175.2, 173.6, 172.4, 172.2, 172.0, 171.8, 171.3, 102.0, 101.7, 81.2 (br), 77.8, 74.8, 74.0, 73.8, 72.8, 72.2 (br), 71.3 (br), 69.8, 65.8 (br), 63.9, 63.0, 56.2, 55.5, 33.0, 30.7, 30.6, 30.4, 27.1, 24.7 (br), 23.6 (d, J = 141.5 Hz), 23.0, 22.9, 21.1, 20.9, 20.7, 20.6, 20.5, 14.5; <sup>31</sup>P NMR (CD<sub>3</sub>OD, 162 MHz) δ 25.1; LRMS (FAB, Cleland) m/z (relative intensity) 995.4 (MK<sup>+</sup>, 4.7%), 979.1 (MNa<sup>+</sup>, 3.4%), 957.2 (MH<sup>+</sup>, 1.0%).

### 4.43. (2*R*,3'*R*)-3-[3-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2deoxy-β-D-glucopyranosyl-(1→4)-2-acetamido-3,6-di-*O*acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphinato]-2-(3',7'-dimethyloctyloxy)propanoic acid (30c)

The procedure used for the synthesis of **29b** was followed. Reaction of **29c** (35 mg, 0.03 mmol) with 10% Pd/C (17 mg) in acetic acid–95% EtOH (1:1 v/v) (3 mL) over 3.25h gave **30c** (27 mg, quant.) as colorless solid: IR (MeOH cast) 3335, 2927, 1748, 1617, 1456 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  5.29 (t, 1H, J = 10.0 Hz), 5.13 (t, 1H, J = 9.1 Hz), 4.96 (t, 1H, J = 9.6 Hz), 4.76 (d, 1H, J = 8.4 Hz), 4.54 (m, 2H), 4.43 (dd, 1H, J = 12.4, 3.7 Hz), 4.15–4.00 (m, 5H), 3.86–3.63 (m, 7H), 3.54 (m, 2H), 2.09 (s, 3H), 2.05 (s, 6H), 1.98, 1.96, 1.93, and 1.90 (4s, 4×3H), 1.82–1.11 (m, 14H), 0.89 (t, 9H, J = 6.6 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz)  $\delta$  173.6,

172.4, 172.2, 172.0, 171.8, 171.3, 102.7, 102.4, 78.1, 76.8 (d, J = 9.6 Hz), 75.1, 74.4, 74.1, 73.1, 71.3 (br), 70.5 (br), 69.4, 64.9 (br), 64.1, 63.2, 56.4, 55.6, 38.5, 37.4, 30.8, 28.9, 25.5, 24.8 (br), 24.4 (d, J = 135.0 Hz), 22.8, 22.7, 22.6, 20.7, 20.5, 20.3, 20.2, 20.1, 19.7; <sup>31</sup>P NMR (CD<sub>3</sub>OD, 81 MHz)  $\delta$  25.1; LRMS (FAB, Cleland) m/z(relative intensity) 1023.2 (MK<sup>+</sup>, 3.8%), 1007.2 (MNa<sup>+</sup>, 4.3%), 985.2 (MH<sup>+</sup>, 0.6%).

### 4.44. Dimethyl (*Z*)-2-hydroxymethyl-3-tetradecylbutenedioate (31)

To a solution of 32 (2.10g, 4.46 mmol) in dry MeCN (40 mL) was added  $BF_3$ ·Et<sub>2</sub>O (0.49 mL, 4.01 mmol) at rt and the mixture was stirred for 2h. The reaction was quenched by adding ice-cold H<sub>2</sub>O (30mL) and further stirred for 5min. Extraction with CH<sub>2</sub>Cl<sub>2</sub>  $(4 \times 50 \text{ mL})$ , drying (Na<sub>2</sub>SO<sub>4</sub>), and evaporation of solvent in vacuo gave 1.69 g of crude product. Further purification by flash chromatography (SiO2, 3:2/petroleum ether-Et<sub>2</sub>O,  $R_f$  0.13) gave **31** (1.56g, 95%) as a white solid: mp 47-48 °C; IR (CD<sub>2</sub>Cl<sub>2</sub> cast) 3506, 2924, 2853, 1726, 1641, 1435, 1316, 1265,  $1082 \text{ cm}^{-1}$ ; <sup>1</sup>H NMR  $(CD_2Cl_2, 300 \text{ MHz}) \delta 4.36 \text{ (d, 2H, } J = 6.6 \text{ Hz}), 3.74 \text{ (s,}$ 6H), 2.39 (t, 2H, J = 7.5 Hz), 2.11 (t, 1H, J = 6.6 Hz), 1.44 (qn, 2H), 1.27 (br s, 22H), 0.88 (t, 3H, J = 6.6 Hz); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>, 75 MHz)  $\delta$  169.7, 167.9, 144.1, 133.2, 58.9, 52.5, 52.4, 32.3, 30.7, 30.08, 30.05, 30.04, 29.99, 29.86, 29.74, 29.71, 29.67, 28.7, 23.1, 14.3; HRMS (EI) calcd for C<sub>21</sub>H<sub>38</sub>O<sub>5</sub> 370.2719, found 370.2715 (M)<sup>+</sup>; Anal. Calcd for  $C_{21}H_{38}O_5$ : C, 68.07; H, 10.34. Found: C, 68.11; H, 10.42.

### 4.45. Dimethyl (Z)-2-(2'-trimethylsilylethoxy)methyl-3tetradecylbutenedioate (32) and dimethyl (E)-2-(2'-trimethylsilylethoxy)methyl-3-tetradecylbutenedioate (33)

Tetradecylmagnesium chloride (20mL of a 1.0M solution in THF, 20 mmol) was added dropwise to a suspension of CuBr·Me<sub>2</sub>S (4.11 g, 20 mmol) in THF (50 mL) at -40 °C. The resulting yellow suspension was stirred at -40 °C for 2h, then cooled to -78 °C, and freshly distilled DMAD (2.22mL, 18mmol) in THF (10mL) was added dropwise to give a dark red brown mixture. After 1h, a HMPA-THF/1:1 solution (20mL) was added dropwise, and the reaction mixture was stirred for 10 min. Trimethylsilylethoxymethyl chloride (7.1 mL, 40mmol) in THF (10mL) was then added dropwise and the reaction mixture was stirred for 1 h at -78 °C. The reaction mixture was warmed to -40 °C and stirred for 5.3h, and then warmed to 0°C. After 1.5h, the reaction mixture was quenched with a saturated aq NH<sub>4</sub>Cl solution (50 mL, adjusted to pH8 with 10% ammonia), and allowed to warm to rt. After 30min, the mixture was filtered through a pad of Celite<sup>®</sup>. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with a saturated aq NH<sub>4</sub>Cl solution, H<sub>2</sub>O, and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. Further purification by flash chromatography  $(SiO_2, 85:15/petroleum ether-Et_2O, R_f 32 0.52 and R_f 33$ 0.47 (3:2/petroleum ether- $Et_2O$ ) gave 32 (2.33 g, 28%) and 33 (4.59 g, 54%) as colorless oils.

Data for **32**: IR (CHCl<sub>3</sub> cast) 2924, 2853, 1728, 1633, 1458, 1434, 1262, 1250, 1079, 859, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.20 (s, 2H), 3.74 and 3.73 (2s, 6H), 3.52 (dd, 2H, J = 9.2, 8.1Hz), 2.39 (t, 2H, J = 7.3 Hz), 1.47–1.20 (m, 24H), 0.94–0.85 (m, 5H), -0.01 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  169.1, 168.0, 142.7, 133.5, 68.3, 65.7, 52.2, 51.9, 32.0, 30.2, 29.7, 29.54, 29.45, 29.40, 28.3, 22.7, 18.1, 14.1, -1.4; HRMS (EI) calcd for C<sub>26</sub>H<sub>50</sub>O<sub>5</sub>Si 470.3427, found 470.3428 [M]<sup>+</sup>; Anal. Calcd for C<sub>26</sub>H<sub>50</sub>O<sub>5</sub>Si: C, 66.34; H, 10.71. Found: C, 66.63; H, 10.80.

Data for **33**: IR (CHCl<sub>3</sub> cast) 2952, 2925, 2854, 1732, 1433 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.28 (s, 2H), 3.77 and 3.76 (2s, 6H), 3.47 (dd, 2H, J = 8.7, 8.1 Hz), 2.39 (t, 2H, J = 7.5 Hz), 1.40 (qn, 2H), 1.29–1.20 (m, 22H), 0.90–0.85 (m, 5H), -0.02 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  168.5, 167.6, 138.9, 133.5, 67.8, 51.6, 51.5, 31.8, 31.3, 29.5, 29.3, 29.2, 29.1, 28.3, 22.5, 17.8, 13.9, -1.6; HRMS (EI) calcd for C<sub>20</sub>H<sub>38</sub>O<sub>5</sub>Si 470.3427, found 470.3422 [M]<sup>+</sup>; Anal. Calcd for C<sub>26</sub>H<sub>50</sub>O<sub>5</sub>Si: C, 66.34; H, 10.71. Found: C, 66.65; H, 10.95.

### 4.46. *O*-(Dimethyl (*Z*)-2-oxymethyl-3-tetradecylbutenedioate) 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy- $\alpha$ -D-glucopyranoside (35)

A mixture of  $\alpha$ -imidate 34 (55 mg, 0.12 mmol) and alcohol 31 (33 mg, 0.09 mmol) in dry Et<sub>2</sub>O (13 mL) was stirred in the presence of powdered activated 4 Å molecular sieves for 30min. TMSOTf (8mg, 6µL, 0.04mmol) was added to the reaction mixture at -20 °C. After being stirred at -20 °C for 3.5h, the reaction mixture was diluted with EtOAc, and filtered through Celite<sup>®</sup>. The filtrate was washed with a saturated aq NaHCO<sub>3</sub> solution, and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Further purification by flash chromatography (SiO<sub>2</sub>; 6:2.5/hexane-EtOAc, R<sub>f</sub> 0.32 (5:3/ hexane-EtOAc)) gave 35 (42 mg, 70%) as a colorless oil:  $[\alpha]_D^{26}$  +69 (c 1.44, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 2925, 2854, 2110, 1751, 1643, 1435, 1367, 1227, 1047 cm<sup>-</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.39 (dd, 1H, J = 10.5, 9.3 Hz), 5.02 (dd, 1H, J = 10.2, 9.3 Hz), 5.01 (d, 1H, J = 3.6 Hz), 4.53 (d, 1H, J = 11.7 Hz), 4.35 (d, 1H, J = 11.7 Hz, 4.27 (dd, 1H, J = 12.3, 4.5 Hz), 4.06 (dd, 1H, J = 12.3, 2.4 Hz), 4.01 (ddd, 1H, J = 10.2, 4.2 Hz, 2.1 Hz), 3.77 and 3.75 (2s, 6H), 3.30 (dd, 1H, J = 10.5, 3.6 Hz), 2.44 (t, 2H, J = 7.8 Hz), 2.06, 2.05 and 2.01 (3s, 9H), 1.48–1.37 (m, 2H), 1.23 (br s, 22H), 0.86 (t, 3H, J = 6.6 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  170.7, 170.1, 169.9, 169.3, 166.8, 147.3, 129.1, 97.6, 70.5, 68.6, 68.2, 63.4, 61.9, 60.9, 52.6, 52.5, 32.1, 31.1, 30.7, 29.8, 29.7, 29.63, 29.55, 29.48, 28.5, 28.3, 22.9, 20.88, 20.85, 20.8, 14.3; HRMS (ES+) calcd for  $C_{33}H_{57}N_4O_{12}$ 701.3973, found 701.3973  $(M+NH_4)^+$ .

### 4.47. *O*-(Dimethyl (*Z*)-2-oxymethyl-3-tetradecylbutenedioate) 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-Dglucopyranoside (36)

To a stirred solution of  $SnCl_2$  (26 mg, 0.14 mmol) in dry MeCN (0.5 mL) was added consecutively thiophenol

 $(56 \mu L, 0.55 \text{ mmol})$ , Et<sub>3</sub>N  $(57 \mu L, 0.41 \text{ mmol})$ , and azide 35 (63 mg, 0.09 mmol) in dry MeCN (2 mL). The reaction mixture was stirred at rt for 20 min, after which time it was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with 2N NaOH. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was dissolved in pyridine (0.84 mL) and  $Ac_2O$ (0.33 mL) and stirred at rt for 17 h. The solution was evaporated to dryness, and then coevaporated with toluene. Further purification by flash chromatography (SiO<sub>2</sub>; 1:1/hexane-EtOAc, R<sub>f</sub> 0.12 or R<sub>f</sub> 0.28 (1:3/hexane-EtOAc)) gave 36 (40 mg, 63%) as a white solid:  $[\alpha]_D^{20}$  +59 (c 3.46, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub> cast) 3362, 2925, 2854, 1747, 1685, 1537, 1435, 1367, 1233, 1047 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.73 (d, 1H, 5.15–5.05 (m, 2H), 4.84  $J = 9.6 \,\mathrm{Hz}$ ), (d, 1H. J = 3.6 Hz, 4.49 (d, 1H, J = 12.0 Hz), 4.35–4.27 (m, 1H), 4.24 (d, 1H, J = 12.0 Hz), 4.21 (dd, 1H. J = 12.3 Hz, 4.5 Hz), 4.08 (dd, 1H, J = 12.3 Hz, 2.4 Hz),3.96-3.90 (m, 1H), 3.77 and 3.76 (2s, 6H), 2.38 (t, 2H, J = 7.5 Hz), 2.06, 1.99, 1.97, and 1.91 (4s, 12H), 1.46-1.33 (m, 2H), 1.22 (br s, 22H), 0.84 (t, 3H, J = 6.6 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  171.2, 170.6, 170.0, 169.3, 168.7, 167.1, 144.8, 130.4, 97.5, 71.2, 68.4, 68.0, 63.7, 61.9, 52.5, 52.4, 51.7, 31.9, 30.5, 29.7, 29.49, 29.45, 29.4, 28.4, 22.7, 23.1, 20.7, 20.6, 14.1; HRMS (ES+) calcd for  $C_{35}H_{57}NO_{13}Na$  722.3728, found 722.3729 (M+Na)<sup>+</sup>.

### 4.48. *O*-(Dimethyl (*Z*)-2-oxymethyl-3-tetradecylbutenedioate) 2-acetamido-2-deoxy-α-D-glucopyranoside (37)

A solution of 36 (35mg, 49 µmol) in MeOH (1mL) was stirred at rt in the presence of a catalytic amount of NaOMe for 1h. The reaction mixture was then neutralized with Amberlite IR-120 (H<sup>+</sup>) resin, filtered, and concentrated under reduced pressure. Further purification by reversed-phase HPLC ( $C_{18}$  Bondpak, flow rate: 15mL/min, gradient elution: 20% MeCN in H<sub>2</sub>O for 2min, 20-80% MeCN in H<sub>2</sub>O over 10min, 100% MeCN for 5min, 100–20% MeCN in H<sub>2</sub>O over 2min) gave 37  $(t_{\rm R} 13.7 \,{\rm min}, 28 \,{\rm mg}, 99\%)$  as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.38 (d, 1H, J = 7.8 Hz), 4.81 (d, 1H, J = 3.9 Hz), 4.47 (d, 1H, J = 12.3 Hz), 4.27 (d, 1H, J = 12.3 Hz, 4.03–3.96, 3.86–3.80, and 3.69–3.55 (3m, 5H), 3.78 and 3.77 (2s, 6H), 3.65 (d, 1H, J = 4.5 Hz), 3.59 (d, 1H, J = 4.5 Hz), 3.52 (br s, 1H), 2.69 (br s, 1H), 2.38 (t, 2H, J = 7.5 Hz), 2.05 (s, 3H), 1.46–1.32 (m, 2H), 1.23 (br s, 22H), 0.86 (t, 3H, J = 6.9 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 172.7, 168.6, 167.9, 143.6, 131.5, 97.6, 73.9, 72.0, 71.4, 63.4, 62.0, 52.5, 52.4, 54.0, 32.0, 30.2, 29.70, 29.65, 29.54, 29.46, 29.40, 28.6, 22.7, 23.1, 14.1; HRMS (ES+) calcd for  $C_{29}H_{51}NO_{10}Na$ 596.3411, found 596.3419 (M+Na)<sup>+</sup>.

### 4.49. Chaetomellic acid A dimethyl ester (38)

The known diester  $38^{48,60,61}$  was prepared using the method described by Ratemi et al.<sup>48</sup> Tetradecylmagnesium chloride (3.6mL of a 1.0M solution in THF, 3.6mmol) was added dropwise to a suspension of Cu-

Br·Me<sub>2</sub>S (0.75g, 3.6mmol) in THF (18mL) at -40 °C. The resulting yellow suspension was stirred at -40 °C for 2h, then cooled to -78 °C, and freshly distilled DMAD (0.42g, 0.36mL, 3.0mmol) in THF (6mL) was added dropwise to give a dark red brown mixture. After 40min, a HMPA-THF/1:1 solution (6mL) was added dropwise, and the reaction mixture was stirred for 45min. Methyl iodide (1.08g, 0.47mL, 7.5mmol) in THF (6mL) was then added dropwise and the reaction mixture was stirred for 5min at -78°C. The reaction mixture was warmed to rt. After 18.5h, the reaction mixture was quenched with a saturated aq NH<sub>4</sub>Cl solution (6mL, adjusted to pH8 with 10% ammonia). After 30 min, the mixture was filtered through a pad of Celite<sup>®</sup>. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with a saturated aq NH<sub>4</sub>Cl solution, H<sub>2</sub>O, and brine, dried  $(Na_2SO_4)$ , and concentrated in vacuo. Further purification by flash chromatography (SiO<sub>2</sub>, 4:1/petroleum ether-Et<sub>2</sub>O) gave **38** (808 mg, 76%) as a colorless oil: IR (CHCl<sub>3</sub> cast) (lit.<sup>48,60</sup>) 2924, 2853, 1725, 1644, 1434 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) (lit.<sup>48,60–62</sup>)  $\delta$ 3.74 and 3.73 (2s, 6H), 2.31 (t, 2H, J = 7.5 Hz), 1.93 (s, 3H), 1.42 (gn, 2H), 1.25–1.24 (br m, 22H), 0.86 (t, 3H, J = 6.5 Hz; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) (lit.<sup>48</sup>)  $\delta$ 169.9, 169.1, 139.7, 131.5, 52.1. 52.0, 31.9, 30.1, 29.6, 29.5, 29.4, 29.3, 27.7, 22.6, 14.9, 14.0; HRMS (EI) calcd for  $C_{21}H_{38}O_4$  354.2770, found 354.2763 (M)<sup>+</sup>.

### 4.50. Dimethyl (Z)-2-geranyl-3-methylbutenedioate (39)

Methylmagnesium bromide (1.33 mL of a 3.0 M solution in THF, 4mmol) was added dropwise to a suspension of CuBr·Me<sub>2</sub>S (0.82 g, 4 mmol) in THF (19 mL) at -40 °C. The resulting yellow suspension was stirred at -40°C for 2h, then cooled to -78°C, and freshly distilled DMAD (0.43 mL, 3.5 mmol) in THF (8 mL) was added dropwise to give a dark red brown mixture. After 40min, a HMPA-THF/1:1 solution (8mL) was added dropwise, which resulted in the heterogeneous mixture becoming nearly homogeneous. After 45min, geranyl bromide (1.39mL, 7mmol) in THF (8mL) was added and stirring was continued at -78°C for 5min. After warming to rt overnight, the reaction mixture was recooled to -20 °C, quenched with a saturated aq NH<sub>4</sub>Cl solution (8mL, adjusted to pH8 with 10% ammonia), and allowed to warm to rt. After 30min, the mixture was filtered through a pad of Celite<sup>®</sup>. The aqueous layer was extracted with Et<sub>2</sub>O, and the combined organic extracts were washed with a saturated aq NH<sub>4</sub>Cl solution, H<sub>2</sub>O, and brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. Further purification by flash chromatography (SiO<sub>2</sub>, 4:1/petroleum ether- $Et_2O$ ,  $R_f$  0.29) gave 39 (867 mg, 84%) as a colorless oil: IR (CDCl<sub>3</sub> cast) 2950, 1724, 1666, 1434 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ 5.01-4.97 (m, 2H), 3.69 and 3.68 (2s, 6H), 3.00 (d, 2H, J = 7.0 Hz, 2.05–1.94 (m, 4H), 1.90 (s, 3H), 1.61, 1.59, and 1.53 (3s, 9H);  ${}^{13}C$  NMR (CDCl<sub>3</sub>, 75MHz)  $\delta$ 169.0, 168.9, 137.9, 137.8, 131.9, 131.3, 123.8, 118.4, 51.9, 51.8, 39.4, 28.7, 26.4, 25.5, 15.9, 14.9; HRMS (EI) calcd for C<sub>17</sub>H<sub>26</sub>O<sub>4</sub> 294.1831, found  $294.1828 (M)^+$ .

### 4.51. Dimethyl (Z)-2-farnesyl-3-methylbutenedioate (40)

The reaction of methylmagnesium bromide (0.67 mL of a 3.0 M solution in THF, 2 mmol), CuBr·Me<sub>2</sub>S (0.41 g, 2mmol) in THF (9.8mL), freshly distilled DMAD (0.23mL, 1.9mmol) in THF (4mL), a HMPA-THF/ 1:1 solution (4mL), and farnesyl bromide (1.08mL, 4mmol) in THF (4mL) was performed as described for the synthesis of 39. Further purification by flash chromatography (SiO<sub>2</sub>, 4:1/petroleum ether-Et<sub>2</sub>O,  $R_{\rm f}$ 0.39) gave 40 (567 mg, 82%) as a colorless oil: IR (CDCl<sub>3</sub> cast) 2949, 2920, 1725, 1643, 1434 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.10–5.00 (m, 3H), 3.71 and 3.70 (2s, 6H), 3.03 (d, 2H, J = 6.9 Hz), 2.05-1.93 (m, 8H),1.93 (s, 3H), 1.65 and 1.63 (2s, 6H), 1.57 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 169.3, 169.2, 138.23, 138.19, 135.3, 132.1, 131.3, 124.4, 123.9, 118.4, 52.2, 52.1, 39.7, 29.0, 26.8, 26.6, 25.7, 17.1, 16.2, 16.0, 15.3, 15.2; HRMS (EI) calcd for C<sub>22</sub>H<sub>34</sub>O<sub>4</sub> 362.2457, found  $362.2449 (M)^+$ .

### 4.52. Dimethyl (Z)-2-nerolyl-3-methylbutenedioate (41)

**4.52.1.** Preparation of nerolyl bromide. To a solution of nerol (1.59 mL, 9 mmol) in THF (10 mL) was added dropwise a solution of phosphorous tribromide (0.36 mL, 3.77 mmol) in THF (5 mL) at  $-10^{\circ}$ C. The reaction mixture was stirred for 15 min, and concentrated in vacuo. The residue obtained was dissolved in a hexane-diisopropyl ether/1:1 solution (15 mL), washed with 5% aq NaHCO<sub>3</sub>, H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to give crude nerolyl bromide (1.92 g, 98%) as a pale yellow oil. This product was used without further purification for the preparation of dimethyl (Z)-2-nerolyl-3-methylbutenedioate (41).

4.52.2. Preparation of 41. The reaction of methylmagnesium bromide (1.33 mL of a 3.0 M solution in THF, 4mmol), CuBr·Me<sub>2</sub>S (0.82g, 4mmol) in THF (19mL), freshly distilled DMAD (0.43mL, 3.5mmol) in THF (8mL), a HMPA-THF/1:1 solution (8mL), and freshly prepared nerolyl bromide (1.92g, 8.8mmol) was performed as described for the synthesis of 39. Further purification by flash chromatography (SiO<sub>2</sub>, 4:1/petroleum ether-Et<sub>2</sub>O,  $R_f$  0.23) gave 41 (751 mg, 73%) as a colorless oil: IR (CDCl<sub>3</sub> cast) 2951, 1725, 1644, 1434, 1265 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.10–4.98 (m, 2H), 3.72 and 3.71 (2s, 6H), 3.03 (d, 2H, J = 6.9 Hz), 2.05–2.02 (m, 4H), 1.93 (s, 3H), 1.67, 1.66, and 1.59 (3s, 9H);  ${}^{13}C$  NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$ 169.21, 169.20, 138.2, 138.1, 132.3, 131.9, 124.0, 119.2, 52.2, 52.1, 32.1, 28.7, 26.4, 25.7, 23.3, 17.7, 15.2; HRMS (EI) calcd for  $C_{17}H_{26}O_4$  294.1831, found 294.1823 (M)<sup>+</sup>.

## 4.53. (Z)-2-Geranyl-3-methylbutenedioic acid dilithium salt (42)

The procedure used for the synthesis of **6** was followed. Reaction of 1.75 N LiOH (0.58 mL, 5.3 equiv) with diester **39** (57 mg, 0.19 mmol) in a THF–H<sub>2</sub>O/1:1 solution (2.3 mL) over 2 days gave **42** (48 mg, 90%) as a white solid: IR (CHCl<sub>3</sub> cast) 2920, 1590, 1543, 1435, 1401 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 360 MHz)  $\delta$  5.24–5.21 and 5.10–5.07 (2m), 2.99 (d, 2H, J = 6.6 Hz), 2.10–1.90 (m, 4H), 1.83 (s, 3H), 1.67 (s, 3H), 1.61 (s, 6H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 75 MHz)  $\delta$  180.5, 179.5, 137.5, 135.9, 133.8, 132.3, 125.5, 124.1, 33.1, 30.1, 27.6, 25.9, 23.6, 16.5; MS (FAB Cleland) *m/z* (relative intensity) 279 (MH<sup>+</sup>, 9%).

## 4.54. (Z)-2-Farnesyl-3-methylbutenedioic acid dilithium salt (43)

The procedure used for the synthesis of **6** was followed. Reaction of 1.75 N LiOH (0.46 mL, 5.3 equiv) with diester **40** (55 mg, 0.15 mmol) in a THF–H<sub>2</sub>O/1:1 solution (2.2 mL) over 3 days gave **43** (54 mg, 99%) as a white solid: IR (CHCl<sub>3</sub> cast) 2920, 1590, 1543, 1435, 1401 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 360 MHz)  $\delta$  5.25–5.20 (m, 1H), 5.10–5.06 (m, 2H), 2.99 (d, 2H, J = 6.7 Hz), 2.11–1.93 (m, 8H), 1.83 (s, 3H), 1.66 and 1.65 (2s, 6H), 1.58 (s, 6H); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 75 MHz)  $\delta$  180.5, 179.5, 137.5, 136.2, 135.9, 134.0, 132.4, 125.5, 125.2, 123.1, 40.7, 40.6, 30.1, 27.6, 27.5, 25.9, 17.8, 16.4, 16.1; MS (CI, NH<sub>3</sub>) *m/z* (relative intensity) 364 (MNH<sub>4</sub><sup>+</sup>, 6%).

## 4.55. (Z)-2-Nerolyl-3-methylbutenedioic acid dilithium salt (44)

The procedure used for the synthesis of **6** was followed. Reaction of 1 N LiOH (0.53 mL, 3.5 equiv) with diester **41** (31 mg, 0.11 mmol) in a THF-H<sub>2</sub>O/1:1 solution (2 mL) over 2 days gave **44** (29 mg, 99%) as a white solid: IR (CDCl<sub>3</sub> cast) 2920, 1590, 1543, 1435, 1401 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  5.24–5.20 and 5.17–5.13 (2m, 2H), 2.99 (d, 2H, J = 6.6 Hz), 2.12–2.08 (m, 4H), 1.83 (s, 3H), 1.67 and 1.61 (2s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  180.5, 179.5, 137.5, 135.9, 133.8, 132.3, 125.5, 124.1, 33.1, 30.1, 27.6, 25.9, 23.6, 17.7, 16.5; MS (FAB, Cleland) m/z (relative intensity) 279 (MH<sup>+</sup>, 28%).

### 4.56. PBP1b transglycosylase inhibition assays

Enzymatic assays were done as previously described in Chen et al.<sup>18</sup> The typical reaction assay contained PBP1b (30 nM, pre-incubated with decyl-PEG), [<sup>14</sup>C]GlcNAc-labeled lipid II analog containing a 35 carbon lipid chain (4 $\mu$ M), inhibitors (100 or 200 $\mu$ M as indicated in Table 2) and buffer (50mM HEPES at pH7.5, 10mM CaCl<sub>2</sub>, 1000 units/mL penicillin G, 0.2mM decyl-PEG). After incubation at rt for 15min, reactions were stopped by adding ice-cold 10mM Tris (pH8.0) containing NaCl (150mM) and Triton X-100 (0.2%). Radiolabeled products and starting material were separated from lipid II by paper chromatography (5:3/isobutyric acid–1M NH<sub>4</sub>OH) and quantitated by scintillation counting.

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