UNIVERSITY OF ALBERTA

Design and Syntheses of Inhibitors of Peptidoglycan Polymerization by Transglycosylase

BY

© Lei QIAO

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Design and Syntheses of Inhibitors of Peptidoglycan Polymerization by Transglycosylase submitted by Lei QIAO in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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To my parents and my wife, L

ABSTRACT

Several compounds, (*2R,3'R*)-3-[(3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphinato]-2-(3',7'-dimethyloctyloxy)propanoic acid (**106**), (*R*)-3-{[4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]methylphosphinato}-2-octyloxypropanoic acid (**139**), (2*R*,3'*R*)-3-{[4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]methylphosphinato}-2-(3',7'-dimethyloctyloxy)propanoic acid (**140**), and (2*R*,3'*S*)-3-{[4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]methylphosphinato}-2-(3',7'-dimethyloctyloxy)propanoic acid (**141**), are synthesized as potential antibiotics and inhibitors of transglycosylase, an enzyme responsible for the formation of the polysaccharide backbone of bacterial peptidoglycan. The target skeletons are obtained in a convergent fashion involving a trichloroacetonitrile-mediated condensation of benzyl (*R*)-glycerate-alkyl ethers with corresponding carbohydrate-containing phosphonic acids.

The syntheses of benzyl (*R*)-glycerate-alkyl ethers, benzyl (*R*)-3-hydroxy-2-octyloxypropanoate (**90**), benzyl (2*R*,3'*R*)-3-hydroxy-2-(3',7'-dimethyloctyloxy)-propanoate (**91**), and benzyl (2*R*,3'*S*)-3-hydroxy-2-(3',7'-dimethyloctyloxy)propanoate (**92**), begin with alkylation of 1,3:4,6-di-*O*-benzylidene-D-mannitol (**93**) with corresponding alkyl bromides followed by debenzylidenation to the tetraols, oxidative cleavage, and esterification of the resulting acids to afford **90**, **91**, and **92** (11-52 % overall yield).

To examine the importance of the first sugar unit of moenomycin A, a known transglycosylase inhibitor, with respect to antibiotic activity, target **106** is synthesized (9 steps in 12.6 % overall yield) by attachment of **91** to 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphonic acid (**77**), which is prepared by glycosylation of 3-bromopropanol with triacetyl oxazoline **65**, Arbuzov reaction with

triethyl phosphite, and dealkylation of the resulting phosphonate **84** with bromotrimethylsilane.

Compounds **139**, **140**, and **141**, combining structural features of both the active portion of moenomycin A and the substrate of the transglycosylase, are synthesized (10 steps in 6.9-8.7 % overall yield) from benzyl (*R*)-glycerate-alkyl ethers **90**, **91**, **92**, and 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (**107**). Wittig reaction of **107** with methylenetriphenylphosphorane affords olefin **120**, which undergoes mercury-induced cyclization and iodination to give the α-*C*-glycosyl iodide **108**. Reductive ring opening of the benzylidene ring, Arbuzov reaction, and glycosylation provide diethyl [4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]methylphosphonate (**129**). Hydrazinolysis and acetylation convert **129** to the corresponding *N*-acetyl derivative **130**. Removal of the ethyl groups from the phosphonate, subsequent condensation with **90**, **91** and **92**, and final deprotection produce targets **139**, **140**, and **141**. Studies also demonstrate that the anomeric methylenephosphonate moiety present in diethyl (3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylphosphonate (**54**) decreases the reactivity of the C-2 center dramatically compared to the corresponding C-2 of the *O*-glycoside toward glycosylation and reductive amination.

(*R*)-3-*O*-Phosphoryl-2-*O*-farnesylpropanoic acid, designed as a potential inhibitor of squalene synthetase by mimicking its substrate, farnesyl pyrophosphate, is obtained as its trisodium salt **143** by modification of the synthetic methodology developed for (*R*)-glycerate-alkyl ethers.

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LIST OF ABBREVIATIONS

$[\alpha]$	specific rotation
Ac	acetyl
Ala	alanine
anhyd	anhydrous
APT	attached proton test
Ar	aryl
Bn	benzyl
bp	boiling point
br	broad
i-Bu	isobutyl
n-Bu	butyl
Bz	benzoyl
calcd	calculated
CI	chemical ionization
concd	concentrated
COSY	correlation spectroscopy
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet
m-DAP	*meso*-diaminopimelate
DAST	diethylaminosulfur trifluoride
DEAD	diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide

DMSO	dimethyl sulfoxide
EI	electron impact
Et	ethyl
FAB	fast atom bombardment
FPP	farnesyl pyrophosphate
Glc	glucose
GlcN	glucosamine
GlcNAc	*N*-acetylglucosamine
Glu	glutamic acid
HMQC	inverse 2D ^{13}C-^{1}H heteronuclear multiple quantum coherence
HRMS	high-resolution mass spectrum
IR	infrared
J	coupling constant
m	multiplet
m/z	mass to charge ratio
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
MurNAc	*N*-acetylmuramic acid
NAD	nicotinamide adenine dinucleotide
NADH	reduced NAD
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

Nu	nucleophile
PBP	penicillin binding protein
PGM	peptidoglycan monomer
Ph	phenyl
Phth	phthalimido
P_i	phosphate
ppm	parts per million
pyr	pyridine
q	quartet
rt	room temperature
s	singlet
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane
Tr	triphenylmethyl (trityl)
UDP	uridine diphosphate
UMP	uridine monophosphate
UTP	uridine triphosphate
UV	ultraviolet

INTRODUCTION

Despite the great success of antibiotics over the past four decades, the need for new antibacterial agents remains urgent. Introduction of effective antimicrobial drugs to clinical usage has been followed by the rapid emergence of resistant bacterial strains through chromosomal mutations or the exchange of genetic material.[1] This problem has seriously reduced the therapeutic value of many important antibiotics, and it has also been the major stimulus for the development of newer and more effective antibacterial drugs.

Antibiotics can be classified into five groups according to their mechanism of action (Table 1).[1,2] They may interfere with: the synthesis of the bacterial cell wall; the synthesis of proteins; the metabolism of nucleic acids; the function of bacterial membranes; or the energy metabolism of bacteria. Since the bacterial cell wall is produced by a biosynthetic pathway that is non-existent in mammals, it has been a classical target for development of antibiotics with great selectivity and low toxicity.[3,4]

Table 1 Classification of Antimicrobial Agents by Mechanism of Action

Mechanism of action	Antibiotics
Cell wall disruption	Penicillins, Cephalosporins, Monobactams, Carbapenems, Bacitracin, Vancomycin, Cycloserine, Moenomycin
Protein biosynthesis	Aminoglycosides, Clindamycin, Mupirocin, Tetracyclines, Chloramphenicol, Spectinomycin, Erythromycin,
Nucleic acids	Quinolones, Rifampin, Nitrofurantoins, Nitroimidazoles
Cytoplasmic membrane	Polymyxins, Polyene
Energy metabolism	Sulfonamides, Trimethoprim, Dapsone, Isoniazid

The bacterial cell wall is a complex structure composed of various macromolecules which function as an envelope to protect the delicate inner structures of the bacterial cell.[5] Among these macromolecules, peptidoglycan, the major component of the bacterial cell wall, plays a central and dominant role. It provides much of the strength and rigidity necessary to maintain the structural integrity of the wall and shape of the cell; defects or disruption of the peptidoglycan layer leads to cell lysis and death of the bacteria.[2]

Peptidoglycan consists of a framework of polysaccharide backbone chains cross-linked by short peptide chains through peptide bonds (Figure 1). The polysaccharide chains consist of two alternating amino sugars, *N*-acetylglucosamine

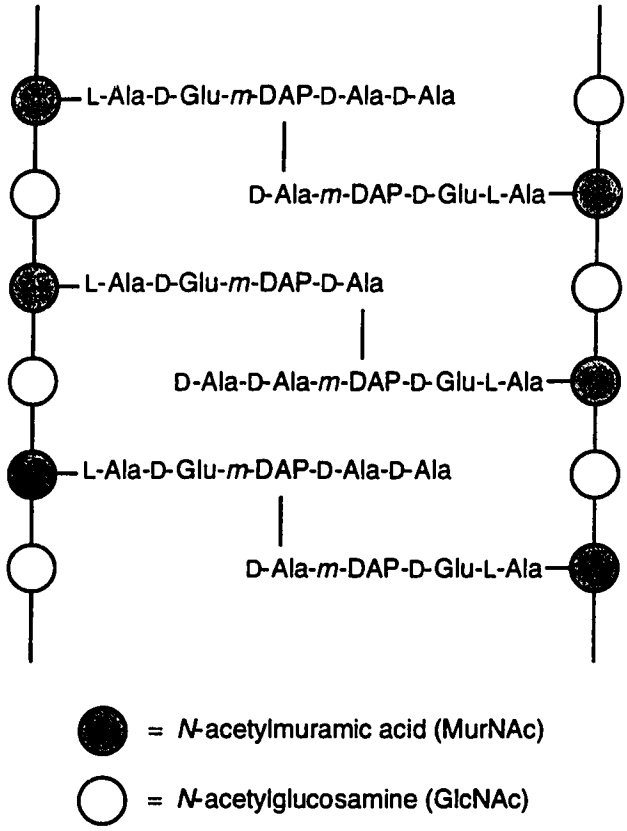


Figure 1 Representation of cross-linked peptidoglycan layer in *E. coli*

(GlcNAc) and *N*-acetylmuramic acid (MurNAc), the latter being attached to a pentapeptide side chain. The sequence of the pentapeptide varies slightly with bacterial species but is generally L-Ala-D-Glu-X-D-Ala-D-Ala, where X is usually *meso*-diaminopimelate (*m*-DAP) for Gram-negative bacteria, and L-Lys for Gram-positive bacteria. Cross-linking of peptidoglycan chains occurs between the terminal amino group in residue X and the D-Ala residue of an adjacent peptide. The presence of D-amino acids also contributes to the stability of the peptidoglycan by providing resistance to external degradative enzymes.[4]

Peptidoglycan is present in all groups of bacteria except the *Halobacterium* and *Mycoplasmas*, which grow in environments that provide osmotic support. In Gram-negative bacteria, there is a thin peptidoglycan sacculus in the inner layer of the cell envelope, while Gram-positive bacteria contain peptidoglycan across the whole width of the wall.[2]

Muramyl peptides are peptidoglycan fragments and many of them can be detected in mammalian organisms. They are believed to originate from the digestion of bacteria by macrophages[6] and bacterial enzymatic degradation of peptidoglycan.[7] These muramyl peptides display a variety of biological effects in mammals and are believed to be responsible for many of the host responses during bacterial infections; e.g., excess slow-wave sleep (SWS) and fever.[6,8,9] The most active compound that has been isolated is the disaccharide tetrapeptide GlcNAc-1,6-anhydro-MurNAc-L-Ala-D-Glu-*m*-DAP-D-Ala.[10,11] The biological properties and structure-activity relationships of muramyl peptides have been reviewed recently.[7,12,13]

The biosynthesis of peptidoglycan may be conveniently divided into three stages: the synthesis of precursors; the assembly of peptidoglycan monomer (PGM) units; and polymerization of PGM.[2,4,5,14]

1. Synthesis of precursors.

The low molecular weight precursors: UDP-*N*-acetylglucosamine (UDPGlcNAc) and UDPMurNAc-L-Ala-D-Glu-*m*-DAP-D-Ala-D-Ala (UDPMurNAc-pentapeptide), are synthesized in the cytoplasm (Figure 2). UDP-*N*-acetylglucosamine is formed from *N*-acetylglucosamine-1-phosphate (GlcNAc-1-P) and UTP, both products of the normal metabolic pool, *via* a reaction involving elimination of pyrophosphate (PP_i) catalyzed by a transferase. The nucleotide then reacts with phosphoenolpyruvate in a reaction catalyzed by UDPGlcNAc enoylpyruvyl transferase to give the corresponding 3-enoylpyruvyl ether. Reduction by a NADPH-dependent reductase produces UDP-*N*-acetylmuramic acid (UDPMurNAc), a unique amino sugar found exclusively in the bacterial cell wall.

Subsequently, five amino acid residues are coupled to the carboxyl group of the muramic acid nucleotide by a series of ATP-dependent amino acid ligases. The final two amino acids are added as a D-Ala-D-Ala dipeptide to give the UDPMurNAc-pentapeptide.

2. Assembly of peptidoglycan monomer units.

Formation of the peptidoglycan monomer occurs on the cytoplasmic membrane (Figure 3). UDPMurNAc-pentapeptide becomes attached to an undecaprenyl lipid carrier by coupling with undecaprenylphosphate (Undecaprenyl-P) catalyzed by UDPMurNAc-pentapeptide phosphotransferase to form undecaprenyl diphospho-MurNAc-pentapeptide. A further *N*-acetylglucosamine residue is then appended through a glycosidation reaction, catalyzed by undecaprenyl-PP-MurNAc-pentapeptide GlcNAc transferase, to form the peptidoglycan monomer (PGM), a complete repeating unit of peptidoglycan attached to the lipid carrier.

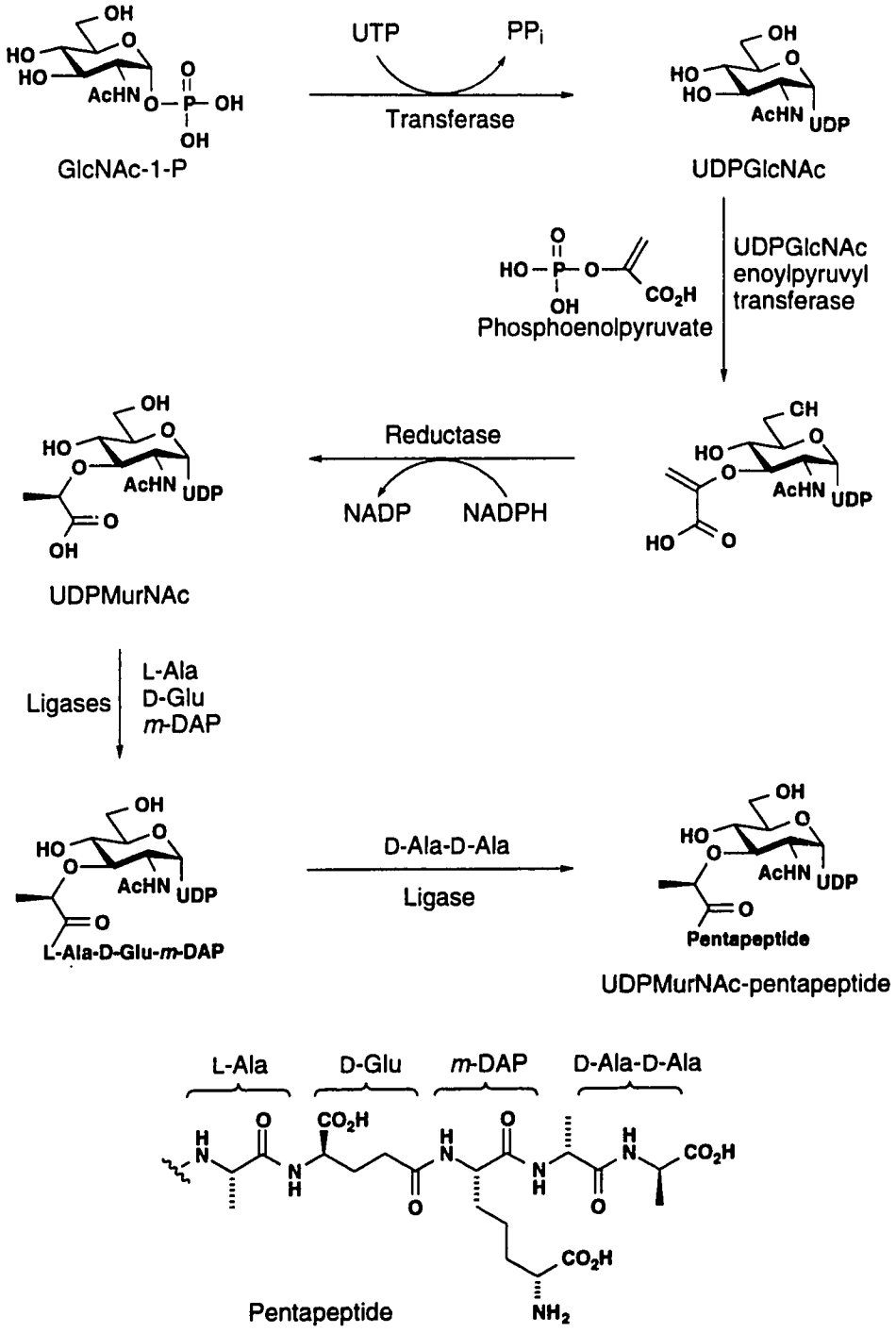


Figure 2 The synthesis of peptidoglycan precusors

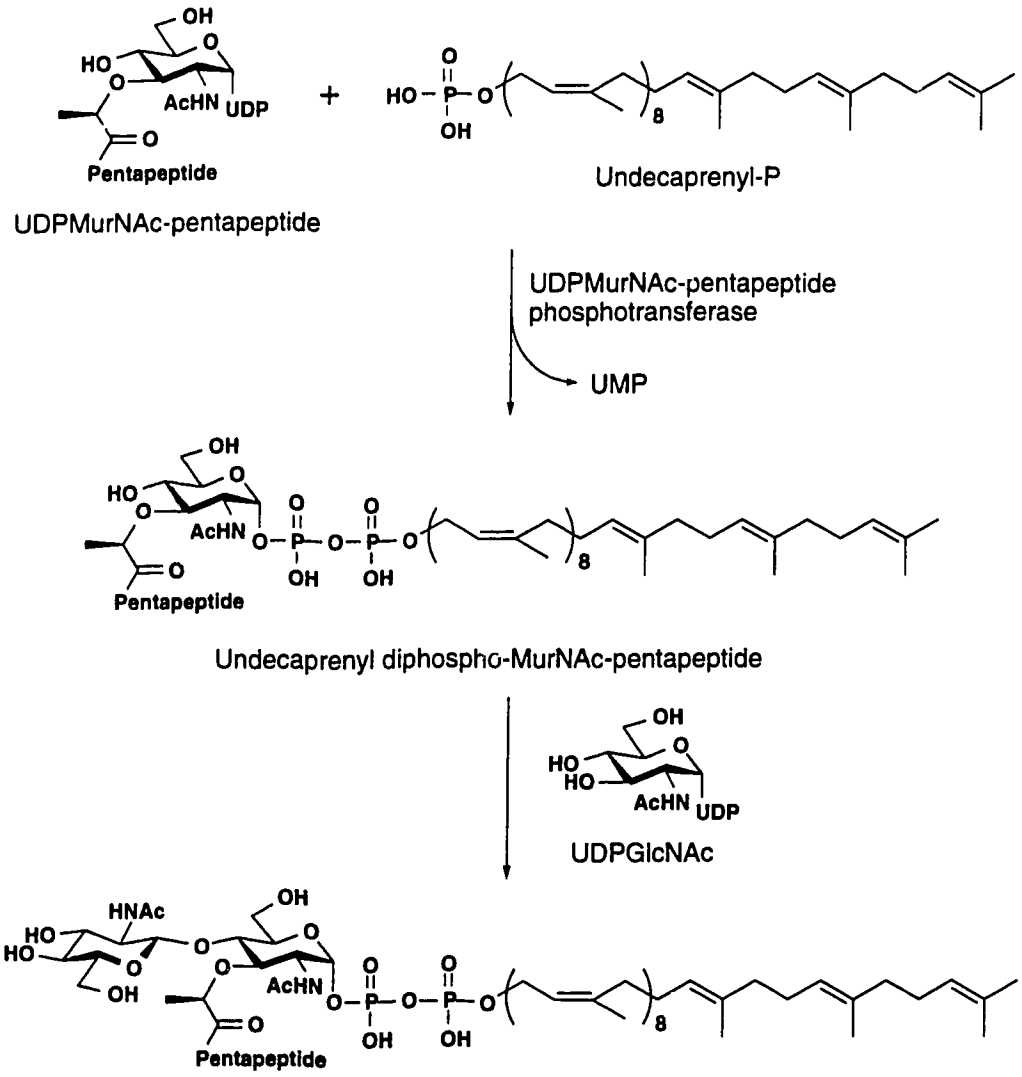


Figure 3 The assembly of peptidoglycan monomer unit

3. Polymerization

The third stage begins with transfer of the peptidoglycan monomer across the cytoplasmic membrane. Two successive reactions, transglycosylation and transpeptidation, then lead to the formation of the peptidoglycan framework. The

transglycosylation process involves the formation of a β-1,4 glycoside linkage between an *N*-acetylmuramic acid residue of the peptidoglycan monomer and the terminal *N*-acetylglucosamine residue of the growing polysaccharide chain (Figure 4). Thus the

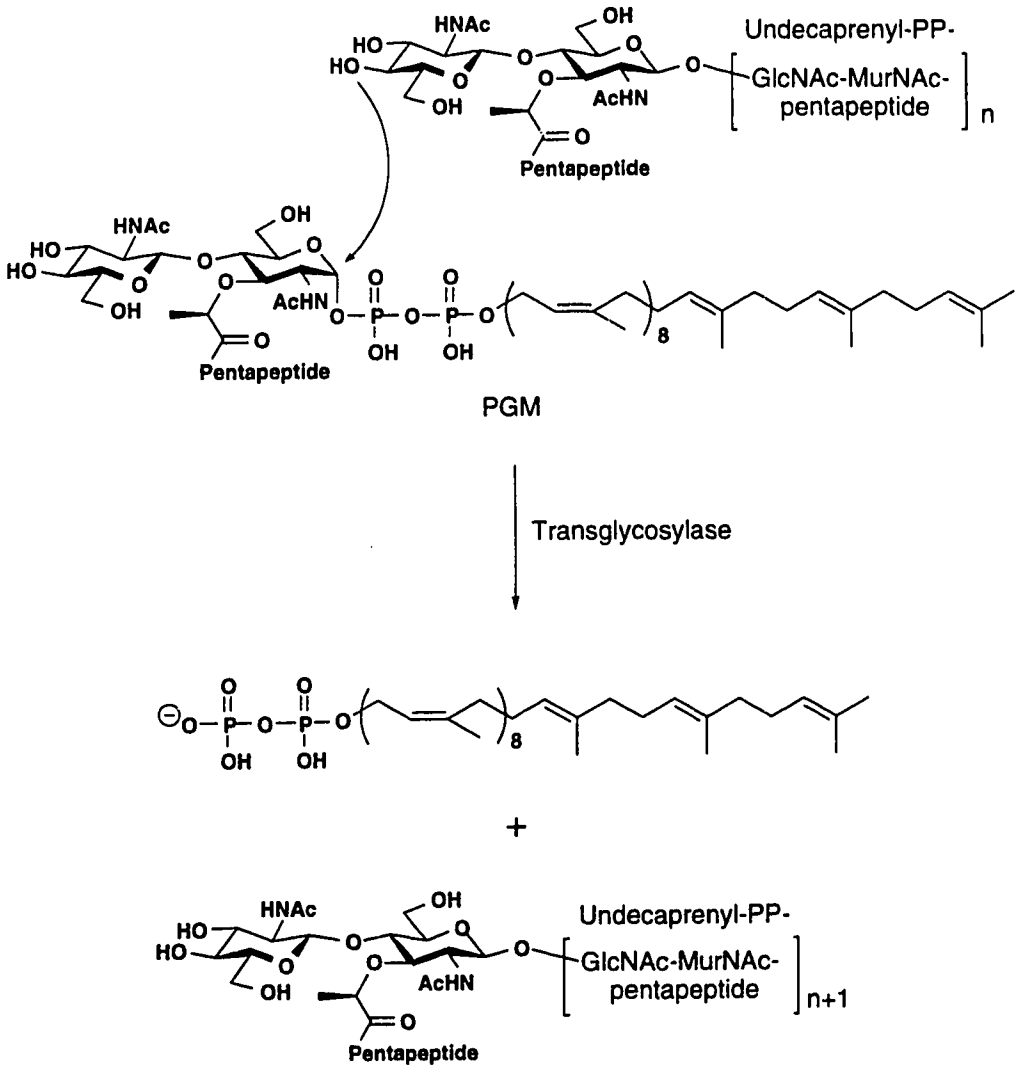


Figure 4 Transglycosylation reaction

growth of the peptidoglycan chains occurs by successive addition of disaccharide units. The membrane lipid carrier is released as undecaprenyl pyrophosphate and is then

reconverted by a specific pyrophosphatase to the corresponding phosphate ready for another cycle of intramembrane reactions (Figure 5).

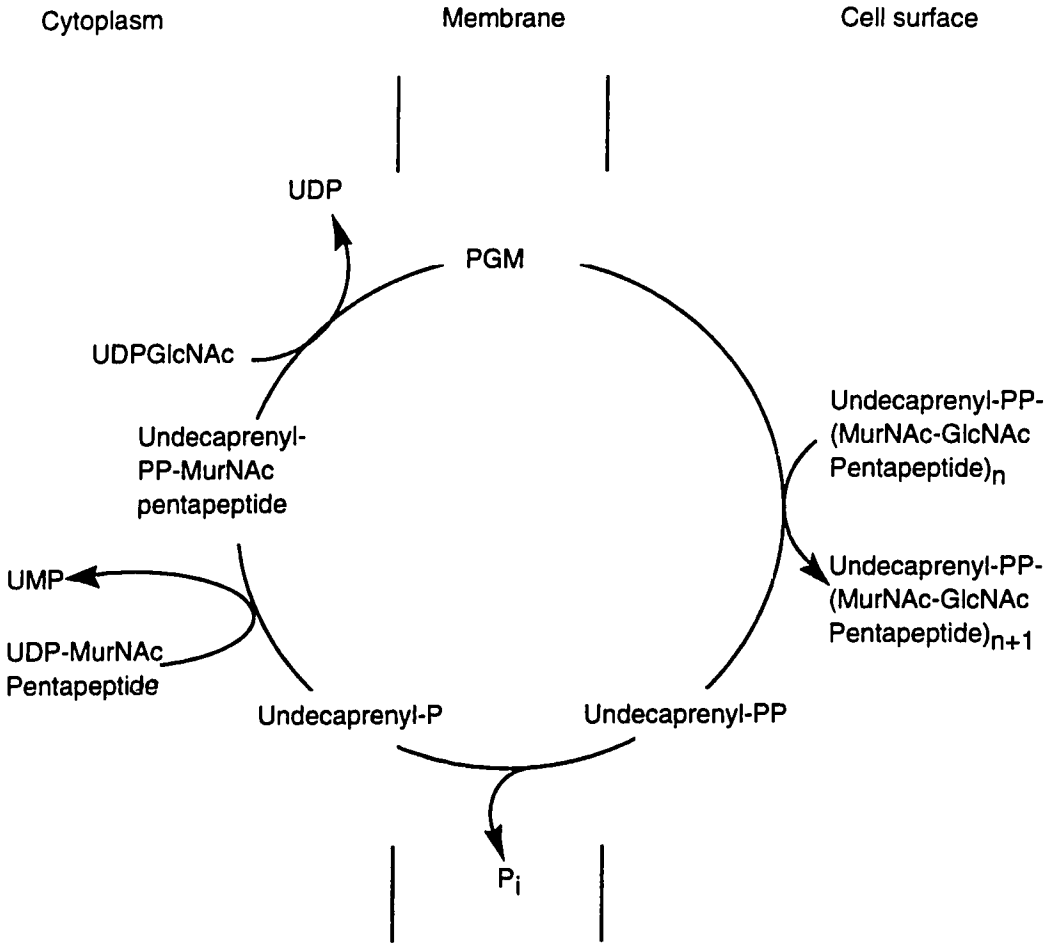


Figure 5 The intramembrane undecaprenylphosphate cycle

In the transpeptidation reaction, the linear peptidoglycan chains are cross-linked through the pentapeptide units (Figure 6). This involves attack of the ε-amino group of the *m*-DAP or L-Lys residue at the penultimate D-Ala of another chain, resulting in the loss of the terminal D-Ala and peptide bond formation.

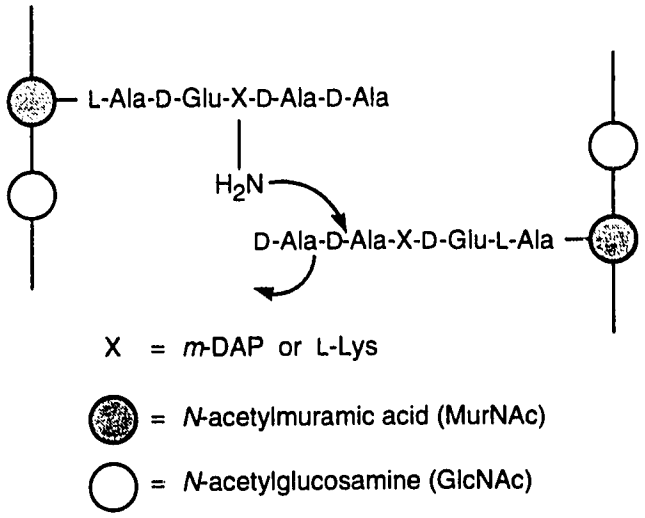


Figure 6 Representation of transpeptidation step

A battery of enzymes, known as penicillin binding proteins (PBPs), is involved in transglycosylation and transpeptidation.[5,15] Interestingly, PBP 1a and 1b in *E. coli* have been identified as bifunctional enzymes that catalyze both transglycosylation and transpeptidation reactions.[16-19] The transglycosylation activity of the enzymes can be uncoupled from the transpeptidation activity by the addition of penicillin, the best known inhibitor of the transpeptidation step. Purified PBP 1b catalyzes the *in vitro* formation of cross-linked peptidoglycan from peptidoglycan monomer or analogues with shorter peptide chains, since it has been found that *in vivo* the *E. coli* peptidoglycan biosynthesis system can accept modifications in the peptide moiety.[19,20]

A large number of naturally occurring antibiotics are known to function by inhibition of various stages of peptidoglycan biosynthesis (Table 2).[4] Many of these, such as β-lactams and glycopeptides, are widely used in clinical situations. However, only one class of antibiotics, the phosphoglycolipids,[21] is believed to have a mechanism based on the selective inhibition of the transglycosylation step. Phosphoglycolipid

Table 2 Peptidoglycan Biosynthesis as a Target for Antibiotics

Target	Antibiotics
Cell wall alanine racemase	Ala-P, D-cycloserine
D-Ala-D-Ala ligase	D-cycloserine
GlcNAc enolpyruvyl transferase	Phosphonomycin
Translocation across membrane	Bacitracin, tunicamycin
Transpeptidation of peptidoglycan	β-Lactams
Binding of peptidyl-D-Ala-D-Ala	Vancomycin
Transglycosylation	Phosphoglycolipids,

antibiotics include moenomycin (Flavomycin®), prasinomycin, diumycins (marcarbomycins), quebemecin, ensachomycin, prenomycin, teichomycin, and pholipomycin which are produced by various species of *Streptomyces* and are usually obtained as mixtures of very similar compounds.[21] They are highly active against Gram-positive bacteria; however, higher concentrations are required for the observation of activity against Gram-negative bacteria. Owing to their specific mode of action, they are non-toxic to mammals (LD_{50} >2000 mg/kg). They are practically not absorbed from the intestine, and presently have only been used as feed additives in animal nutrition.

Structurally, phosphoglycolipid antibiotics are rather complex, consisting of an oligosaccharide part, phosphoglyceric acid, a C_{25}-lipid alcohol, moenocinol, and frequently a UV chromophore (257-258 nm). They are characterized by a relatively high molecular weight ranging from 1600 to 2100 and the possession of one phosphorus atom per molecule. Even with sophisticated instrumentation, the structure elucidation of these compounds is not simple; none of the phosphoglycolipid antibiotics have been obtained in crystalline form, thus making X-ray analysis impossible. ^1H NMR spectroscopy is

usually of little value, since in most instances very broad peaks are observed, probably due to the formation of high molecular weight aggregates in aqueous solution.[21] Only the structures of moenomycin A and a few related compounds seem to have been firmly established by extensive degradation and spectroscopic studies.[22-26]

Moenomycin A (Figure 7), first reported in 1965,[27] has been extensively used as a animal growth promoter under the trade name of Flavomycin.® Studies have demonstrated that moenomycin A inhibits the formation of the linear peptidoglycan chain from peptidoglycan monomer by interfering with the transglycosylation step. Moreover, it has been established that moenomycin A inhibits the polymerization of peptidoglycan monomer by selective inhibition of PBP 1b.[28,29] With both the cell free system and the purified PBP 1b enzyme, moenomycin A has an inhibitory effect at concentrations between 10^{-8} and 10^{-7} M.[30]

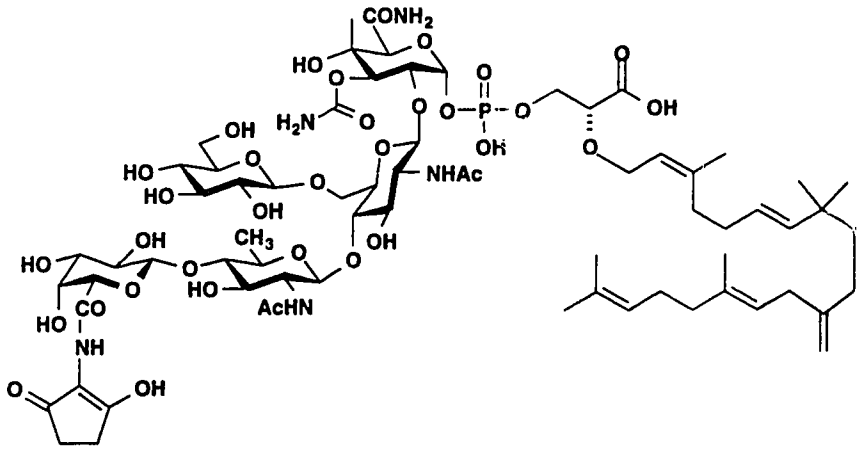


Figure 7 Moenomycin A

Systematic degradations have shown that only a portion of the moenomycin A structure is essential for antibiotic activity. The substructure containing the central disaccharide, the phosphoglyceric acid section, and the lipid tail (which can be saturated), retains the full antibiotic activity (Figure 8) of the parent compound.[22,23]

Comparison of the structure of this active portion with that of the transglycosylase substrate, the peptidoglycan monomer, indicates that the antibiotic activity of moenomycin A results from the structural analogy between these two compounds.[22,28]

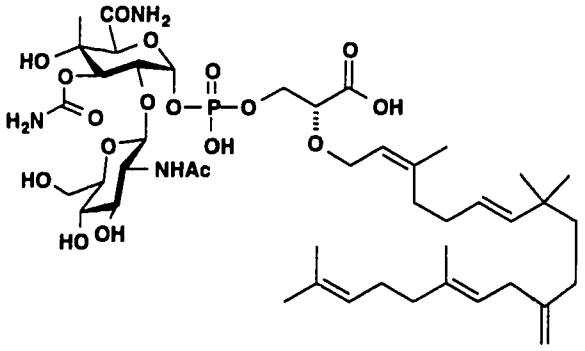
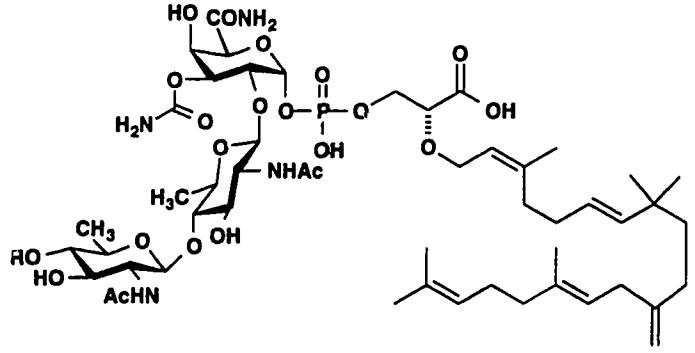
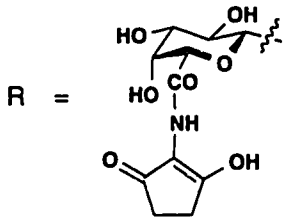


Figure 8 Moenomycin A active portion

Very recently, the antibiotic moenomycin C_1 was reported, which has a D-galacto configuration sugar attached to the phosphate (Figure 9). In this series, the



Moenomycin C_1 Moenomycin C_1 active portion



R = R = H

Figure 9 Moenomycin C_1 and the active portion

trisaccharide degradation product was demonstrated to be the minimum structure required for the full antibiotic activity.[26]

The degradation studies suggest that other small, synthetically accessible molecules could be inhibitors of transglycosylase. Since 1987, several analogues of the active portions of moenomycins A and C_1 have appeared in the literature. Welzel and coworkers reported the synthesis of two disaccharide analogues of the moenomycin C_1 active portion (Figure 10),[31,32] and in 1990, Hecker *et al.* reported the synthesis of

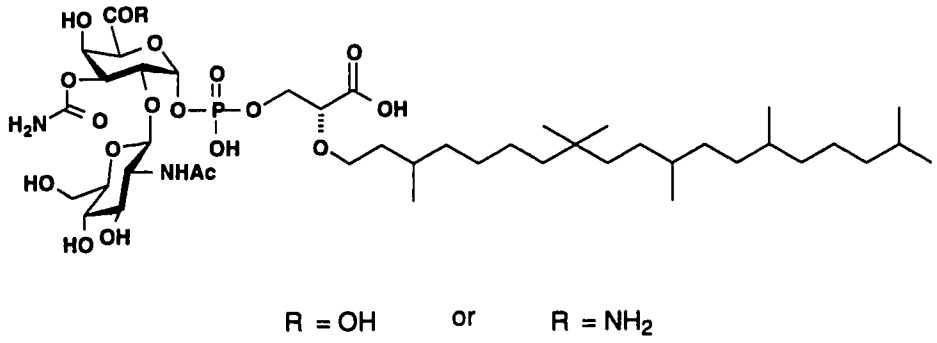


Figure 10 Disaccharide analogues of moenomycin C_1

two monosaccharide analogues designed to inhibit the transglycosylation step (Figure 11).[33] Unfortunately, these synthetic analogues display no antibacterial activity. However, recently Welzel and coworkers synthesized a trisaccharide analogue of

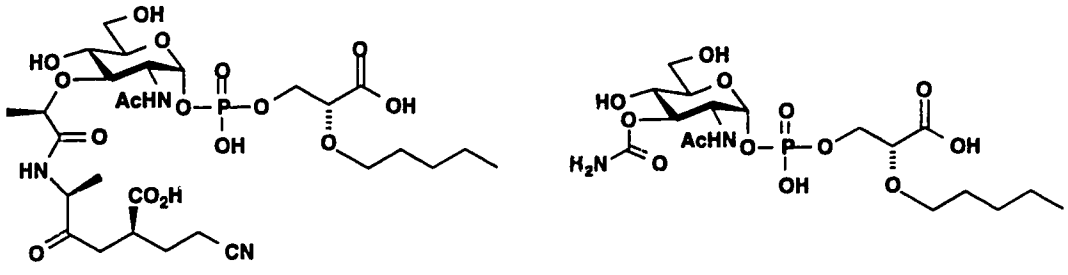


Figure 11 Monosaccharide analogues

moenomycin C_1 which has been shown to be as active as moenomycin A toward PBP 1b (Figure 12).[34]

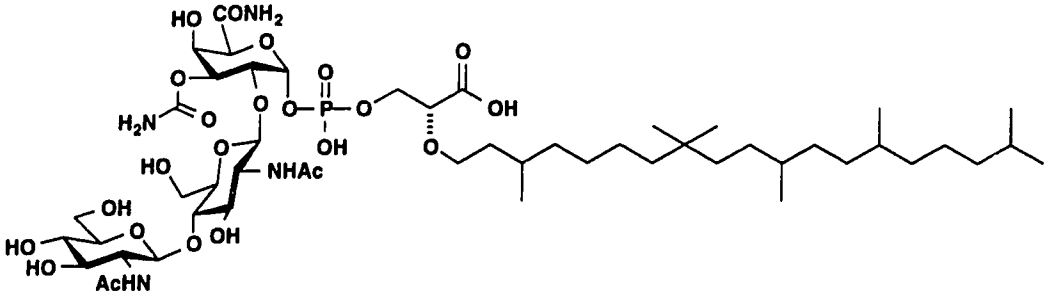
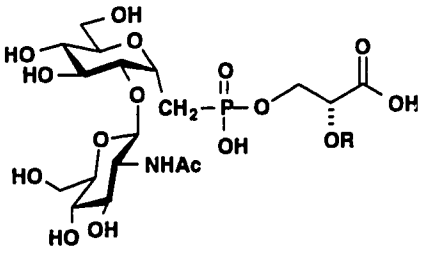


Figure 12 Trisaccharide analogue of moenomycin C_1

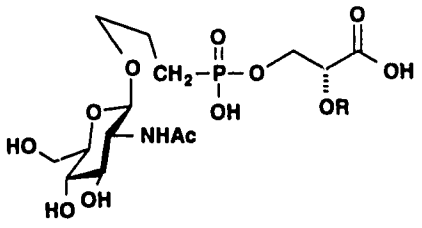
Since transglycosylase inhibitors with better physical properties (e.g. improved absorption from the intestine) may be effective against organisms resistant to current therapy, we embarked on the synthesis of a series of such potential inhibitors.

Three types of targets were designed as exemplified in Figure 13. Type **A** closely resembles the naturally occurring inhibitor, moenomycin A, having the *N*-acetylglucosamine residue attached at the 2-position of the first sugar unit. In type **B** compounds, the distance between the *N*-glucosamine unit and the phosphorus atom is similar to that in moenomycin A, and this type of molecule was targeted to examine the importance of the first sugar unit with respect to antibiotic activity. Type **C** targets were designed by combining features of both the active portion of moenomycin A and the structure of peptidoglycan monomer, the natural inhibitor and natural substrate of the transglycosylase, respectively. All three targets lack the physiologically active peptide chain which contributes to multiple biological effects (e.g. somnogenic and pyrogenic effects) in mammals. However they do contain many of the characteristics expected for recognition by transglycosylase, namely, a terminal *N*-acetylglucosamine unit, a lipid tail, and a phosphoglycerate anionic group. Moreover, in these molecules, the non-

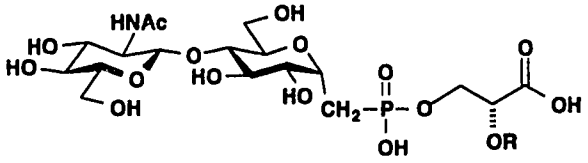
cleavable *C*-glycoside and phosphonate moieties were chosen to serve as the stable surrogates of *O*-glycosides and phosphate esters respectively. In addition to potentially inhibiting transglycosylase, they could also "end-cap" the growing polysaccharide chain if they are incorporated into peptidoglycan.



Type **A**



Type **B**

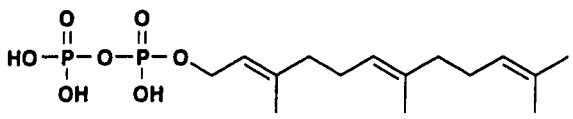


R = Lipid alkyl group

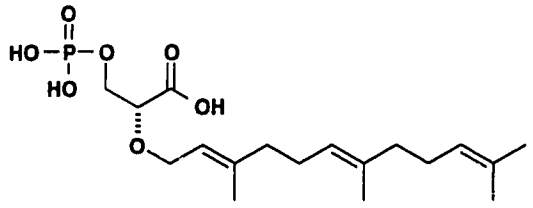
Type **C**

Figure 13 Synthetic Target Molecules

In addition to the above targets, pyrophosphate mimics were also of interest. The mode of action of moenomycin A and related antibiotics suggests that the phosphoglycerate anionic group may mimic the pyrophosphate moiety present in the peptidoglycan monomer. In order to observe the function of this moiety in other systems, we designed target **D** which could serve as an inhibitor of squalene synthetase[35] by mimicking its substrate, farnesyl pyrophosphate (FPP) (Figure 14).



FPP



target **D**

Figure 14 FPP and target **D**

Successful analogues would be useful tools to study the structure requirements for substrate recognition by transglycosylase. The information obtained could also facilitate rational inhibitor design. In the following sections, the results of synthetic studies toward these targets are described.

RESULTS AND DISCUSSION

Part 1: Synthetic Studies toward Methylenephosphonate α-*C*-Glycosides

In recent years, carbon-linked glycosyl compounds (*C*-glycosides), resulting from the replacement of the anomeric oxygen of a glycoside by a carbon atom, have been the object of significant efforts in carbohydrate chemistry and biological chemistry. They serve as stable isosteric analogues of the naturally occurring glycosides due to their geometrical similarity and the stability of the *C*-glycosidic bond. Functionally substituted *C*-glycosides also occur as sub-units of a variety of natural products having significant biological activities; thus, a wide range of synthetic methods involving carbanionic, carbocationic and free radical intermediates has been successfully developed.[36-43]

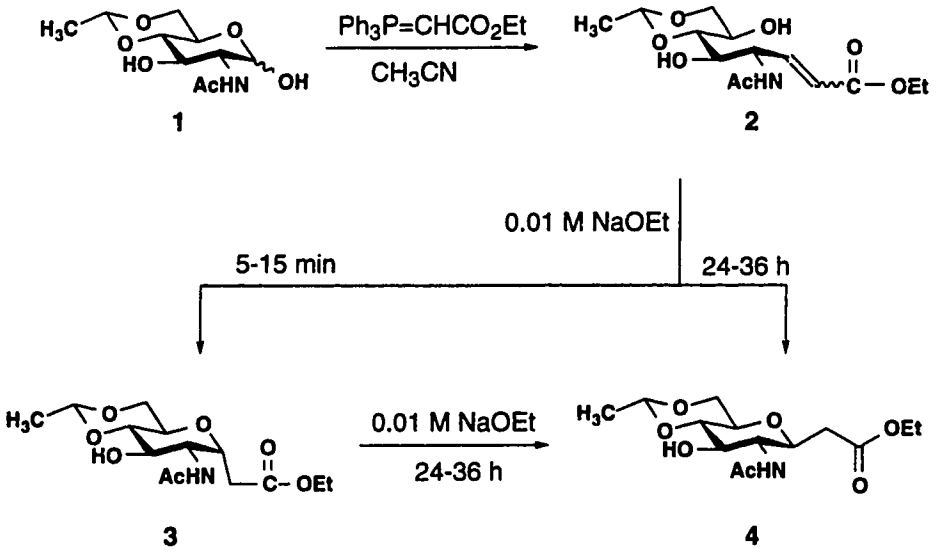
Our approach towards the targets of type **A** and type **C** began with attempts to prepare methylenephosphonate *C*-glycosides with the α-configuration. Although many methods are available for *C*-glycoside syntheses, the placement of a methylenephosphonate moiety onto the anomeric center is a much more difficult problem. A literature survey revealed very few precedents, though promising methods included a Wittig olefination-Michael cyclization route[44,45] and a multistep synthesis involving a mercury-assisted cyclization, halodemercuration and subsequent Arbuzov reaction.[46,47]

1.1 The Wittig Olefination-Michael Cyclization Route

The Wittig olefination has found significant utility in *C*-glycoside synthesis.[48-55] Reducing sugars which exist predominantly as cyclic hemiacetals participate well in

Wittig reactions. With stabilized ylides, the reactions initially produce open chain α,β-unsaturated olefins, which may be isolated under carefully controlled conditions. However, since these conjugated olefins may be subject to Michael addition on exposure to bases, including excess ylide, they often proceed directly to the *C*-furanoside or *C*-pyranoside. This constitutes the "Wittig-Michael" route for the synthesis of *C*-glycosides.

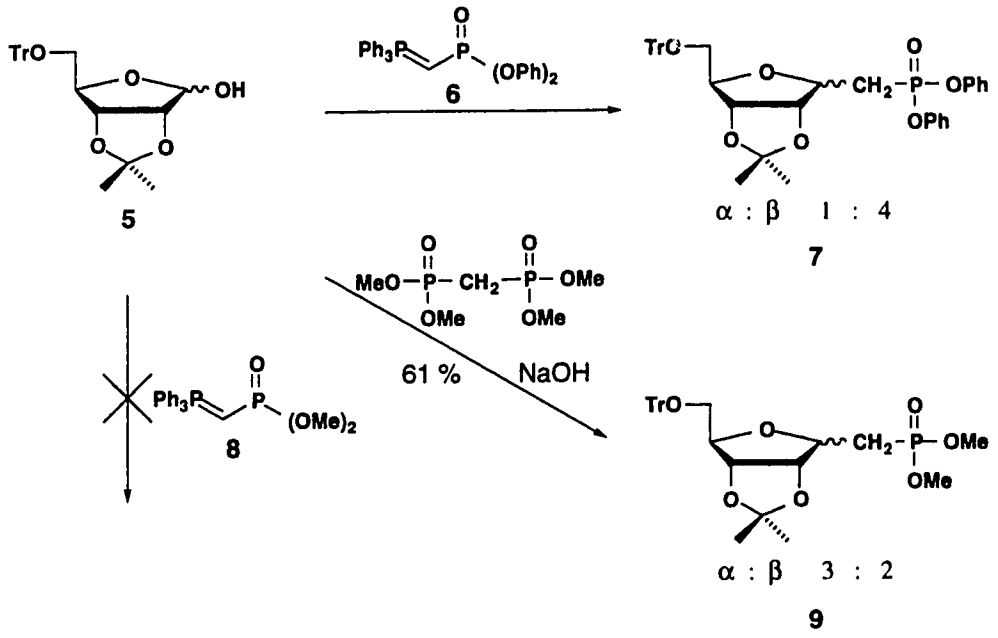
The following example reported by Giannis and Sandhoff illustrates this process (Scheme 1).[53] Reaction of 2-acetylamido-2-deoxy-4,6-ethylidene-D-glucopyranose (**1**) with the α-carbonyl-stabilized ylide, $Ph_3P{=}CHCO_2Et$, yields the (*E*)- and (*Z*)-isomers of the α,β-unsaturated ester **2**. Upon treatment with a catalytic amount of sodium ethoxide, these esters undergo intramolecular Michael addition to yield the α- and β-*C*-glycosides **3** and **4**. The α-*C*-glycoside **3** is formed under kinetic control, but can be converted exclusively into the thermodynamically more stable β-isomer **4** upon treatment with base for a longer period of time. The mechanism for the epimerization most likely involves base catalyzed ring opening to **2** followed by Michael addition as before.



1 2 3 4

Scheme 1

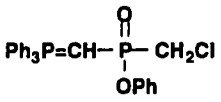
Unlike the α-carbonyl stabilized ylides, the corresponding α-phosphoryl stabilized ylides have demonstrated only limited success in *C*-glycoside synthesis. McClard reported the reaction of 5-trityl-2,3-di-*O*-isopropylidene-D-ribose (**5**) with the α-phosphoryl stabilized ylide **6** to give the methylenephosphonate *C*-glycoside **7** as a mixture of α- and β-isomers in a 1 : 4 ratio, respectively (Scheme 2).[44] In a similar study conducted by Meyer *et al.*, the reaction of the ylide **8** with the same sugar fails to give the desired phosphonate. However, condensation of the Wadsworth-Emmons reagent $CH_2[P(O)(OCH_3)_2]_2$ with sugar **5** produces a 3 : 2 mixture of α and β-*C*-glycosides **9**.[45] In neither case was the observation of the α, β–unsaturated phosphonate intermediate reported.



Scheme 2

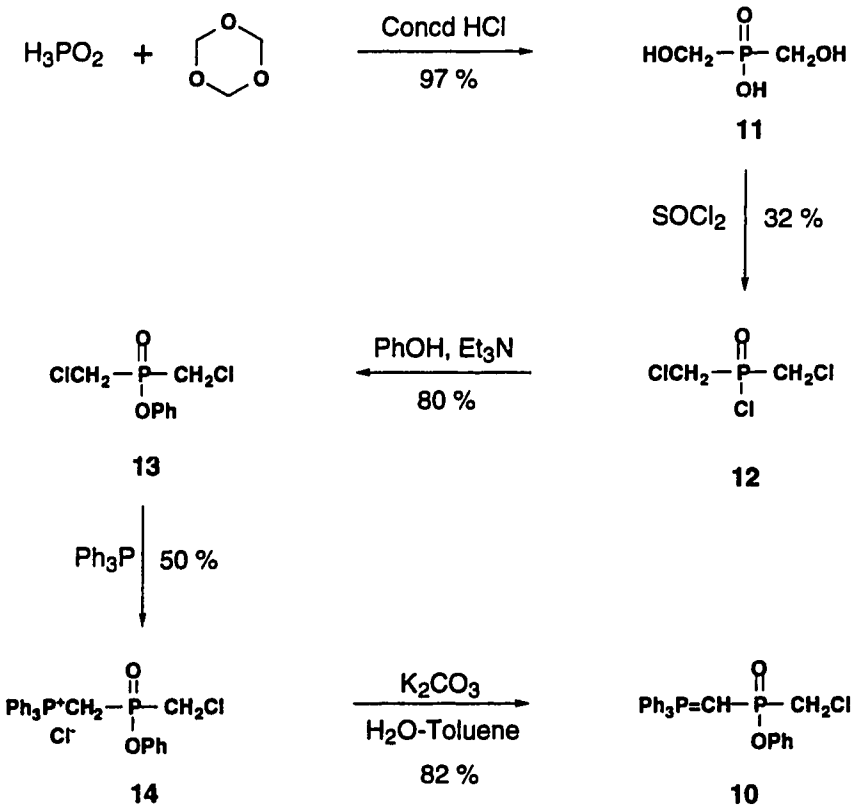
In the hope of obtaining either the α,β-unsaturated phosphonate intermediates or the methylenephosphonate *C*-glycosides directly, we applied this methodology to the six-membered pyranose substrates.

The α-phosphoryl stabilized ylide **10** which was used by Rosenthal and coworkers in the synthesis of a phosphonate-phosphinate analogue of a lipid-linked nucleotide[56,57]



10

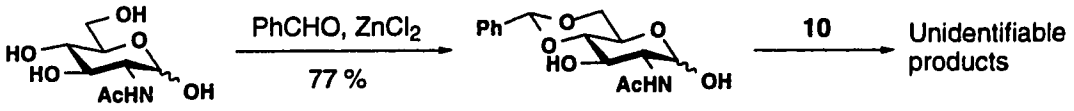
was chosen. The chloromethyl functionality can subsequently participate in an Arbuzov reaction[58,59] for the introduction of a further phosphorus atom. Ylide **10** is available by following the literature procedure (Scheme 3). Reaction of hypophosphorous acid (50 % aqueous solution) and paraformaldehyde in the presence of concentrated hydrochloric



Scheme 3

acid provides bis(hydroxymethyl)phosphinic acid (**11**). Treatment of acid **11** with thionyl chloride generates bis(chloromethyl)phosphinic chloride (**12**).[60] Subsequent esterification of **12** with phenol affords phenyl bis(chloromethyl)phosphinate (**13**),[61] which reacts with triphenylphosphine in refluxing toluene to precipitate the pure monophosphonium chloride **14**. Treatment of **14** with potassium carbonate in toluene-H_2O generates the ylide **10** as a solid.[56] Compound **10** undergoes hydrolysis of the phenyl ester on prolonged exposure to aqueous conditions. Fortunately the final reaction occurs rapidly, and the ylide **10** can be efficiently extracted into the co-solvent toluene.

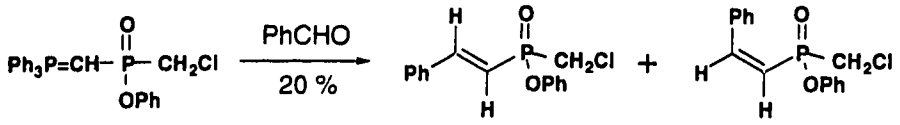
Benzylidenation of commercially available *N*-acetyl-D-glucosamine by reaction with benzaldehyde and freshly fused zinc chloride provides 4,6-di-*O*-benzylidene glucosamine **15** (Scheme 4).[62] Treatment of **15** with ylide **10** following the literature precedent[56,57] fails to give the desired products. Various conditions with different solvents and at different temperatures all prove fruitless; in some cases, the reaction produces phenol as a by-product, which may originate from the decomposition of the ylide.



15

Scheme 4

As a model reaction to test the feasibility of this process, a refluxing solution of ylide **10** and benzaldehyde in benzene affords the α, β-unsaturated phosphinates as a mixture of (*E*)- and (*Z*)-isomers, **16a** and **16b**, respectively, in 20 % yield after 48 hours (Scheme 5). This yield is comparable to the 32 % reported by Vargas and Rosenthal for a similar reaction on a more reactive substrate, *p*-nitrobenzaldehyde.[56]

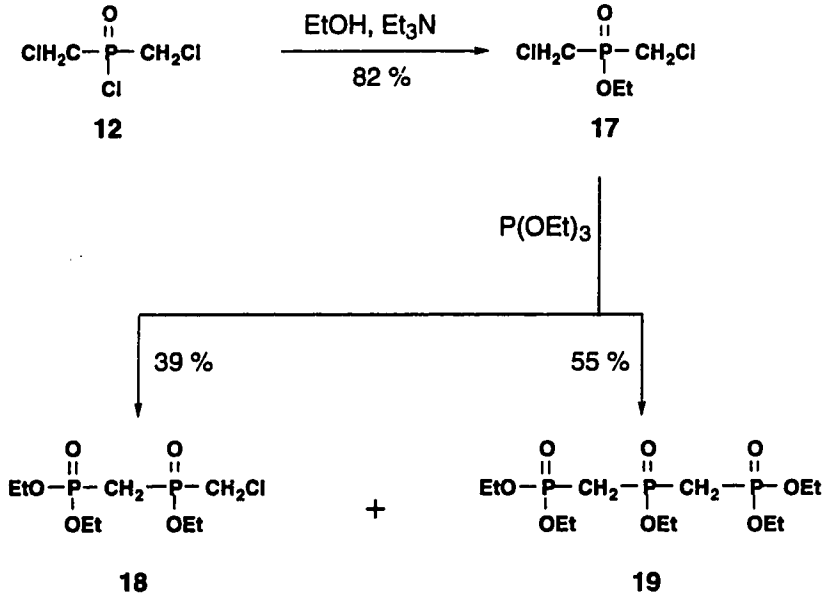


10 **16a** **16b**

Scheme 5

Based on the above observations, it appears that the low reactivity of ylide **10** with sugar **15** could be responsible for the failure of these reactions. The cleavage of the phenyl ester of the phosphinate under the reaction conditions could also play a role. To solve these problems, the more reactive Wadsworth-Emmons reagents and an acyclic *aldehydo* sugar were employed.

The Wadsworth-Emmons reaction[63] broadens the general utility of the Wittig olefination by enhancing the reactivity of unreactive phosphoranes. The requisite reagents **18** and **19** are readily accessible from chloride **12** by literature procedure (Scheme 6).[61] Treatment of chloride **12** with absolute ethanol and triethylamine affords

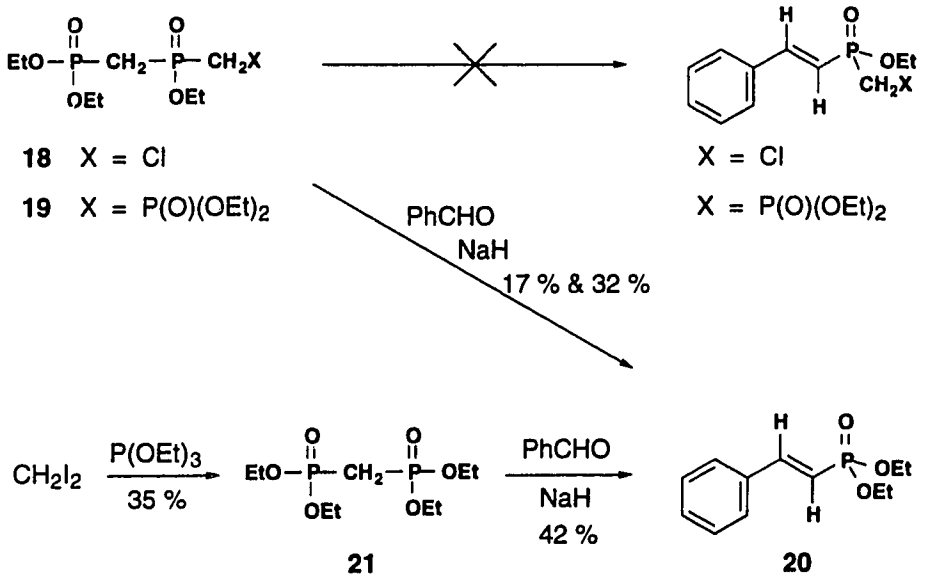


12 **17** **18** **19**

Scheme 6

the more stable ethyl ester **17**. An Arbuzov reaction with triethyl phosphite then generates Wadsworth-Emmons reagents **18** and **19**.

Model reactions of **18** and **19** with benzaldehyde,[64] surprisingly, give the same product, the α,β-unsaturated phosphonate **20** (Scheme 7). An authentic sample of **20** prepared by the reaction of benzaldehyde with tetraethyl methylenediphosphonate (**21**)[65] displays identical spectroscopic properties.



Scheme 7

It is not immediately obvious why the C-P bond of a phosphinate is cleaved (Route A) in preference to a C-P bond of a phosphonate (Route B) (Figure 15). It may be that the electron-withdrawing effect of the CH_2Cl group attached to the phosphinate makes it more prone to nucleophilic attack by the negatively charged oxygen. A similar argument may explain the behavior of the intermediate derived from **19**. Since the reactions of the three Wadsworth-Emmons reagents **18**, **19** and **21** give the same product, in the following studies **21** was used because of its ready availability.

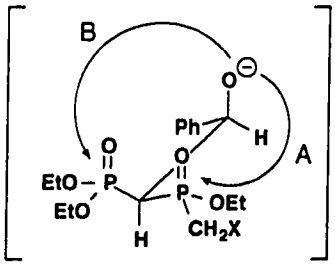
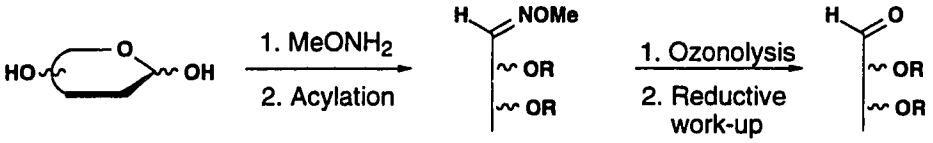


Figure 15

To enable the carbohydrate to participate more readily in the Wittig reaction, a completely protected acyclic *aldehydo* sugar is desired. This would potentially also allow the isolation of the α,β-unsaturated phosphonate intermediates. Thus, the Wittig olefination-intramolecular Michael addition could be conducted in a stepwise fashion in order to obtain the kinetically favored α-*C*-glycoside selectively.

Recently, Weitz and Bednarski reported a method for the synthesis of an acyclic sugar aldehyde based on the ozonolysis of *O*-methyloxime-protected aldoses (Scheme 8).[66] Reducing sugars were treated with methoxyamine hydrochloride and then acylated *in situ.* The resulting protected methyloximes were ozonized to generate the

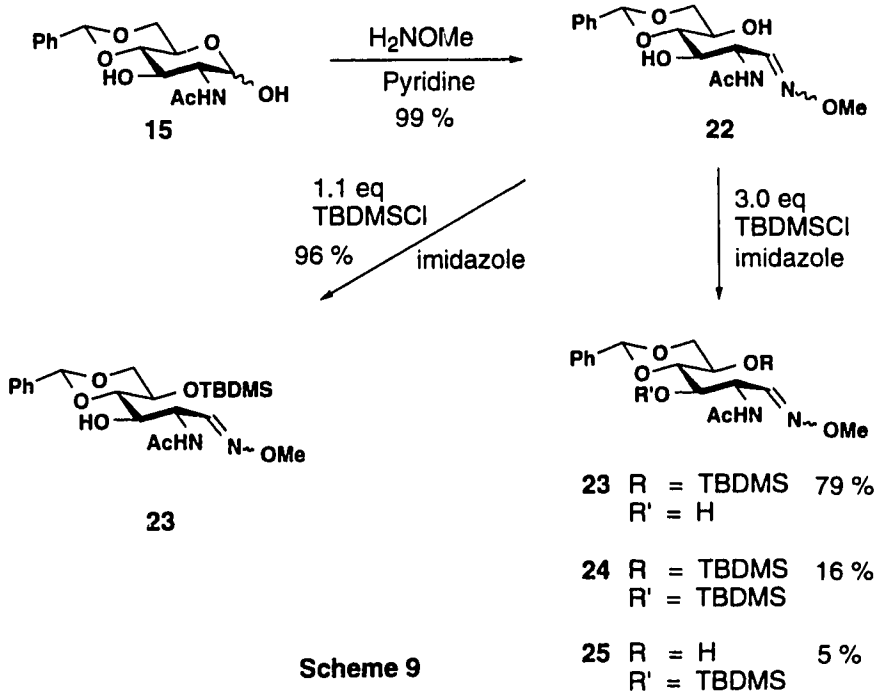


Scheme 8

acyclic *aldehydo* sugars. Hence, treatment of 4,6-di-*O*-benzylidene-*N*-acetyl-D-glucosamine (**15**) with methoxyamine hydrochloride in pyridine produces the diol **22** as a pair of oxime isomers (*E : Z*, 3.8 : 1) in almost quantitative yield (Scheme 9).

The *t*-butyldimethylsilyl ether is an appropriate protecting group for the 5-hydroxyl of **22** since it is able to withstand both ozonolysis and the subsequent Wittig

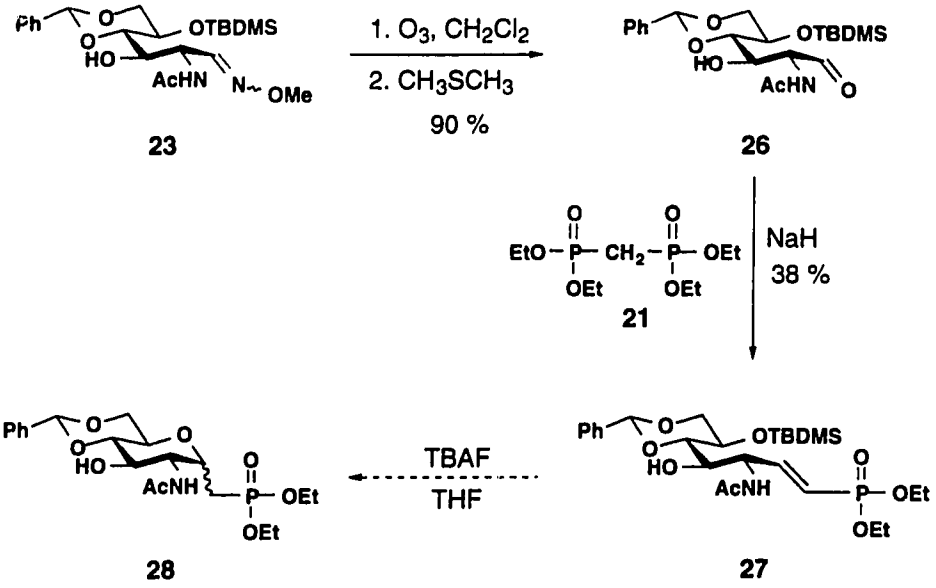
reaction.[67] It can also be removed selectively with fluoride ion without affecting the acid labile benzylidene group, thereby allowing the desired Michael addition to occur. Thus, reaction of oxime diol **22** with 3.0 equivalents of *t*-butyldimethylsilyl chloride and imidazole[67] produces the 5-*O*-silylated material **23** as the major product, and the 3,5-di-*O*-silyl **24** and 3-*O*-silyl ethers **25** as the minor products. However, by using less silylating reagent (1.1 equivalents), the 5-OH can be selectively protected to afford the silyl ether **23** in 96 % yield.



Scheme 9

Ozonolysis of oxime **23** followed by reduction with dimethyl sulfide furnishes the properly protected aldehyde **26** (Scheme 10). Wadsworth-Emmons reaction of **26** with tetraethyl methylenediphosphonate (**21**) and sodium hydride provides the (*E*)-α,β-unsaturated phosphonate **27**, along with many other components as indicated by TLC. Treatment of **27** with dry tetrabutylammonium fluoride (TBAF) in THF generates

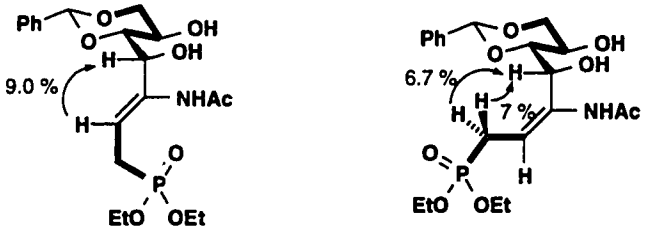
two closely related products. It initially seemed that since fluoride ion in dry THF is a strong base,[67] it had effected the Michael addition to give the α- and β-*C*-glycosides **28**.



23 **26** **21** **28** **27**

Scheme 10

Unfortunately, extensive NMR studies reveal that the two products are the rearranged (*Z*)- and (*E*)-olefins **29a** (75 %) and **29b** (19 %) (Figure 16). The hydrogen-hydrogen connectivity (bold line) determined by two-dimensional ^{1}H-^{1}H COSY[68] clearly displays the missing-link between H-2 and H-4. ^{1}H-^{13}C COSY[69] unveils the existence and the position of the carbon-carbon double bond, the geometries of which are

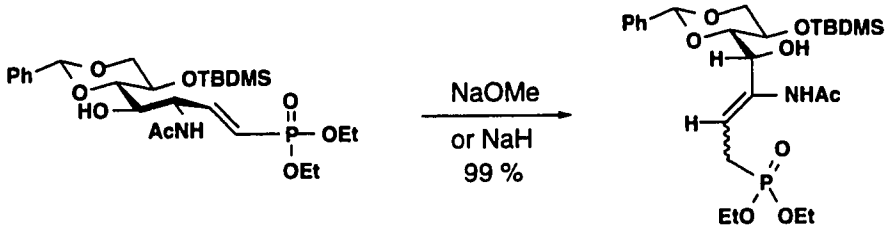


29a **29b**

Figure 16

evident from NOE studies.[70] For isomer **29a**, a strong NOE effect (9.0 %) between H-2 and H-4 indicates that these protons are close in space, in agreement with the (*Z*)-configuration of the double bond. The strong NOEs (7.0 %, 6.7 %) between two methylene protons and H-4 of the other isomer, **29b**, are consistent with the (*E*)-configuration of the molecule.

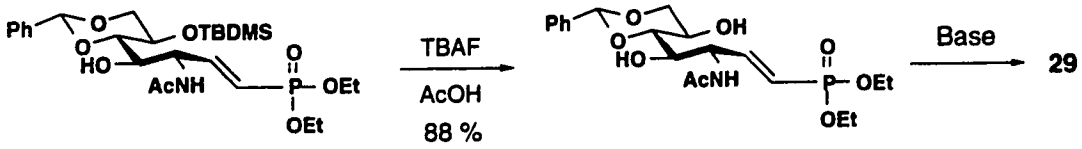
The protected α,β-unsaturated phosphonate **27** also readily undergoes rearrangement to **30** upon treatment with sodium ethoxide; thus the rearrangement is not solely a result of the deprotection (Scheme 11). The product **30** could also be detected by careful analysis of the products obtained from the Wadsworth-Emmons reaction.



27 **30**

Scheme 11

However, desilylation with TBAF in the presence of acetic acid slowly generates the desired α,β-unsaturated phosphonate **31** (Scheme 12). Unfortunately, different bases such as sodium alkoxides and sodium hydride, which were tried to accomplish the projected Michael addition of **31**, all give rearrangement to **29**. Reagents such as

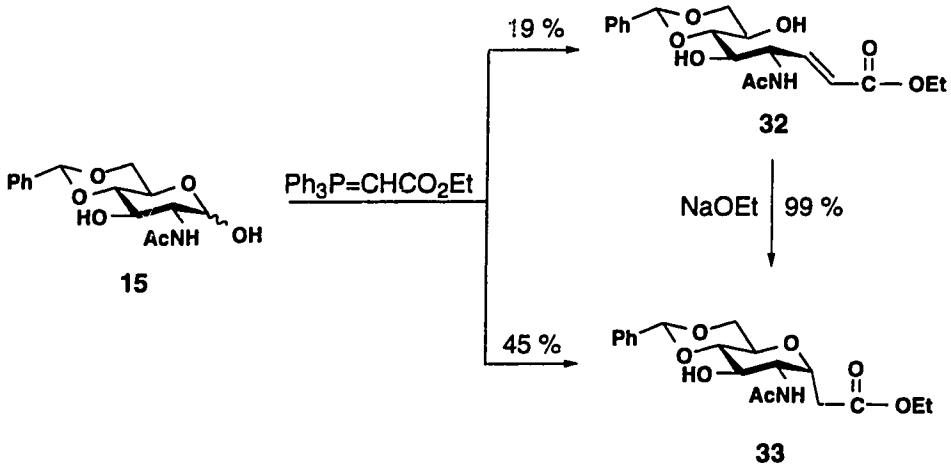


27 **31**

Scheme 12

mercury salts and iodine also prove fruitless in the attempted ring closure.

In order to determine whether the desired Michael ring closure is feasible in principle with this system, the α, β-unsaturated carboxylate **32** was investigated. Wittig reaction of sugar **15** with the stabilized ylide, $Ph_3P{=}CHCO_2Et$, provides the cyclized *C*-glycoside **33** and the intermediate α,β-unsaturated ester **32**.[54] Upon exposure to sodium ethoxide, **32** undergoes smooth cyclization to the *C*-glycoside **33** without any detectable migration of the carbon-carbon double bond (Scheme 13). These observations clearly demonstrate the significant difference in propensity for ring closure between the

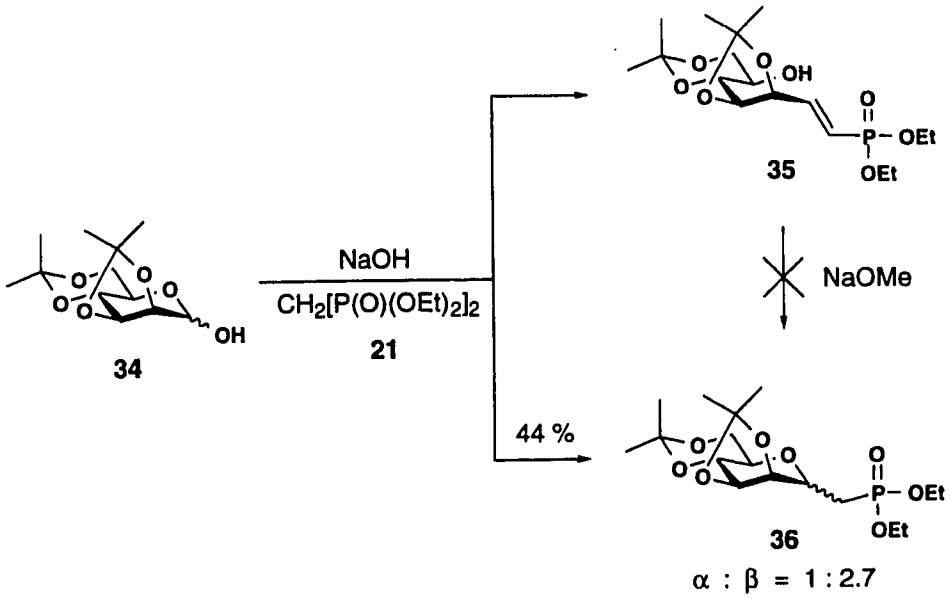


Scheme 13

unsaturated phosphonate **31** and the α,β-unsaturated carboxylate **32**. This may be explained by electronic and steric arguments. Not only does the phosphonate have a weaker ability to stabilize an α-anion than the corresponding carboxylate, but it is also much more sterically demanding. These factors could be responsible for the failure of the cyclization of the α,β-unsaturated phosphonate **31**.

While our work was in progress, a related report appeared in the literature.[71] In this study, treatment of the fully protected D-mannose derivative **34** with tetraethyl

methylenediphosphonate (**21**) and NaOH yields the α,β-unsaturated phosphonate **35** and a mixture of α- and β-*C*-glycosides **36a** and **36b** in a 1:2.7 ratio, respectively (Scheme 14). However, an attempted intramolecular Michael addition of **35** in the presence of sodium methoxide in methanol fails to produce the *C*-glycoside **36**. The mechanism of formation of **36** is unclear, but the results suggest that it does not form *via* Michael addition of the alkoxide derived from **35**.



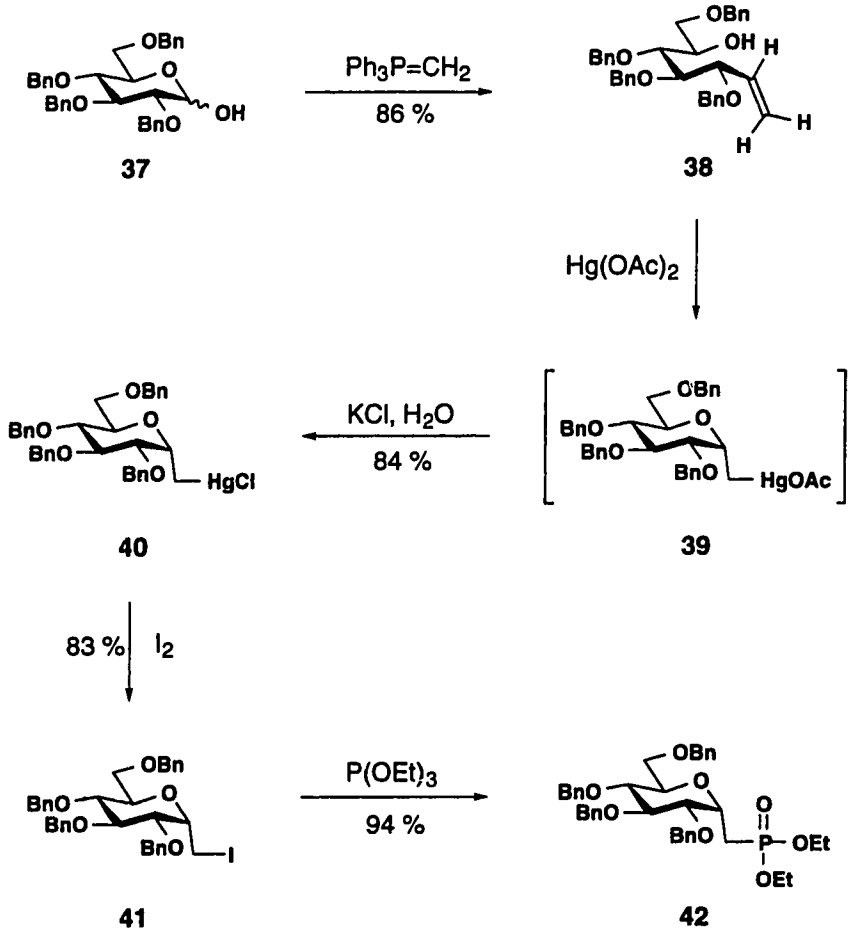
Scheme 14

Based on our own results and related reports, it seems that the Wittig-Michael route to *C*-glycosides depends heavily on the particular substrates and that the stereochemical outcomes are hard to control. It appeared that this approach could be problematic in more complicated systems, and this promoted us to explore alternative, more reliable methods to introduce the phosphonate group into carbohydrates.

1.2 The Wittig Olefination followed by Mercury-Assisted Cyclization Approach

In 1981, Sinaÿ and coworkers reported a mercury-assisted cyclization route to α-D-*C*-glucopyranosyl derivatives.[72] In the following year, Nicotra *et al.* employed this method to prepare methylene halide *C*-glycosides, which were subsequently converted to methylene phosphonate *C*-glycosides *via* an Arbuzov reaction.[46,47]

We examined and optimized this route (Scheme 15). Wittig reaction of the commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**37**) with methylene-triphenylphosphorane produces olefin **38**. Upon treatment with mercury acetate, **38**



Scheme 15

undergoes cyclization to selectively provide the α-*C*-glycoside as an unstable mercury acetate **39**, but this could be stabilized by conversion to the mercury chloride **40** using aqueous potassium chloride. Iododemercuration of **40** provides methylene iodide *C*-glycoside **41**, which can be converted to the methylenephosphonate α-*C*-glycoside **42** by an Arbuzov reaction with triethyl phosphite.

When the Wittig olefination was done according to the literature procedure, the reactions proceeded slowly and incompletely. Moreover, forcing conditions (e.g. heating) caused elimination of benzyl ethers from the sugar substrate. Modification of this method by increasing the amount of ylide gives better and reproducible results; the reaction was complete in 2 hours at 45 °C to provide olefin **38** in 86 % yield with no elimination. Mercury-assisted cyclization of **38** and subsequent iododemercuration of **40** was performed under an inert atmosphere due to the possible radical mechanism involved.[73] This optimized route produces methylenephosphonate α-*C*-glycoside **42** in 56 % overall yield which compares favorably to the 23 % yield reported in the literature preparation.[72,47] The observed facial diastereoselectivity of the cyclization is believed to originate from the suitably orientated 2-*O*-benzyl group which exerts a strong directing effect by co-ordinating with the incoming mercury species (Figure 17).[74] However, this explanation also reveals the limitation of this approach, namely, the choice of protecting group at C-2 is restricted to *O*-benzyl.

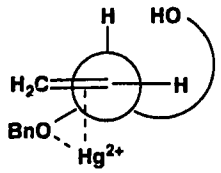
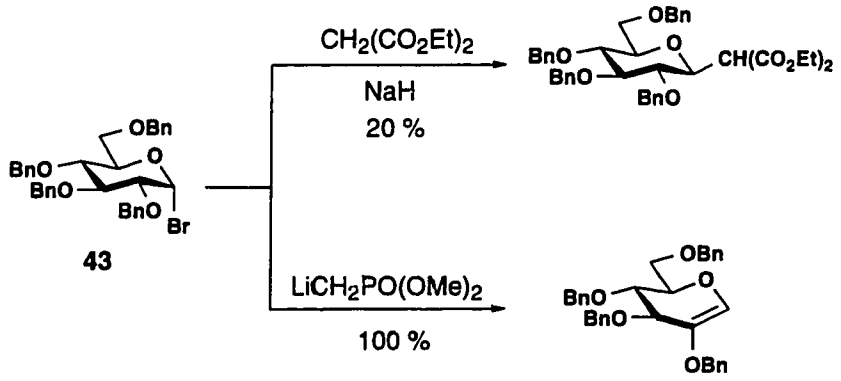


Figure 17

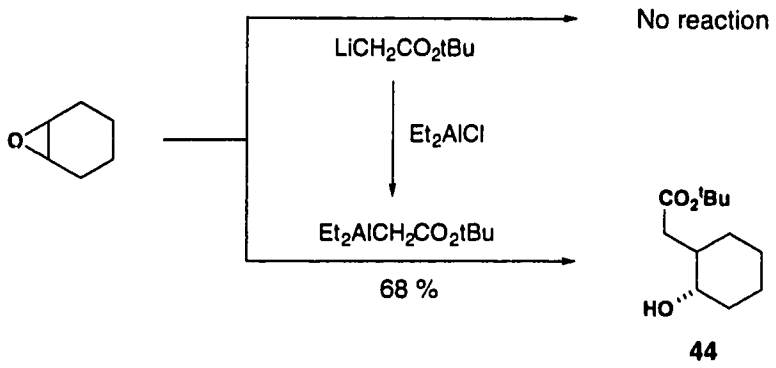
1.3 Nucleophilic Substitution at the Anomeric Center

Several other methods for *C*-glycoside synthesis were also considered for introduction of the methylenephosphonate group, or alternatively, of a methylene halide which could be potentially converted to it by an Arbuzov reaction. The most common preparation of α-linked *C*-glycosyl compounds involves the nucleophilic substitution at the anomeric center by carbon nucleophiles.[43] Hanessian and Pernet condensed sodium diethylmalonate with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**43**) to yield β-*C*-glucosyl malonates (Scheme 16).[75] However, a study by Russo and coworkers demonstrated that treatment of the same sugar substrate with phosphorus counterpart, $LiCH_2PO(OCH_3)_2$, resulted in quantitative elimination of hydrogen bromide.[47] Hence, the key to success seems to revolve around enhancing the softness of the nucleophile.



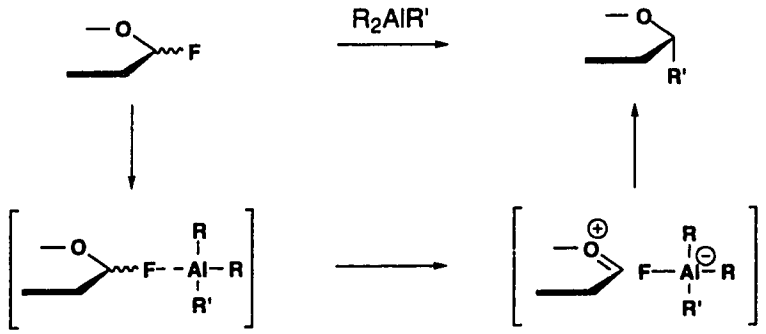
Scheme 16

Danishefsky *et al.* reported some useful applications of aluminum derivatives of *t*-butyl acetate in the opening of epoxides (Scheme 17).[76] No reaction was observed between lithium *t*-butylacetate and cyclohexane epoxide; however, upon addition of diethylaluminum chloride, the product **44** was obtained in 68 % yield. It was suggested



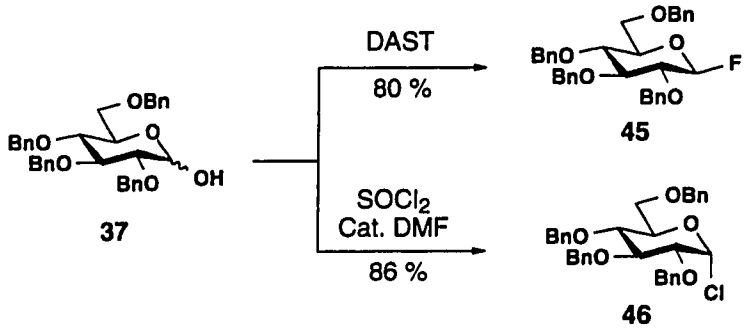
Scheme 17

that diethylcarbo-*t*-butoxymethylalane was the reactive species in this case. Interestingly, organoaluminum reagents have also found applications in *C*-glycoside synthesis.[77, 78] Various organoaluminum reagents react with glycosyl fluorides to form α-*C*-glycosides (68-93 %). It was suggested that the organoaluminum reagents activated glycosyl fluorides due to the strong affinity of aluminum for fluoride ions, and that this reaction could involve the formation of an oxonium ion along with a tetravalent aluminum/fluoro complex (Scheme 18) .



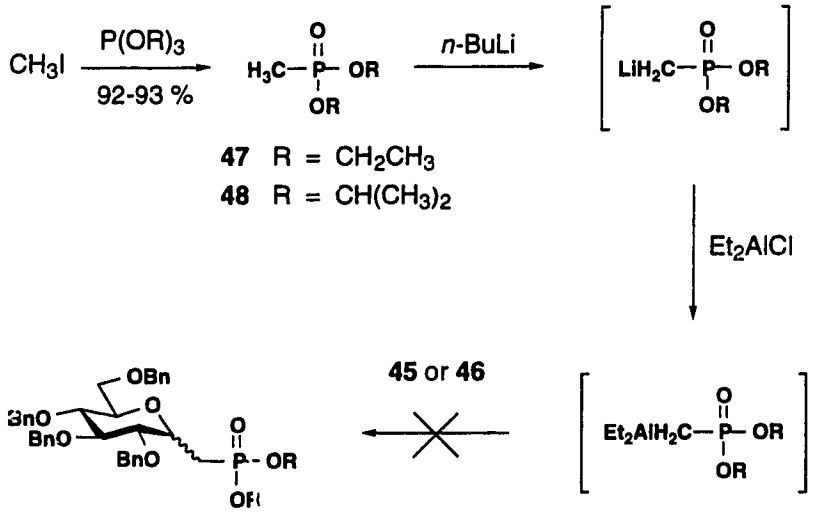
Scheme 18

Thus, treatment of the 2,3,4,6-tetra-O-benzyl-D-glucopyranose (**37**) with diethylaminosulfur trifluoride (DAST) affords the known β-glycosyl fluoride **45** (Scheme 19).[79] For comparison, the corresponding chloride **46** was also synthesized following the literature procedure[80] by the reaction of **37** with thionyl chloride and a catalytic amount of DMF.



Scheme 19

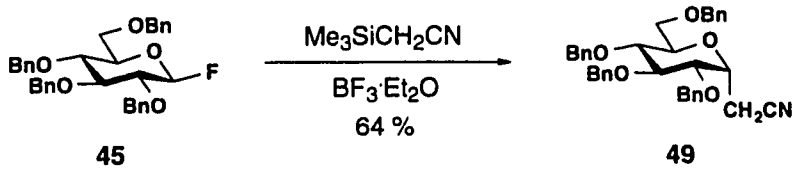
Arbuzov reaction of methyl iodide with triethyl phosphite provides diethyl methylphosphonate (**47**) (Scheme 20).[59] Treatment of **47** with *n*-butyl lithium at -78 °C generates the phosphonate anion,[81] which is treated with diethylaluminum chloride



Scheme 20

followed by glycosyl fluoride **45**. However, work-up only produces the hydrolyzed glycosyl fluoride; similar reactions with the carbanion from diisopropyl methylphosphonate **48** and glycosyl chloride **46** are also unsuccessful.

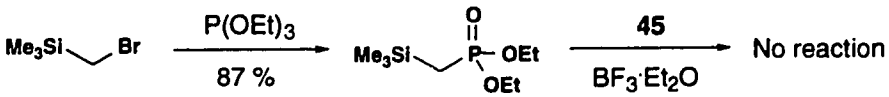
The Lewis-acid catalyzed addition of alkyl silanes to activated carbohydrate derivatives has been a successful route for the preparation of α-*C*-glycosides.[43] Nicolaou *et al.* reported the synthesis of *C*-glycosides by treatment of glycosyl fluorides with a number of silanes.[82] For example, the reaction of glycosyl fluoride **45** with trimethylsilylacetonitrile in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ provides the corresponding α-*C*-glycoside **49** (Scheme 21).



45 **49**

Scheme 21

In an attempt to introduce the methylenephosphonate functionality in a similar manner, an analogous reaction was attempted with diethyl (trimethylsilyl)-methylphosphonate (**50**), which is available by reaction of bromomethyltrimethylsilane with triethyl phosphite (Scheme 22).[83] Disappointingly, treatment of the glycosyl fluoride **45** with the phosphonate **50** in the presence of $BF_3{\cdot}Et_2O$ does not yield any desired *C*-glycoside, and a significant amount of the phosphonate reagent **50** is recovered. Neither heating the reaction mixture nor the addition of CsF to assist the

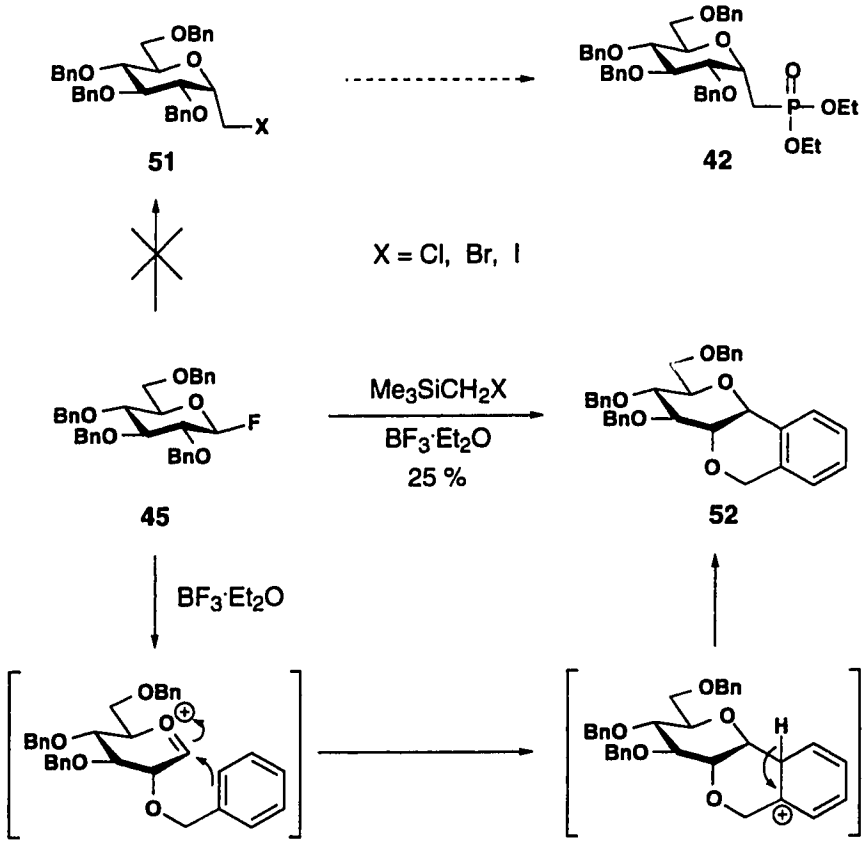


50

Scheme 22

desilylation is successful in effecting the condensation. Use of the glycosyl chloride **46** as the electrophile also gives disappointing results.

In an attempt to prepare the *C*-glycoside methylene halides **51**, from which the corresponding phosphonate **42** could hopefully be generated, the glycosyl fluoride **45** was reacted with either chloromethyltrimethylsilane, bromomethyltrimethylsilane or iodomethyltrimethylsilane (Scheme 23). Interestingly, each reaction generates the intramolecular Friedel-Crafts product **52**, which can also be produced simply by treatment of the glycosyl fluoride **45** with $BF_3{\cdot}Et_2O$ in the absence of these reagents. In future work, this reaction could potentially be extended to the synthesis of aryl *C*-glycosides which have been shown to possess various interesting physiological



Scheme 23

properties,[84] such as antiviral and antibiotic activities.

The lack of success of these approaches demonstrates that the Wittig methylenation of the reducing sugar followed by the mercury-assisted cyclization of the olefinic intermediate is the current method of choice for making methylenephosphonate α-*C*-glycosides. With this optimized synthetic method available, we launched the construction of our target molecules.

Part 2: Synthetic Studies on Type A Targets

2.1 Studies on Synthesis of the Type A Targets

The synthetic strategy for the construction of targets of type **A** is based on the retrosynthetic analysis outlined in Figure 18. The target molecule could be envisaged to be derived from a disaccharide phosphonic acid **53** and a glycerate lipid. Disaccharide **53** could be prepared by glycosylation of a suitably protected methylene phosphonate *C*-glycoside **54** with a D-glucosaminyl donor.

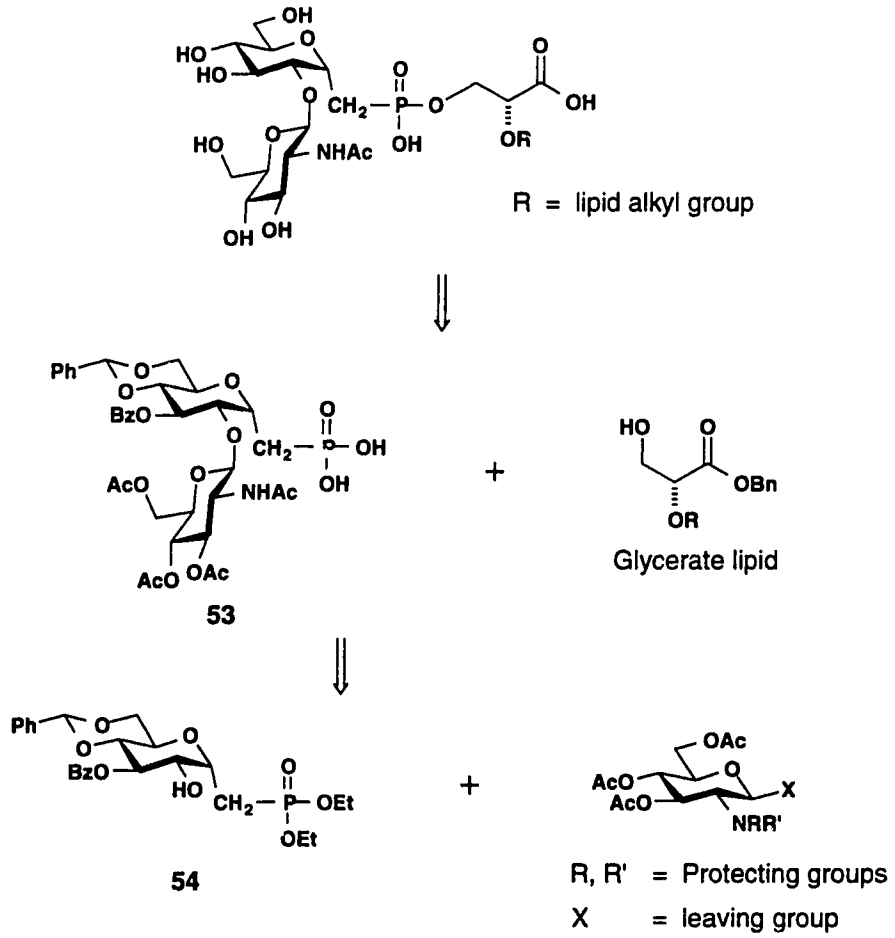
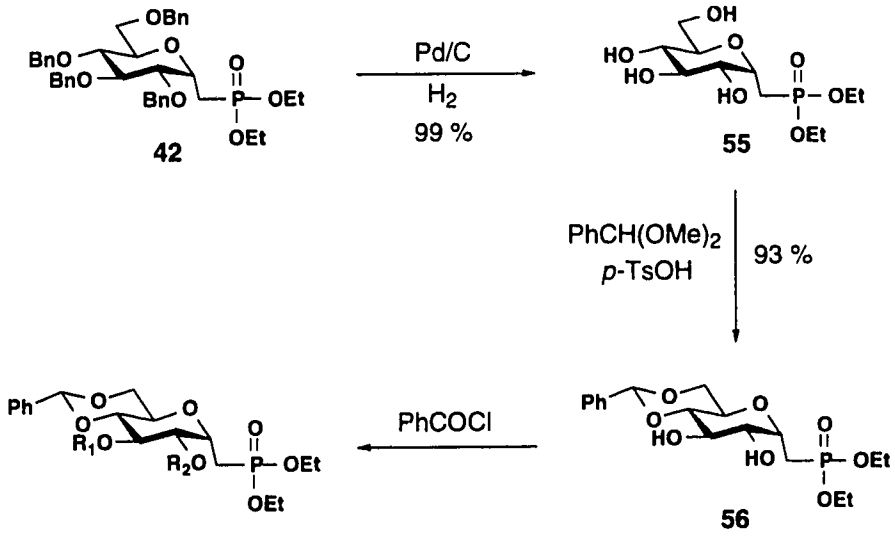


Figure 18

The synthesis of glycosyl acceptor **54** begins with (tetra-*O*-benzyl-D-glucosyl)methylphosphonate **42**, which can be prepared as discussed in part 1 of this thesis. Hydrogenation of **42** with Pd/C generates the tetraol **55** in quantitative yield (Scheme 24). Subsequent benzylidenation of **55** with benzaldehyde and freshly fused zinc chloride produces the diol **56** in 38 % yield. The low yield of this step partially results from purification problems caused by the large excess of benzaldehyde and by the



	R_1	R_2	
54	Bz	H	74 %
57a	H	Bz	< 5 %
57b	Bz	Bz	9.5 %

Scheme 24

presence of benzoic acid, formed by its oxidation. To circumvent this difficulty, the procedure reported by Evans[85] was attempted. Treatment of tetraol **55** with benzaldehyde dimethyl acetal and a catalytic amount of *p*-toluenesulfonic acid in DMF under reduced pressure produces the diol **56** in 93 % yield. Benzoylation of diol **56** with benzoyl chloride[86] initially gives an approximately 1:1 mixture of regioisomers **54** and **57a** as indicated by NMR (^1H, ^{13}C, and ^{31}P) spectrometry. Better selectivity is obtained when the method is modified to ensure a low concentration of benzoyl chloride in the

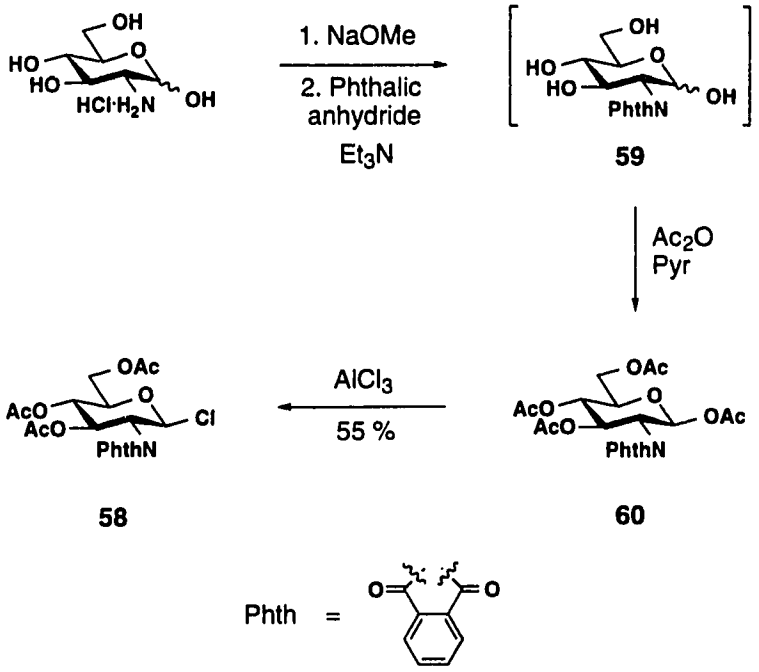
reaction mixture. Addition of a solution of benzoyl chloride in CH_2Cl_2 to the diol **56** over 4 hours at -78 °C produces the desired 3-benzoylated ester **54** in 74 % yield along with the 2,3-dibenzoylated compound **57b** (9.5 %) and a trace amount of 2-benzoylated material **57a**. The glycosyl acceptor **54** should be a versatile intermediate since the 2-hydroxyl group could potentially undergo a variety of transformations.

With the successful elaboration of the glycosyl acceptor **54** complete, attention focused on the preparation of glycosyl donors. The 2-amino-2-deoxy-β-D-glucopyranoside moiety occurs widely in natural oligosaccharides and glycoconjugates, and consequently many synthetic methodologies to incorporate it have been developed.[87-90] Of these, the Koenigs-Knorr method using a phthalimido-glucopyranosyl halide in conjunction with the silver triflate and *s*-collidine complex as the promoter has been a very reliable method.[91] The high stereoselectivity is believed to originate from the phthalimido group which shelters the α-face of the pyranose ring and provides the neighboring-group participation at the anomeric center during the glycosylation reactions (Figure 19). Hence, phthalimido-glucopyranosyl chloride (**58**)

Figure 19

was prepared according to the literature procedure (Scheme 25).[91] Sequential treatment of D-glucosamine hydrochloride with sodium methoxide, phthalic anhydride, and

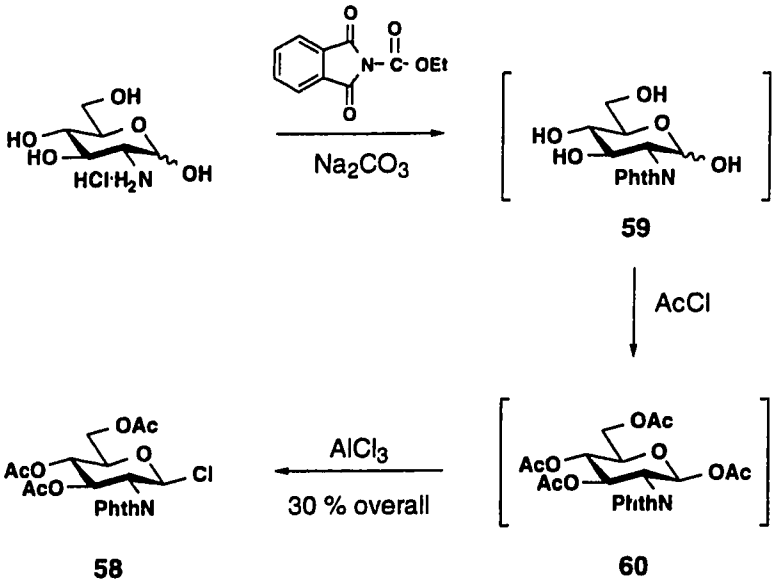
triethylamine followed by *in situ* acetylation of the resulting phthalimido-D-glucopyranose (**59**) provides the tetraacetate **60**. Treatment of **60** with aluminium



Scheme 25

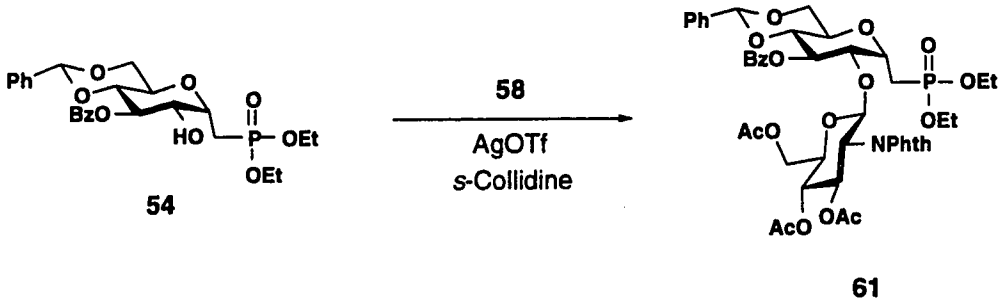
chloride yields the chloride **58** in 55 % yield. This procedure repeatedly afforded very low yields (≤ 2.2 %) of tetraacetate **60**; several workers in the research group of Professor O. Hindsgaul have also experienced similar problems.[92]

The method reported by Derome and co-workers[93] is more reliable and convenient (Scheme 26). Treatment of 2-amino-2-deoxy-D-glucopyranose with commercially available *N*-ethoxycarbonylphthalimide in aqueous sodium carbonate solution yields phthalimido-D-glucopyranose (**59**). Acetylation and substitution *in situ* by reaction of **59** with acetyl chloride-aluminium chloride provides β-chloride **58** in 30 % overall yield.



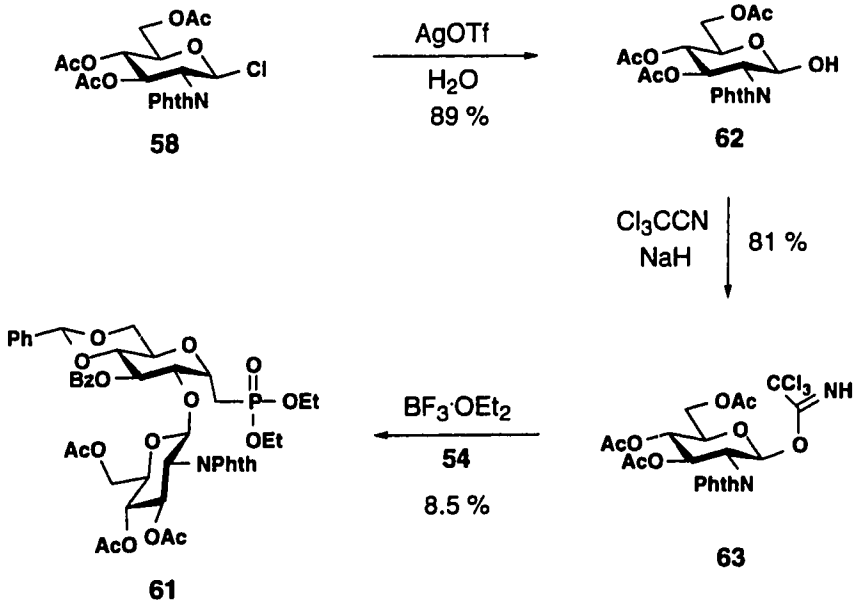
Scheme 26

Unfortunately, glycosylation of the acceptor **54** with the donor **58** in the presence of silver triflate and *s*-collidinc yields only trace amounts of disaccharide **61** and significant recovery of alcohol **54** (56-77 %) (Scheme 27).[91] Both **54** and **61** have very similar mobilities by single-elution TLC, but can be separated by multiple development of the plate using CH_2Cl_2-MeOH (30:1, v/v) system. Due to the low yield of this process, other approaches were investigated.



Scheme 27

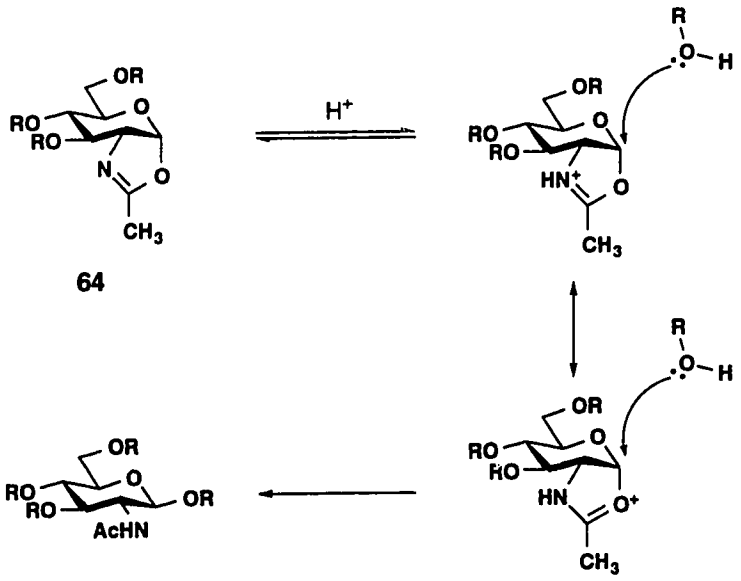
The glycosylation procedure using *O*-glycosyl trichloroacetimidate as the glycosyl donor[87-89] is a valuable alternative to the classical Koenigs-Knorr process for the synthesis of oligosaccharides and other sugar containing natural products. Trichloroacetimidates are thermally and chemically stable and are readily accessible from the corresponding 1-hydroxyl sugars. The glycosylation is promoted by mild Lewis acid catalysis. Hence, hydrolysis of chloride **58** in the presence of silver triflate yields phthalimido-D-glucopyranose derivative **62** (Scheme 28). Treatment of **62** with trichloroacetonitrile and NaH affords the *O*-glycosyl trichloroacetimidate **63**. Glycosylation of alcohol **54** with the trichloroacetimidate **63** in the presence of boron trifluoride etherate generates disaccharide **61** in 8.5 % yield.[94] The low yields may be



Scheme 28

due to the steric hindrance presented by the methylenephosphonate moiety; the presence of the phthalimido group in the glycosyl donor may make this problem even more severe. A smaller glycosyl donor could potentially alleviate this problem, and thus an oxazoline procedure was explored.

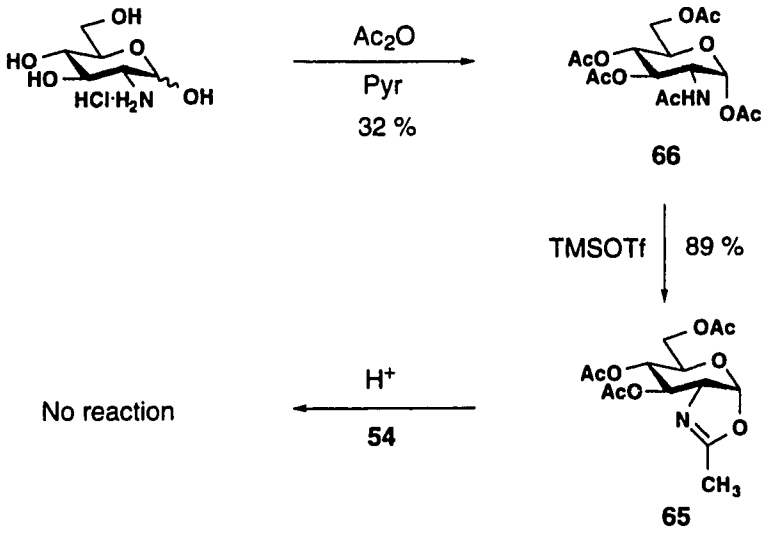
Although the 2-acetamido group can provide neighboring-group participation in the synthesis of 2-amino-2-deoxy-β-D-glucopyranosides, the corresponding glycosyl halides usually produce stable oxazolines. The oxazolines **64** can be used as glycosyl donors under strong acidic catalysis with glycosyl acceptors possessing the required acid stability (Scheme 29).[88,90] Protonation of the oxazoline followed by nucleophilic attack at the glycosidic center results in ring opening with inversion of configuration at C-1 to give a 1,2-trans-glycosidic bond. The apparent advantage of the oxazoline method is that the correct functionality, the acetamido group, can be installed directly, but this method also suffers the drawbacks of low oxazoline reactivity and harsh reaction conditions.



Scheme 29

The procedure reported by Jeanloz and coworkers was adopted to prepare oxazoline **65** (Scheme 30).[95] Acetylation of D-glucosamine hydrochloride affords the pentaacetate **66**. Treatment of **66** with trimethylsilyl trifluoromethanesulfonate then yields the oxazoline **65**. Attempted glycosylation of alcohol **54** with oxazoline **65** in the

presence of camphorsulfonic acid[32] produces none of the desired disaccharide; both alcohol **54** and oxazoline **65** are recovered unchanged.



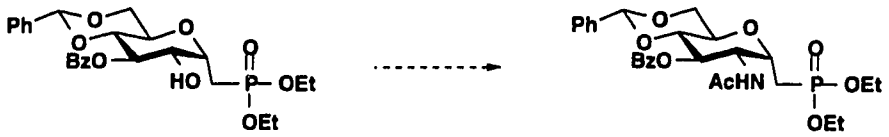
Scheme 30

The above study demonstrates the low reactivity of the 2-hydroxyl of alcohol **54** toward glycosylation. This may be due to the methylenephosphonate moiety obstructing the incoming glycosyl donor from the α-face of the molecule and thus preventing formation of the disaccharide. The adjacent electron-withdrawing benzoyl and phosphonate groups may also contribute to the low reactivity of this functionality.

From disaccharide **61**, six more steps are required to reach the type A target; efforts are currently underway to accumulate sufficient disaccharide to complete the subsequent reactions. Studies are also in progress to investigate conditions under which the glycosylation reaction may be improved by using different protective groups and coupling strategies.

2.2 Attempted Transformation of the α-D-Glucopyranosyl Skeleton into the 2-Amino-2-deoxy-α-D-glucopyranosyl System

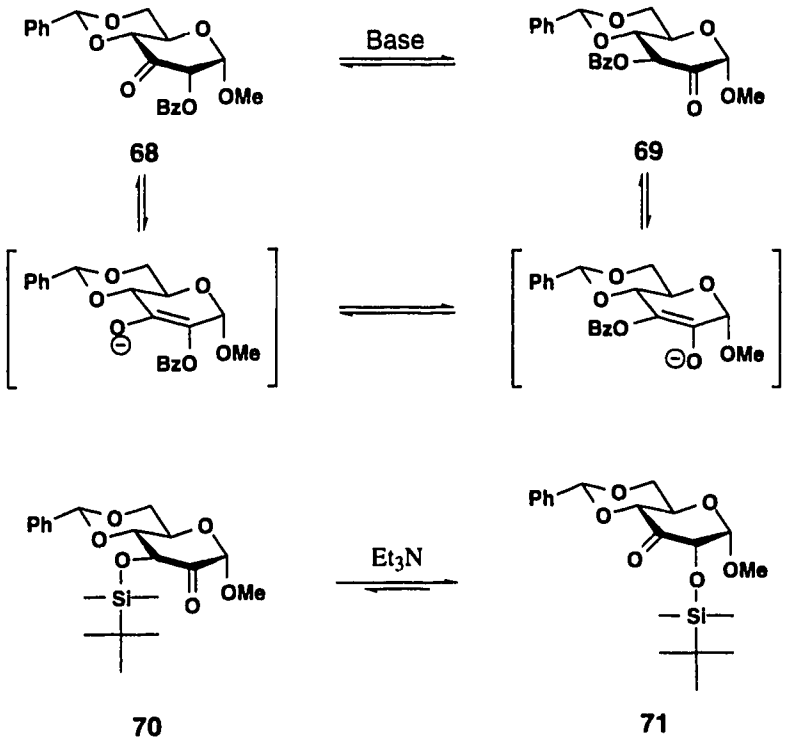
Strategies for the conversion of the α-D-glucopyranosyl skeleton **54** into the 2-acetamido-2-deoxy-α-D-glucopyranosyl system **67** were also examined (Scheme 31). This transformation could allow access to the D-glucosamine series of the methylenephosphonate *C*-glycosides. With suitable protecting groups, oxidation of **54**



54 **67**

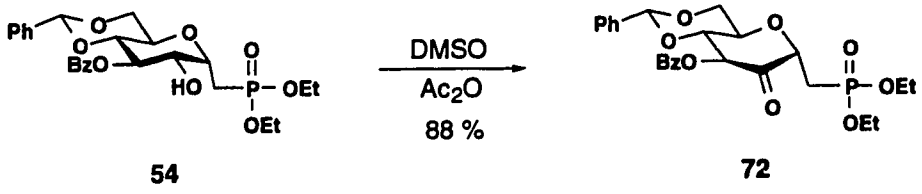
Scheme 31

would produce a ketone, which could be further converted to **67** by a reductive amination. Steric hindrance created by the methylenephosphonate moiety could direct the reduction to occur from the less hindered β-face to yield the desired equatorial amino group. Many carbonyl sugars have successfully been used in the syntheses of amino sugars, β-D-mannopyranosides, and branched-chain sugars,[96-100] but unexpected transformations can occur. Yoshimura and coworkers reported a rearrangement of methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-ribo-hexopyranosid-3-uloside (**68**) during attempted Wittig olefination to the corresponding 3-*O*-benzoyl-D-arabino-hexopyranosid-2-uloside **69** (Scheme 32).[100] In studies with the silyl ether protected sugars **70** and **71**, Wood and coworkers observed that treatment of either regioisomer with triethylamine resulted in an equilibrium mixture of 2-uloside **70** and 3-uloside **71** in a ratio of 1 : 4, respectively.[99] This equilibrium may also involve the migration of the silyl group *via* 2,3-enediol intermediates.



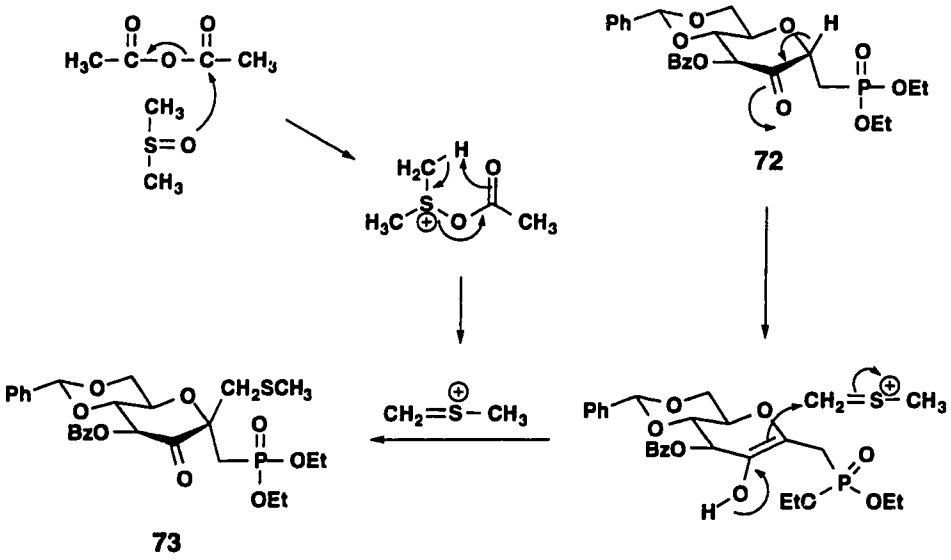
Scheme 32

It was uncertain whether the 2-ulo-*C*-glycoside **72**, potentially available by oxidation of alcohol **54**, would display similar properties. More importantly, it was unclear whether the C-1 center would epimerize to form the thermodynamically more stable β-*C*-glycoside after the introduction of the 2-oxo function. Therefore, a mild modification of the Pfitzner-Moffatt oxidation procedure was adopted.[101] Treatment of alcohol **54** with DMSO and acetic anhydride provides the 2-uloside **72** (Scheme 33).



Scheme 33

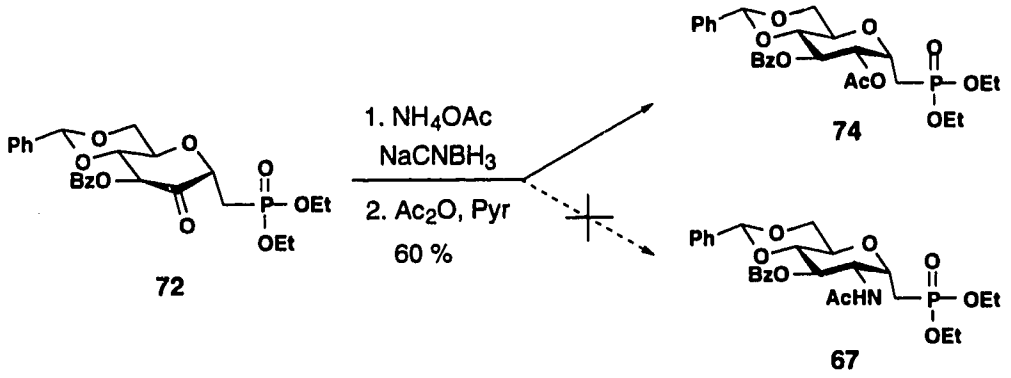
The position of the carbonyl group is easily established by a ^{1}H-^{1}H COSY experiment which shows a coupling connectivity gap between H-1 and H-3. The oxidation also generates a by-product which is tentatively assigned as the thioether **73** (7.0 %), although the stereochemistry at C-1 is not yet unequivocally established. The methylene protons display geminal coupling and P-H coupling, indicating the absence of the H-1; an attached proton test (APT) ^{13}C NMR spectrum is also consistent with this assignment. A possible mechanism for the formation of **73** is shown in Scheme 34.



Scheme 34

Introduction of the amino group was attempted using the reductive amination procedure of Borch *et al.*[102] Reaction of the ketone **72** with ammonium acetate and sodium cyanoborohydride followed by acetylation *in situ* with acetic anhydride in pyridine produces the acetate ester **74**, rather than the desired amide **67** (Scheme 35). The reduction of the ketone occurs, as predicted, from the less hindered β-face. Formation of acetate **74** implies that neither migration of the benzoyl group nor epimerization of the C-1 center occurs under the reductive amination condition. Since a

difference of only one mass unit exists between the amide **67** and the acetate **74**, the structural elucidation of **74** depends mainly upon NMR spectroscopy. ^{1}H and ^{13}C NMR spectra can be fully assigned with the aid of ^{1}H-^{1}H and ^{1}H-^{13}C shift correlation spectra.

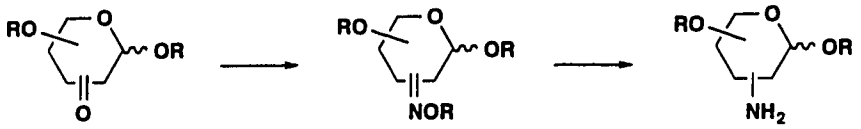


Scheme 35

The H-2 proton resonating at δ 4.66 displays three coupling constants in a ddd pattern: $J_{H\text{-}2,P}$ = 2.5 Hz, $J_{H\text{-}1,\,2}$ = 6.0 Hz, $J_{H\text{-}2,\,3}$ = 10.0 Hz, clearly indicating the axial orientation of H-2. The chemical shift of this proton is downfield relative to the protons adjacent to acetamido groups, which usually appear at approximately δ 4. Furthermore, after D_2O exchange, the H-2 coupling pattern is unchanged and no exchangeable NH amide signal can be detected. These studies rule out the presence of acetamido compound **67**. Independent synthesis of the acetate ester **74** *via* acetylation of the alcohol **54** confirms the assignment.

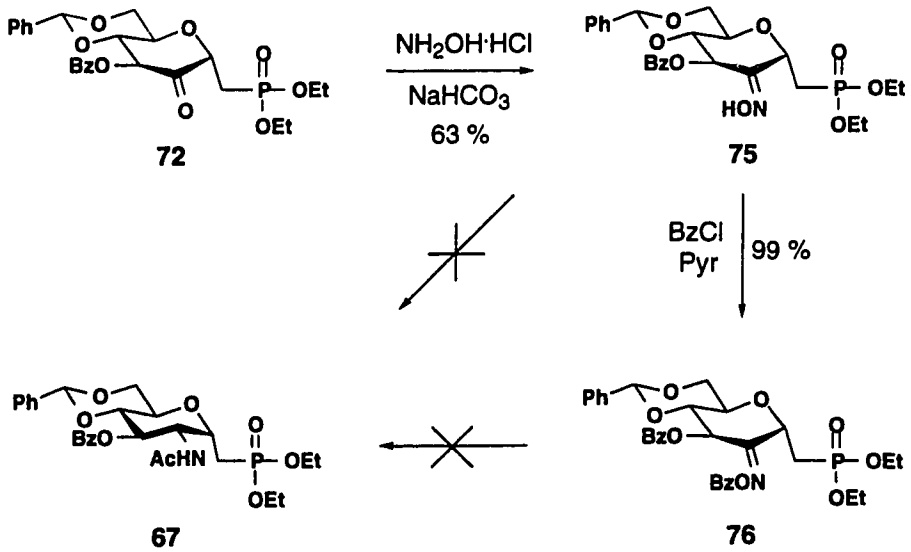
The formation of acetate **74** suggests that the imine precursor of the acetamido sugar did not form. Thus, it might be possible to effect the reductive amination using a more reactive ammonium equivalent.[103] However, treatment of the 2-uloside **72** with allyl amine and sodium cyanoborohydride results in the cleavage of the benzoyl group and the epimerization of the C-1 center without introduction of nitrogen.

An alternative procedure for the transformation of oxo-glycosides into amino-sugars involves the reduction of sugar oximes derived from the corresponding ketones (Scheme 35).[104-108,96] Thus, reaction of the 2-uloside **72** with hydroxylamine



Scheme 36

hydrochloride in the presence of sodium bicarbonate provides oxime **75** (Scheme 37).[109] However, attempts to reduce the oxime **75** with $LiAlH_4$, Raney nickel/H_2, and nickel/H_2, all fail to give the amino derivative. Benzoylation of oxime **75** with benzoyl chloride and



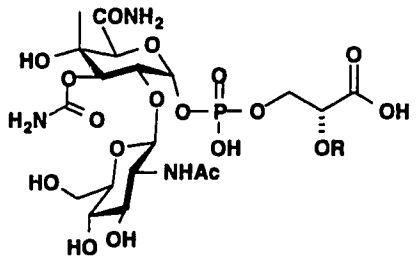
Scheme 37

pyridine generates benzoyloximino derivative **76** in quantitative yield. Attempted reduction with excess BH_3·THF, followed by *in situ* acetylation did not lead to the formation of the acetamido compound **67** (Scheme 37).[106,108]

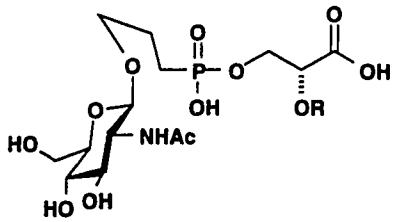
From these studies, it appears that the introduction of the methylenephosphonate moiety at the anomeric center of the glucopyranose changes the reactivity of the C-2 center in a fundamental way. Many reactions that normally occur at the corresponding C-2 center of an *O*-glycoside fail in this series. The change in reactivity presumably results from the steric hindrance created by the methylene phosphonate moiety, which precludes facile introduction of the desired nitrogen.

Part 3: The Synthesis of the Type B Target

The structural features of active portions of moenomycin antibiotics indicate that the terminal glucosamine unit may play an essential role in the enzymatic recognition.[22,26] Further support for this idea is provided by the observation that synthetic monosaccharide analogues are devoid of antimicrobial activity.[33] However, the relative contribution of the central sugar unit to the antibiotic activity is not so evident. In order to address this question, a type **B** target was designed (Figure 20), where a three-carbon chain replaces the sugar unit between the phosphorus atom and the terminal glucosamine unit. Although it is more flexible, this chain can be very similar in length to the corresponding portion of moenomycin antibiotics in the correct conformation. The replacement of the phosphate moiety with a phosphonate group also lends general metabolic and chemical stability to the structure.



Moenomycin A active portion



Type **B** target

R = Lipid alkyl group

Figure 20

A retrosynthetic analysis (Figure 21) of the Type **B** compound indicates that the key intermediate would be (2-acetamido-2-deoxy-β-D-glucopyranosyl)propanyl-phosphonic acid **77**. This would then be coupled with (*R*)-glycerate-alkyl ethers to

afford the protected target molecule. Two possible routes were envisaged for the construction of **77**. One is a convergent strategy involving the coupling of a D-glucosaminyl donor with diethyl 3-hydroxypropanylphosphonate (**78**), followed by dealkylation of the phosphonate. The second possibility is a linear synthetic route entailing glycosylation of 3-bromopropanol (**79**) and subsequent introduction and deprotection of the phosphonate function.

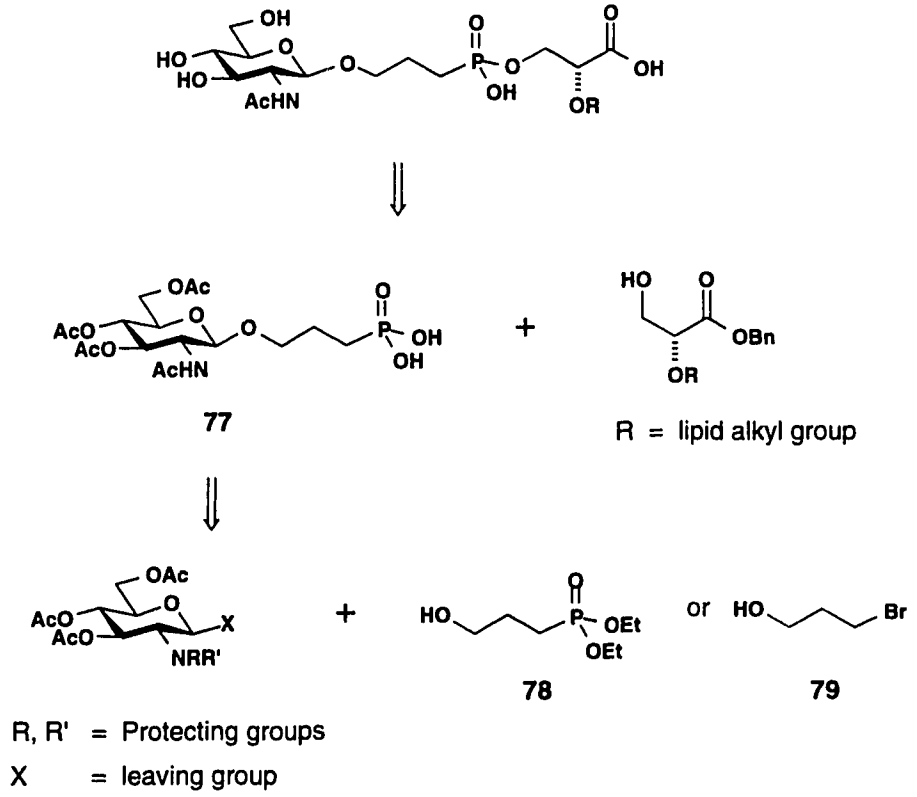
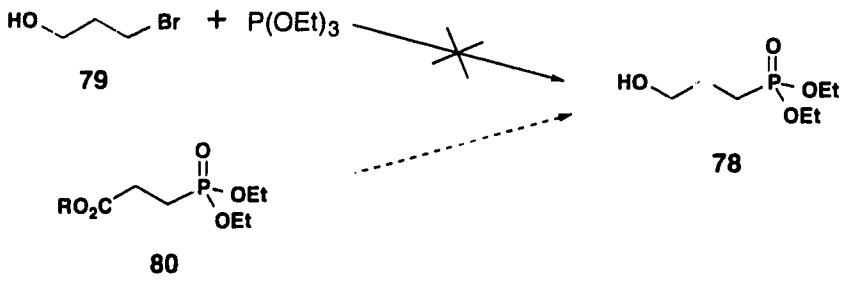


Figure 21

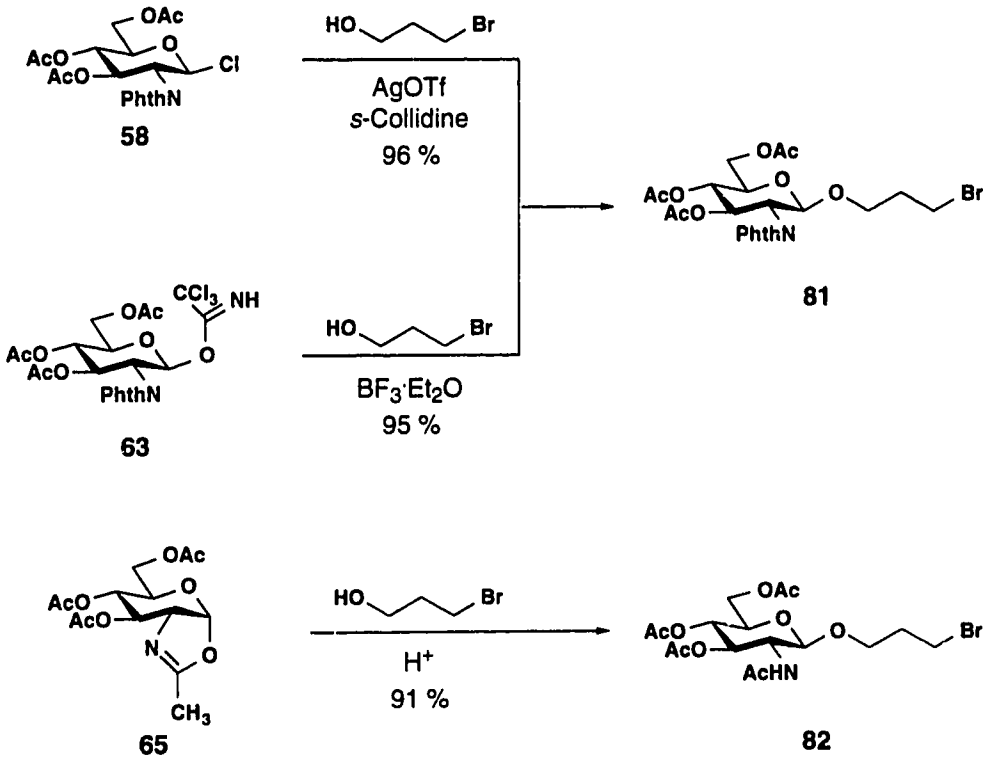
Arbuzov reaction of commercially available 3-bromopropanol (**79**) with triethyl phosphite was expected to afford the glycosyl acceptor diethyl 3-hydroxy-propylphosphonate (**78**). However, the reaction produces none of the desired product, possibly due to the sensitivity of the bromo alcohol and the harsh reaction conditions

(Scheme 38). Other approaches, such as the reduction of the carboxylate functions in diethyl alkoxycarbonylpropanylphosphonates **80** may lead to many side reactions such as cyclization. Hence, this approach was quickly abandoned.



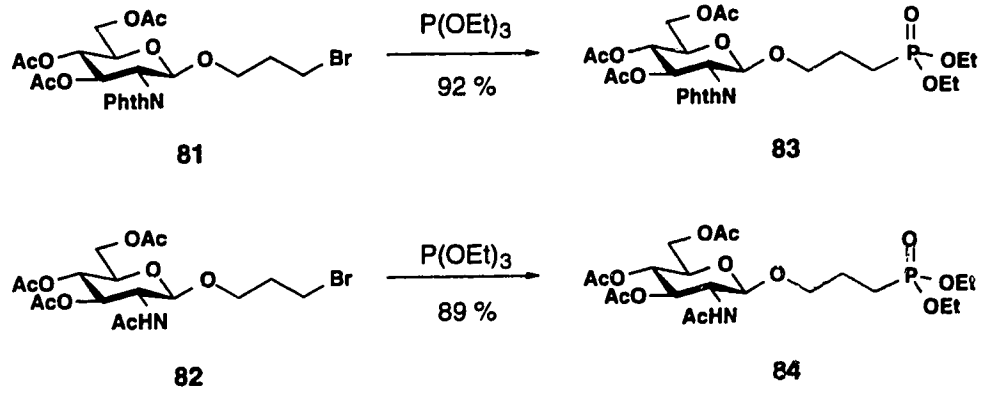
Scheme 38

The linear synthetic route involving glycosylation of 3-bromopropanol (**79**) was explored next (Scheme 39). With three different glycosyl donors available, glycosyl chloride **58**, glycosyl trichloroacetimidate **63,** and oxazoline **65**, the relative efficiency of the three corresponding coupling reactions could be compared. Condensation of 3-bromopropanol (**79**) with glycosyl chloride **58** under modified Koenigs-Knorr reaction conditions (silver trifluoromethanesulfonate/s-collidine)[91] provides the phthalimido-β-glycoside **81** in 96 % yield. The β-configuration of the glycosidic linkage was apparent from the 8.5 Hz trans-diaxial coupling constant of H-1 seen with ^{1}H NMR spectrum. Glycosylation promoted by boron trifluoride etherate of 3-bromopropanol (**79**) with glycosyl trichloroacetimidate **63** produces the same glycoside **81** in a comparable yield (95 %).[94] However, due to the absence of heavy-metal salts and proton acceptors, the latter method does have the advantage of simple purification. Reaction of 3-bromopropanol (**79**) with oxazoline **65** in the presence of camphorsulfonic acid[32] at 42 °C for 12 hours also proceeds remarkably well, providing the acetamido-β-glycoside **82** in 91 % yield.



Scheme 39

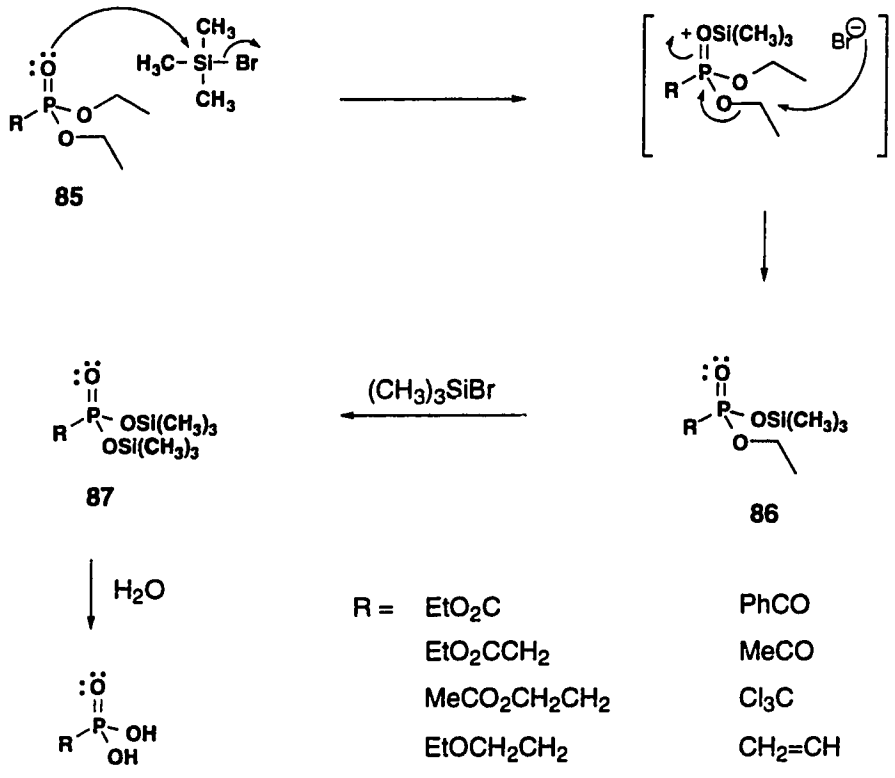
The Arbuzov reaction of glycosides **81** and **82** using triethyl phosphite produces the corresponding phosphonates **83** and **84** in 92 % and 89 % yields, respectively (Scheme 40). Since no difficulties occur along the oxazoline route, and the required



Scheme 40

functionality, the 2-acetamido group, is in position already, this approach is the method of choice for preparing the glycosylpropanylphosphonate **84**. Thus, the phthalimido phosphonate **83** was not further manipulated.

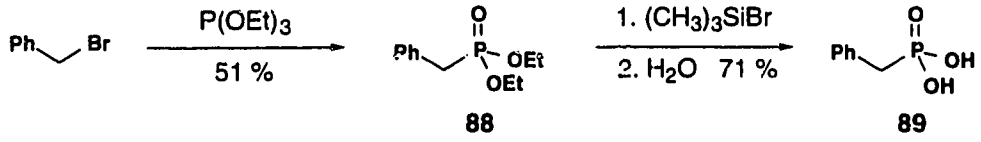
The next objective was the selective cleavage of the ethyl esters from the phosphonate. Dealkylation of phosphonates can be effectively achieved by acid or base-catalyzed hydrolysis,[110,111] however these conditions may also interfere with other sensitive functional groups. McKenna *et al.* demonstrated that bromotrimethylsilane (TMSBr) smoothly converts a variety of dialkyl phosphonates to the corresponding bis(trimethylsilyl) esters, which are readily hydrolyzed to the phosphonic acids under neutral conditions (Scheme 41).[112,113] This process involves attack on the silicon of TMSBr by the phosphoryl oxygen of **85**, followed by an S_N2 displacement by bromide ion on an alkyl group to yield the trimethylsilyl phosphonate **86**. A repetition of this



Scheme 41

reaction sequence yields the bis(trimethylsilyl)phosphonate **87**. These reaction conditions are mild and compatible with many sensitive functional groups, as shown in Scheme 41.

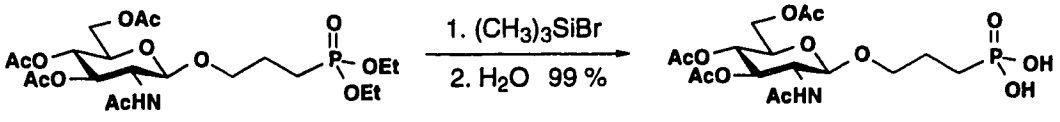
In a model system (Scheme 42), treatment of diethyl benzylphosphonate **88** (readily derived from benzyl bromide and triethyl phosphite) with neat bromotrimethylsilane at room temperature, followed by hydrolysis with a small excess of H_2O produces the phosphonic acid **89**.



88 **89**

Scheme 42

Hence, dealkylation of glycosyl phosphonate **84** was attempted (Scheme 43). Use of a large excess of TMSBr (> 5 equivalents) results in cleavage of the glycosidic bond along with removal of the ethyl groups. However, dealkylation using 2.8 equivalents of TMSBr proceeds smoothly and subsequent hydrolysis furnishes the phosphonic acid **77**.



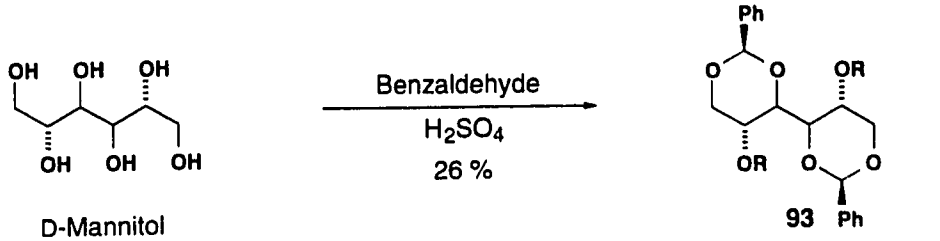
84 **77**

Scheme 43

The final piece necessary for the target compounds is a lipid-containing glyceric acid moiety. The (*R*)-glycerate-alkyl ethers are accessible by modification of the

procedure originally devised by Schubert and Welzel[114] and adopted by Hecker and coworkers[33] for the synthesis of related compounds. Three (*R*)-glycerates **90**, **91**, and **92** with octyl, (*R*)- and (*S*)-3,7-dimethyloctyl side chains respectively, were chosen for our studies.

Benzylidenation of D-mannitol by reaction with benzaldehyde in the presence of an acid catalyst gives the bis-benzylidene mannitol **93** (Scheme 44).[115] Alkylation of the two remaining free hydroxyl groups with octyl, (*R*)-citronellyl, or (*S*)-citronellyl bromide produces **94**, **95**, or **96**. Removal of the benzylidene acetals of **95** and **96** by hydrogenolysis simultaneously saturates the carbon-carbon double bond of the citronellyl moieties to afford tetraols **98** and **99**. In the case of the octyl derivative **94**, acidic hydrolysis provides the expected tetraol **97**. Oxidative cleavage of tetraols **97**, **98**, and **99** with sodium metaperiodate generates the intermediate aldehydes, which were initially subjected to oxidation with silver oxide without separation in an attempt to generate carboxylic acids **100**, **101** and **102**. After several unsuccessful attempts, a component presumed to be the intermediate aldehyde of the octyl derivative was isolated and subjected to spectroscopic studies. Mass spectrometry (CI, NH_3) gives the required molecular weight; however, ^1H NMR and ^{13}C NMR spectra reveal no characteristics expected for aldehydes, and provide little information due to extensive overlap of signals. It may be that the formation of aldehyde dimers might account for these phenomena (Scheme 45). The formation of acetals and hemiacetals would preclude the observation of an aldehyde carbonyl signal, and the existence of four possible dimeric structures would result in complex spectra. The cyclized six-membered ring systems could also make such molecules more stable toward oxidation.



R = H

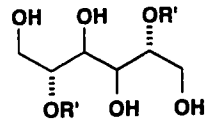
NaH, RBr, 52-71 %

R =

94 Octyl

95 (*R*)-Citronellyl

96 (*S*)-Citronellyl



for **97** HCl, EtOH

for **98** & **99** H_2, Pd/C

40-88 %

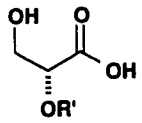
R' =

97 Octyl

98 (*R*)-3,7-dimethyloctyl

99 (*S*)-3,7-dimethyloctyl

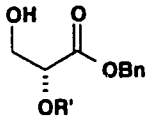
85-94 %: 1. $NaIO_4$ 2. Ag_2O, NaOH



BnBr, DMF

$NaHCO_3$

62-89 %



R' =

100 Octyl

101 (*R*)-3,7-dimethyloctyl

102 (*S*)-3,7-dimethyloctyl

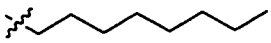
R' =

90 Octyl

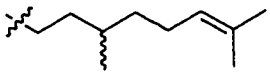
91 (*R*)-3,7-dimethyloctyl

92 (*S*)-3,7-dimethyloctyl

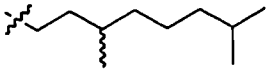
Octyl



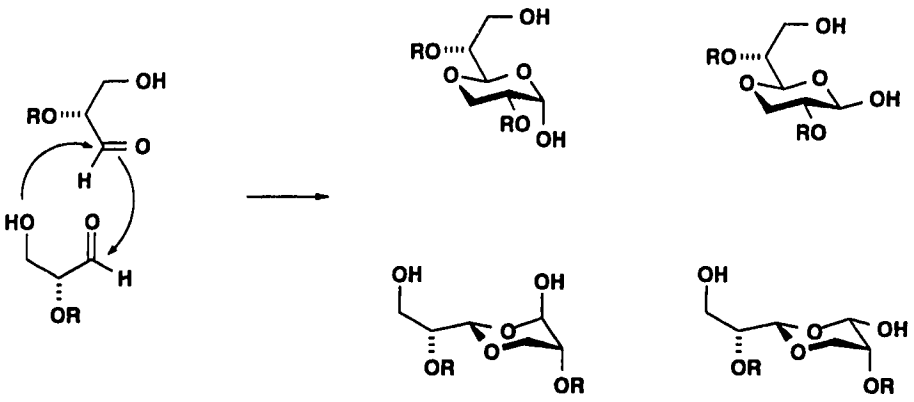
Citronellyl



3,7-dimethyloctyl



Scheme 44

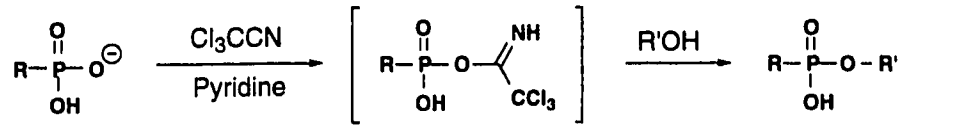


R = Lipid alkyl groups

Scheme 45

In agreement with this proposal, the oxidation under basic conditions using NaOH produces carboxylic acids **100**, **101**, and **102** in 85 %, 94 %, and 85 % yield, respectively. Esterification of the acids with benzyl bromide and sodium bicarbonate furnishes the (*R*)-glycerate-alkyl ether subunits **90**, **91** and **92**.

Attention was now directed toward finding efficient coupling methods. Since organic phosphoric acids occur in a number of biologically important substances, such as nucleic acids and phospholipids, extensive efforts have been made to construct these systems. A vast array of phosphorylation methods have been developed,[116] including a trichloroacetonitrile-mediated coupling reaction which has previously been used in the synthesis of pyrophosphate and phosphoric acid esters.[117] Upon treatment with trichloroacetonitrile and pyridine (Scheme 46), phosphoric acid is converted to a reactive trichloroacetimidoyl phosphate intermediate **103** which undergoes condensation with a further phosphoric acid molecule or an alcohol to produce either a pyrophosphate or a phosphoric monoester.



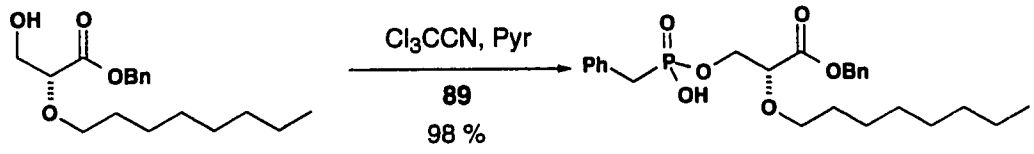
103

R = OH or alkyl goup

R' = $PO(OH)_2$ or alkyl group

Scheme 46

To test the efficiency of this coupling process, a model reaction was conducted (Scheme 47). Thus condensation of benzyl phosphonic acid (**89**) with benzyl glycerate-octyl ether (**90**) in the presence of trichloroacetonitrile and pyridine[57,117] produces the corresponding phosphonic acid monoester **104** in almost quantitative yield.



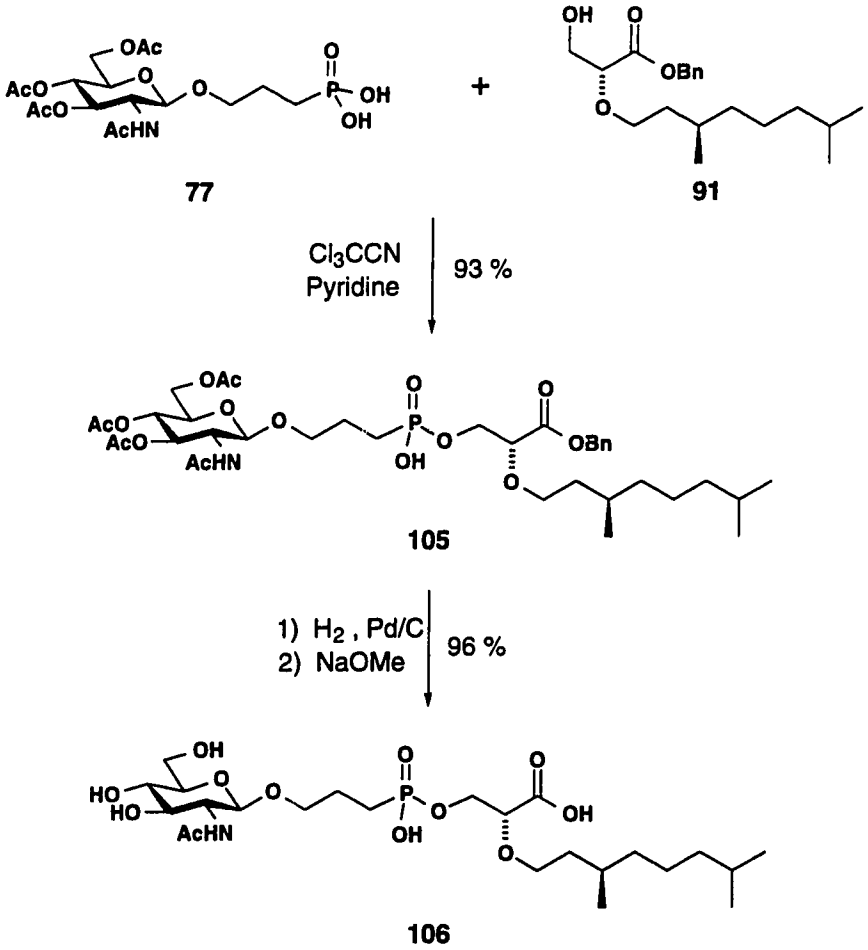
90 **104**

Scheme 47

For analysis of the ^{1}H and ^{13}C NMR spectra of the product, a mixture of CD_2Cl_2, CD_3OH, and pyridine-d_5 (2 : 1 : 0.5) gives the most informative spectra; other solvents cause the resonances to broaden. This may be due to the presence of both hydrophilic phosphonic acid and hydrophobic lipid moieties which causes pure **104** to form aggregates in solution. This behavior is inhibited by impurities such as trichloroacetamide, a by-product of the coupling reaction. A similar phenomenon was also observed by the Welzel group with moenomycin A degradation products.[25]

The desired coupling reaction was then conducted. Reaction of the phosphonic acid **77** with glycerate **91**, under standard conditions (trichloroacetonitrile/pyridine),

produces the target skeleton **105**. Hydrogenolysis over 10 % palladium on carbon removes the benzyl ester, and saponification with 4 equivalents of methanolic sodium methoxide affords the desired product **106** (Scheme 48).



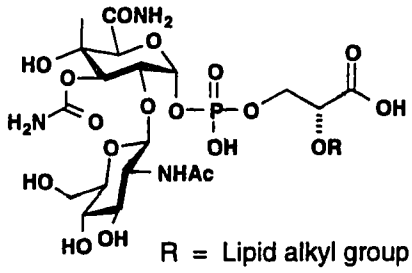
Scheme 48

In summary, type B target **106**, designed to determine the relative contribution of the central sugar unit to the antibiotic activity, can be synthesized (9 steps in 12.6 % overall yield from known compounds) through trichloroacetonitrile-mediated condensation of the phosphonic acid **77** with the glycerate-alkyl ether **91**. The synthesis

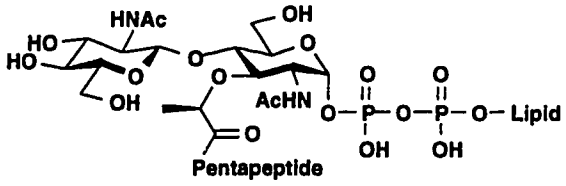
of **77** proceeds readily by glycosylation of 3-bromopropanol with oxazoline **65**, followed by Arbuzov reaction and subsequent dealkylation. The required (*R*)-glycerate-alkyl ethers are readily prepared from D-mannitol by modification of the literature procedures. The development of the methodologies involved in the synthesis of moenomycin A anologues such as **106** provides valuable information for the extension of this synthetic strategy to more complicated systems. Investigations on the potential antibiotic properties and transglycosylase inhibition by **106** are in progress in collaboration with the group of Professor van Heijenoort in France.

Part 4: The Synthesis of Type C Targets

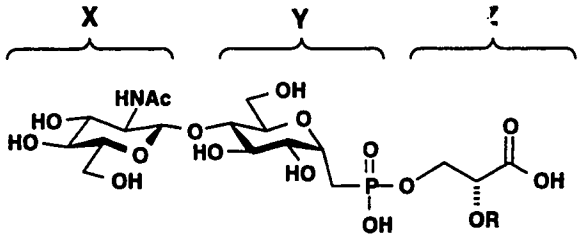
The previous target analogues designed by us and others[31,32] mimicked the active disaccharide portion of the natural moenomycin antibiotics as blockers of transglycosylase. However, the natural substrate of the enzyme, the peptidoglycan monomer (PGM), also provides a structural motif for inhibitor design. Type **C** targets combine structural features of both the active portion of moenomycin A and the PGM (Figure 22). The disaccharide portion of the targets bears a close resemblance to that of the transglycosylase substrate with the terminal D-glucosamine unit expected for recognition. The pyrophosphate group of PGM is replaced by a *C*-glycoside phosphonate; a stable surrogate of the *O*-glycoside phosphate portion found in the natural inhibitors.



Moenomycin A active portion



Peptidoglycan monomer

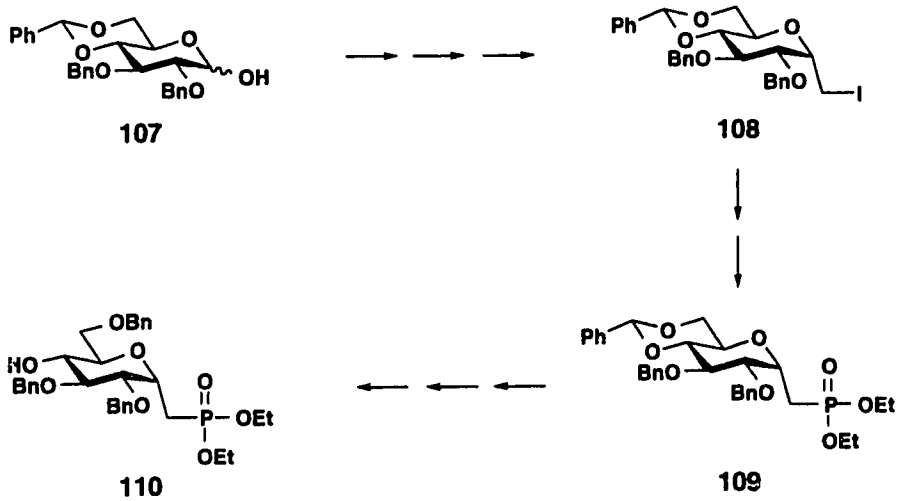


Type **C** targets R = Lipid alkyl group

Figure 22

Analogous to the type **A** and **B** targets, the synthetic approach toward type **C** is also a convergent one involving the sequential coupling of suitably protected fragments **X**, **Y**, and **Z** and final deprotection. With the availability of the fragments **X** and **Z** (from Parts 2 and 3), our attention focused on the preparation of the central D-glucose *C*-phosphonate **Y** unit. The subunit **Y** should contain a temporary blocking group at O-4 to allow the selective removal at the required stage for construction the disaccharide **XY** system. In addition, **Y** must bear a group which permits selective deprotection at the phosphonate end for attachment of the (*R*)-glycerate subunit **Z**.

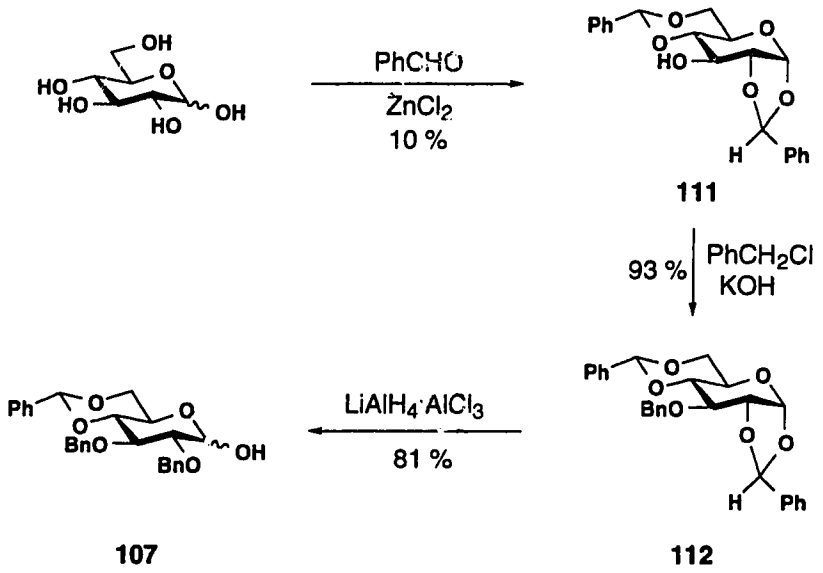
Although such a system could be potentially derived from the (α-glucosyl)methylenephosphonate **55** (from Part 2), it was of interest to examine the applicability of the mercury-assisted cyclization approach on different sugar substrates. Sugar **107** was projected as the requisite substrate (Scheme 49). It contains the 2-*O*-benzyl group required for the stereoselective cyclization and possesses the 4,6-benzylidene moiety as a temporary blocking group. Potentially this fully protected reducing sugar could undergo the Wittig olefination, mercury-assisted cyclization, and



Scheme 49

iododemercuration sequence to give the *C*-glycoside **108** with the required α-configuration. Arbuzov reaction followed by regioselective ring opening of the benzylidene group of **109** would give the properly protected subunit **Y**, compound **110**.

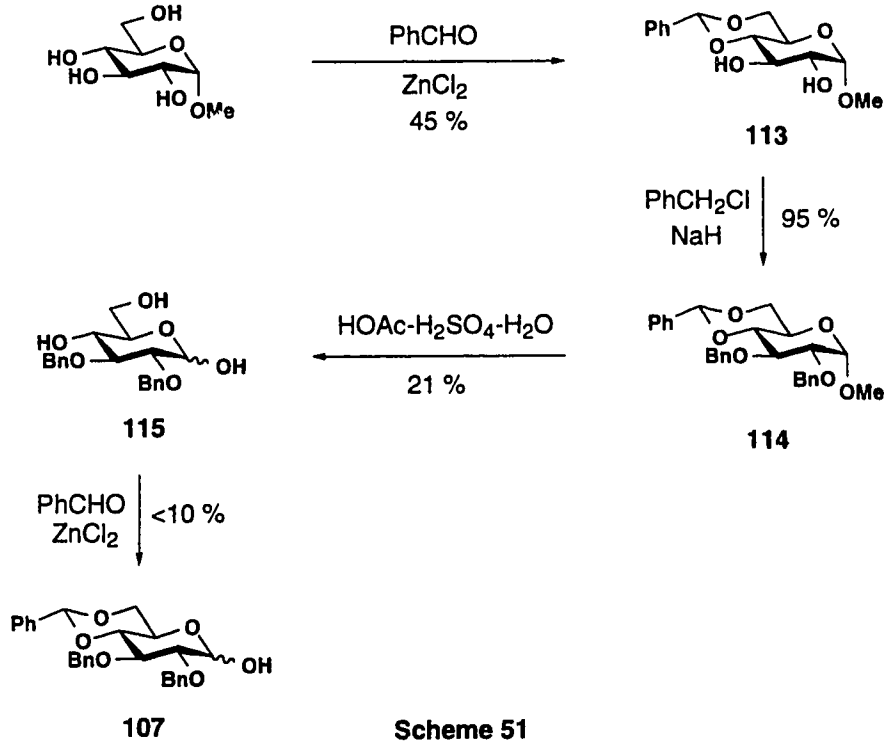
A survey of the literature produced two precedents for the synthesis of sugar **107**. Sharpless and coworkers utilized this material to prepare the *C*-glycoside by Wittig olefination, asymmetric epoxidation, and subsequent cyclization.[118] However, the preparation of this sugar is not described. Lipták *et al.* reported a multistep synthesis of **107** (Scheme 50) involving benzylidenation of D-glucose to give 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose (**111**), followed by benzylation of the 3-position to generate **112**, and finally, $LiAlH_4$-$AlCl_3$ induced selective 1,2-*O*-benzylidene ring



Scheme 50

opening to afford the reducing sugar **107** in an overall yield of 8.0 %.[119] A more efficient procedure was required to provide sufficient amounts of **107** so that the further transformations could proceed effectively.

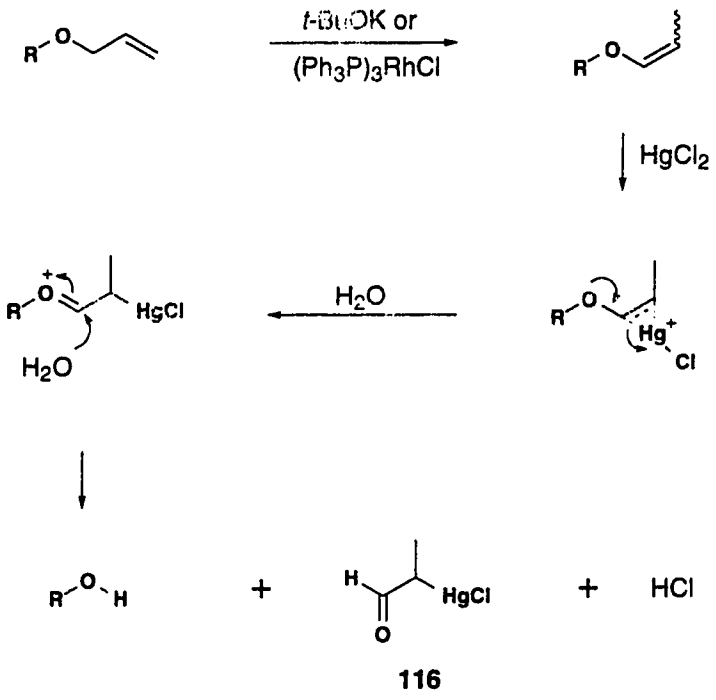
A classical route beginning with methyl α-D-glucopyranoside was attempted first (Scheme 51). Benzylidenation of methyl α-D-glucopyranoside with benzaldehyde and freshly fused zinc chloride affords 4,6-O-benzylidene methyl glycoside **113**. Subsequent benzylation of the 2- and 3-positions with NaH and benzyl chloride provides the fully



Scheme 51

protected methyl glycoside **114**. Hydrolysis of methyl glycoside **114** in acetic acid-sulphuric acid results in the removal of the benzylidene ring and subsequent cleavage of the glycosidic bond.[120] However, the hydrolytic step gives extremely low yields of **115** under a variety of conditions. Heating a solution of glycoside **114** in acetic acid and 2 N sulphuric acid (1:1, v/v) at 85 °C for 6 days provides the highest yield (21 %). Isolation of the triol **115** from the large quantity of acidic media is also difficult. Benzylidenation of **115** with benzaldehyde and freshly fused zinc chloride gives **107** in low yield (< 10 %).

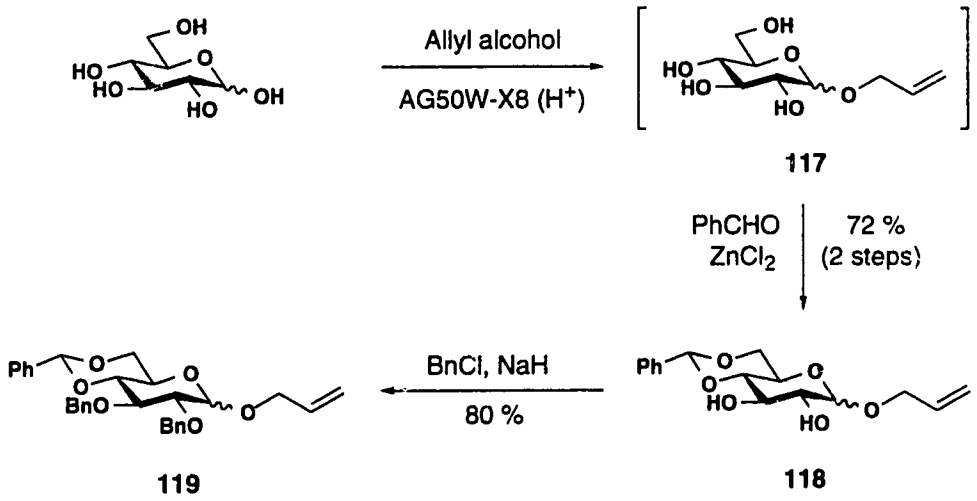
Due to the problems associated with the preparation of **115**, an alternative method which contains a more labile anomeric group was needed. The anomeric group should be removable under mild conditions after all protecting groups have been installed. Consequently, the allyl glycoside was chosen for this purpose. Allyl ethers are relatively stable to acids and bases and can be isomerized upon treatment with potassium *t*-butoxide[121] or Wilkinson's catalyst, tris(phenylphosphine)rhodium (I) chloride[122] (Scheme 52). The resultant prop-1-enyl ethers can be removed under a variety of conditions, such as hydrolysis or oxidative cleavage. In particular, the method described by Gigg and coworkers,[123] using mercuric chloride and mercury oxide to afford the free alcohol and chloromercuripropionaldehyde **116**, has seen extensive use because of the mild conditions. The hydrogen chloride liberated in the reaction is removed by mercury oxide to retain the neutrality of the medium.



116

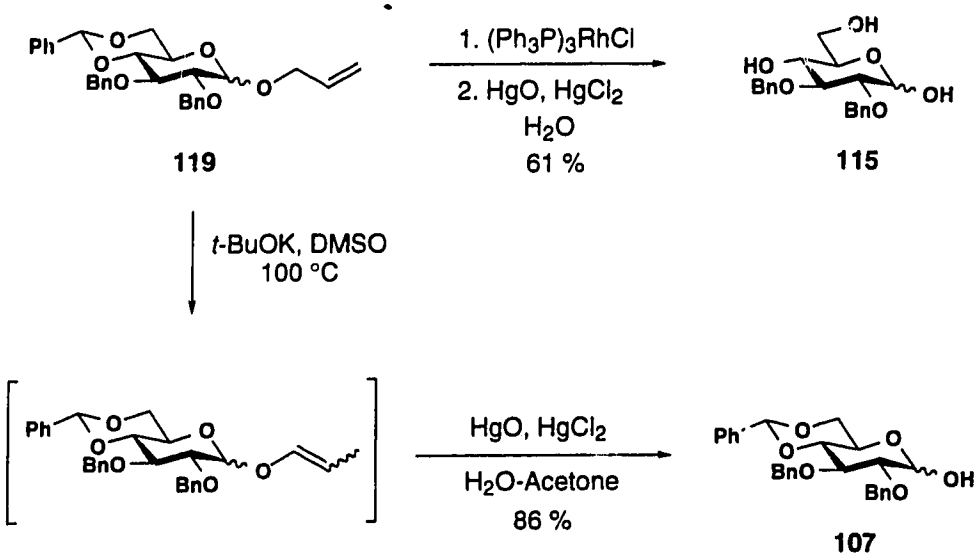
Scheme 52

Thus, Fischer glycosylation[88] of D-glucose with allyl alcohol using pre-dried AG50W-X8 (H^+) ion exchange resin as catalyst gives the allyl glycoside **117**[124] (Scheme 53), which is treated with benzaldehyde and zinc chloride without separation to produce the benzylidene allyl glycoside **118** as a 1.1 : 1 mixture of α- and β-anomers in 72 % overall yield. Use of pre-dried cation exchange resins significantly improves the yield over that reported in the literature (26 %).[124] Benzylation of the two remaining hydroxyl groups with NaH and benzyl chloride produces the fully blocked allyl glycoside **119**.



Scheme 53

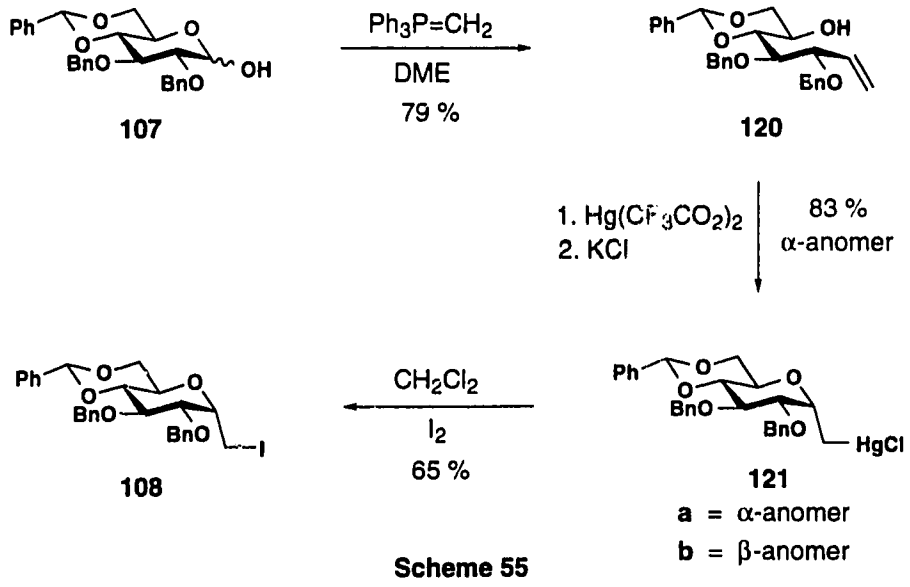
The next task was the removal of anomeric allyl group. Reaction of allyl glycoside **119** with Wilkinson's catalyst followed by hydrolysis with mercury chloride and mercury oxide gives triol **115** (Scheme 54). Unfortunately, under the conditions, the benzylidene group is also removed. An alternative but more drastic treatment with potassium *t*-butoxide in DMSO at 100 °C completes isomerization of the allyl glycoside **119** in 2 hours. Hydrolysis with mercury chloride and yellow mercury oxide then provides the reducing sugar **107**.



Scheme 54

In summary, a highly efficient 4-step route was developed to produce the reducing sugar **107** in 50 % overall yield from D-glucose which compares far superior to the 8.0 % yield in the literature preparation. This sets the stage for a detailed study of the Wittig olefination, mercury-assisted cyclization, and iododemercuration reaction sequence on this particular substrate.

Reaction of the sugar **107** with freshly prepared ylide in DME gives the olefin **120** (Scheme 55). However, upon treatment with mercury acetate, olefin **120** fails to cyclize to the desired *C*-glycoside. Fortunately, exposure to the more reactive mercury trifluoroacetate[125] induces cyclization to a mixture of α and β-isomers **121a** and **121b** in 96 % yield in a 4.3 : 1 ratio as indicated by ^{1}H NMR spectrometry. Apparently, the strain imposed by the two trans-fused six-membered rings seriously hinders the cyclization process.



Scheme 55

Iododemercuration of the mixture of organomercury compounds **121a** and **121b** provides the corresponding iodo derivatives, which are readily separated by flash chromatography to give **108** (Scheme 54). The α configuration of **108** is unequivocally assigned on the basis of NMR studies. The ^1H-^1H COSY experiment allows the definitive identification of individual protons, and the coupling constant, $J_{1,2} = 4.5$ Hz, clearly indicates an equatorial-axial relationship of these two protons. Further evidence comes from a nuclear Overhauser enhancement (NOE) experiment. Irradiation of H-1 produces a 14 % enhancement of H-2, which is consistent with the α-anomer (Figure 23).

Figure 23

With the formation of the α-*C*-glycoside secured, the introduction of the phosphonate moiety could be addressed. Compound **122** with a (phosphinyl)-phosphonate moiety appeared to also be an interesting target analogue of the corresponding pyrophosphate derivatives.[126] Potentially, Arbuzov reaction of **108** with phosphorus(III) intermediate (**123**) could generate compound **122** (Figure 24).

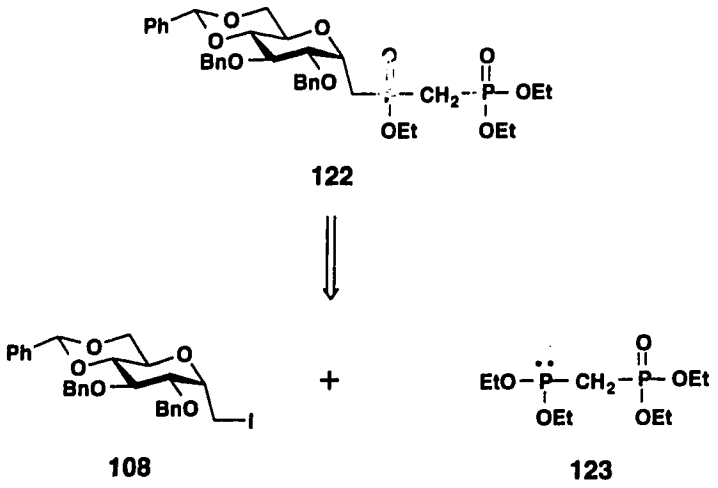
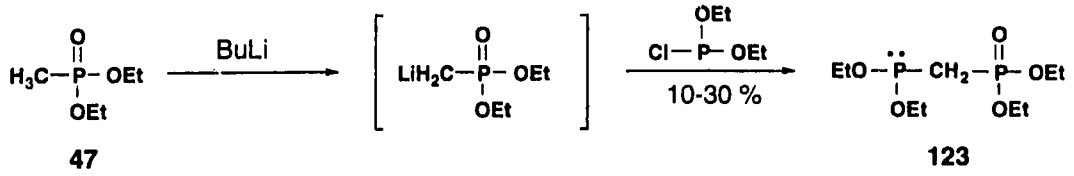


Figure 24

Novikova *et al.* first reported the synthesis of **123**.[127] Poulter and coworkers subsequently utilized this reagent in the synthesis of isopentenyl diphosphate analogues.[128] In Novikova's study, condensation of $LiCH_2P(O)(OEt)_2$ with diethyl phosphorochloridite produces the **123** in 30 % yield. However, Poulter *et al* were unable to repeat this synthesis and used a multistep sequence instead. Despite the possible difficulties, Novikova's approach was explored (Scheme 56). Reaction of *n*-BuLi with diethyl phosphonate (**47**) at -78 °C generates the phosphonate anion, which is then exposed to three equivalents of the commercially available diethyl phosphorochloridite. Filtration followed by distillation under argon atmosphere provides **123** in low yield (10-30 %). Several trials demonstrate that **123** is indeed difficult to make due to its

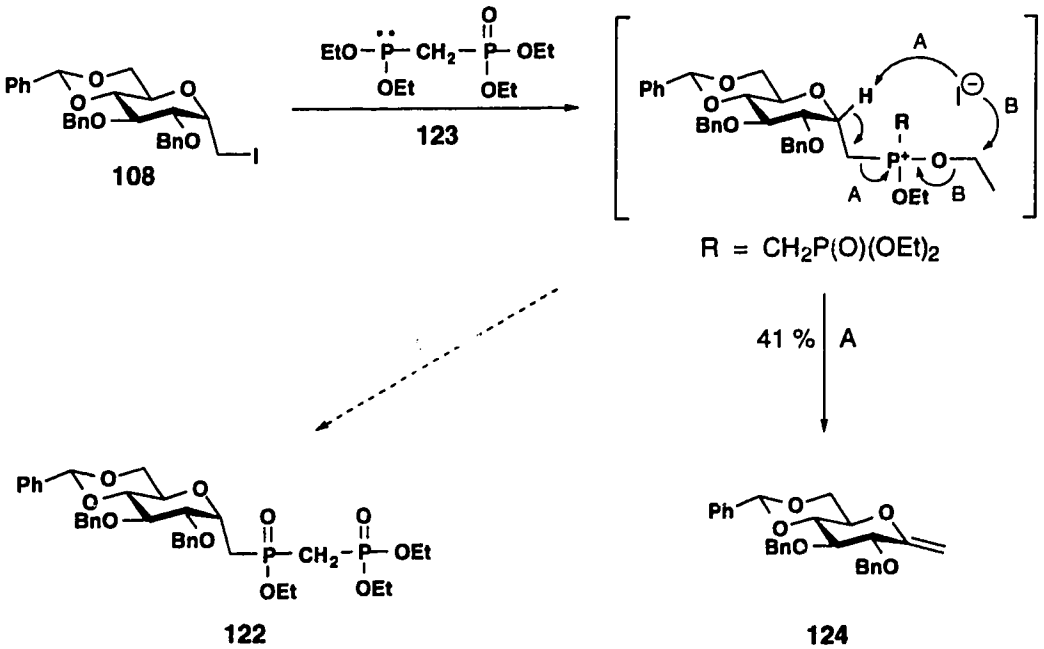
extreme sensitivity to aerobic oxidation. The entire reaction process must be rigorously conducted under argon atmosphere, especially during solvent removal and vacuum distillation. Compound **123** is stable at -20 °C under argon for approximately a week and appears to be oxidized upon storage. In addition to its sensitive nature, **123** also possesses a very unpleasant smell and causes severe headaches.



47 **123**

Scheme 56

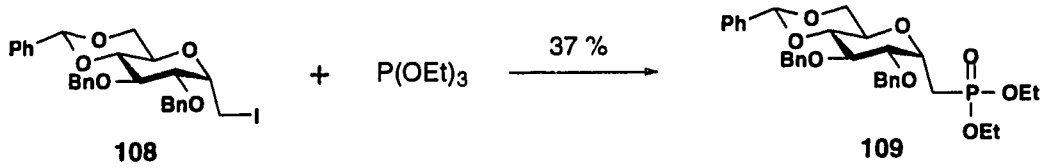
Attempted Arbuzov reaction of **108** and **123** fails to give the expected product **122**. Instead, the elimination product, the exo-methylene sugar **124**, is produced (Scheme 57). With variation of reaction conditions, **108** remains intact when the reaction



108 **122** **124**

Scheme 57

temperature is below 100 °C, but elimination inevitably occurs at higher temperature (100 to 170 °C). It is possible that the mechanism involves abstraction of the anomeric hydrogen to cause elimination (Route A), rather than the desired S_N2 attack on the ethyl carbon to complete the Arbuzov reaction (Route B). However, Arbuzov reaction of **108** with triethyl phosphite under such forcing conditions (160 °C for 24 h) affords the expected *C*-glycoside phosphonate **109** in 37 % yield (Scheme 58).

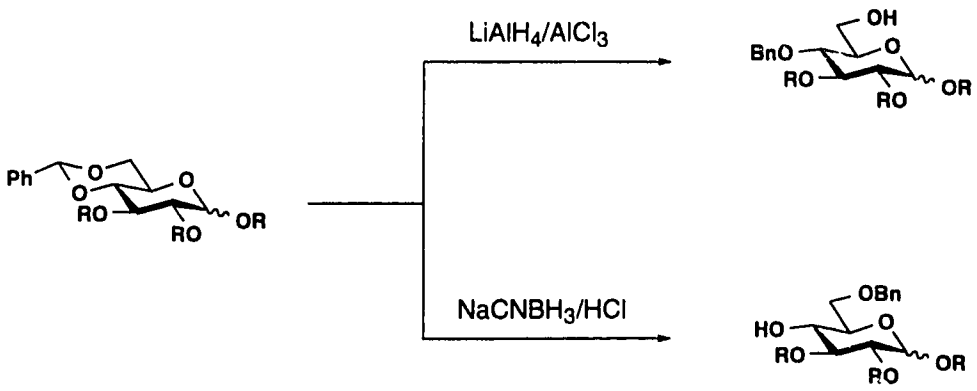


108 **109**

Scheme 58

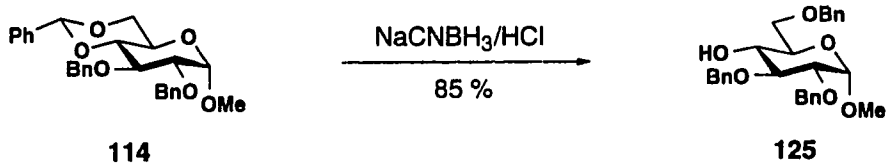
It seemed that the sterically hindered environment of the *C*-glycosyl iodide could be responsible for the difficulties experienced with the Arbuzov reaction. The electrophilic center is located beneath two trans-fused six-membered rings, and consequently approach of the phosphite reagent may be hindered. Removal of the benzylidene ring would give the molecule more flexibility and could aid substitution of the iodide. Reductive ring opening of the benzylidene ring at an earlier stage could therefore assist the Arbuzov process.

Depending on the nature of the reagents and the reaction conditions, the reductive ring opening of benzylidene acetals proceeds with different regioselectivity (Scheme 59). Lipták *et al.* demonstrated that $LiAlH_4/AlCl_3$ system cleaves 4,6-*O*-benzylidene acetals to produce predominantly the 4-*O*-benzyl compound with the 6-OH free.[129] Garegg *et al.* subsequently established that $NaCNBH_3$-HCl in THF provides a regioselectivity opposite to the one observed for the $LiAlH_4/AlCl_3$ reaction.[97,130,131] These two complementary methods have found wide application in carbohydrate synthesis.



Scheme 59

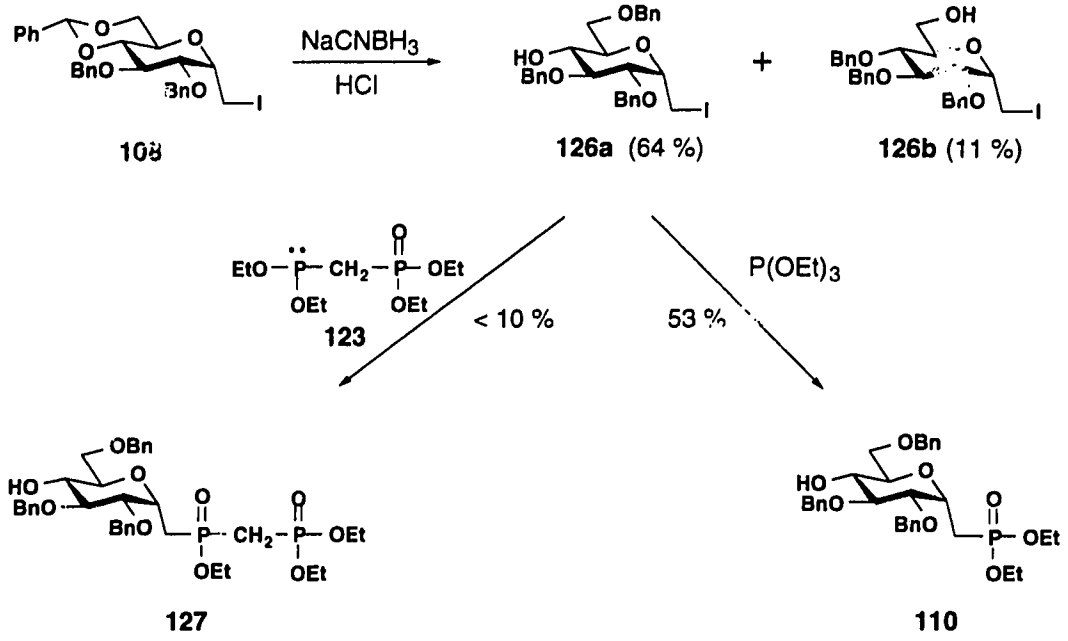
To preserve valuable materials, a model reaction was conducted (Scheme 60). Reaction of 4,6-benzylidene methyl glycoside **114** with sodium cyanoborohydride in



114 **125**

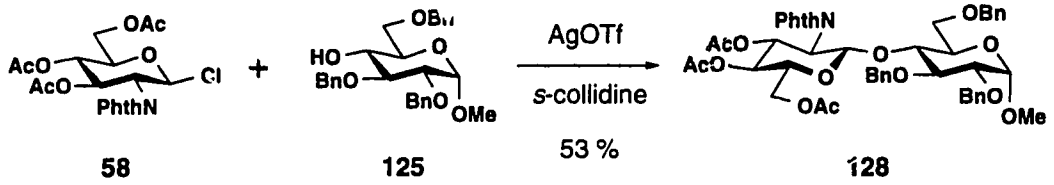
Scheme 60

acidic ether-THF frees the 4-OH to generate the 6-benzyl glycoside **125**.[130] Similarly, reduction of the benzylidene ring of *C*-glycoside **198** with $NaCNBH_3$-HCl in THF-ether gives the required 4-OH *C*-glycoside **126a** along with the side product 6-OH *C*-glycoside **126b** (Scheme 61). Arbuzov reaction of **126a** with **123** produces phosphonate **127** in low yield (<10 %). This route was not investigated further because of the sensitivity and possible toxicity associated with **123**. Reaction of **126a** with triethyl phosphite furnishes the phosphonate **110** required for subunit **Y**.



Scheme 61

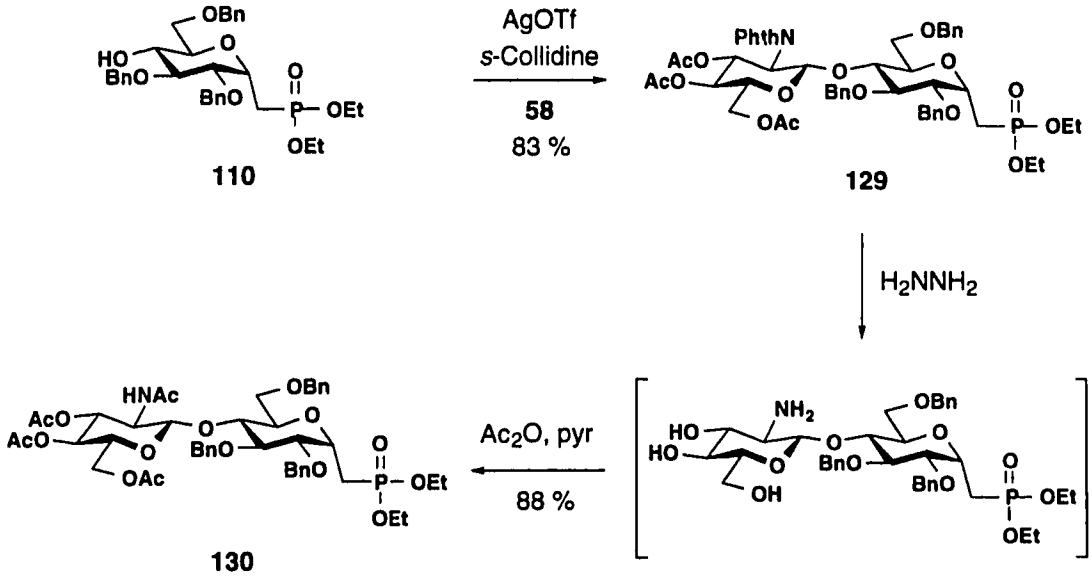
With the successful preparation of subunit **Y**, the construction of the disaccharide appears feasible. In a model to test the glycosylation of the 4-OH, reaction of methyl glycoside **125**, phthalimido chloride **58**, silver trifluoromethanesulfonate, and *s*-collidine produces the β-linked disaccharide **128** (Scheme 62). Glycosylation of **110** with chloride



Scheme 62

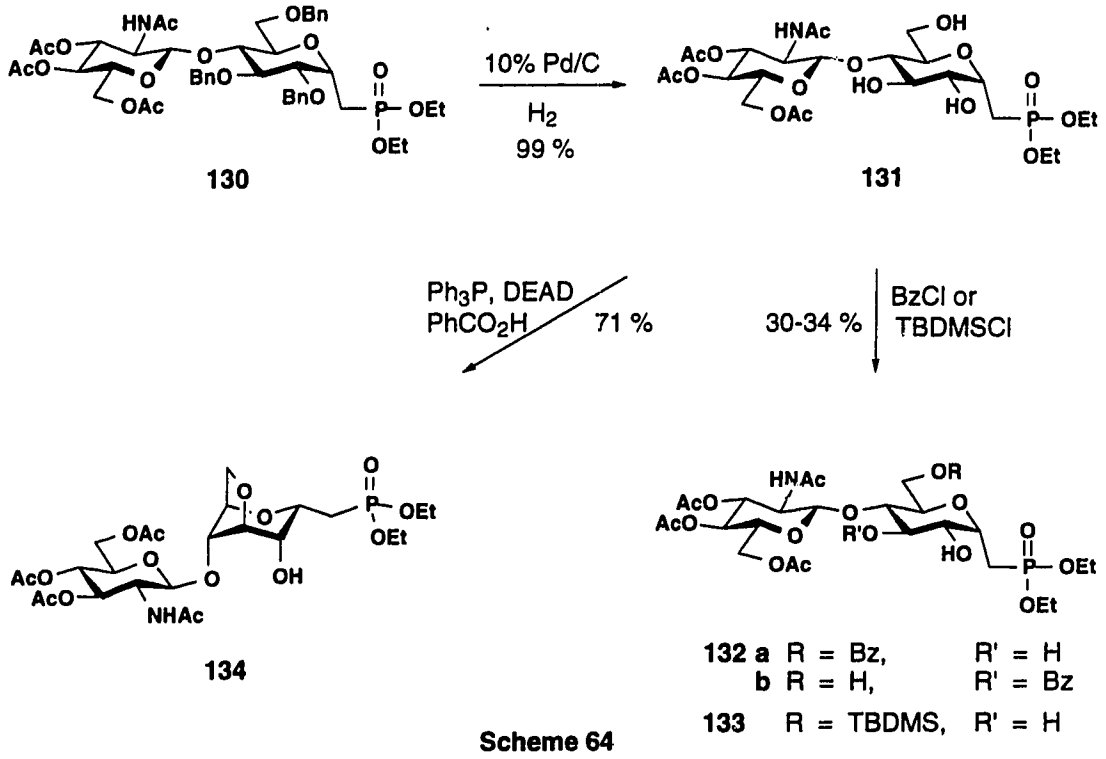
58 under the same conditions yields the disaccharide **129** in 83 % yield without complications (Scheme 63). The β configuration of the glycosidic linkage is readily assigned since the H-1' occurs as a doublet at δ 5.60 with a 8.0 Hz coupling constant.

The disaccharide **129** is converted readily to the corresponding *N*-acetyl derivative **130** by the well-established hydrazinolysis and *N*-acetylation sequence.[132]



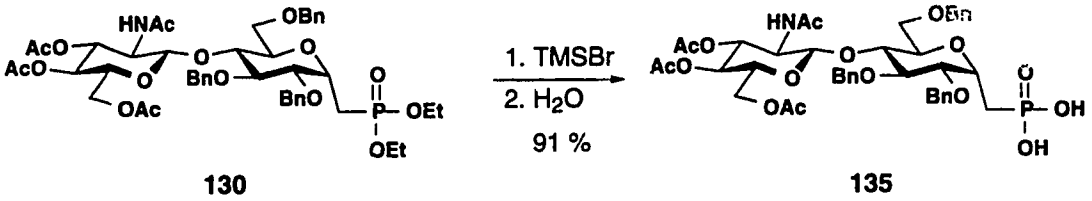
Scheme 63

Since moenomycin A has a urethane group attached on the first sugar moiety, the potential modification of the central glucose unit of **130** was briefly explored (Scheme 64). These studies began with the hydrogenation of **130** over 10 % Pd/C to produce triol **131**. Subsequently, several reactions were attempted to protect the primary hydroxyl group. Treatment of **131** with trityl chloride[133] fails to give the trityl ether, presumably due to steric crowding. Benzoylation of **131** with benzoyl chloride provides a mixture of non-separable regioisomers **132** as indicated by ^{1}H NMR spectrometry in low yield (30 %). Reaction of **131** with *t*-butyldimethylsilyl chloride and imidazole affords the desired silyl ether **133**. However, this group proved incompatible with the bromotrimethylsilane dealkylation of the phosphonate. Mitsunobu reaction[134] of **131** with benzoic acid, diethyl azodicarboxylate (DEAD), and triphenylphosphine produces the dehydration product **134**. Further investigations were not attempted.

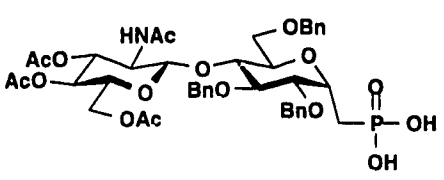


Scheme 64

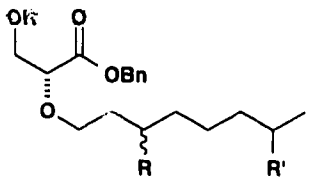
Dealkylation of the disaccharide phosphonate **130** with bromotrimethylsilane provides the "**XY** component" **135** ready for the attachment of the lipid-bearing subunit **Z** (Scheme 65). Condensation of three available glycerate lipids, **90**, **91**, and **92** (prepared in part 3) with the disaccharide phosphonic acid **135** using trichloroacetonitrile and pyridine as the coupling reagents completes the synthesis of the target skeletons **136**, **137**, and **138** (Scheme 66). 2-D ^{1}H-^{1}H COSY and inverse 2D ^{13}C-^{1}H heteronuclear multiple quantum coherence (HMQC)[133] experiments allow the complete



Scheme 65



135

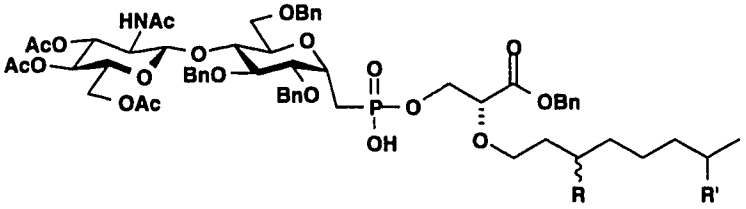


90 R = H, R' = H

91 R = (*R*)-CH_3, R' = CH_3

92 R = (*S*)-CH_3, R' = CH_3

78-95 % | Cl_3CCN, Pyridine

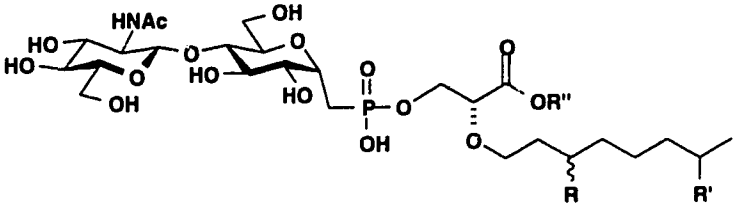


136 R = H, R' = H

137 R = (*R*)-CH_3, R' = CH_3

138 R = (*S*)-CH_3, R' = CH_3

92-96 % | 1. H_2 Pd/C; 2. NaOMe



139 R = H R' = H R'' = H

140 R = (*R*)-CH_3 R' = CH_3 R'' = H

141 R = (*S*)-CH_3 R' = CH_3 R'' = H

142 R = H R'=H R'' = CH_3

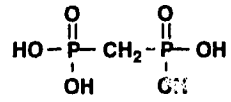
Scheme 66

assignment of the proton and carbon signals. Hydrogenolysis of the benzyl groups with 10 % Pd/C followed by de-O-acetylation using methanolic sodium methoxide generates the amphiphilic targets **139**, **140**, and **141**. In the case of the octyl derivative **136**, reversal of the deprotection steps produces the corresponding methyl ester **142**.

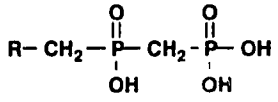
In summary, the synthesis of type **C** targets which combine structural features of both moenomycin A and peptidoglycan monomer has been achieved. As part of this synthesis, a route was also developed to offer improved access to sugar **107**. The Wittig olefination followed by the mercury induced cyclization sequence was successfully extended to this sugar substrate with good

Part 5: The Synthesis of a Potential Inhibitor of Squalene Synthetase.

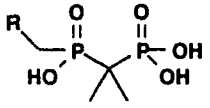
The biological importance of natural phos . . s and their instability toward hydrolytic enzymes continue to spur efforts to develop effective phosphate surrogates. Methylenediphosphonic acid and related structures have long been used as analogues of inorganic pyrophosphate.(Figure 25).[126] In the last few years, (phosphinyl)methyl-phosphonate (PMP) and related phosphinato(dimethylmethyl)phosphonate systems (PDMMP) have found application as stable pyrophosphate analogues in the design of inhibitors of prenyl transferase and squalene synthetase.[128,136-138] Very recently, chaetomellic acids have proven to be potent and highly specific farnesyl pyrophosphate (FPP) mimic inhibitors of a farnesyl-protein transferase involved in *ras* oncogene processing.[139,140]



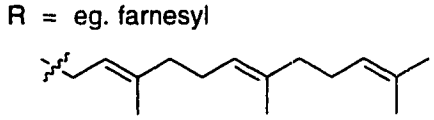
methylenediphosphonic acid



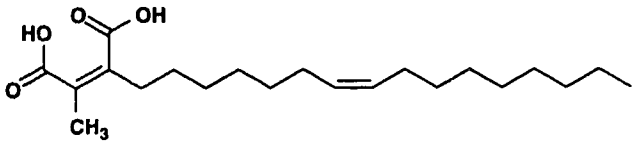
(phosphinylmethyl)phosphonate (PMP)



phosphinato(dimethylmethyl) phosphonate (PDMMP)



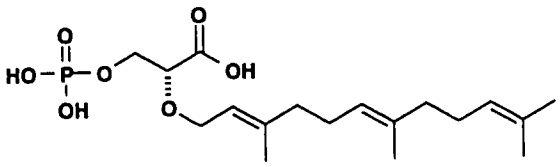
R = eg. farnesyl



chaetomellic acid B

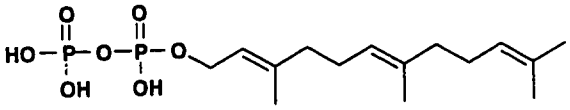
Figure 25

The mode of action of moenomycin antibiotics suggests that the phosphoglycerate moiety mimics the pyrophosphate moiety present in the peptidoglycan monomer. Thus, target **D** molecule **143** was designed as a mimic of farnesyl pyrophosphate (FPP) (Figure 26). Since **143** contains a phosphoglycerate moiety, it could therefore potentially be a potent inhibitor of FPP-utilizing enzymes such as squalene synthetase or farnesyl protein transferases.



Target **D**

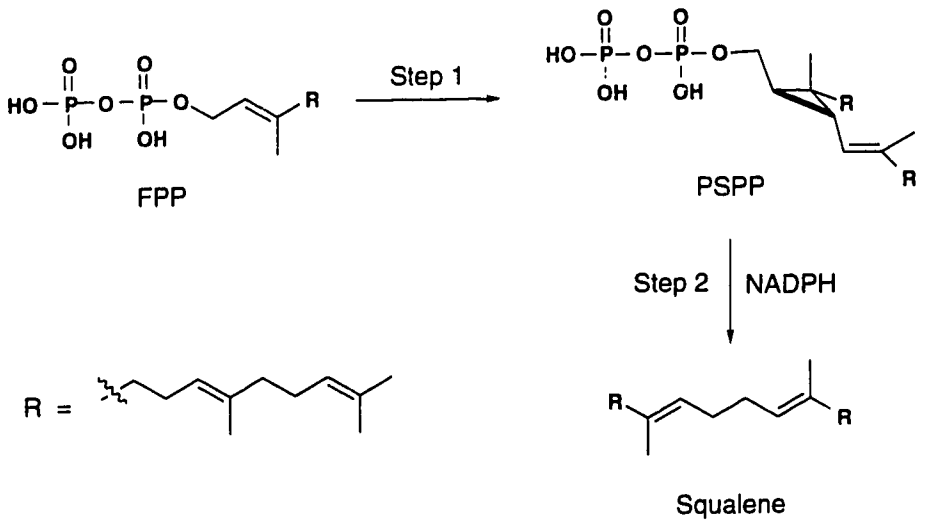
143



Farnesyl pyrophosphate (FPP)

Figure 26

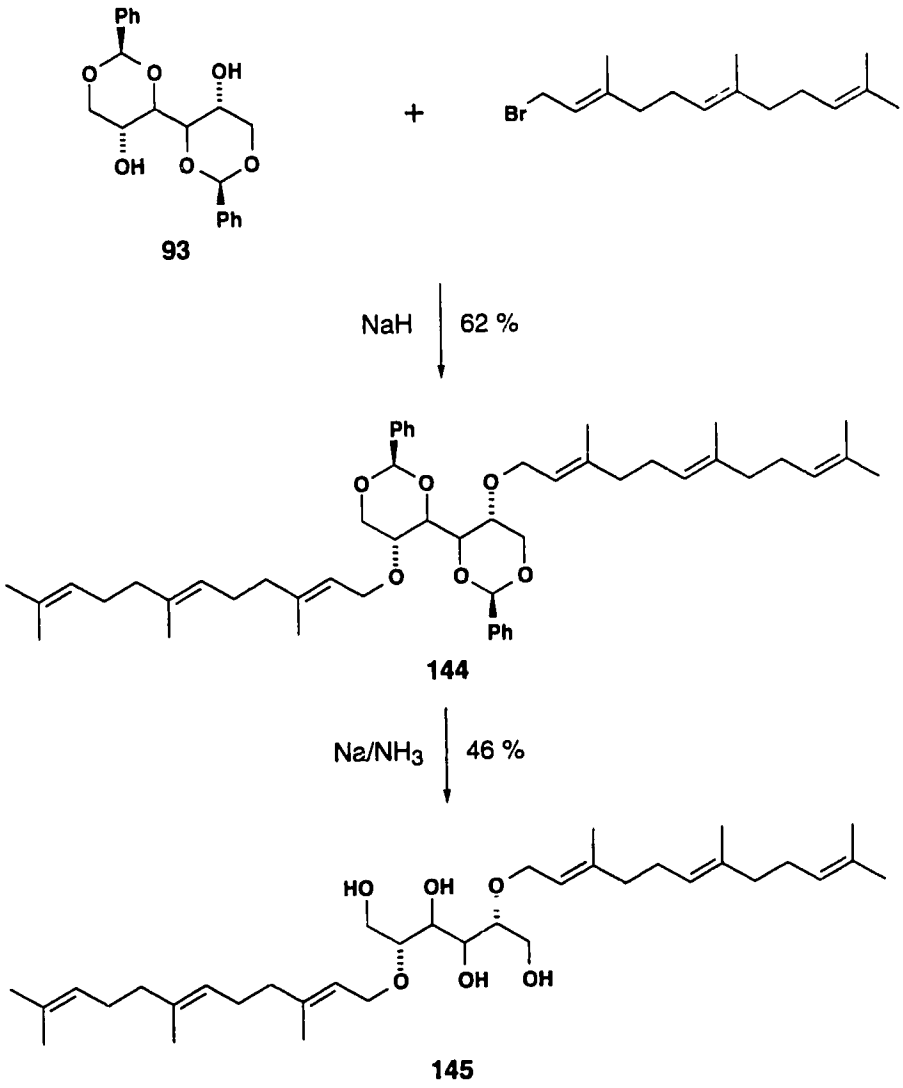
Squalene synthetase is a key enzyme involved in the cholesterol biosynthetic pathway.[35] It catalyzes the transformation of farnesyl diphosphate (FPP) to squalene in two steps. The first step condenses two molecules of FPP to presqualene diphosphate (PSPP), whereas the second step involves the reductive rearrangement of PSPP to squalene (Scheme 67).



Scheme 67

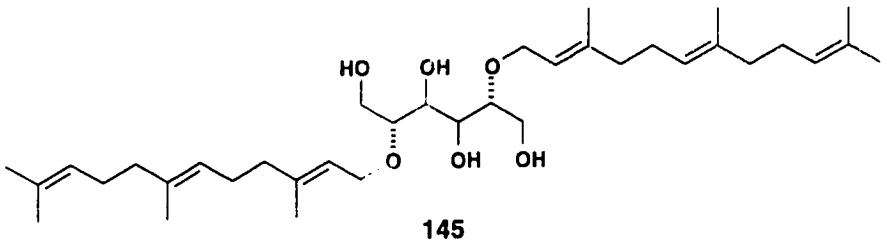
The successful methodology for the synthesis of glycerate-alkyl ethers developed previously appeared applicable to the synthesis of target **143**. Alkylation of the diol **93** with commercially available farnesyl bromide proceeds readily to give **144** (Scheme 68). The removal of the two benzylidene rings is difficult. Hydrolysis of **144** with either acetic acid or hydrochloric acid inevitably results in complicated mixtures, presumably due to the labile nature of the farnesyl moiety. Since the carbon-carbon double bonds are essential, a promising alternative is chemical reduction by sodium in liquid ammonia.[141] Thus, treatment of **144** with sodium in liquid ammonia in the presence of *t*-BuOH produces the desired tetraol **145** as a waxy solid.

At this juncture, instead of oxidative cleavage of the vicinal diol followed by oxidation to carboxylic acid, we decided to introduce the two phosphate groups to circumvent the problem associated with carboxylic acid protection. Phosphorylation of

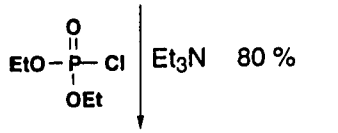


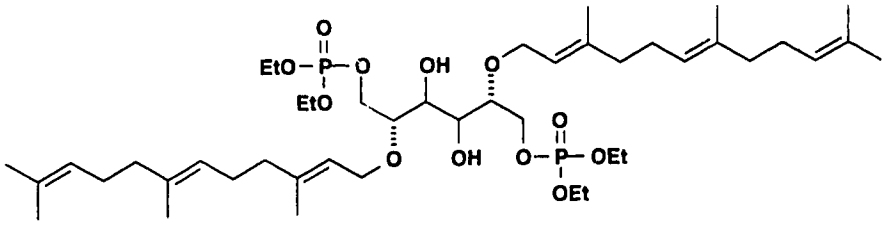
Scheme 68

the two primary hydroxyl groups with commercially available diethyl chlorophosphate in the presence of triethylamine yields the diphosphoryl mannitol **146** (Scheme 69). Treatment of diol **146** with sodium metaperiodate provides the intermediate aldehyde, which was oxidized without separation with silver oxide in the presence of sodium hydroxide. Attempts to generate the corresponding acid of salt **147** by acidification

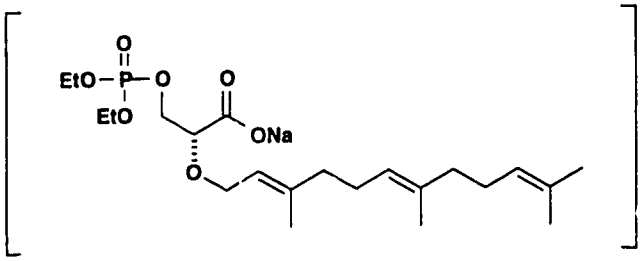


145

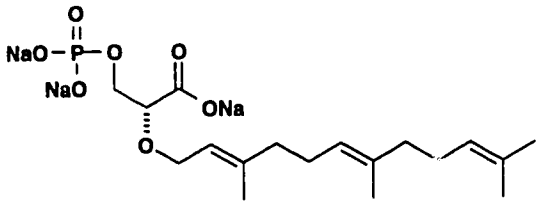




146



147



143

Scheme 69

results in complete decomposition, presumably due to the lability of this material. Hence the dealkylation following the oxidation was done without purification of the intermediate. Thus, reaction of sodium salt **147** with TMSBr in the presence of *s*-collidine as an acid scavenger[136,137] followed by salt formation (> 3 equivalents of NaOH) provides the trisodium salt of the target **143**.

In summary, the trisodium salt of target **143**, a potential mimic of farnesyl diphosphate, has been synthesized. The synthesis strategy is based on that developed in part 3 for glycerate-alkyl ethers, which is modified extensively for the synthesis of sensitive materials. Biological and enzyme inhibition studies are planned in the near future.

EXPERIMENTAL PROCEDURES

General Methods.

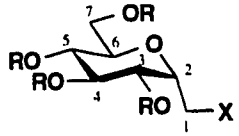
All processes involving air or moisture sensitive reactants were done under an atmosphere of dry argon using oven-dried glassware. Reagents and solvents were reagent grade and used as supplied unless otherwise mentioned. Solvents for anhydrous reactions were dried according to Perrin *et al.*[142] Tetrahydrofuran (THF), diethyl ether, 1,2-dimethoxyethane (DME), benzene, and toluene were distilled over sodium benzophenone ketyl under an argon atmosphere. Acetonitrile, dichloromethane, *N,N*-dimethylformamide (DMF), triethylamine, and pyridine were distilled over calcium hydride, and nitromethane was fractionated from P_2O_5. Methanol and ethanol were distilled over magnesium turnings and a catalytic amount of iodine. Dimethyl sulfoxide (DMSO) was distilled over calcium hydride and stored over CaH_2. Water was obtained from a Milli-Q reagent water system. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl, $NaHCO_3$, KOH, and NaOH refer to aqueous solutions. Solvent evaporation was performed under reduced pressure below 40 °C using a Büchi rotary evaporator, followed by evacuation (< 0.1 torr) to constant sample weight. Reactions involving triethyl phosphite and other phosphate reagents were performed in a fume hood.

Reactions and fractions from column chromatography were monitored and analyzed by thin-layer chromatography (TLC) using glass plates with a UV fluorescent indicator (normal silica, Merck 60 F_{254}; reverse phase, Merck RP-8 and RP-18 F_{254}). One or more of the following methods were used for visualization: UV absorption by fluorescence quenching; iodine staining; phosphomolybdic acid/ceric sulfate/sulfuric acid (10 g : 1.25 g : 8 % 250 mL) spray; 50 % sulfuric acid spray; and 0.1 % $KMnO_4$ spray. Flash column chromatography was performed by the method of Still[143] using

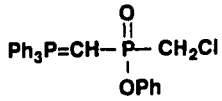
230-400 mesh silica (Merck, silica gel). Ion exchange resins AG1-X8 (Cl^- form, 100-200 mesh) and AG50W-X8 (H^+ form, 50-100 mesh) were purchased from Bio-Rad.

Melting points were determined on a Thomas-Hoover or Büchi oil immersion apparatus using open capillary tubes and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter with a microcell (10.0 cm path length, 0.9 mL) at ambient temperature. All specific rotations reported were measured at the sodium D line and were referenced against air. Infrared spectra (IR) were recorded on a Nicolet 7199 FT-IR spectrometer. Cast refers to the evaporation of a solution on a NaCl plate. Mass spectra (MS) were recorded on Kratos AEI MS-50 (high resolution mass spectrometry (HRMS), electron impact ionization (EI)), MS-12 (chemical ionization (CI), NH_3), and MS-9 (fast atom bombardment (FAB), argon) instruments. Cleland matrix used in FAB refers to a 5:1 mixture of dithiothreitol and dithioerythritol. Microanalyses were obtained on Perkin Elmer 240 or Carlo Erba 1180 elemental analyzers. ^1H NMR spectra were obtained at 80, 200, 300, 400, and 500 MHz; ^{13}C at 50, 75, 100, and 125 MHz; and ^{31}P at 81 and 162 MHz on Bruker or Varian instruments. ^1H NMR chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) using the solvent resonance as the reference: $CDCl_3$ δ 7.24, CD_2Cl_2 δ 5.32, CD_3OD δ 3.30, and $(CD_3)_2SO$ δ 2.49. ^{13}C shifts are reported relative to $CDCl_3$ δ 77.0, CD_2Cl_2 δ 53.8, CD_3OD δ 49.0, and $(CD_3)_2SO$ δ 39.5. ^{31}P shifts are relative to external 85 % H_3PO_4 set at 0.0 ppm. Selective homonuclear decoupling, shifts correlation spectroscopy (COSY), attached proton test (APT), and ^1H-^{13}C correlation experiments were occasionally used for signal assignments. ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), number of protons, coupling constant (s) in Hertz (Hz), and assignment. When appropriate, the multiplicity is proceeded by br, indicating that the signal was broad.

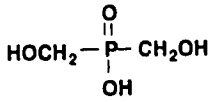
For NMR assignment only, protons of the (D-glucopyranosyl)methyl group present in the compounds described are numbered as indicated below. The methylene protons are defined as Ha and Hb, with the exception of the six-membered benzylidene ring system, wherein H-e and H-a are used to refer to the equatorial and axial protons,



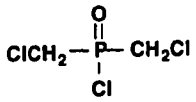
respectively. All literature compounds had IR, ^{1}H NMR, and mass spectra consistent with the reported data.



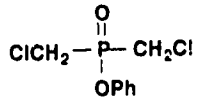
Phenyl (Chloromethyl)[triphenylphosphoranylidene)methyl]phosphinate (10). The procedure of Vargas and Rosenthal was modified.[56] Salt **14** (198 mg, 0.299 mmol) was dissolved in warm water (6.2 mL) and the solution was cooled to room temperature. Toluene (2.0 mL) was then added followed by a 20 % solution of K_2CO_3 (0.62 mL). The reaction mixture was stirred vigorously for one min and then the organic layer was separated and the aqueous layer was extracted with toluene (2 x 3 mL). The combined organic extracts were dried (K_2CO_3) and concentrated *in vacuo* to give the ylide **10** (150 mg, 82 %) as a solid: IR ($CHCl_3$ cast) 1592, 1490, 1210, 1199, 1162, 1105, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.70-7.10 (m, 20 H, Ar*H*), 4.96 (dd, 1 H, J = 13.0, 11.5 Hz, PC*H*HCl), 4.77 (dd, 1 H, J = 13.0, 6.2 Hz, PCH*H*Cl), 1.60 (dd, 1 H, J = 1.7, 1.1 Hz, P=C*H*P); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 21.1; MS (CI, NH_3) *m/z* (relative intensity) 467 (18), 466 (13), 465 (MH^+, 45), 264 (20), 263 (100).



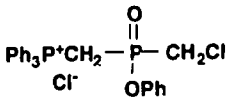
Bis(hydroxymethyl)phosphinic Acid (11). The literature procedure was followed.[60] A mixture of hypophosphorous acid (30.5 g of a 50 % aqueous solution, 231 mmol), paraformaldehyde (14.5 g, 161 mmol), and conc HCl (17.5 mL) was stirred at 40-45 °C until a clear solution was obtained, and this was then refluxed for 24 h. The reaction mixture was cooled to room temperature and then concentrated *in vacuo* to give acid **11** (28.5 g, 97 %) as a highly viscous, pale yellow oil: IR (neat, film) 3347 (br), 2900, 2830, 2291, 1657, 1423, 1168, 1048, 969, 852 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 3.60 (d, 4 H, J = 5.2 Hz, 2 x CH_2OH); ^{13}C NMR (D_2O, 200 MHz) δ 55.9 (d, J = 107.6 Hz); ^{31}P NMR (D_2O, 81 MHz) δ 45.6; HRMS (EI) Calcd for $C_2H_7O_4P$ (M^+): 126.0082. Found: 126.0086.



Bis(chloromethyl)phosphinic Chloride (12). The literature procedure was followed.[60] Freshly distilled thionyl chloride (28.0 mL, 353 mmol) was added dropwise over a period of 40 min to a stirred solution of bis(hydroxymethyl)phosphinic acid (10.0 g, 79.4 mmol) in anhydrous benzene (60 mL). After completion of the addition, the reaction mixture was heated slowly to reflux and kept at that temperature for 12 h. Distillation at atmospheric pressure and then under vacuum gave **12** (7.40 g, 32 %) as a colorless liquid: bp 89-90 °C (0.5-0.6 torr) (lit.[60] bp 80-85 °C (0.05-0.1 torr)); IR (neat, film) 2996, 2937, 1389, 1262, 1205, 972, 844, 662, 524 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.15-3.85 (m, 4 H, 2 x PCH_2Cl); ^{31}P NMR ($CDCl_3$, 81 MHz), δ 51.2; HRMS (EI) Cacld for $C_2H_4Cl_3OP$ (M^+): 183.9006 (2 x ^{37}Cl), 181.9036 (^{35}Cl, ^{35}Cl), 179.9065 (2 x ^{35}Cl). Found: 183.9005, 181.9034, 179.9064.

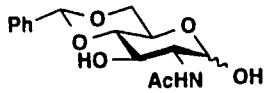


Phenyl Bis(chloromethyl)phosphinate (13). Phenol (2.02 g, 21.5 mmol) in anhydrous ether (20 mL), and then triethylamine (2.17g 21.5 mmol), were added dropwise to a stirred solution of chloride **12** (3.90 g, 2.15 mmol). The resulting mixture was then stirred at room temperature for 12 h and filtered. Evaporation of the filtrate *in vacuo* gave a pink liquid which was distilled under vacuum to produce the title compound **13** (4.10 g, 80 %) as a colorless liquid: bp 115-120 °C (0.10-0.15 torr) (lit.[144] bp 117-20 °C (0.02 torr)); IR (CCl_4 cast) 3000, 2940, 1590, 1490, 1267, 1194, 934 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.30-7.20 (m, 5 H, Ar*H*), 3.75 (d, 4 H, *J* = 9.0 Hz, 2 x CH_2Cl); HRMS (EI) Calcd for $C_8H_9Cl_2O_2P$ (M^+): 241.9659 (2 x ^{37}Cl), 239.9688 (^{37}Cl, ^{35}Cl), 237.9718 (2 x ^{35}Cl). Found: 241.9669, 239.9695, 237.9724.

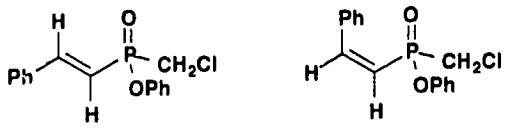


Phenyl (Chloromethyl)[(triphenylphosphoranylidene)methyl]phosphinate Chloride (14). The procedure of Vargas and Rosenthal was modified.[56] Phenyl bis(chloromethyl)phosphinate (**13**) (3.16 g, 13.2 mmol) and triphenylphosphine (3.85 g, 14.7 mmol) in toluene (40 mL) were heated to reflux under argon for 3 days. The crystalline product which formed was separated by filtration, washed with toluene (3 x 10 mL) and hexane (3 x 10 mL), and dried *in vacuo* to give pure **14** (2.65 g, 40 %) as white crystals. The filtrates and washings were combined and concentrated *in vacuo*. The residue was redissolved in toluene and the solution was heated at reflux for 4 days to give another crop of product (0.79 g, 10 %): IR (KBr disk) 1590, 1487, 1438, 1248, 1218, 1203, 1163, 1106, 941, 919, 824 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 8.00-7.35 (m, 20 H, Ar*H*), 6.90 (d, 2 H, *J* = 8.3 Hz, PCH_2P), 4.12 (dd, 2 H, *J* = 8.0, 1.6 Hz, PCH_2Cl);

^{13}C NMR (CD_3OD, 50 MHz) δ 168.6, 150.6, 150.5, 136.5, 135.4, 135.0, 135.2, 135.1, 131.4, 131.2, 130.4, 127.2, 121.6, 121.5, 120.9, 120.5, 119.1, 116.2, 37.2 (d, J = 100.6 Hz); MS (FAB, Clelan:) *m/z* (relative intensity) 467 (42.2), 466 (35.4), 465 (M^+-Cl, 100).



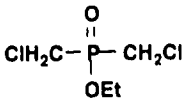
2-Acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose (15). The literature procedure was followed.[62] A suspension of *N*-acetyl-D-glucosamine (8.0 g, 0.036 mol) and freshly fused zinc chloride (4.80 g, 0.048 mol) in freshly distilled benzaldehyde (20 mL) was stirred at room temperature under argon for 3 days. The resulting clear solution was then added to petroleum ether (100 mL), and the reaction mixture solidified slowly. It was then filtered and the solid obtained was washed with petroleum ether (2 x 100 mL) and water (3 x 50 mL). The white solid was dried under high vacuum to give **15** (8.65 g, 77 %) as a mixture of α- and ß-isomers in a 1:1 ratio (by ^1H NMR). An analytical sample was obtained by recrystallisation from water: mp 242-243 (dec.) (Lit.[62] mp 247-248 °C); IR (KBr disk) 3456 (br), 3297 (br), 1623, 1567, 1373, 1118, 1099, 1033, 992 cm^{-1}; ^1H NMR (DMSO-d_6 + trace of D_2O, 200 MHz) δ 7.45-7.35 (m, 5 H, Ar*H*), 5.52 (s, 1 H, PhC*H*O_2), 4.96 (d, 0.5 H, J = 3.3 Hz, H-1$_\alpha$), 4.56 (d, 0.5 H, J = 8.3 Hz, H-1$_\beta$), 4.20-4.00 (m, 1 H, H-6e), 3.90-3.02 (m, 5 H, H-2, H-3, H-4, H-5, H-6a), 1.82 (s, 3 H, C*H*$_3$CO); ^{13}C NMR (DMSO-d_6 + trace of D_2O, 50 MHz) δ 171.2, 171.11, 138.1, 129.5, 128.6, 126.9, 101.5, 101.3, 96.3, 91.6, 82.5, 81.7, 71.0, 68.8, 68.4, 67.7, 66.4, 62.7, 58.3, 55.2, 23.3, 22.9; HRMS (EI) Calcd for $C_{15}H_{19}NO_6$: 309.1212. Found: 309.1188; MS (CI, NH_3) *m/z* (relative intensity) 309 (MH^+, 100), 292 (24.8), 209 (16.2), 186 (16.6); Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.13; H, 6.27; N, 4.48.



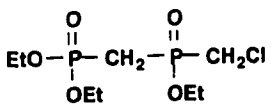
Phenyl (2-Phenylethenyl)(chloromethyl)phosphinate (16). The procedure of Vargas and Rosenthal for a similar compound was followed.[56] A solution of the freshly prepared ylide **10** (76 mg, 0.163 mmol) in benzene (4 mL) was added dropwise to a solution of freshly distilled benzaldehyde (56 mg, 0.528 mmol) in anhydrous benzene (10 mL) under argon. The resulting mixture was heated at reflux under argon for 48 h. The reaction mixture was then concentrated *in vacuo* and the residue obtained was subjected to flash chromatography (silica, CH_2Cl_2-EtOAc-MeOH, 33:1:0.05) to give the title compound as two isomers: **16a** :(*E*)-isomer (5.18 mg, 11 %), **16b**: (*Z*)-isomer (4.20 mg, 9.0 %).

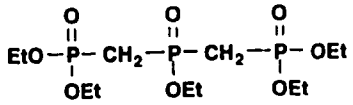
For **16a**: IR (CH_2Cl_2, cast) 2927, 1606, 1591, 1489, 1199, 923, 902, 689 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.70-7.05 (m, 11 H, Ar*H*, PhC*H*=), 5.98 (dd, 1 H, *J* = 17.2, 14.2 Hz, =C*H*P), 3.51(dd, 1 H, *J* = 14.3, 9.9 Hz, PC*H*HCl), 3.42 (dd, 1 H, *J* = 14.3, 6.3 Hz, PCH*H*Cl); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 151.7, 130.3, 130.2, 130.1, 128.8, 125.7, 121.3 (d, *J* = 3.0 Hz), 116.9 (d, *J* = 134.9 Hz), 35.8 (d, *J* = 103.7 Hz); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 32.4; HRMS (EI) Calcd for $C_{15}H_{14}ClO_2P$ (M^+): 294.0390 (^{37}Cl), 292.0420 (^{35}Cl). Found: 294.0392, 292.0419.

For **16b**: IR (CH_2Cl_2, cast) 2927, 1606, 1591, 1489, 1199, 923, 902, 689 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.60 (dd, 1 H, *J* = 20.9, 17.4 Hz, PhC*H*=), 7.50-7.10 (m, 10 H, ArH), 6.50 (dd, 1 H, *J* = 22.1, 17.4 Hz, =C*H*P), 3.70 (dd, 1 H, *J* = 13.9, 9.6 Hz, PC*H*HCl), 3.62 (dd, 1 H, *J* = 13.9, 7.1 Hz, PCH*H*Cl); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 152.5, 134.7, 131.3, 130.3, 129.4, 128.5, 125.6, 121.2 (d, *J* = 3.5 Hz), 113. 6 (d, *J* = 140.4 Hz), 36.7 (d, *J* = 107.2 Hz); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 33.5; HRMS (EI) Calcd for $C_{15}H_{14}ClO_2P$ (M^+): 294.0390 (^{37}Cl), 292.0420 (^{35}Cl). Found: 294.0398, 292.0421.



Ethyl Bis(chloromethyl)phosphinate (17). The literature procedure was followed.[61] Anhydrous EtOH (7.5 mL, 128 mmol) was added dropwise to a solution of bis(chloromethyl)phosphonic chloride (**12**) (11.7 g, 46.2 mmol) in dry THF (20 mL) at 0 °C. Triethylamine (6.52g, 64.4 mmol) was added and the resulting mixture was stirred at room temperature under argon for 2 days and then filtered. The solvent was evaporated and the remaining liquid was distilled under vacuum to give **17** (9.95 g, 82 %) as a colorless liquid: bp 95-100 °C (0.45-0.50 torr) (lit.[61] bp 104-106 °C (1 torr)); IR ($CHCl_3$ cast) 2992, 2937, 1394, 1257, 1205, 1033, 967, 851 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 4.20 (dq, 2 H, J = 7.2, 7.2 Hz, $POCH_2CH_3$), 3.72 (d, 4 H, J = 8.4 Hz, 2 x OCH_2Cl), 1.35 (t, 3 H, J = 7.2 Hz, $POCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) 62.7 (d, J = 7.0 Hz), 32.5 (d, J = 105.9 Hz), 16.2 (d, J = 4.8 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 39.3; HRMS (EI) Calcd for $C_4H_9Cl_2O_2P$ (M^+): 193.9658 (2 x ^{37}Cl), 191.9687 (^{37}Cl, ^{35}Cl), 189.9717 (2 x ^{35}Cl). Found: 193.9672; 191.9698; 189.9729.



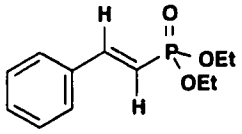


Ethyl (Chloromethyl)(diethyl phosphonomethyl)phosphinate (18) and Ethyl Bis(diethyl phosphonomethyl)phosphinate (19). The literature procedure was followed.[61] A mixture of **17** (2.51 g, 13.2 mmol) and freshly distilled triethyl phosphite (2.89 g, 17.2 mmol) was heated at 170 °C under argon for 40 h. Distillation under reduced pressure gave **18** (1.52 g, 39 %) as a colorless liquid. The viscous yellow residue was identified as **19** (2.8 g, 55 %).

For **18**: bp 140-150 °C (0.10-0.20 torr) (lit.[145] 178-180 °C (1 torr)); IR ($CHCl_3$ cast) 2983, 2935, 2908, 1444, 1394, 1368, 1249, 1029, 968, 829 cm^{-1}; ^1H NMR ($CDCl_3$,

200 MHz) δ 4.25-4.05 (m, 6 H, 3 x OCH_2CH_3), 3.85-3.60 (m, 2 H, PCH_2Cl), 2.85-2.60 (dd, 4 H, J = 20.0, 18.0 Hz, 2 x PCH_2P), 1.40-1.20 (m, 9 H, 3 x OCH_2CH_3); HRMS (EI) Calcd for $C_8H_{19}ClO_5P_2$ (M^+): 294.0366 (^{37}Cl), 292.0396 (^{35}Cl). Found: 294.0368; 292.0402.

For **19**: IR (CH_2Cl_2 cast) 2984, 2934, 2909, 1248, 1166, 1096, 1027, 972, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.25-4.05 (m, 10 H, 5 x $POCH_2CH_3$), 2.70 (dd, 4 H, J = 20.0, 18.0 Hz, 2 x PCH_2P), 1.40-1.20 (m, 15 H, 5 x $POCH_2CH_3$); HRMS (EI) Calcd for $C_{12}H_{29}O_8P_3$ (M^+): 394.1075. Found: 394.1071.

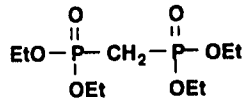


Diethyl 2-Phenylethenylphosphonate (20). The literature procedure was followed.[64] Phosphonate **21** (150 mg, 0.521 mmol) in THF (1.0 mL) was added to a suspension of sodium hydride (23.0 mg, 60 % dispersion in oil, 0.567 mmol) in dry THF (9.0 mL). The mixture was stirred at 22 °C for 30 min and then benzaldehyde (55 mg, 1.32 mmol) was added dropwise. The solution was stirred for a further 15 h and then concentrated *in vacuo*. Purification of the oily residue by flash chromatography (silica, CH_2Cl_2-MeOH, 40:1) gave **20** (52 mg, 42 %) as a colorless oil.

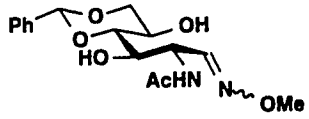
Similiar reaction of **18** (364 mg, 1.24 mmol) with sodium hydride (52.0 mg, 1.31 mmol) and benzaldehyde (140 mg, 1.32 mmol) in THF (10 mL) gave a colorless oil (50 mg, 17 %) which was also identified as **20**.

Similiar reaction of **19** (200 mg, 0.507 mmol) with sodium hydride (21.3 mg, 60 % dispersion in oil, 0.532 mmol) and benzaldehyde (53.8 mg, 0.507 mmol) gave a yellowish oil. Purification by flash chromatography (CH_2Cl_2-MeOH, 35:1) gave a colorless oil (39 mg, 32 %) which was identified as **20**.

For **20**: IR ($CHCl_3$ cast) 1615, 1246, 1223, 1052, 1027, 961, 744 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.50-7.25 (m, 6 H, Ar*H*, PhC*H*=), 6.19 (dd, 1 H, *J* = 17.6, 17.6 Hz, =C*H*P), 4.08-3.92 (dq, 4 H, *J* = 8.0, 7.2 Hz, 2 x OCH_2CH_3), 1.25 (t, 6 H, *J* = 7.2 Hz, 2 x OCH_2CH_3); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 18.9; HRMS (EI) Calcd for $C_{12}H_{17}O_3P$ (M^+): 240.0915. Found: 240.0919.

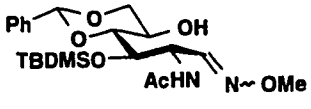


Tetraethyl Methylenediphosphonate (21). The procedure of Kosolapoff was modified to give a better yield.[65] Triethyl phosphite (20.0 g, 120 mmol) and methylene iodide (15.0 g, 56.0 mmol) were placed in a three-neck round-bottomed flask equipped with a dropping funnel and distillation apparatus. The mixture was heated to 160 °C and the lower boiling point by-products were allowed to distill over. After 1 h of heating, a further portion of triethyl phosphite (20.0 g, 120 mmol) was added dropwise to the solution over a period of 5 h. The reaction mixture was then kept at 160 °C for a further 18 h. Fractional distillation under reduced pressure gave the title compound **21** (5.63 g, 35 %) as a colorless liquid: bp 120-125 °C (0.50 torr) (lit.[65] bp 135-137(0.4 torr)); IR ($CHCl_3$ cast) 2983, 2909, 1393, 1256, 1193, 1165, 1098, 1027, 970, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.10 (m, 8 H, 4 x OCH_2CH_3), 2.31 (ABq, 2 H, *J* = 21.0 Hz, PCH_2P), 1.30 (t, 12 H, *J* = 5.0 Hz, 4 x OCH_2CH_3); ^{31}P (CD_2Cl_2, 81 MHz) δ 19.5; HRMS (EI) Calcd for $C_9H_{22}O_6P_2$ (M^+): 288.0892. Found: 288.0893.



2-Acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucose Methyloxime (22). The procedure of Weitz and Bednarski for similar compounds was followed.[66] A mixture of

15 (1.00 g, 3.26 mmol) and methoxyamine hydrochloride (0.32 g, 3.85 mmol) in anhydrous pyridine (5.0 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and the syrup obtained was subjected to flash chromatography (silica, EtOH-EtOAc, 1:1) to give the title compound **22** (1.08 g, 99 %) as a mixture of (*E*)-and (*Z*)-isomers (ratio, 3.8:1 by ^{1}H NMR): mp 164-165 °C; IR (KBr disk) 3371 (br), 3320 (br), 1650, 1543, 1398, 1371, 1088, 1067, 1011 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ (data for major isomer only) 8.05 (br s, 1 H, NH), 7.50-7.30 (m, 6 H, H-1, Ar*H*), 5.45 (s, 1 H, PhC*H*O$_2$), 5.14 (d, 1 H, *J* = 6.0 Hz, 5-OH), 5.00 (d, 1 H, *J* = 7.2 Hz, H- 2), 4.15 (dd, 1 H, *J* = 10.2, 5.0 Hz, H-6e), 4.00 (dd, 1 H, *J* = 7.2, 7.2 Hz, H-3), 3.75-3.60 (m, 4 H, H-5, NOC*H*$_3$), 3.60-3.40 (m, 2 H, H-4, H-6a), 1.82 (s, 3 H, C*H*$_3$CO); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.1, 168.9, 150.0, 149.3, 138.2, 128.4, 127.8, 126.1, 100.0, 99.8, 81.8, 80.8, 71.1, 67.5, 66.7, 61.4, 60.9, 60.0, 59.8, 51.3, 48.0, 22.7; MS (CI, NH_3) *m/z* (relative intensity) 356 (MNH_4^+, 3.7), 339 (MH^+, 64.6), 321 (26.2), 209 (11.3), 35 (100); Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.50; H, 6.41; N, 8.13.



2-Acetamido-4,6-*O*-benzylidene-5-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-glucose Methyloxime (23), 2-Acetamido-4,6-*O*-benzylidene-3,5-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-glucose Methyloxime (24), and 2-Acetamido-4,6-*O*-benzylidene-3-*O*-*t*-butyldimethylsilyl-2-deoxy-D-glucose Methyloxime (25). Diol **22** (2.09 g, 6.18 mmol) was treated with *t*-butyldimethylsilyl chloride (1.02 g, 6.80 mmol) and imidazole (1.05 g, 15.4 mmol) in DMF (10 mL) at room temperature for 48 h. The reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in Et_2O and washed with brine. The organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a

white foam. Purification by flash chromatography (silica, CH_2Cl_2-MeOH, 25:1) afforded **23** (2.69 g, 96 %) as a mixture of (*E*)- and (*Z*)-isomers, with some fractions containing pure (*E*)- and (*Z*)-isomer. When 3.0 equiv. of *t*-butyldimethylsilyl chloride was used, 3,5-di-O-silylated **24** (16 %), 5-O-silylated **23** (79 %), and 3-O-silylated **25** (5 %) were isolated.

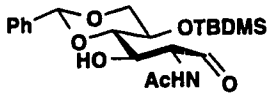
For **23** ((*E*)-isomer): mp 111-113 °C; IR ($CHCl_3$ cast) 3300 (br), 2956, 2930, 2857, 1656, 1650, 1547, 1390, 1254, 1110, 1076, 1029, 839 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.30 (m, 6 H, H-1, Ar*H*), 6.40 (d, 1 H, *J* = 7.0 Hz, NH), 5.50 (s, 1 H, PhC*H*O_2), 4.75 (ddd, 1 H, *J* = 7.0, 5.5, 4.5 Hz, H-2), 4.24 (dd, 1 H, *J* =10.5, 5.0 Hz, H-6a), 4.10 (ddd, 1 H, *J* = 8.0, 5.5, 1.5 Hz, H-3), 3.96 (ddd, 1 H, *J* = 10.5, 9.0, 5.0 Hz, H-5), 3.84 (s, 3 H, NOC*H*$_3$), 3.65 (dd, 1 H, *J* = 9.0, 1.5 Hz, H-4), 3.60 (dd, 1 H, *J* =10.5, 10.5 Hz, H-6b), 3.05 (d, 1 H, *J* = 8.0 Hz, 3-OH), 1.85 (s, 3 H, C*H*$_3$CO), 0.90 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.15, 0.13 (2 x s, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 170.8, 147.7, 138.1, 129.3, 128.5, 126.6, 101.1, 81.7, 72.1, 69.3, 62.2, 62.1, 52.7, 25.9, 23.3, 16.2, -4.2, -4.7; MS (CI, NH_3) *m/z* (relative intensity) 453 (MH^+, 100), 436 (31); Anal. Calcd for $C_{22}H_{36}N_2O_6Si$: C, 58.38; H, 8.02; N, 6.19. Found: C, 58.56; H, 8.04; N, 5.89.

For **23** ((*Z*)-isomer): mp 121-122 °C; IR ($CHCl_3$ cast) 3320 (br), 2956, 2930, 2857, 1648, 1547, 1401, 1390, 1253, 1112, 1052, 859 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.48-7.38 (m, 5 H, Ar*H*), 6.64 (d, 1 H, *J* = 6.5 Hz, H-1), 6.30 (d, 1 H, *J* = 6.7 Hz, N*H*), 5.02 (ddd, 1 H, *J* = 6.5, 6.4, 6.4 Hz, H-2), 4.22 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-6e), 4.12 (ddd, 1 H, *J* = 10.0, 6.5, 1.0 Hz, H-3), 3.95 (ddd, 1 H, *J* = 10.5, 9.0, 5.0 Hz, H-5), 3.88 (s, 3 H, NOC*H*$_3$), 3.62 (dd, 1 H, *J* = 9.0, 1.0 Hz, H-4), 3.59 (dd, 1 H, *J* = 10.5, 10.5 Hz, H-6a), 2.55 (d, 1 H, *J* = 10.0 Hz, 3-OH), 1.80 (s, 3 H, C*H*$_3$CO), 0.90 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.12, 0.11 (2 x s, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 170.6, 149.5, 138.1, 129.4, 128.6, 126.5, 101.3, 82.8, 72.0, 68.1, 62.4, 62.1, 50.6, 25.6, 23.2, 18.1, -4.2, -5.0; MS (CI, NH_3) *m/z* (relative intensity) 453 (MH^+, 8.94), 395 (2.06), 130

(1.90), 28 (100); Anal. Calcd for $C_{22}H_{36}N_2O_6Si$: C, 58.38; H, 8.02; N, 6.19. Found: C, 58.20; H, 7.89; N, 6.00.

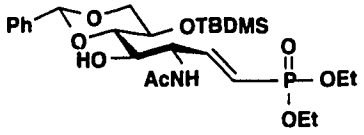
For **24**: mp 186-187 °C; IR (CH_2Cl_2 cast) 3200 (br), 3045, 2955, 2933, 2858, 1640, 1551, 1471, 1407, 1254, 1103, 1089, 1025, 885 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.50-7.30 (m, 6 H, Ar*H*, H-1), 6.30 (d, 1 H, *J* = 6.4 Hz, N*H*), 5.40 (s, 1 H, PhC*H*O_2), 4.65 (dt, 1 H, *J* = 6.4, 3.6 Hz, H-2), 4.41 (dd, 1 H, *J* = 10.5, 5.5 Hz, H-6e), 3.90-3.75 (m, 4 H, H-5, NOC*H*$_3$), 3.65-3.50 (m, 2 H, H-4, H-6a), 1.90 (s, 3 H, C*H*$_3$CO), 0.95-0.85 (m, 18 H, 2 x SiC(C*H*$_3$)$_3$), 0.20-0.05 (m, 12 H, 2 x Si(C*H*$_3$)$_2$); MS (CI, NH_3) *m/z* (relative intensity) 568 (MH^+, 100), 510 (13.5).

For **25**: IR ($CHCl_3$ cast) 3400 (br), 2929, 2857, 1658, 1511, 1472, 1463, 1255, 1096, 1071, 1029, 838 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.35-7.48 (m, 6 H, H-1,Ar*H*), 6.32 (d, 1 H, *J* = 4.0 Hz, N*H*), 5.42 (s, 1 H, PhC*H*O_2), 5.01 (dt, 1 H, *J* = 7.6, 2.6 Hz, H-2), 4.29 (dd, 1 H, *J* = 5.0, 2.6 Hz, H-2), 4.24 (dd, 1 H, *J* = 10.4, 5.0 Hz, H-6e), 3.86 (m, 4 H, H-5, NOC*H*$_3$), 3.61 (dd, 1 H, *J* = 9.2, 5.0 Hz, H-4), 3.55-3.48 (m, 2 H, H-6a, 5-OH), 2.01 (s, 3 H, C*H*$_3$CO), 0.86 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.10 (s, 3 H, SiC*H*$_3$), -0.2 (s, 3 H, SiC*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.7, 148.5, 138.1, 129.3, 128.43, 71.9, 63.4, 61.9, 52.2, 26.1, 23.5, 18.5, -4.4, -4.6; MS (CI, NH_3) *m/z* (relative intensity) 453 (MH^+, 100); Anal. Calcd for $C_{22}H_{36}N_2O_6Si$: C, 58.38; H, 8.02; N, 6.19. Found: C, 58.14; H, 8.03; N, 6.11.



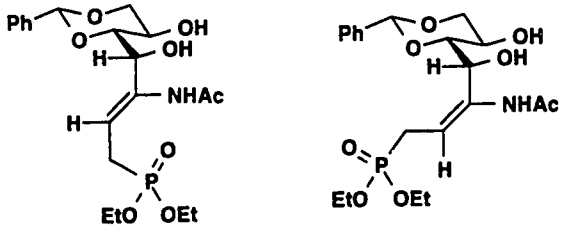
2-Acetamido-4,6-*O*-benzylidene-5-*O*-*tert*-butyldimethylsilyl-2-deoxy-*aldehydo*-D-glucose (26). A solution of oxime **23** (175 mg, 0.387 mmol) in dry CH_2Cl_2 (40 mL) was cooled to -78 °C. Ozone was bubbled through the solution for 40 minutes to give a light blue solution. The reaction mixture was kept at -78 °C for an additional 12 h and was

then purged with O_2 to remove the excess ozone. Dimethyl sulfide (0.33 mL) was then added to the reaction and the resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction solution was then washed with brine-$NaHCO_3$ (1:1 v/v, 100 mL) and the organic layers were separated, dried (Na_2SO_4), and concentrated *in vacuo* to give **26** (148 mg, 90 %) as a foam. The compound was unstable on silica gel and could not be further purified: IR (CH_2Cl_2 cast) 3400 (br), 2955, 2930, 2857, 1730, 1656, 1389, 1373, 1254, 1112, 1028, 855, 839, 779 cm^{-1}, ^1H NMR (CD_2Cl_2, 200 MHz) δ 9.65 (s, 1 H, H-1), 7.50-7.30 (m, 5 H, Ar*H*), 6.50 (d, *J* = 5.8 Hz, NH), 5.50 (s, 1 H, PhC*H*O_2), 4.62 (dd, 1 H, *J* = 6.0, 5.0 Hz, H-2), 4.41 (dd, 1 H, *J* = 5.0, 1.0 Hz, H-3), 4.25 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-6e), 4.04-3.90 (ddd, 1 H, *J* = 10.0, 9.0, 5.0 Hz, H-5), 3.69 (dd, 1 H, *J* = 9.0, 1.0 Hz, H-4), 3.59 (dd, 1 H, *J* = 10.5, 10.0 Hz, H-6a), 1.92 (s, 3 H, C*H*$_3$CO), 0.90 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.15-0.05 (2s, 6 H, Si(C*H*$_3$)$_2$); MS (CI, NH_3) *m/z* (relative intensity) 425 (28.4), 424 (MH^+, 100), 406 (36.0), 300 (32.7).



(*E*)-3-Acetamido-5,7-*O*-benzylidene-6-*O*-*t*-butyldimethylsilyl-1-(diethoxyphosphinyl)-1,2,3-trideoxy-D-*gluco*-hept-1-enitol (27). A solution of **21** (316 mg, 1.10 mmol) in dry THF (1.0 mL) was added dropwise to a slurry of NaH (44.0 mg, 60 % dispersion in oil, 1.10 mmol, washed with petroleum ether before use) in dry THF (0.5 ml). The resulting mixture was stirred for 15 min, and then a solution of aldehyde **26** (210 mg, 0.496 mmol) in dry THF (1.0 mL) was rapidly added with stirring. After 6 h, water (0.5 mL) was added. The resulting solution was concentrated *in vacuo*, and the residue obtained was dissolved in Et_2O (10 mL) and brine (10 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation *in vacuo* gave a residue which was

purified by flash chromatography (silica, CH_2Cl_2-MeOH, 30:1) to yield phosphonate **27** (104 mg, 38 %) as a syrup: IR ($CHCl_3$ cast) 3290 (br), 2930, 1658, 1550, 1251, 1229, 1108, 1028 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.50-7.40 (m, 5 H, Ar*H*), 6.68 (ddd, 1 H, *J* = 21.4, 17.5, 5.8 Hz, H-2), 6.10 (d, 1 H, *J* = 8.0 Hz, NH), 5.85 (ddd, 1 H, *J* = 19.3, 17.5, 1.5 Hz, H-1), 5.50 (s, 1 H, PhC*H*O_2), 4.75-4.65 (m, 1 H, H-3), 4.20 (dd, *J* = 10.5, 5.0 Hz, H-7e), 4.10-3.75 (m, 6 H, H-5, H-6, 2 x O*CH*$_2$CH$_3$), , 3.65 (dd, 1 H, *J* = 9.4, 1.1 Hz, H-4), 3.55 (dd, 1 H, *J* = 10.5, 10.5 Hz, H-7a), 2.72 (d, 1 H, *J* = 9.4 Hz, 4-OH), 1.85 (s, 3 H, C*H*$_3$CO), 1.30 (dt, 6 H, *J* = 7.5, 0.5 Hz, 2 x OCH$_2$C*H*$_3$), 0.90 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.11, 0.10 (2 x s, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 170.5, 149.8 (d, *J* = 15.6 Hz), 138.11, 129.4, 128.6, 126.6, 119.1 (d, *J* = 186.7 Hz), 101.4, 82.4, 72.1, 70.0, 62.5, 62.2 (m), 55.7 (d, *J* = 21.6 Hz), 25.9, 23.3, 16.2, 16.5 (d, *J* = 6.5 Hz), -4.2, -4.8; ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 17.3; MS (CI, NH_3) *m/z* (relative intensity) 575 (MNH_4^+, 59.4), 55.8 (MH^+, 100); Anal. Calcd for $C_{26}H_{44}NO_8PSi$: C, 56.00; H, 7.95; N, 2.51. Found: C, 55.79; H, 7.73; N, 2.40.

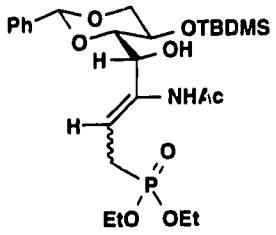


(*Z*)-3-Acetamido-5,7-*O*-benzylidene-1-(diethoxyphosphinyl)-1,2,3-trideoxy-D-*arabino*-hept-2-enitol (29a) and (*E*)-3-Acetamido-5,7-*O*-benzylidene-1-(diethoxyphosphinyl)-1,2,3-trideoxy-D-*arabino*-hept-2-enitol (29b). *n*-Bu_4NF (0.167 mL of a 1.0 M solution in THF, 0.167 mmol) was added dropwise to a stirred solution of **27** (46.6 mg, 0.0835 mmol) in dry THF (2.0 mL). The reaction mixture was then stirred at room temperature for a further 1 h at which time no starting material was visible by TLC.

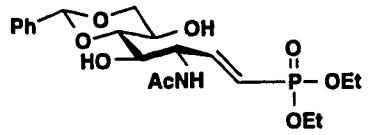
The mixture was concentrated *in vacuo* and purified by column chromatography (silica, EtOAc-MeOH, 10:1) to give the (*Z*)-isomer **29a** (27.8 mg, 75 %) and the (*E*)-isomer **29b** (7.2 mg, 19 %).

For **29a**: IR ($CHCl_3$ cast) 3342 (br), 2984, 1664, 1393, 1246, 1220, 1089, 1050, 1026 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 8.16 (s, 1 H, NH), 7.50-7.30 (m, 5 H, Ar*H*), 5.58 (dt, 1 H, *J* = 8.0, 8.0 Hz, H-2), 5.50 (s, 1 H, PhC*H*O_2), 4.60 (br s, 1 H, H-4), 4.40 (br s, 1 H, OH), 4.22 (dd, 2 H, *J* = 10.8, 5.2 Hz, H-7e), 4.20 (br s, 1 H, OH), 4.10-3.98 (m, 4 H, 2 x OC*H*$_2$$CH_3$), 3.80 (ddd, 1 H, *J* = 10.0, 9.6, 5.2 Hz, H-6), 3.70 (dd, 1 H, *J* = 9.6, 5.0 Hz, H-5), 3.58 (dd, 1 H, *J* = 10.8, 10.2 Hz, H-7a), 2.60 (dd, 2 H, *J* = 21.6, 8.0 Hz, H-1a, H-1b), 2.01 (s, 3 H, C*H*$_3$CO), 1.30-1.20 (2 x t, 6 H, *J* = 7.7 Hz, 2 x OCH_2C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 170.6 (d, *J* = 1.5 Hz), 139.4 (d, *J* = 13.5 Hz), 138.3, 129.3, 128.5, 126.6, 113.3 (d, *J* = 11.2 Hz), 101. 3, 83.5 (d, *J* = 3.5 Hz), 73.6 (d, *J* = 3.0 Hz), 71.3, 63.1 (d, *J* = 6.8 Hz), 62.9 (d, *J* = 7.0 Hz), 61.8, 25.5 (d, *J* = 137.4 Hz), 23.6, 16.6 (d, *J* = 6.0 Hz), 16.5 (d, *J* = 6.0 Hz); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 28.8; MS (CI, NH_3) *m/z* (relative intensity) 444 (MH^+, 100), 426 (46.3).

For **29b**: ^1H NMR (toluene-d_8, 200 MHz) δ 7.81 (br s, 1 H, NH), 7.50-6.95 (m, 5 H, ArH), 6.80 (dt, 1 H, *J* = 8.0, 8.0 Hz, H-2), 5.30 (s, 1 H, PhC*H*O_2), 5.25 (br s, 1 H, H-4), 4.40 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-7e), 4.25-3.70 (m, 6 H, H-5, H-6, 2 x OC*H*$_2$$CH_3$), 3.50 (dd, 1 H, *J* = 10.5, 10.0 Hz, H-7a), 2.90-2.50 (m, 2 H, H-1a, H-1b), 1.62 (s, 3 H, C*H*$_3$CO), 1.15-0.95 (m, 6 H, 2 x CH_2C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 169.4, 139.1, 138.8, 138.0, 129.4, 128.6, 126.4, 104.8 (d, *J* = 11.6 Hz), 101.3, 84.0, 71.7, 65.5, 63.2 (d, *J* = 7.0 Hz), 61.6, 25.0 (d, *J* = 139.9 Hz), 24.7, 16.6 (d, *J* = 4.5 Hz); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 27.6.

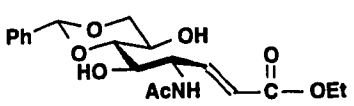


(*Z*)-3-Acetamido-5,7-*O*-benzylidene-6-*O*-*t*-butyldimethylsilyl-1-(diethoxyphosphinyl)-1,2,3-trideoxy-D-*arabino*-hept-2-enitol (30). Sodium ethoxide (0.20 mL of a 0.25 M solution in ethanol, 0.050 mmol) was added to a solution of **27** (11.0 mg, 0.0201 mmol) in absolute ethanol (0.8 mL). The reaction mixture was stirred at room temperature for 1 h and cation exchange resin (AG50W-X8 (H^+)) was then added to quench the reaction. Filtration followed by evaporation of the solvent *in vacuo* gave **30** (11 mg, 99 %) as a syrup: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.70 (br, 1 H, NH), 7.45-7.30 (m, 5 H, ArH), 5.50 (s, 1 H, PhC*H*O_2), 5.42 (dt, 1 H, *J* = 8.0, 8.0 Hz, H-2), 4.71 (br s, 1 H, H-4), 4.20 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-7e), 4.10-4.00 (m, 3 H, H-6, OC*H*$_2$CH$_3$), 3.98-3.88 (m, 2 H, OC*H*$_2$CH$_3$), 3.65 (dd, 1 H, *J* = 9.0, 1.8 Hz, H-5), 3.59 (dd, 1 H, *J* = 10.5, 10.5 Hz, H-7a), 2.56 (dd, 2 H, *J* = 22.0, 8.0 Hz, 2 x H-1), 1.89 (s, 3 H, C*H*$_3$CO), 1.28 (t, 3 H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 1.12 (t, 3 H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 0.92 (s, 9 H, C(C*H*$_3$)$_3$), 0.15, 0.12 (2 x s, 6 H, Si (C*H*$_3$)$_2$); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 28.5; MS (CI, NH_3) *m/z* (relative intensity) 559 (MH^+, 100), 541 (51.1), 454 (64).



(*E*)-3-Acetamido-5,7-*O*-benzylidene-1-(diethoxyphosphinyl)-1,2,3-trideoxy-D-*gluco*-hept-1-enitol (31). *n*-Bu_4NF (129 μL of a 1.0 M solution in THF, 0.129 mmol) was added dropwise to a stirred solution of silyl ether **27** (36.0 mg, 0.0645 mmol) and acetic acid (3 drops) in THF (1 mL). The resulting solution was stirred at room temperature for 12 h and was then concentrated *in vacuo*. The residue obtained was subjected to flash

chromatography (silica, EtOAc-MeOH, 10:1) to yield **31** (25.0 mg, 88 %) as a white foam: IR ($CHCl_3$ cast) 3312(br), 2983, 1653, 1546, 1394, 1371, 1224, 1089, 1050 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.30 (m, 5 H, Ar*H*), 6.97 (d, 1 H, *J* = 8.5 Hz, NH), 6.80 (ddd, 1 H, *J* = 22.4, 17.2, 5.2 Hz, H-2), 5.89 (ddd, 1 H, *J* = 20.2, 17.2, 1.8 Hz, H-1), 5.45 (s, 1 H, PhC*H*O_2), 4.97-4.89 (m, 1 H, H-3), 4.70 (br d, 1 H, *J* = 4.0 Hz, H-4), 4.24 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-7e), 4.12-4.07 (m, 1 H, 6-OH), 4.04 (dt, 4 H, *J* = 7.0, 6.8 Hz, 2 x O*C*$H_2$$CH_3$), 3.90-3.80 (m, 2 H, H-6, 4-OH), 3.60 (dd, 1 H, *J* = 8.8, 4.0 Hz, H-5), 3.56 (dd, 1 H, *J* = 10.8, 10.5 Hz, H-7a), 1.90 (s, 3 H, CH_3CO), 1.29 (t, *J* = 7.0 Hz 6 H, 2 x OCH_2CH_3); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 171.4, 151.6 (d, *J* = 5.5 Hz) 138.3, 129.4, 128.6, 126.7, 118.1 (d, *J* = 187.2 Hz), 101.5, 82.6, 71.8, 70.9, 62.8 (d, *J* = 4.5 Hz), 62.2, 55.3, 23.2, 16.5 (d, *J* = 6.0 Hz), ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 18.4; MS (CI, NH_3) *m/z* (relative intensity) 461 (MNH_4^+, 4.9), 444 (MH^+, 60.2), 426 (100); Anal. Calcd for $C_{20}H_{30}NO_8P$: C, 54.17; H, 6.82; N, 3.16. Found: C, 53.82; H, 6.58; N, 3.24.

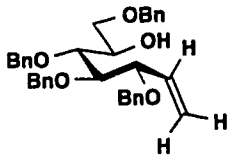


(*E*)-3-Acetamido-5,7-*O*-benzylidene-1-(ethoxycarbonyl)-1,2,3-trideoxy-D-*gluco*-hept-1-enitol (32) and Ethyl (2-Acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosyl)acetate (33). The literature procedure was modified.[54] A mixture of **15** (262 mg, 0.848 mmol) and (carbethoxymethylene)triphenylphosphorane (325 mg, 0.933 mmol) in acetonitrile (8 mL) was heated at reflux under argon for 4 h. The solvent was then evaporated *in vacuo* and the residue was purified by flash chromatography (silica, CH_2Cl_2-MeOH, 25:1) to give (*E*)-α, β-unsaturated ester **32** (60 mg, 19 %) and *C*-glycoside **33** (144 mg, 45 %).

An ethanolic solution of sodium ethoxide (0.2 mL of a 0.1 M solution) was added to a solution of **32** (21 mg, 0.0554 mmol) in anhydrous EtOH (1.8 mL). The resulting

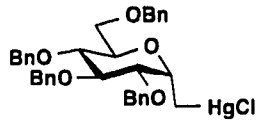
solution was stirred for 5 min and then AG50W-X8 (H^+) resin was added . Filtration and evaporation of the filtrate *in vacuo* afforded *C*-glycoside **33** (21 mg, 99 %) as a solid. For **32**: mp 189-190 °C; IR (KBr disk) 3385 (br), 3273 (br), 1719, 1653, 1397, 1371, 1287, 1191, 1080, 1022, 985 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace CD_3OD, 300 MHz) δ 7.50-7.35 (m, 4 H, Ar*H*), 6.91 (dd, 1 H, *J* = 15.5, 5.0 Hz, H-3), 5.98 (dd, 1 H, *J* = 15.5, 1.5 Hz, H-2), 5.49 (s, 1 H, PhC*H*O_2), 4.90 (dd, 1 H, *J* = 4.0, 1.5 Hz, H-4), 4.25 (dd, 1 H, *J* = 10.5, 5.5 Hz, H-8e), 4.17 (q, 2 H, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 3.99 (dd, 1 H, *J* = 4.0, 4.0 Hz, H-5), 3.81 (ddd, 1 H, *J* = 10.5, 9.0, 5.5 Hz, H-7), 3.59 (dd, 1 H, *J* = 9.0, 4.0 Hz, H-6), 3.56 (dd, 1 H, *J* = 10.5, 10.5 Hz, H-8a), 2.00 (s, 3 H, C*H*$_3$CO), 1.24 (t, 3 H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); MS (CI, NH_3) *m/z* (relative intensity) 380 (MH^+, 78), 362 (100); Anal. Calcd for $C_{19}H_{25}O_7N$: C, 60.14; H, 6.64; N, 3.69. Found: C, 59.77; H, 6.52; N, 3.67.

For **33**: ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.30 (m, 4 H, Ar*H*), 6.40 (d, 1 H, *J* = 6.3 Hz, N*H*), 5.51 (s, 1 H, PhC*H*O_2), 4.70 (ddd, 1 H, *J* = 10.0, 5.5, 5.5 Hz, H-3), 4.20-3.50 (m, 9 H, H-4, H-5, H-6, H-7, H-8a, H-8b, OC*H*$_2$CH$_3$, O*H*), 2.80-2.60 (dd, 1 H, *J* = 15.2, 8.8 Hz, H-2a), 2.60-2.50 (dd, 1 H, *J* = 15.2, 4.8 Hz, H-2b), 1.95 (s, 3 H, C*H*$_3$CO), 1.25 (t, 3 H, *J* = 6.5 Hz, OCH$_2$C*H*$_3$); MS (CI, NH_3) *m/z* (relative intensity) 380 (MH^+, 100), 362 (99.5).

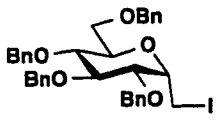


3,4,5,7-Tetra-*O*-benzyl-1,2-dideoxy-D-*gluco*-hept-1-enitol (38). The literature procedure was modified.[72] *n*-Butyllithium (19.3 mL of a 1.6 M solution in hexanes, 30.8 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (11.0 g, 30.8 mmol) in dry DME (50 mL) at -78 °C under an argon atmosphere. After completion of the addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for 30 min to give a bright yellow suspension of

the ylide. To a suspension of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **37** (6.00 g, 11.1 mmol) in dry DME (46 mL) was added *n*-butyllithium (6.94 mL of a 1.6 M solution in hexanes, 11.1 mmol) over a period of 10 min at -78 °C under argon. The cooling bath was removed and the mixture was stirred at room temperature for 20 min to give a clear solution. The ylide prepared above was added to this latter solution rapidly *via* cannula and the resulting suspension was heated at 45 °C for 2 h. TLC analysis indicated complete consumption of carbohydrate starting material. Acetone (60 mL) was added to quench the reaction, and the resulting solution was stirred at 22 °C for an additional 2 h. The solvents were evaporated *in vacuo*, and the yellowish residue was suspended in brine and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellowish syrup. Purification by flash chromatography (silica, petroleum ether-ethyl acetate, gradient, 10:1 to 3:1) afforded olefin **38** (5.29 g, 86 %) as a waxy solid: IR (CH_2Cl_2 cast) 3474(br), 3063, 3030, 2864, 1453, 1354, 1208, 1090, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.30 (m, 20 H, Ar*H*), 5.90 (ddd, 1 H, *J* = 17.0, 10.0, 7.5 Hz, H-2), 5.32-5.22 (m, 2 H, H-1a, H-1b), 4.83 (d, 1 H, *J* = 11.5 Hz, Ph*H*HO), 4.69 (d, 1 H, *J* = 11.5 Hz, Ph*H*HO), 4.62 (d, 1 H, *J* = 11.5 Hz, Ph*H*HO), 4.60-4.52 (2 d, 2 H, *J* = 11.5 Hz, 2 x Ph*H*HO), 4.52-4.46 (ABq, 2 H, *J* = 11.5 Hz, Ph*HH*O), 4.40 (d, 1 H, *J* = 11.5 Hz. Ph*H*HO), 4.20 (dd, 1 H, *J* = 7.5, 5.0 Hz, H-3), 4.05-4.01 (m, 1 H, H-6), 3.78-3.72 (m, 2 H, H-4, H-5), 3.65-3.55 (m, 2 H, H-7a, H-7b); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 139.1, 139.0, 138.7, 136.0, 128.74, 128.65, 128.3, 128.1, 128.0, 127.9, 119.4, 82.1, 79.0, 75.2, 73.69, 73.65, 71.8, 71.1, 70.8; MS (CI, NH_3) *m/z* (relative intensity) 556(MNH_4^+, 39.7), 539 (MH^+, 10.7), 431 (8.8), 91 (100); Anal. Calcd for $C_{35}H_{38}O_5$: C, 78.04, ; H, 7.11. Found: C, 77.83; H, 7.12.

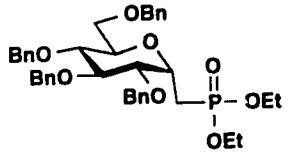


(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)methylmercuric Chloride (40). The literature procedure was modified.[72] Mercuric acetate (4.69 g, 14.5 mmol) was added to a stirred solution of olefin **38** (5.99 g, 11.1 mmol) in dry THF (160 mL) under an argon atmosphere. The resulting solution was stirred at 22 °C for 20 h, and then a solution of potassium chloride (8.3 g, 111 mmol) in H_2O (60 mL) was added. The resultant mixture was stirred at room temperature for an additional 4 h and then the organic layer was separated. The aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Flash chromatography (silica, petroleum ether-ethyl acetate-methanol, 25:5:1) of the residue afforded **40** (7.26 g, 84 %) as a syrup: IR (CH_2Cl_2 cast) 3062, 3029, 2908, 2866, 1453, 1362, 1115, 1085, 1073, 1027, 736 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.40-7.15 (m, 20 H, Ar*H*), 4.90-4.78 (m, 4 H, 4 x Ph*H*HO), 4.68 (d, 1 H, *J* = 11.5 Hz, PhH*H*O), 4.55-4.46 (m, 3 H, 3 x PhH*H*O), 4.20 (m, 1 H, H-2), 3.76-3.50 (m, 6 H, H-3, H-4, H-5, H-6, H-7a, H-7b), 2.10 (dd, 1 H, *J* = 11.5, 10.0 Hz, H-1a), 1.93 (dd, 1 H, *J* = 11.5, 7.0 Hz, H-1b); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 139.1, 138.8, 138.7, 138.1, 129.0, 128.9, 128.7, 128.5, 128.3, 128.24, 128.17, 128.01, 127.98, 127.94, 82.0, 79.3, 78.8, 75.5, 75.1, 74.5, 73.7, 73.6, 71.5, 69.8, 26.5; MS (CI, NH_3) *m/z* (relative intensity) 556 (11.7), 448 (6.2), 431 (6.8), 181 (10.4), 91 (100); Anal. Calcd for $C_{35}H_{37}ClHgO_5$: C, 54.25; H, 4.82. Found: C, 54.10 H, 4.77.



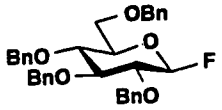
(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)methyl Iodide (41). A solution **40** (3.50 g, 4.53 mmol) in dry CH_2Cl_2 (110 mL) was stirred under an argon atmosphere for

0.5 h to remove traces of oxygen. Iodine (3.45 g, 13.6 mmol) was then added. After 11 h of stirring, a further portion of iodine (1.20 g, 4.74 mmol) was added and the stirring was continued for an additional 3 h. The reaction mixture was then treated with a 10 % aqueous sodium sulfite solution (100 mL) and stirred at room temperature for 1 h. The organic layer was separated and washed successively with 5 % aqueous KI and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The syrup obtained was subjected to flash chromatography (silica, petroleum ether-ethyl acetate, gradient, 20:1 to 10:1) to yield the title compound **41** (2.49 g, 83 %) as a white crystalline solid: mp 78-79 °C; IR ($CHCl_3$ cast) 3030, 2909, 2868, 1496, 1453, 1364, 1208, 1147, 1095 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.38-7.18 (m, 20 H, Ar*H*), 4.87 (d, 1 H, *J* = 11.0 Hz, Ph*H*HO), 4.79 (d, 1 H, *J* = 11.0 Hz, Ph*H*HO), 4.78 (d, 1 H, *J* = 11.0 Hz, Ph*H*HO), 4.70 (d, 1 H, *J* = 11.0 Hz, Ph*H*HO), 4.63 (d, 1 H, *J* = 11.0 Hz, PhH*H*O), 4.59 (d, 1 H, *J* = 11.0 Hz, PhH*H*O), 4.55 (d, 1 H, *J* = 11.0 Hz, PhH*H*O), 4.50 (d, 1 H, *J* = 11.0 Hz, PhH*H*O), 4.16 (ddd, 1 H, *J* = 11.0, 5.0, 4.5 Hz, H-2), 3.78-3.68 (m, 4 H, H-4, H-5, H-7a, H-7b), 3.65-3.58 (m, 2 H, H-1a, H-3), 3.50 (ddd, 1 H, *J* = 10.0, 4.0, 2.5 Hz, H-6), 3.44 (dd, 1 H, *J* = 11.0, 11.0 Hz, H-1b); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 139.1, 138.8, 138.7, 138.1, 128.8, 128.6, 128.2, 128.0, 127.9, 81.8, 79.9, 78.1, 75.4, 75.1, 74.8, 73.73, 73.68, 72.0, 69.5, 3.1; MS (CI, NH_3) *m/z* (relative intensity) 682 (MNH_4^+, 58.6), 181 (17.2), 91 (100); Anal. Calcd for $C_{35}H_{37}IO_5$: C, 63.26; H, 5.61. Found: C, 62.90; H, 5.52.



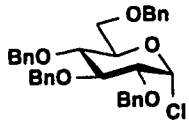
Diethyl (3,4,5,7-Tetra-*O*-benzyl-α-D-glucopyranosyl)methylphosphonate (42). The literature procedure was modified.[47] A solution of iodide **41** (2.47 g, 3.72 mmol) in freshly distilled triethyl phosphite (50 mL) was heated at 150 °C for 3 h under an argon atmosphere. Further triethyl phosphite (20 mL) was added and the heating was

continued for an additional 5 h. The reaction mixture was distilled at reduced pressure below 100 °C and the remaining syrup was then concentrated under high vacuum to give a colorless oily residue. Flash chromatography (silica, CH_2Cl_2-MeOH, gradient, 200:1 to 80:1) of this residue provided phosphonate **42** (2.35 g, 94 %) as a colorless syrup: IR (CH_2Cl_2 cast) 3030, 2904, 2867, 1454, 1363, 1249, 1156, 1093, 1070, 1027 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.35-7.20 (m, 20 H, ArH), 4.90 (d, 1 H, J = 11.0 Hz, PhC*H*HO), 4.81 (ABq, 2 H, J = 11.0 Hz, PhC*HH*O), 4.68 (s, 2 H, PhC*HH*O), 4.60-4.48 (m, 4 H, H-2, 3 x PhC*H*HO), 4.11-4.02 (m, 4 H, 2 x O$CH_2$$CH_3$), 3.80-3.64 (m, 6 H, H-3, H-4, H-5, H-6, H-7a, H-7b), 2.30-2.10 (m, 2 H, H-1a, H-1b), 1.29 (dt, 6 H, J = 7.0 Hz, 2 x O$CH_2$$CH_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 139.3, 139.0, 138.8, 138.6, 128.7, 128.64, 128.61, 128.3, 128.2, 128.1, 127.9, 127.8, 82.1, 79.7 (d, J = 12.1 Hz), 78.2, 75.5, 75.1, 73.8, 73.3, 72.4, 70.0 (d, J = 5.0 Hz), 69.4, 62.1 (d, J = 6.0 Hz), 61.8 (d, J = 5.0 Hz), 22.8 (d, J = 144.9 Hz), 16.7 (d, J = 6.0 Hz); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 29.1; MS (CI, NH_3) *m/z* (relative intensity) 678 (38.3), 675 (MH^+, 100).



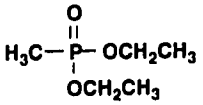
2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl Flouride (45). The procedure of Posner and Haines was followed.[79] Diethylaminosulfur trifluoride (0.26 mL, 1.99 mmol) was rapidly added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1.08 g, 2.0 mmol) in dry THF (12 mL) at -30 °C under an argon atmosphere. The cooling bath was removed immediately after completion of the addition and the stirring was continued for 20 min. The reaction mixture was cooled to -30 °C and MeOH (10 mL) was added to quench the reaction. The resulting solution was allowed to warm to room temperature over a period of 10 min and was then concentrated *in vacuo* to give a syrup, which was dissolved in CH_2Cl_2 (150 mL), washed with brine, and dried (Na_2SO_4). The solvent

was evaporated *in vacuo* and the residue was purified by flash chromatography (silica, petroleum ether-ethyl acetate, 11:1) to give the fluoride **45** (0.86 g, 80 %) as a syrup: IR (CH_2Cl_2 cast) 3031, 2905, 2870, 1497, 1454, 1362, 1151, 1100, 1065, 1028 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.40-7.20 (m, 20 H, Ar*H*), 5.28 (dd, 1 H, *J* = 53.0, 6.5 Hz, H-1), 4.90-4.70 (m, 5 H, 5 x PhC*H*HO), 4.62-4.50 (m, 3 H, 3 x PhC*H*HO), 3.76-3.52 (m, 6 H, H-2, H-3, H-4, H-5, H-6a, H-6b); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 138.9, 138.6, 138.5, 138.4, 128.8, 128.71, 128.66, 128.50, 128.3, 128.24, 128.21, 128.05, 127.95, 110.3 (d, *J* = 213.6 Hz), 83.7 (d, *J* = 12.6 Hz), 81.8 (d, *J* = 23.3 Hz), 77.3, 75.5, 75.2, 75.1, 74.6, 73.8, 69.0; MS (CI, NH_3) *m/z* (relative intensity) 560 (MNH_4^+, 47.9), 450 (14.9), 324 (24.5), 254 (28.6), 91 (100).

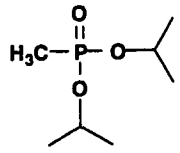


2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl Chloride (46). A mixture of thionyl chloride (3.4 mL) and DMF (50 μL) was stirred at 50 °C for 5 min. To this solution, 2, 3, 4, 6-tetra-*O*-benzyl-D-glucopyranose (1.06 g, 1.96 mmol) was added, and the resulting mixture was stirred at 50 °C for 20 min. The reaction mixture was then cooled to room temperature and toluene (20 mL) was added. Evaporation of the solvent *in vacuo* followed by flash chromatography (silica, petroleum ether-EtOAc, 12 : 1) gave the known[80] chloride **46** (0.944 g, 86 %) as a colorless oil: IR ($CHCl_3$ cast) 3030, 2866, 1497, 1454, 1363, 1117, 1102, 1073, 1028, 736 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.40-7.15 (m, 20 H, Ar*H*), 6.18 (d, 1 H, *J* = 3.7 Hz, H-1), 4.95 (d, 1 H, *J* = 10.5 Hz, PhC*H*HO), 4.86 (d, 1 H, *J* = 10.5 Hz, PhC*H*HO), 4.81 (d, 1 H, *J* = 10.5 Hz, PhCH*H*O), 4.70 (s, 2 H, PhCH_2O), 4.57 (d, 1 H, *J* = 10.5 Hz, PhCH*H*O), 4.50 (ABq, 2 H, *J* = 10.5 Hz, PhCH_2O), 4.10-3.60 (m, 6 H, H-2, H-3, H-4, H-5, H-6a, H-6b); MS (CI, NH_3)

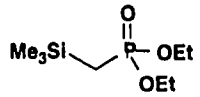
m/z (relative intensity) 558 (4.5), 540 (13.6), 91 (100); Anal. Calcd for $C_{34}H_{35}ClO_5$: C, 73.04; H, 6.31; Cl, 6.34. Found: C, 72.93; H, 6.33; Cl, 6.36.



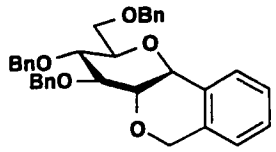
Diethyl Methylphosphonate (47). Iodomethane (12.8 g, 90.0 mmol) was added dropwise to triethyl phosphite (10.0 g, 60.0 mmol) at 50 °C. The resulting mixture was heated slowly to reflux (80 °C) and kept at this temperature for 5 h. Distillation at atmospheric pressure and then under vacuum gave the title compound **47** (8.46 g, 93 %) as a colorless liquid: bp 70-75 °C (6.3 torr) (lit.[146] bp 80 °C (15 torr)); IR (neat film) 2984, 1314, 1245, 1099, 1057, 1031, 905, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.10-3.90 (m, 4 H, 2 x OCH_2CH_3), 1.35 (d, 3 H, J =17.5 Hz, PCH_3), 1.20 (t, 6 H, J = 7.0 Hz, 2 x OCH_2CH_3); HRMS (EI) Calcd for $C_5H_{13}O_3P$ (M^+): 152.0602. Found: 152.0600.



Diisopropyl Methylphosphonate (48). A mixture of triisopropyl phosphite (10.4 g, 50 mmol) and methyl iodide (10.6 g, 75 mmol) was heated gently to 60 °C, at which point a vigorous reaction occurred. Heating was discontinued until there was no more refluxing, and then the reaction mixture was heated at 80 °C for an additional 5 h. Distillation at atmospheric pressure and then under vacuum yielded **48** (8.26 g, 92 %) as a colorless liquid; bp 52 °C (1 torr) (lit.[147] bp 60 °C (1 torr)); IR ($CHCl_3$ cast) 2979, 2934, 1386, 1375, 1312, 1245, 1142, 1110, 1011, 983, 917, 791 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.70-4.50 (m, 2 H, 2 x $CH(CH_3)_2$), 1.36 (d, 3 H, J = 17.6 Hz, PCH_3), 1.24 (d, 12 H, J = 6.2 Hz, 2 x $CH(CH_3)_2$).

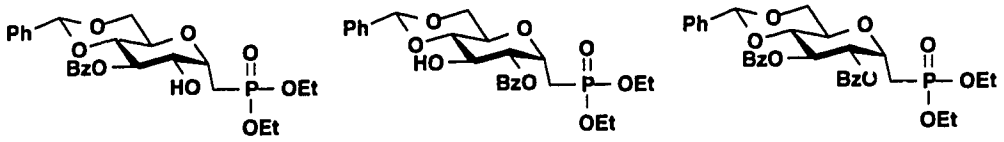


Diethyl Trimethylsilylmethylphosphonate (50). A mixture of bromomethyltrimethylsilane (2.16 g, 12.9 mmol) and triethyl phosphite (5.60 g, 33.7 mmol) was heated at 150 °C for 8 h. A further portion of triethyl phosphite (4.40 g, 26.5 mmol) was then added, and the reaction mixture was kept at 150 °C for an additional 16 h. Distillation at atmospheric pressure and then under vacuum gave the title compound **50** (2.52 g, 87 %) as a colorless liquid: bp 70-80 °C (1.0 torr); IR(CH_2Cl_2 cast) 2981, 2957, 2903, 1391, 1242, 1108, 1060, 1029, 847 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 4.10-3.90 (m, 4 H, 2 x OCH_2CH_3), 1.30 (t, J = 7.0 Hz, 2 x OCH_2CH_3), 1.10 (d, 2 H, J = 21.5 Hz, PCH_2), 0.10 (s, 9 H, 3 x $SiCH_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 61.2 (d, J = 5.4 Hz), 16.6 (d, J = 7.2 Hz), 14.8 (d, J = 127.5 Hz), -0.3 (d, J = 3.6 Hz); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 32.4; HRMS (EI) Calcd for $C_8H_{21}O_3PSi$ (M^+): 224.0997. Found: 224.0987.



2',1''-Anhydro-1-(3,4,6-tri-*O*-α-D-glucopyranosyl)-2-hydroxymethylbenzene (52). Bromomethyltrimethylsilane (33.0 μL, 0.228 mol), followed by boron trifluoride (3.0 μL), were added to a solution of glycosyl fluoride **45** (62.0 mg, 0.114 mmol) in dry CH_2Cl_2 (0.5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for a further 30 min. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (silica, petroleum ether-EtOAc, gradient, 16:1 to 10:1) to give *C*-glycoside **52** (15.0 mg, 25 %) as a colorless syrup: IR ($CHCl_3$ cast) 3029, 2916, 2863, 1496, 1453, 1364, 1155, 1117, 1091, 1073, 1028, 749 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.00 (m, 19 H, ArH), 5.09 (d, 1 H, J = 6.0 Hz,

H-1), 4.90 (d, 1 H, J = 11.5 Hz, PhC*H*HO), 4.83-4.75 (ABq, 2 H, J = 11.5 Hz, PhC*HH*O), 4.80 (d, 1 H, J = 16.0 Hz, PhC*H*HO), 4.70 (d, 1 H, J = 16.0 Hz, PhCH*H*O), 4.60 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.57 (d, 1 H, J = 11.5 Hz, PhC*H*HO), 4.52 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.18 (dd, 1 H, J = 8.0, 6.0 Hz, H-2), 3.82 (dd, 1 H, J = 8.0, 8.0 Hz, H-3), 3.78-3.68 (m, 3 H, H-4, H-6a, H-6b), 3.50 (dt, J = 9.5, 3.0 Hz, H-5); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 139.3, 138.90, 138.87, 135.6, 132.5, 128.70, 128.67, 128.61, 128.18, 128.15, 127.9, 127.8, 127.5, 127.2, 124.2, 79.0, 78.0, 75.7, 74.8, 74.1, 73.7, 73.3, 70.0, 69.0, 63.8; MS (CI, NH_3) *m/z* (relative intensity) 540 (MNH_4^+, 31.0), 342 (10.5), 180 (100).



Diethyl (3-*O*-Benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylphosphonate (54), Diethyl (2-*O*-Benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylphosphonate (57a), and Diethyl (2,3-*O*-Dibenzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylphosphonate (57b). A mixture of diol **56** (1.10 g, 2.73 mmol), DMAP (0.100 g, 0.819 mmol) and anhydrous pyridine (1.0 mL) in dry CH_2Cl_2 (50 mL) was cooled to -78 °C. Benzoyl chloride (0.26 mL, 2.18 mmol) in dry CH_2Cl_2 (3.8 mL) was added dropwise to this solution over a period of 1 h. The resulting mixture was stirred at -78 °C for 3 h and then a further portion of benzoyl chloride (80 μL, 0.72 mmol) in CH_2Cl_2 (1.2 mL) was added. After an additional 4 h of stirring, more benzoyl chloride (30 μL, 0.29 mmol) was added. The reaction mixture was allowed to warm to room temperature, and the stirring was continued for a further 16 h. The reaction was quenched by addition of MeOH and all solvents were then removed *in vacuo*. The foam obtained was subjected to flash chromatography (silica, CH_2Cl_2-MeOH, gradient, 90:1 to 60:1) to afford **54** (1.02 g, 74 %) as a white foam. The 2,3-di-

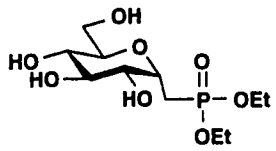
O-benzoylated compound **57b** (158 mg, 9.5 %) and a trace amount of the 2-*O*-benzoylated compound **57a** were also isolated.

For **54**: IR (CH_2Cl_2 cast) 3299 (br), 2981, 2906, 1727, 1452, 1369, 1315, 1270, 1221, 1125, 1085, 1076, 1027 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of D_2O, 300 MHz) δ 8.08, 7.60-7.30 (m, 10 H, Ar*H*), 5.50 (s, 1 H, PhC*H*O_2), 5.41 (dd, 1 H, *J* = 10.0, 9.0 Hz, H-4), 4.58 (dddd, 1 H, *J* = 10.0, 10.0, 6.0, 4.5 Hz, H-2), 4.28 (m, 1H, H-7e), 4.18-4.00 (m, 5 H, H-3, 2 x POC*H*$_2$CH$_3$), 3.82-3.70 (m, 3 H, H-5, H-6, H-7a), 2.50-2.20 (m, 2 H, H-1a, H-1b), 1.30 (dt, 6 H, *J* = 7.0, 4.5 Hz, 2 x POCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 166.7, 137.7, 133.6, 130.3, 130.1, 129.3, 128.8, 128.5, 126.5, 126.4, 101.9, 80.0, 73.5, 73.3 (d, *J* = 3.8 Hz), 71.0 (d, *J* = 12.1 Hz), 69.6, 64.9, 62.6 (d, *J* = 6.8 Hz), 62.3 (d, *J* = 6.8 Hz), 23.5 (d, *J* = 143.4 Hz), 16.7, 16.6 (2 d, *J* = 6.0 Hz); MS (CI, NH_3) *m/z* (relative intensity) 524 (MNH_4^+, 17.4), 507 (MH^+, 58.0), 478 (49.9), 35 (100); Anal. Calcd for $C_{25}H_{31}O_9P$: C, 59.29; H, 6.17. Found: C, 59.21; H, 6.17.

For **57a**: IR (CH_2Cl_2 cast) 3332 (br), 2980, 2927, 1724, 1452, 1269, 1100, 1069, 1045, 1027 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 8.05, 7.65-7.35 (m, 10 H, Ar*H*), 5.50 (s, 1 H, PhC*H*O_2), 5.26 (ddd, 1 H, *J* = 9.5, 6.0, 2.5 Hz, H-3), 4.68 (m, 1 H, H-2), 4.27 (dd, 1 H, *J* = 10.0, 4.0 Hz, H-7e), 4.12-3.95 (m, 5 H, H-4, 2 x OC*H*$_2$CH$_3$), 3.80-3.60 (m, 3 H, H-5, H-6, H-7a), 3.12 (d, 1 H, *J* = 3.5 Hz, 4-OH), 2.50-2.33 (ddd, 1 H, *J* = 16.5, 15.5, 11.5 Hz, H-1a), 2.13-2.00 (ddd, 1 H, *J* = 19.5, 15.5, 3.5 Hz, H-1b), 1.25 (dt, 6 H, *J* = 7.0, 1.5 Hz, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 165.9, 137.8, 133.9, 130.3, 130.1, 129.8, 129.5, 128.9, 128.6, 126.7, 101.3, 82.1, 73.8 (d, *J* = 12.8 Hz), 70.3 (d, *J* = 5.3 Hz), 69.7, 69.4, 64.5, 62.4(d, *J* = 6.0 Hz), 62.1 (d, *J* = 6.0 Hz), 24.4 (d, *J* = 144.9 Hz), 16.6 (d, *J* = 5.3 Hz); MS (CI, NH_3) *m/z* (relative intensity) 507 (MH^+, 100), 419 (55.6).

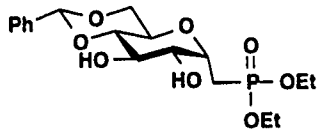
For **57b**: IR (CH_2Cl_2 cast) 2981, 1728, 1452, 1385, 1315, 1275, 1179, 1103, 1070, 1027, 711 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 7.95, 7.60-7.30 (m, 15 H, Ar*H*),

5.85 (dd, 1 H, J = 9.5, 9.5 Hz, H-4), 5.55 (ddd, 1 H, J = 9.5, 6.0, 2.5 Hz, H-3), 4.91-4.81 (m, 1 H, H-2), 4.36 (dd, 1 H, J = 10.0, 4.0 Hz, H-7e), 4.15-4.05 (m, 4 H, 2 x OCH_2CH_3), 4.00-3.95 (m, 2 H, H-5, H-6), 3.84 (m, 1 H, H-7a), 2.60 (ddd, 1 H, J = 16.5, 15.5, 12.0 Hz, H-1a), 2.14 (ddd, 1 H, J = 19.5, 15.5, 3.5 Hz, H-1b), 1.30 (dt, 6 H, J = 7.0, 3.0 Hz, 2 x OCH_2CH_3); MS (CI, NH_3) m/z (relative intensity) 628 (MNH_4^+, 26.3), 611 (MH^+, 36.1), 523 (23.1), 35 (100); Anal. Calcd for $C_{32}H_{35}O_{10}P$: C, 62.95; H, 5.78. Found: C, 63.04; H, 5.76.



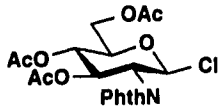
Diethyl (α-D-Glucopyranosyl)methylphosphonate (55). A mixture of **42** (1.70 g, 2.52 mmol) and 10 % palladium on carbon (0.34 g) in 95 % ethanol-acetic acid (3:1 v/v, 40 mL) was stirred under a hydrogen atmosphere overnight. The reaction mixture was then filtered through a pad of Celite which was washed with MeOH, and the filtrate was concentrated *in vacuo* to yield a clear syrup. Both ^1H NMR and TLC indicated that the reaction was not complete. The syrup was redissolved in 95 % ethanol-acetic acid (2:1, v/v, 15 mL) and hydrogenated in the presence of 10 % palladium on carbon (0.17 g) at room temperature for a further 12 h. Filtration and concentration as above afforded a syrup. Flash chromatography (silica, EtOAc-MeOH, gradient, 6:1 to 3:1) yielded tetraol **55** (0.79 g, 99 %) as a clear syrup; IR (CH_2Cl_2 cast) 3359 (br), 2930, 2911, 1394, 1222, 1107, 1075, 1048, 1024 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of D_2O, 400 MHz) δ 4.38 (m, 1 H, H-2), 4.20-4.06 (m, 4 H, 2 x OCH_2CH_3), 3.80-3.40 (m, 6 H, H-3, H-4, H-5, H-6, H-7a, H-7b), 2.45-2.35 (m, 1 H, H-1a), 2.28-2.15 (m, 1 H, H-1b), 1.31 (dt, 6 H, J = 7.0, 2.5 Hz, 2 x OCH_2CH_3); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 74.3, 74.1, 71.4, 71.3, 70.6, 62.8 (d, J = 6.6 Hz), 62.4 (d, J = 6.6 Hz), 62.0, 22.6 (d, J = 143.2 Hz), 16.6 (d, J = 5.7 Hz);

^{31}P NMR δ 31.3; MS (CI, NH_3) *m/z* (relative intensity) 343 (13.3), 315 (MNH_4^+, 100), 297 (12.5); Anal. Calcd for $C_{11}H_{23}O_8P$: C, 42.04; H, 7.38. Found: C, 42.04; H, 7.65.



Diethyl (4,6-Di-*O*-benzylidene-α-D-glucopyranosyl)methylphosphonate (56). Tetraol **55** (0.938 g, 2.98 mmol), α,α-dimethoxytoluene (0.500 mL, 3.33 mmol), anhydrous DMF (3 mL), and a few crystals of *p*-toluenesulfonic acid monohydrate were placed in a 25 mL round-bottomed flask fitted with an air-cooled condenser. The condenser was connected to a vacuum line and the mixture was heated at 60 °C under reduced pressure. After 3.5 h of heating, the condenser was switched to a water aspirator. The reaction mixture began to reflux, and was maintained under these conditions for an additional 1 h. The reaction mixture was then warmed to 85 °C over a period of 1 h, and all of the solvent was allowed to evaporate to give a thick syrup. The crude product was subjected to flash chromatography (silica, ethyl acetate-MeOH, gradient, 20:1 to 5:1) to give diol **56** (1.12 g, 93 %) as a foam: IR (CH_2Cl_2 cast) 3357 (br), 2981, 2906, 1218, 1188, 1134, 1080, 1061, 1026, 986 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of D_2O, 400 MHz) δ 7.50-7.35 (m, 5 H, Ar*H*), 5.50 (s, 1 H, PhC*H*O_2), 4.45 (dddd, 1 H, *J* = 10.0, 10.0, 6.0, 3.5 Hz, H-2), 4.20 (dd, 1 H, *J* = 9.5, 4.5 Hz, H-7e), 4.08 (m, 4 H, 2 x OC*H*$_2$CH$_3$), 3.80 (ddd, 1 H, *J* = 9.0, 6.0, 2.0 Hz, H-3), 3.70 (dd, 1 H, *J* = 9.0, 9.0 Hz, H-4), 3.68 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-7a), 3.61 (ddd, 1 H, *J* = 10.0, 9.0, 4.5 Hz, H-6), 3.45 (dd, 1 H, *J* = 9.0, 9.0 Hz, H-5), 2.15-2.35 (m, 2 H, H-1a, H-1b), 1.30 (dt, 6 H, *J* = 7.0, 2.5 Hz, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 137.9, 129.4, 128.5, 126.7, 102.1, 81.8, 72.8 (d, *J* = 5.0 Hz), 72.2 (d, *J* = 13.1 Hz), 71.3, 69.5, 64.6, 62.5 (d, *J* = 7.0 Hz), 62.3 (d, *J* = 6.0 Hz), 22.6 (d, *J* = 144.9 Hz), 16.60 (d, *J* = 5.0 Hz), 16.55 (d, *J* = 6.0 Hz); ^{31}P NMR (CD_2Cl_2,

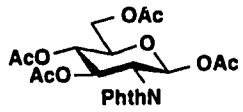
162 MHz) δ 30.4; MS (CI, NH_3) *m/z* (relative intensity) 403 (MH^+, 100), 357 (30.7), 315 (43.6); Anal. Calcd for $C_{18}H_{27}O_8P$: C, 53.73; H, 6.76. Found: C, 53.52; H, 6.79.



3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl Chloride (58). The literature procedure was followed.[148] A mixture of pentaacetate **60** (150 mg, 0.314 mmol), $AlCl_3$ (200 mg, 1.49 mmol) in anhydrous CH_2Cl_2 (92 mL) was stirred at room temperature for 50 min. The solution was then poured into ice-water and extracted with CH_2Cl_2. The combined organic phases were dried ($CaCl_2$) and concentrated *in vacuo*. Purification of the residue by flash chromatography (silica, petroleum ether-ethyl acetate, 3:1) gave glycosyl chloride **58** (74 mg, 52 %) as a white solid.

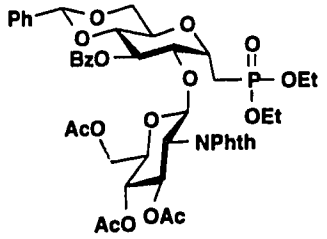
An alternative literature procedure was also employed.[93] A mixture of D-glucosamine hydrochloride (2.16 g, 10.0 mmol), *N*-ethoxycarbonyl phthalimide (2.10 g, 10.0 mmol), and sodium carbonate (0.60 g, 6.0 mmol) in water (30 mL) was stirred at room temperature for 2 days. The reaction solution was then concentrated *in vacuo*, and the residue was dried under high vacuum to constant weight. The solid obtained was then stirred with acetyl chloride (20 mL) overnight, and then $AlCl_3$ (1.6 g, 120 mmol) was added. After a further 18 h of stirring, the brown reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$, brine, and dried (Na_2SO_4). Concentration *in vacuo* followed by flash chromatography (petroleum ether-ethyl acetate, gradient, 4:1 to 3:1) afforded glycosyl chloride **58** (1.36 g, 30 %) as a white solid: mp 139-141 °C (lit.[148] mp 149 °C); IR (CH_2Cl_2 cast) 1779, 1750, 1720, 1385, 1227, 1098, 1043, 721 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.88 (dd, 2 H, *J* = 5.5, 3.0 Hz, Ar*H*), 7.79 (dd, 2 H, *J* = 5.5, 3.0 Hz, ArH), 6.20 (d, 1 H, *J* = 9.5 Hz, H-1), 5.76 (dd, 1 H, *J* = 10.5, 9.5 Hz, H-3), 5.20

(dd, 1 H, J = 10.5, 9.5 Hz, H-4), 4.49 (dd, 1 H, J = 10.5, 9.5 Hz, H-2), 4.29 (dd, 1 H, J = 12.5, 5.0 Hz, H-6a), 4.20 (dd, 1 H, J = 12.5, 2.5 Hz, H-6), 4.00 (ddd, 1 H, J = 10.5, 5.0, 2.5 Hz, H-5), 2.10, 2.02, 1.84 (3 x s, 9 H, 3 x CH_3CO); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.7, 170.2, 169.7, 135.0, 131.7, 124.1, 86.2, 76.3, 70.9, 68.7, 62.2, 58.0, 20.9, 20.8, 20.6; MS (CI, NH_3) *m/z* (relative intensity) 473 (9.3), 471 (MNH_4^+, 25), 435 (19), 29.8 (52), 35 (100); Anal. Calcd for $C_{20}H_{20}ClNO_9$: C, 52.93; H, 4.44; N, 3.09. Found: C, 52.96; H, 4.30; N, 3.05.



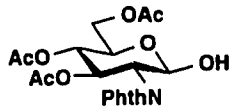
1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (60). The literature procedure was followed.[91] D-Glucosamine hydrochloride (10.8 g, 50.0 mmol) was added to a freshly prepared solution of sodium methoxide (2.72 g, 50.4 mmol) in MeOH (50 mL). The resulting mixture was stirred at room temperature for 1 h and then filtered. To the filtrate was added finely ground phthalic anhydride (3.70 g, 25.0 mmol) followed by triethylamine (5.05 g, 50.0 mmol). A further portion of phthalic anhydride (4.05 g, 27.3 mmol) was then added, and the resulting mixture was stirred at 22 °C for 30 min, and then at 50 °C for a further 30 min. The solvents were then evaporated *in vacuo* to give a yellowish solid which was treated with pyridine (100 mL) and acetic anhydride (50 mL) for 16 h. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with brine, 0.2 N H_2SO_4, saturated $NaHCO_3$, and dried ($MgSO_4$). Evaporation *in vacuo* followed by flash chromatography (silica, petroleum ether-ethyl acetate, 2:1) gave **60** (531 mg, 2.2 %) as a white solid: mp 88-90 °C (lit.[91] mp 90-94 °C); $[\alpha]_D$ +61.15° (c 1.13, $CHCl_3$); IR (CH_2Cl_2 cast) 1755, 1720, 1386, 1368, 1218, 1101, 1047, 1015, 723 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.86 (dd, 2 H, J = 5.5 Hz, 3.0 Hz, ArH), 7.78 (dd, 2 H, J = 5.5, 3.0 Hz, ArH), 6.48 (d, 1 H, J = 9.0 Hz,

H-1), 5.84 (dd, 1 H, J = 11.0, 9.0 Hz, H-3), 5.17 (dd, 1 H, J = 10.5, 9.0 Hz, H-4), 4.42 (dd, 1 H, J = 11.0, 9.0 Hz, H-2), 4.31 (dd, 1 H, J = 12.5, 4.5 Hz, H-6a), 4.11 (dd, 1 H, J = 12.5, 2.5 Hz, H-6b), 4.02 (ddd, 1 H, J = 10.5, 4.5, 2.5 Hz, H-5), 2.08, 2.04, 1.98, 1.82 (4 x s, 12 H, 4 x CH_3CO); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.7, 170.3, 169.8, 169.0, 167.8, 134.9, 131.8, 124.0, 90.1, 73.2, 70.8, 68.9, 62.1, 53.9, 20.93, 20.85, 20.79, 20.6; MS (CI, NH_3) *m/z* (relative intensity) 495 (MNH_4^+, 100), 435 (96), 375 (13), 298 (48); Anal. Calcd for $C_{22}H_{23}NO_{11}$: C, 55.34; H, 4.86; N, 2.93. Found: C, 55.42; H, 5.22; N, 2.71.



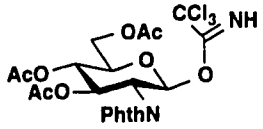
Diethyl [2-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl]methylphosphonate (61). A mixture of alcohol **54** (52.0 mg, 0.102 mmol), trichloroacetimidate **63** (97.0 mg, 0.167 mmol), and powdered 4 Å molecular sieves (0.10 g) in dry CH_2Cl_2 (2.0 mL) was stirred at 0 °C for 20 min, and then boron trifluoride etherate (0.4 mL of a 0.1 M solution in CH_2Cl_2, 0.041 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for a further 20 min and was then allowed to warm to room temperature. After 4 h, a further portion of boron trifluoride etherate (0.4 mL of a 0.3 M solution in CH_2Cl_2, 0.123 mmol) was added to the reaction mixture, and the stirring was continued for 24 h. The reaction mixture was then diluted with CH_2Cl_2 and filtered, and the filtrate was evaporated *in vacuo*. Purification of the residue by flash chromatography (silica, CH_2Cl_2-MeOH, gradient, 100:1 to 60:1) gave disaccharide **61** (8.0 mg, 8.5 %) and the starting alcohol **54** (40 mg, 77 % recovery): IR (CH_2Cl_2 cast) 1748, 1720, 1386, 1368, 1242, 1229, 1068,

1028 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.65-7.20 (m, 10 H, Ar*H*), 5.66 (dd, 1 H, *J* = 11.0, 9.0 Hz, H-1'), 5.51 (d, 1 H, *J* = 8.0 Hz, H-1'), 5.40-5.32 (m, 2 H, PhC*H*O_2, H-4), 5.11 (dd, 1 H, *J* = 10.0, 9.0 Hz, H-4'), 4.82-4.76 (m, 1 H, H-2), 4.30-3.64 (m, 1. H, H-3, H-5, H-6, H-7a, H-7b, H-2', H-5', H-6'a, H-6'b, 2 x O*C*$H_2$$CH_3$), 2.45-2.32 (m, 2 H, H-1a, H-1b), 2.10, 2.00, 1.75 (3s, 9 H, 3 x *C*H_3CO), 1.34 (dt, J = 7.0, 2.0 Hz, 2 x OCH_2*C*H_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.9, 170.2, 169.7, 165.3, 137.5, 134.4, 133.3, 131.1, 130.1, 129.8, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 126.4, 123.4, 101.8, 99.7, 80.1, 79.8, 79.4, 79.3, 73.8, 73.1, 72.2, 71.0, 70.5, 69.4, 69.1, 64.9, 64.3, 62.4, 62.2, 61.7, 54.8, 23.6 (d, J = 142.9 Hz), 20.8, 20.8, 20.5, 16.7, 16.7; ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 27.9; MS (FAB, Cleland) *m/z* (relative intensity) 946.6 (MNa^+, 0.07), 923.5 (M^+, 0.14), 507 (32.1).

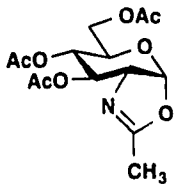


3, 4, 6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-ß-D-glucopyranose (62). Silver triflate (0.360 g, 1.42 mmol) was added to a solution of **58** (430 mg, 0.947 mmol) in acetone-H_2O (10:1 v/v, 11 mL) and the resulting mixture was stirred at 22 °C for 2 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue obtained was dissolved in CH_2Cl_2 and washed with brine-saturated $NaHCO_3$ (1 : 1, v/v), dried ($MgSO_4$), and concentrated. Recrystallisation from CH_2Cl_2-petroleum ether gave the sugar **62** (367 mg, 89 %) as a white solid: mp 178-179 °C (lit.[148] mp 166-167 °C); IR (CH_2Cl_2, cast) 3504 (br), 1781, 1749, 1713, 1388, 1365, 1230, 1159, 1088, 1075, 1032 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of D_2O, 200 MHz) δ 7.95-7.65 (m, 4 H, Ar*H*), 5.90 (dd, 1 H, *J* = 10.5, 9.5 Hz, H-3), 5.60 (d, 1 H, *J* = 8.5 Hz, H-1), 5.05 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-4), 4.30-4.10 (m, 3 H, H-2, H-6a, H-6b), 3.95 (ddd, 1 H, *J* =10.0, 4.5, 2.5 Hz, H-5), 2.05, 2.00, 1.90 (3 s, 9 H, 3 x *C*H_3CO); MS (CI,

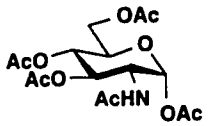
NH_3) *m/z* (relative intensity) 453 (MNH_4^+, 81), 393 (24), 298 (100); Anal. Calcd for $C_{20}H_{21}NO_{10}$: C, 55.17; H, 4.86; N, 3.22. Found: C, 55.38; H, 4.90; N, 3.16.



3, 4, 6-Tri-*O* -acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl Trichloroacetimidate (63). The literature procedure was followed.[94] A mixture of **62** (117 mg, 0.268 mmol), powdered 4 Å molecular sieves (0.1 g) and trichloroacetonitrile (0.50 mL, 5.0 mmol) in anhydrous CH_2Cl_2 (2 mL) was stirred at room temperature for 10 min, and then sodium hydride (11.0 mg, 60 % dispersion in oil, 0.268 mmol, washed with 2 x 1.0 mL of petroleum ether before use) was added portionwise. The resulting mixture was stirred for 20 min and then AG50W-X8 (H^+) ion exchange resin was added to quench the reaction. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated *in vacuo*. Flash column chromatography (silica, petroleum ether-ethyl acetate, gradient, 5:1 to 3:1) of the residue produced the title compound **63** (125 mg, 81 %) as a white solid: IR (CH_2Cl_2 cast) 1780, 1750, 1720, 1385, 1367, 1227, 1041 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 8.70 (s, 1 H, N*H*), 7.90-7.70 (m, 4 H, Ar*H*), 6.60 (d, 1 H, *J* = 8.9 Hz, H-1), 5.90 (dd, 1 H, *J* = 10.5, 9.2 Hz, H-3), 5.25 (dd, 1 H, *J* = 10.0, 9.2 Hz, H-4), 4.59 (dd, 1 H, *J* = 10.5, 8.9 Hz, H-2), 4.35 (dd, 1 H, *J* = 12.5, 4.5 Hz, H-6a), 4.20-4.02 (m, 2 H, H-6b, H-5), 2.13, 2.06, 1.85 (3 x s, 9 H, 3 x C*H*$_3$CO), ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.8, 170.3, 169.8, 167.8, 160.9, 134.9, 131.6, 123.9, 93.9, 73.3, 70.5, 68.8, 62.0, 53.9, 20.9, 20.8, 20.6; MS (CI, NH_3) *m/z* (relative intensity) 453 (13), 435 (49), 298 (100).



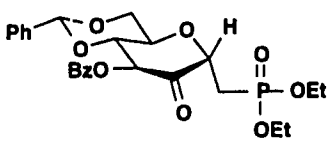
2-Methyl-(3, 4, 6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-Δ^2-oxazoline (65). The literature procedure was followed.[95] A mixture of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (**66**) (0.37 g, 0.94 mmol) and trimethylsilyl trifluoromethanesulfonate (0.27 mL, 1.41 mmol) in 1,2-dichloroethane (10 mL) was stirred at 50 °C under argon for 24 h. The reaction mixture was cooled to room temperature and then triethylamine (5.0 mL) was added. The resulting mixture was concentrated *in vacuo* to a brown syrup. Purification by flash chromatography (silica, CH_2Cl_2-MeOH-Et_3N, 160:2:1) gave the oxazoline **65** (292 mg, 89 %) as a syrup: IR (CH_2Cl_2 cast) 1745, 1674, 1370, 1234, 1039, 941 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.90 (d, 1 H, J = 7.5 Hz, H-1), 5.20 (dd, 1 H, J = 2.5, 2.5 Hz, H-3), 4.85 (ddd, 1 H, J = 9.0, 2.0, 1.0 Hz, H-4), 4.10-4.00 (m, 3 H, H-2, H-6a, H-6b), 3.55 (dt, 1 H, J = 9.0, 4.5 Hz, H-5), 2.05-2.00 (m, 12 H, 4 x C*H*$_3$CO); ^{13}C NMR (CD_3Cl, 100 MHz) δ 170.4, 169.4, 169.0, 166.4, 99.2, 70.2, 69.2, 67.3, 64.8, 63.2, 20.7, 20.66, 20.56, 13.8; MS (CI, NH_3) *m/z* (relative intensity) 330 (MH^+, 100).

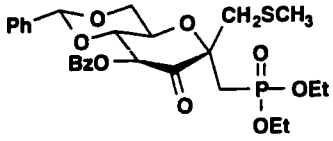


2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (66)

A mixture of *N*-acetyl-α-D-glucosamine (1.10 g, 5.00 mmol), DMAP (0.040 g), pyridine (5.0 mL), and acetic anhydride (5.0 mL) was stirred at room temperature for 6 h. Methanol (10 mL) was then added slowly and stirring was continued for a further 20 min. The reaction mixture was concentrated *in vacuo*, and the resultant syrup was dissolved in CH_2Cl_2 (50 mL) and washed with 1 N HCl, brine, and saturated $NaHSO_4$.

The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to give a solid. Recrystallisation from EtOAc-petroleum ether gave the known[149] compound **66** (0.61 g, 31 %) as a white solid: mp 128-130 °C; IR (CH_2Cl_2 cast) 3295 (br), 1751, 1664, 1369, 1222, 1042, 1013 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 6.1 (d, 1 H, J = 3.5 Hz, H-1), 5.64 (d, 1 H, J = 9.0 Hz, N*H*), 5.25 (dd, 1 H, J =10.6, 9.5 Hz, H-3), 5.18 (dd, 1 H, J = 10.0, 10.0 Hz, H-4), 4.41 (ddd, 1 H, J = 10.5, 9.0, 3.5 Hz, H-2), 4.20 (dd, 1 H, J = 12.0, 4.0 Hz, H-6a), 4.08 (dd, 1 H, J = 12.5, 2.5 Hz, H-6b), 4.00 (ddd, 1 H, J = 10.0, 4.0, 2.5 Hz, H-5), 2.18 (s, 3 H, C*H*$_3$CO), 2.05 (s, 3 H, C*H*$_3$CO), 2.02 (s, 3 H, C*H*$_3$CO), 1.90 (s, 3 H, C*H*$_3$CO); MS (CI, NH_3) *m/z* (relative intensity) 407 (MNH_4^+, 5.2), 330 (100).

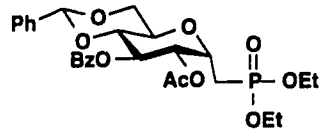




Diethyl (3-*O*-Benzoyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranos-2-ulosyl)methylphosphonate (72) and Diethyl (3-*O*-Benzoyl-4,6-*O*-benzylidene-1-methylthiomethyl-α-D-*arabino*-hexopyranos-2-ulosyl)methylphosphonate (73). Freshly distilled acetic anhydride (0.80 mL, 8.4 mmol) was added dropwise to a solution of alcohol **54** (103 mg, 0.203 mmol) in dry DMSO (3.0 mL). The resulting mixture was stirred at 22 °C for 30 h to give a bright yellowish solution. The solvent was removed *in vacuo*, and the remaining solution was further concentrated under high vacuum for 12 h. Purification of the syrup by flash chromatography (silica, CH_2Cl_2-MeOH, 60:1) gave ketone **72** (90 mg, 88 %) as an oil. When the reaction was performed at a larger scale (**54** (1.02 g, 2.01 mmol), DMSO (20 mL), and Ac_2O (10 mL)), a side product **73** (79 mg, 7.0 %) was also isolated.

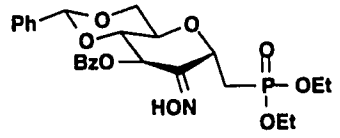
For **72**: IR (CH_2Cl_2 cast) 2926, 1729, 1270, 1179, 1101, 1070, 1053, 1026 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 8.10, 7.65-7.30 (m, 10 H, Ar*H*), 5.85 (d, 1 H, *J* = 10.0 Hz, H-4), 5.60 (s, 1 H, PhC*H*O_2), 4.75 (ddd, 1 H, *J* = 10.5, 10.5, 5.0 Hz, H-2), 4.45 (dd, 1 H, *J* = 10.0, 4.5 Hz, H-7e), 4.30-4.20 (m, 2 H, H-5, H-6), 4.20-4.08 (m, 4 H, 2 x OC*H*$_2$CH$_3$), 3.86 (dd, *J* = 10.5, 9.5 Hz, H-7a), 2.56 (ddd, *J* = 17.0, 15.5, 10.5 Hz, H-1a), 2.20 (ddd, 1 H, *J* = 20.0, 15.5, 5.0 Hz, H-1b), 1.35 (dt, 6 H, *J* = 7.0, 3.0 Hz, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 199.2 (d, *J* = 13.9 Hz), 165.8, 137.3, 134.0, 130.2, 130.1, 129.6, 129.4, 128.9, 128.8, 128.6, 128.5, 126.6, 126.5, 101.7, 79.6, 78.5 (d, *J* = 5.6 Hz), 75.8, 69.2, 65.5, 62.7 (d, *J* = 5.6 Hz), 62.5 (d, *J* = 6.9 Hz), 27.2 (d, *J* = 142.9 Hz), 16.6 (2 d, *J* = 5.5 Hz); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 24.3; MS (CI, NH_3) *m/z* (relative intensity) 505 (MH^+, 6), 383 (40), 105 (25), 35 (100).

For **73**: IR (CH_2Cl_2 cast) 2980, 2925, 1725, 1452, 1385, 1271, 1239, 1106, 1026 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 8.10-7.30 (m, 10 H, Ar*H*), 5.95 (d, 1 H, *J* = 10.5 Hz, H-4), 5.65 (s, 1 H, PhC*H*O_2), 4.68 (dd, 1 H, *J* = 10.5, 9.5 Hz, H-5), 4.43 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-7e), 4.28 (ddd, 1 H, *J* = 9.5, 9.5, 5.0 Hz, H-6), 4.18-4.06 (m, 2 H, OC*H*$_2$CH$_3$), 4.05-3.98 (m, 2 H, OC*H*$_2$CH$_3$), 3.86 (dd, 1 H, *J* = 9.5, 9.5 Hz, H-7a), 3.25 (dd, 1 H, *J* = 14.5, 5.5 Hz, CH$_3$SC*H*H), 2.85 (dd, 1 H, *J* = 18.0, 15.0 Hz, H-1a), 2.80 (dd, 1 H, *J* = 19.0, 15.0 Hz, H-1b), 2.69 (dd, 1 H, *J* = 14.5, 1.2 Hz, CH$_3$SCH*H*), 2.23 (s, 3 H, C*H*$_3$SCH$_2$), 1.36 (t, 3 H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 1.30 (t, 3 H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 200.9 (d, *J* = 2.6 Hz), 186.1, 137.5, 133.8, 130.3, 129.7, 129.5, 128.9, 128.6, 126.6, 101.6, 86.6 (d, *J* = 6.0 Hz), 77.9, 75.6, 69.2, 66.5, 62.3 (d, *J* = 6.0 Hz), 61.8 (d, *J* = 6.0 Hz), 40.3 (d, *J* = 16.6 Hz), 34.4 (d, *J* = 141.1 Hz), 17.7, 16.6 (d, *J* = 6.8 Hz), 16.5 (d, *J* = 6.8 Hz); MS (CI, NH_3) *m/z* (relative intensity) 565 (41), 564 (MH^+, 100), 476 (9), 442 (10), 105 (32).

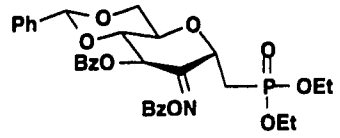


Diethyl (2-*O*-Acetyl-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylphosphonate (74). A mixture of ketone **72** (47.0 mg, 0.093 mmol), ammonium acetate (76.0 mg, 0.992 mmol), sodium cyanoborohydride (12.0 mg, 0.190 mmol) and powdered 3 Å molecular sieves (0.1 g) in absolute methanol (2.0 mL) was stirred at room temperature under an argon atmosphere. After 48 h, the reaction mixture was diluted with methanol, filtered through a pad of Celite, and concentrated *in vacuo*. The residue was dissolved in dichloromethane (10 mL) and washed with brine (2 x 5 mL). The aqueous phase was basified with 1 N NaOH and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then stirred with anhydrous pyridine (2.0 mL) and acetic anhydride (2.0 mL) at room temperature for 30 h. MeOH (5 mL) was then added slowly to decompose the excess anhydride. Evaporation *in vacuo* followed by flash chromatography (silica, CH_2Cl_2-MeOH, 90:1) of the residue gave the acetate **74** (30.6 mg, 60 %) as a white solid: IR (CH_2Cl_2 cast) 2980, 2928, 1751, 1729, 1369, 1269, 1224, 1107, 1061, 1028 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 8.00, 7.60-7.30 (m, 10 H, Ar*H*), 5.61 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-4), 5.35 (ddd, 1 H, *J* = 10.0, 6.0, 2.5 Hz, H-3), 4.70-4.60 (m, 1 H, H-2), 4.30 (dd, 1 H, *J* = 10.0, 4.0 Hz, H-7e), 4.11 (dt, 4 H, *J* = 7.5, 7.0 Hz, 2 x OCH_2CH_3), 3.84-3.74 (m, 2 H, H-5, H-6), 3.78 (dd, 1 H, *J* = 10.0, 10.0 Hz, H-7a), 2.46 (ddd, 1 H, *J* = 16.5, 16.5, 11.5 Hz, H-1a), 2.13 (ddd, 1 H, *J* = 21.5, 16.5, 3.5 Hz, H-1b), 1.94 (s, 3 H, CH_3CO), 1.32 (t, 6 H, *J* = 7.0 Hz, 2 x OCH_2CH_3); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 169.9, 166.0, 137.5, 133.7, 130.0, 129.9, 129.4, 128.8, 128.5, 126.5, 102.0, 80.0, 70.8 (d, *J* = 12.1 Hz), 70.5 (d, *J* = 10.6 Hz), 70.4, 69.3, 64.9, 62.5 (d, *J* = 6.8 Hz), 62.2 (d, *J* = 6.0 Hz), 24.1 (d, *J* = 144.1 Hz), 20.9, 16.7 (2 d, *J* = 4.5 Hz); MS (CI, NH_3) *m/z* (relative

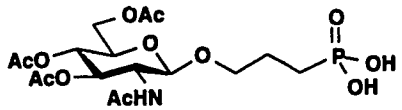
intensity) 566 (MNH_4^+, 65), 549 (NH^+, 78), 53 (17), 461 (65), 105 (100); Anal. Calcd for $C_{27}H_{33}O_{10}P$: C, 59.12; H, 6.06. Found: C, 58.71; H, 5.76.



Diethyl (3-*O*-Benzoyl-4,6-*O*-benzylidene-2-deoxy-2-oximino-α-D-*arabino*-hexopyranosyl)methylphosphonate (75). A mixture of **72** (42.0 mg, 0.0833 mmol), hydroxylammonium chloride (29.0 mg, 0.417 mmol) and sodium bicarbonate (46.0 mg, 0.458 mmol) in anhydrous MeOH (3.0 mL) was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue obtained was purified by flash chromatography (silica, CH_2Cl_2-MeOH, 48:1) to give **75** (27.0 mg, 63 %) as a white crystalline solid; IR (CH_2Cl_2 cast) 3186 (br), 3069, 2983, 2910, 2871, 1726, 1452, 1274, 1105, 1055, 1026, 976 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 10.18 (br s, 1 H, N*H*), 8.11-7.30 (m, 10 H, Ar*H*), 6.09 (dd, 1 H, *J* = 10.0, 1.0 Hz, H-4), 5.64 (ddd, 1 H, *J* = 12.0, 9.0 3.0 Hz, H-2), 5.58 (s, 1 H, PhC*H*O_2), 4.30 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-7e), 4.10-3.92 (m, 6 H, H-5, H-6, 2 x OCH_2CH_3), 3.74 (dd, 1 H, *J* = 10.5, 10.0 Hz, H-7a), 2.51 (ddd, 1 H, *J* = 15.5, 15.5 12.0 Hz, H -1a), 2.02 (ddd, 1 H, *J* = 19.5, 15.5, 3.0 Hz, H-1b), 1.29 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 1.24 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 166.1, 151.0 (d, *J* = 14.3 Hz), 137.6, 133.7, 130.2, 130.0, 129.4, 128.9, 128.5, 126.6, 101.8, 79.5, 69.9, 69.2, 67.0 (d, *J* = 5.3 Hz), 65.1, 62.8 (d, *J* = 6.0 Hz), 62.6 (d, *J* = 6.0 Hz), 26.1 (d, *J* = 141.9 Hz), 16.6 (d, *J* = 6.0 Hz), 16.5 (d, *J* = 6.0 Hz); MS (CI, NH_3) *m/z* (relative intensity) 537 (MNH_4^+, 7), 520 (MH^+, 26), 400 (9), 180 (57), 144 (54), 115 (100); Anal. Calcd for $C_{25}H_{30}NO_9P$: C, 57.80; H, 5.82; N, 2.70. Found: C, 57.79; H, 5.81; N, 2.69.

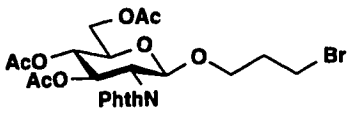


Diethyl [3-*O*-Benzoyl-2-(benzoyloximino)-4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranosyl]methylphosphonate (76). Benzoyl chloride (29 μL, 0.25 mmol) was added to a stirred solution of oxime **75** (13.0 mg, 0.025 mmol) and a catalytic quantity DMAP in dry pyridine (0.5 mL). After 4 h, the reaction was quenched with MeOH (0.5 mL). Solvent removal *in vacuo* gave a residue which was dissolved in CH_2Cl_2 (5.0 mL) and washed with 1 N HCl and brine. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give **76** (15 mg, 99 %) as a syrup; IR (CH_2Cl_2 cast) 2924, 1760, 1728, 1273, 1242, 1104, 1052, 1023 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 8.15-8.05 (m, 4 H, Ar*H*), 7.65-7.30 (m, 11 H, Ar*H*), 6.22 (dd, 1 H, *J* = 10.5, 1.0 Hz, H-4), 5.90 (ddd, 1 H, *J* = 10.5, 10.5, 4.0 Hz, H-2), 5.65 (s, 1 H, PhC*H*O_2), 4.40 (dd, 1 H, *J* = 10.0, 4.5 Hz, H-7e), 4.25-4.05 (m, 6 H, H-5, H-6, 2 x O*CH*$_2$CH$_3$), 3.84 (dd, 1 H, *J* = 10.0, 10.0, H-7a), 2.70 (ddd, 1 H, *J* = 16.5, 15.5, 10.5 Hz, H-1a), 2.30 (ddd, 1 H, *J* = 20.0, 15.5, 4.0 Hz, H-1b), 1.35 (dt, 6 H, *J* = 7.0, 7.0 Hz, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 165.9, 162.7, 160.7 (d, *J* = 13.6 Hz), 137.3, 134.1, 133.9, 133.8, 130.3, 130.1, 129.7, 129.6, 129.1, 128.8, 128.6, 126.6, 102.1, 79.7, 69.6, 69.1, 68.2 (d, *J* = 4.0 Hz), 65.4, 63.0 (d, *J* = 7.5 Hz), 62.9 (d, *J* = 7.5 Hz), 27.3 (d, *J* = 142.6 Hz), 16.7 (d, *J* = 6.0 Hz), 16.6 (d, *J* = 6.0 Hz); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 24.2; MS (CI, NH_3) *m/z* (relative intensity) 507 (13), 504 (34), 503 (20), 502 (63), 382 (15), 105 (63), 35 (100).



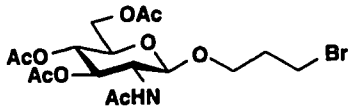
3-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)propylphosphonic Acid (77). Bromotrimethylsilane (80.0 μL, 0.61 mmol) was added dropwise to a solution of phosphonate **84** (119 mg, 0.227 mmol) in dry CH_2Cl_2 (4.0 mL). The

resulting mixture was stirred at room temperature for 2 h and then a further portion of bromotrimethylsilane (5.0 μL, 0.038 mmol) was added. After an additional 1 h of stirring, the reaction mixture was concentrated to dryness *in vacuo*. Acetone (1.5 mL) and water (10 mL) were added to the residue, and the resulting solution was stirred at 22 °C for 30 min. The solvent was evaporated *in vacuo* to yield **77** (106 mg, 99 %) as a glassy solid: IR (CH_2Cl_2 cast) 3246 (br), 3064 (br), 2940, 2888, 1749, 1561, 1369, 1230, 1166, 1043 cm^{-1}; ^1H NMR (CD_2Cl_2 + CD_3OD, 400 MHz) δ 5.15 (dd, 1 H, J = 10.0, 10.0, H-3), 4.98 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-4), 4.58 (d, 1 H, *J* = 8.5 Hz, H-1), 4.22 (dd, 1 H, *J* = 12.0, 4.5 Hz, H-6a), 4.09 (dd, 1 H, *J* = 12.0, 2.5 Hz, H-6b), 3.90-3.80 (m, 2 H, H-1', H-2), 3.70 (ddd, 1 H, *J* = 9.5, 4.5, 2.5 Hz, H-5), 3.60-3.50 (m, 1 H, H-1'), 2.04, 1.98, 1.97, 1.91 (4 x s, 12 H, 4 x C*H*$_3$CO), 1.90-1.70 (m, 4 H, 2 x H-2', 2 x H-3'); ^{13}C NMR (CD_2Cl_2 + CD_3OD, 100 MHz) δ 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; ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 32.6; MS (FAB, Cleland) *m/z* (relative intensity) 492.4 (MNa^+, 3.3), 470.5 (MH^+, 11), 454.5 (4.7), 428 (5.1), 103 (100).



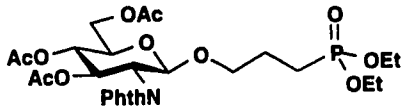
3-Bromopropyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranoside (81). A mixture of silver trifluoromethanesulfonate (86 mg, 0.335 mmol), *s*-collidine (41 mg, 0.335 mmol), and powdered 4 Å molecular sieves (100 mg) in dry CH_2Cl_2 (1.0 mL) was cooled to -78 °C and stirred for 10 min. Freshly distilled 3-bromopropanol (139 mg, 1.00 mmol) was then added, and stirring was continued for 5 min, at which time a solution of chloride **58** (152 mg, 0.335 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. The resulting mixture was warmed to -30 °C and was stirred at this temperature for 40 min. It was then allowed to warm to room temperature and was

stirred for 20 h. The mixture was then diluted with CH_2Cl_2, washed with 1 N HCl, and brine. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography (silica, CH_2Cl_2-MeOH, gradient, 170:1 to 120:1) of the residue gave glycoside **81** (182 mg, 96 %) as a colorless syrup; IR ($CHCl_3$ cast) 1777, 1747, 1717, 1387, 1226, 1081, 1038, 722 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.85-7.75 (m, 4 H, Ar*H*), 5.78 (dd, 1 H, *J* = 10.5, 9.5 Hz, H-3), 5.36 (d, 1 H, *J* = 8.5 Hz, H-1), 5.12 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-4), 4.30 (dd, 1 H, *J* = 12.5, 5.0 Hz, H-6a), 4.24 (dd, 1 H, *J* = 10.5, 8.5 Hz, H-2), 4.15 (dd, 1 H, *J* = 12.5, 2.5 Hz, H-6b), 4.00-3.85 (m, 2 H, H-5, H-1'a), 3.61 (ddd, 1 H, *J* = 10.0, 8.0, 5.0 Hz, H-1'b), 3.31-3.19 (m, 2 H, H-3'a, H-3'b), 2.09, 2.01, 1.82 (3 x s, 9 H, 3 x C*H*$_3$CO), 2.05-1.85 (m, 2 H, H-2'a, H-2'b); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 170.8, 170.3, 169.8, 134.7, 131.8, 123.8, 98.7, 72.3, 70.9, 69.4, 67.9, 62.4, 55.0, 32.6, 30.4, 20.9, 20.8, 20.6; MS (CI, NH_3) *m/z* (relative intensity) 576 (26), 575 (M(^{81}Br)NH_4^+, 96), 573 (M(^{79}Br)NH_4^+, 100), 529 (40), 511(16), 298 (33).



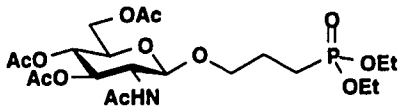
3-Bromopropyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (82). 10-(*R*)-Camphorsulfonic acid (0.30 g, 1.28 mmol) which had been azeotropically dried with benzene (10 mL) was added to a mixture of oxazoline **65** (1.05g, 3.19 mmol) and powdered 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (35 mL). Freshly distilled 3-bromopropanol (5.0 mL, 55.0 mmol) was then added. The reaction vessel was sealed and heated behind a safety shield at 42 °C overnight and then at 60 °C for 1 h. The reaction mixture was cooled and washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated under high vacuum to remove 3-bromopropanol. Purification of the residue by flash chromatography (silica, CH_2Cl_2-MeOH, gradient elution, 100:1 to 50:1) afforded the glycoside **82** (1.36 g, 91 %) as a white solid: mp 129-131 °C; $[\alpha]_D$ + 0.137°

(c, 1.16, $CHCl_3$); IR ($CHCl_3$ cast) 3283 (br), 1748, 1659, 1551, 1369, 1229, 1044 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 5.68 (d, 1 H, *J* = 9.0 Hz, N*H*), 5.21 (dd, 1 H, *J* = 10.6, 9.5 Hz, H-3), 5.01 (dd, 1 H, *J* = 9.5, 9.5 Hz, H-4), 4.60 (d, 1 H, *J* = 8.5 Hz, H-1), 4.24 (dd, 1 H, *J* = 12.5, 5.0 Hz, H-6a), 4.10 (dd, 1 H, *J* = 12.5, 2.5 Hz, H-6b), 3.95 (ddd, 1 H, *J* = 10.0, 5.0, 5.0 Hz, H-1'a), 3.85 (ddd, 1 H, *J* = 10.5, 9.0, 8.5 Hz, H-2), 3.71 (ddd, 1 H, *J* = 9.5, 5.0, 2.5 Hz, H-5), 3.65 (ddd, 1 H, *J* = 10.0, 8.5, 5.0 Hz, H-1'b), 3.52-3.48 (m, 2 H, H-3'a, H-3'b), 2.20-1.90 (m, 14 H, H-2'a, H-2'b, 4 x CH_3CO), ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 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, 20.84; MS (CI, NH_3) *m/z* (relative intensity) 471 (20), 470 ($M(^{81}Br)H^+$, 90), 469 (24), 468 ($M(^{79}Br)H^+$, 100), 330 (72); 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.

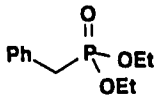


Diethyl 3-O-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranosyl)-propylphosphonate (83). A mixture of **81** (75 mg, 0.135 mmol) and triethyl phosphite (1.5 mL) was heated at 140 °C for 9 h. The reaction mixture was cooled and concentrated under high vacuum. Purification of the residue by flash chromatography (silica, CH_2Cl_2-MeOH, 60:1) afforded **83** (76.5 mg, 92 %) as a syrup; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.85-7.75 (m, 4 H, Ar*H*), 5.75 (dd, 1 H, *J* = 10.5, 9.5 Hz, H-3), 5.36 (d, 1 H, *J* = 8.5 Hz, H-1), 5.11 (dd, 1 H, *J* = 10.5, 9.5 Hz, H-4), 4.30 (dd, 1 H, *J* = 12.5, 5.0 Hz, H-6a), 4.24 (dd, 1 H, *J* = 10.5, 8.5 Hz, H-2), 4.15 (dd, 1 H, *J* = 12.5, 2.5 Hz, H-6b), 3.95-3.80 (m, 6 H, 2 x OCH_2CH_3, H-1a', H-1'b), 3.50 (dt, 1 H, *J* = 9.5 Hz, H-5), 2.05, 2.01, 1.82 (3 x s, 3 x 3 H, 3 x C*H*$_3$CO), 1.75-1.65 (m, 2 H, H-2'a, H-2'b), 1.58-1.45 (m, 2 H, H-3'a, H-3'b), 1.19 (dt, *J* = 7.0, 2.8 Hz, 2 x OCH_2CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.8, 170.3, 169.8, 134.7, 131.8, 123.8, 98.5, 72.3, 70.9,

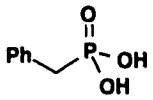
70.0 (d, J = 16.0 Hz), 69.4, 62.4, 61.6 (d, J = 5.0 Hz), 54.9, 23.1 (d, J = 3.0 Hz), 22.1 (d, J = 141 Hz), 20.9, 20.8, 20.6, 16.6 (d, J = 6.0 Hz); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 31.1.



Diethyl 3-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl)propylphosphonate (84). A solution of **82** (800 mg, 1.71 mmol) in triethyl phosphite (10.0 mL) was heated at 120 °C under argon. After 12 h, a further portion of triethyl phosphite (1.5 mL) was added, and the resulting solution was heated at 140 °C for an additional 4 h. The reaction solution was cooled to room temperature and concentrated under high vacuum. Purification of the residue by flash column chromatography (silica, CH_2Cl_2-MeOH, gradient, 35:1 to 25:1) afforded the title compound **84** (803 mg, 89 %) as a syrup: IR ($CHCl_3$ cast) 1749, 1369, 1231, 1041, 962 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 6.42 (br d, 1 H, J = 8.5 Hz, N*H*), 5.18 (dd, 1 H, J = 10.5, 9.5 Hz, H-3), 5.01 (dd, 1 H, J = 10.0, 9.5 Hz, H-4), 4.62 (d, 1 H, J = 8.5 Hz, H-1), 4.25 (dd, 1 H, J = 12.0, 5.0 Hz, H-6a), 4.20-4.00 (m, 5 H, H-6b, 2 x OC*H*$_2$CH$_3$), 3.80-3.92 (m, 2 H, H-2, H-1'a), 3.70 (ddd, 1 H, J = 10.0, 5.0, 2.5 Hz, H-5), 3.64-3.55 (m, 1 H, H-1'b), 2.05, 1.99, 1.98, 1.89 (4 x s, 12 H, 4 x C*H*$_3$CO), 1.30 (dt, 6 H, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.9, 170.8, 170.4, 169.8, 101.2, 73.2, 72.2, 69.4 (d, J = 14.1 Hz), 62.5, 63.0 (d, J = 8.0 Hz), 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); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 31.6; MS (CI, NH_3) *m/z* (relative intensity) 526 (MH^+, 100), 406 (27), 330 (100); Anal. Calcd for $C_{21}H_{36}NO_{12}P$: C, 48.00; H, 6.91; N, 2.67. Found: C, 47.81; H, 7.14; N, 2.63.

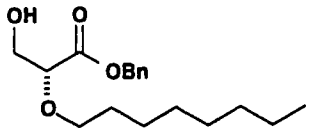


Diethyl Benzylphosphonate (88). Benzyl chloride (5.0 g, 39.5 mmol) was added dropwise to triethyl phosphite (6.90 g, 41.5 mmol). The resulting mixture was heated slowly to 140 °C and was stirred for 2 h at this temperature. Distillation under vacuum gave phosphonate **88** (4.62 g, 51 %) as a colorless liquid: bp 120-122 °C (0.7-0.8 torr) (lit.[150] bp 167-169 °C (25 torr)); IR ($CHCl_3$ cast) 2982, 1496, 1252, 1164, 1098, 1054, 1029, 963 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.35-7.25 (m, 5 H, Ar*H*), 4.00 (dq, 4 H, J = 8.0, 7.0 Hz, 2 x OCH_2CH_3), 3.13 (d, 2 H, J = 21.5 Hz, $PhCH_2P$), 1.25 (t, 6 H, J = 7.0 Hz, 2 x OCH_2CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 132.5 (d, J = 9.0 Hz), 130.1 (d, J = 7.0 Hz), 34.7, 33.3, 16.6 (d, J = 7.0 Hz); ^{31}P NMR (CD_2Cl_2, 81 MHz) δ 26.1; HRMS (EI) Calcd for $C_{11}H_{17}O_3P$ (M^+): 228.0915. Found: 228.0915 ; Anal. Calcd for $C_{11}H_{17}O_3P$: C, 57.89; H, 7.51. Found: C, 57.76; H, 7.54.

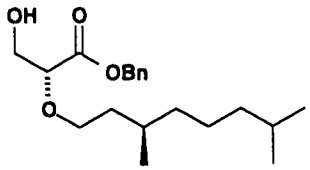


Benzylphosphonic Acid (89). Trimethylsilyl bromide (1.00 mL, 7.63 mmol) was added dropwise to **88** (0.58 g, 2.54 mmol) and the resulting mixture was stirred at room temperature for 3 h. The mixture was concentrated *in vacuo*, water (0.15 mL) was added to the residue, and the resulting slurry was stirred at room temperature for 20 min. Evaporation of the solvent *in vacuo* followed by recrystallisation of the residue from MeOH-CH_2Cl_2-hexane gave known[150] acid **89** (0.309 g, 71 %) as a white solid: mp 167-169 (lit. mp 170-172); IR (KBr disk) 3422 (br), 2914 (br), 2329 (br), 1262, 1160, 1112, 1074, 1008, 992 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of CD_3OD, 400 MHz) δ 7.35-7.25 (m, 5 H, ArH), 3.06 (d, 2 H, J = 21.8 Hz $PhCH_2P$); ^{13}C NMR (CD_2Cl_2 + trace of D_2O, 100 MHz) δ 132.8 (d, J = 1.0 Hz), 130.2 (d, J = 6.0 Hz), 128.8, 127.1 (d, J =

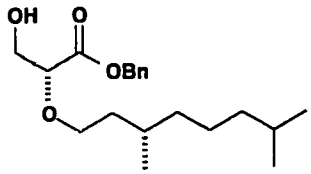
3.0 Hz), 34.5 (d, J = 138.8 Hz); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 26.9; HRMS (EI) Calcd for $C_7H_9O_3P$ (M^+): 172.0289. Found: 172.0289.



Benzyl (*R*)-3-Hydroxy-2-octyloxypropanoate (90). Sodium bicarbonate (92.0 mg, 1.09 mmol) was added to a stirred solution of **100** (78.0 mg, 0.358 mmol) in dry DMF (2.5 mL) and the mixture was heated at 50 °C for 10 min. Benzyl bromide (186 mg, 1.09 mmol) was added and the resulting mixture was heated at 70 °C for 24 h. It was then poured into brine and extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give an oily residue which was purified by flash chromatography (silica, petroleum ether-ethyl acetate, 7:1) to give **90** (98.0 mg, 89 %) as an oil: $[\alpha]_D$ + 37.8° (c 0.60, $CHCl_3$); IR ($CHCl_3$ cast) 3453 (br), 2953, 2927, 1750, 1186, 1127, 1058 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.30–7.40 (m, 5 H, Ar*H*), 5.20 (ABq, 2 H, J = 11.5 Hz, PhCH_2O), 4.00 (dd, 1 H, J = 6.5, 3.6 Hz, H-2), 3.85 (ddd, 1 H, J = 11.0, 6.5, 3.6, H-3a), 3.76 (ddd, 1 H, J =11.0, 6.5, 6.5 Hz, H-3b), 3.68 (dt, 1 H, J = 9.0, 6.5 Hz, OCH*H*CH$_2$), 3.42 (dt, 1 H, J = 9.0, 6.5 Hz, OC*H*HCH$_2$), 2.15 (t, J = 6.5 Hz, O*H*), 1.65-1.55 (m, 2 H, OCH$_2$CH_2CH$_2$), 1.40-1.20 (m, 10 H, OCH$_2$CH$_2$(CH_2)$_5$), 0.86 (t, 3 H, J = 8.0 Hz, CH_3); ^{13}C NMR (CD_2Cl_2, 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; MS (CI, NH_3) *m/z* (relative intensity) 326 (MNH_4^+, 100), 309 (MH^+, 12), 108 (23), 91(72); Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.24; H, 9.30.

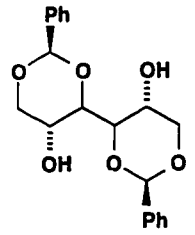


Benzyl (2*R*, 3'*R*)-3-Hydroxy-2-(3',7'-dimethyl-octyloxy)propanoate (91). A procedure analogous to that used to prepare the corresponding octyl derivative **90** was followed. Thus, **101** (192 mg, 0.779 mmol) was treated with sodium bicarbonate (228 mg, 2.72 mmol) and benzyl bromide (466 mg, 2.72 mmol) in dry DMF (5 mL) at 70 °C for 24 h. Purification by flash chromatography (CH_2Cl_2-MeOH, 7:1) gave **91** (202 mg, 77 %) as a colorless oil: IR ($CHCl_3$ cast) 3400 (br), 2954, 2927, 1751, 1183, 1127 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.40-7.36 (m, 5 H, Ar*H*), 5.20 (ABq, 2 H, *J* = 11.5 Hz, PhCH_2O), 4.00 (dd, 1 H, *J* = 6.0, 4.0 Hz, H-2), 3.85 (ddd, 1 H, *J* = 11.0, 7.0, 4.0, H-3a), 3.80-3.70 (m, 2 H, H-3b, OCH*H*CH_2), 3.45 (dt, 1 H, *J* = 9.0, 7.0 Hz, OC*H*HCH_2), 2.10 (t, *J* = 7.0 Hz, O*H*), 1.70-1.10 (m, 10 H, 4 x CH_2, 2 x C*H*), 0.88, 0.84 (2 x s, 9 H, 3 x CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 354 (MNH_4^+, 72), 91(100).



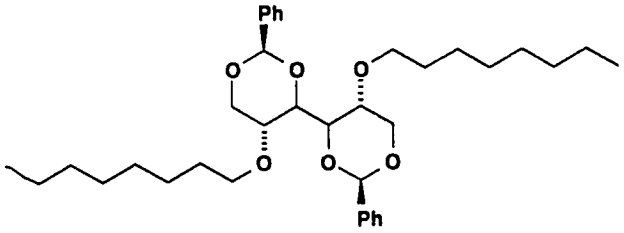
Benzyl (2*R*, 3'*S*)-3-Hydroxy-2-(3',7'-dimethyloctyloxy)propanoate (92). A procedure analogous to that used to prepare the corresponding octyl derivative **90** was followed. Thus, **102** (160 mg, 0.649 mmol) was treated with sodium bicarbonate (163 mg, 1.95 mmol) and benzyl bromide (333 mg, 1.95 mmol) in dry DMF (4 mL) at 70 °C for 24 h. Purification by flash chromatography (silica, CH_2Cl_2-MeOH, gradient, 200:1 to 100:1) gave **92** (135 mg, 62 %) as a colorless oil: IR ($CHCl_3$ cast) 3500 (br), 2954, 2927,

1751, 1184, 1127 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.38-7.32 (m, 5 H, Ar*H*), 5.18 (ABq, 2 H, *J* = 11.5 Hz, COOC*H*$_2$Ph), 4.00 (dd, 1 H, *J* = 6.0, 4.0 Hz, H-2), 3.80-3.90 (m, 1 H, H-3a), 3.77-3.80 (m, 2 H, H-3b, OC*H*HCH$_2$), 3.45 (dt, 1 H, *J* = 9.0, 7.0 Hz, OCH*H*CH$_2$), 2.10 (t, 1 H, *J* = 7.0 Hz, O*H*), 1.65-1.10 (m, 10 H, 4 x C*H*$_2$, 2 x C*H*), 0.88, 0.84 (2 x s, 9 H, 3 x C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 171.0, 136.2, 128.9, 128.7, 128.5, 80.1, 69.9, 66.9, 63.6, 39.7, 37.7, 37.1, 30.2, 28.4, 25.1, 22.8, 22.7, 19.7; MS (C$^+$ NH_3) *m/z* (relative intensity) 355 (10), 354 (MNH_4^+, 46), 181 (3), 91 (100); Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.70; H, 9.69.



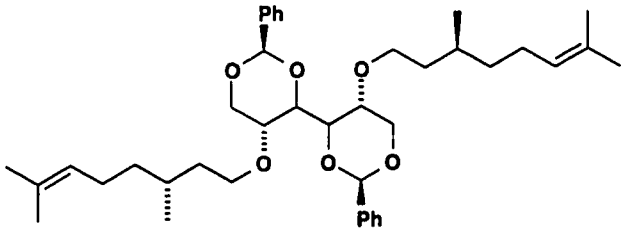
1,3:4,6-Di-*O*-benzylidene-D-mannitol (93). Concentrated sulfuric acid (98 %, 1.0 mL) was added dropwise to a stirred suspension of D-mannitol (5.0 g, 27.4 mmol) and freshly distilled benzaldehyde (6.0 mL) in DMF (15 mL). The resulting mixture was stirred at room temperature for 3 days to give a clear solution. A solution of potassium carbonate (2.0 g) in water (150 mL) was added portionwise to the reaction mixture, and then petroleum ether (50 mL) was added. The resulting mixture was stirred at room temperature for 30 min, and the precipitate which formed was collected by filtration. Purification by flash chromatography (silica, petroleum ether-ethyl acetate, gradient, 4:1 to 3:1) gave **93** (3.52 g, 26 %) as white crystals: mp 173-174 °C (lit.[115] mp 192-193 °C); $[\alpha]_D$ -9.82° (c, 1.10, acetone); IR ($CHCl_3$ cast) 3439 (br), 1456, 1219, 1105, 1065, 1028 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of D_2O, 300 MHz) δ 7.50-7.30 (m, 10 H, ArH), 5.51 (s, 2 H, 2 x PhC*H*O$_2$), 4.29 (dd, 2 H, *J* = 10.0, 5.0 Hz, H-1e, H-6e), 4.05-3.90 (m, 4 H, H-2, H-5, H-3, H-4), 3.61 (dd, 2 H, *J* = 10.0, 10.0 Hz, H-1a, H-6a); ^{13}C NMR (CD_2Cl_2 +

trace of D_2O, 75 MHz) δ 138.4, 129.2, 128.5, 126.6, 101.5, 79.5, 71.6, 60.3; MS (CI, NH_3) *m/z* (relative intensity) 359 (MH^+, 100), 253 (7), 105 (48); Anal. Calcd for $C_{20}H_{22}O_6$, C, 67.03; H, 6.19. Found: C, 66.91; H, 6.28.



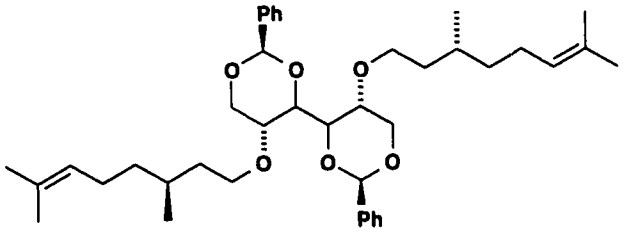
1,3:4,6-Di-*O*-benzylidene-2,5-di-*O*-octyl-D-mannitol (94). A 60 % suspension of sodium hydride in oil (0.30 g, 7.5 mmol) was washed with petroleum ether and was then added in small portions to a solution of 1,3:4,6-di-*O*-benzylidene-D-mannitol (**93**) (760 mg, 2.12 mmol) in dry DMF (5 mL) at room temperature. The resulting mixture was heated at 70 °C for 20 min, and then 1-bromooctane (1.20 g, 6.21 mmol) was added. After stirring at 70 °C for 24 h, the mixture was cooled to room temperature, poured into brine and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was subjected to flash chromatography (silica, petroleum ether-ethyl acetate, 13:1) to give **94** (870 mg, 71 %) as a clear oil: IR (CH_2Cl_2 cast) 3035, 2953, 2925, 2854, 1456, 1410, 1377, 1218, 1107, 1030, 696 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.30-7.50 (m, 10 H, Ar*H*), 5.49 (s, 1 H, PhC*H*O_2), 4.45 (dd, 2 H, J = 10.0, 5.0, H-1e and H-6e), 3.97 (d, 2 H, *J* = 8.5 Hz, H-3, H-4), 3.70 (ddd, 2 H, *J* = 10.0, 8.5, 5, H-2, H-5), 3.62 (dd, 2 H, *J* = 10.0, 10.0, H-1a, H-6a), 3.61 (dt, 2 H, *J* = 9.5, 3.0 Hz, 2 x OCH*H*CH_2CH_2), 3.51 (dt, 2 H, *J* = 9.5, 6.5 Hz, 2 x OC*H*HCH_2CH_2), 1.60-1.50 (m, 4 H, 2 x $OCH_2CH_2CH_2$), 1.40-1.20 (m, 20 H, 2 x $OCH_2CH_2(CH_2)_5$), 0.85 (t, 6 H, *J* = 8 Hz, 2 x CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 600 (MNH_4^+, 4), 583 (MH^+, 50), 291 (33), 212 (22), 156 (44), 105

(45) 71 (69), 91 (42), 57 (100); Anal. Calcd for $C_{36}H_{54}O_6$: C, 74.19; H, 9.34. Found: C, 74.32; H, 9.39.

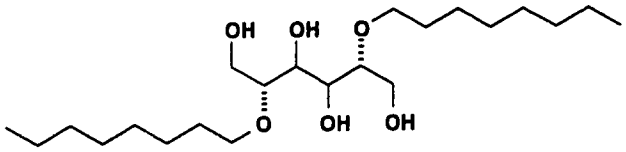


(3'*R*)-1,3:4,6-Di-*O*-benzylidene-2,5-di-*O*-(3',7'-dimethyl-6'-octenyl)-D-mannitol (95). A procedure analogous to that used to prepare the corresponding octyl derivative **94** was followed. Thus, reaction of **93** (1.00 g, 2.79 mmol) with sodium hydride (0.50 g, a 60 % suspension in oil, 12.5 mmol) and (*R*)-citronellyl bromide (1.41 g, 6.42 mmol) in dry DMF (10 mL) at 70 °C for 24 h gave an oil. Purification by flash chromatography (petroleum ether-ethyl acetate, gradient, 125:1 to 100:1) gave **95** (0.93 g, 52 %) as a colorless oil: $[\alpha]_D$ -35.2° (c 1.15, $CHCl_3$); IR ($CHCl_3$ cast) 2962, 2924, 1454, 1377, 1102, 1029 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.40 (m, 10 H, Ar*H*), 5.50 (s, 2 H, PhC*H*O_2), 5.12-5.04 (m, 2 H, *H*C=C$(CH_3)_2$), 4.42 (dd, 2 H, *J* = 10.5, 5.0 Hz, H-1e, H-6e), 3.95 (d, 2 H, *J* = 9.0 Hz, H-3, H-4), 3.78 (ddd, 2 H, *J* = 10.0, 9.0, 5.0 Hz, H-2, H-5), 3.70-3.52 (m, 6 H, H-1a, H-6a, 2 x O*CH*$_2$$CH_2CH_2$), 2.05-1.90 (m, 4 H, 2 x OCH_2CH_2), 1.70, 1.60 (2 x s, 12 H, 2 x C=C$(CH_3)_2$), 1.65-1.50 (m, 4 H, 2 x CH_2CH=C), 1.45-1.30 (m, 4 H, 2 x CH$(CH_3)CH_2CH_2$), 1.20-1.10 (m, 2 H, 2 x C*H*$(CH_3)CH_2CH_2$), 0.90 (d, 6 H, *J* = 6.5 Hz, 2 x CH$(CH_3)CH_2CH_2$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 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; MS (FAB, Cleland) *m/z* (relative intensity) 635.4

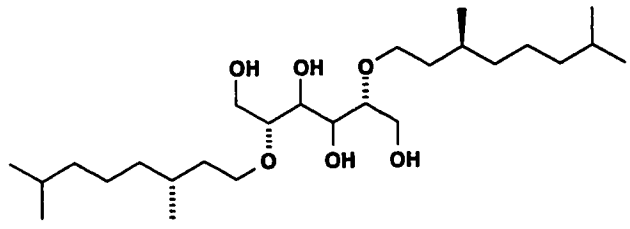
(MH+, 1.2), 633.4 (0.7), 148.8 (12), 137.0 (14), 105 (100); Anal. Calcd for $C_{40}H_{58}O_6$: C, 75.67; H, 9.21. Found: C, 75.82; H, 9.44.



(3'*S*)-1,3:4,6-Di-*O*-benzylidene-2,5-di-*O*-(3',7'-dimethyl-6'-octenyl)-D-mannitol (96). A procedure analogous to that used to prepare the corresponding octyl derivative **94** was followed. Thus, reaction of **93** (1.02 g, 2.79 mmol) with sodium hydride (0.50 g, a 60 % suspension in oil, 12.5 mmol) and (*S*)-citronellyl bromide (1.41 g, 6.42 mmol) in dry DMF (10 mL) at 70 °C for 24 h gave an oil. Purification by flash chromatography (petroleum ether-ethyl acetate, 72:1) gave **96** (1.19 g, 67 %) as a colorless oil; IR ($CHCl_3$ cast) 2962, 2924, 1455, 1377, 1103, 1029 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.30 (m, 10 H, Ar*H*), 5.50 (s, 2 H, PhC*H*O_2), 5.12-5.08 (m, 2 H, 2 x C*H*=C$(CH_3)_2$), 4.45 (dd, 2 H, *J* = 10.5, 4.5, H-1e, H-6e), 3.95 (d, 2 H, *J* = 8.5 Hz, H-3, H-4), 3.80 (ddd, 2 H, *J* = 10.0, 9.0, 5.0, H-2, H-5), 3.70-3.50 (m, 6 H, H-1a, H-6a, 2 x OCH_2CH_2), 2.05-1.90 (m, 4 H, 2 x OCH_2CH_2), 1.70, 1.60 (2 x s, 12 H, 2x C=C$(CH_3)_2$), 1.65-1.55 (m, 4 H, 2 x CH_2CH=C), 1.45-1.25 (m, 4 H, 2 x CH$(CH_3)CH_2CH_2$), 1.22-1.10 (m, 2 H, 2 x C*H*$(CH_3)CH_2CH_2$), 0.90 (d, 6 H, J = 6.5 Hz, 2 x CH$(CH_3)CH_2CH_2$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 138.4, 131.6, 129.1, 128.5, 126.5, 125.1, 101.5, 78.0, 77.1, 69.3, 67.7, 37.6, 37.5, 29.6, 25.8, 19.5, 17.8; MS (FAB, Cleland) *m/z* (relative intensity) 635.4 (MH^+, 1.9), 633.4 (1.1), 191.0 (1.0), 105.2 (100); Anal. Calcd for $C_{40}H_{58}O_6$: C, 75.67; H, 9.21. Found: C, 75.73; H, 9.46.

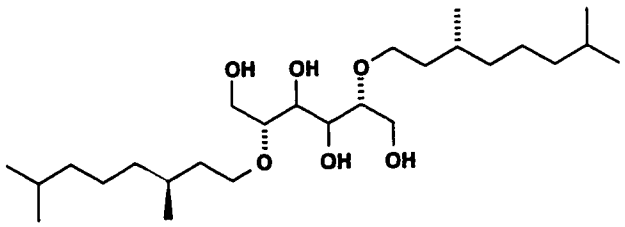


2,5-Di-*O*-octyl-D-mannitol (97). A mixture of **94** (655 mg, 1.12 mmol) and 12 N HCl (1.1 mL) in 80 % ethanol (18 mL) was heated at 70 °C for 20 h. The mixture was cooled to room temperature and saturated Na_2CO_3 solution (20 mL) was added dropwise. The resulting mixture was concentrated *in vacuo*, and the residue was dissolved in brine and extracted with ether. The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, CH_2Cl_2-MeOH, 24:1) to give **97** (402 mg, 88 %) as a colorless oil: IR (CH_2Cl_2 cast) 3363 (br), 3349 (br), 2921, 2871, 2853, 1467, 1111, 1093, 1045 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.87 (dd, 2 H, J = 6.0, 6.0 Hz, H-3, H-4), 3.82-3.68 (m, 4 H, H-1a, H-1b, H-6a, H-6b), 3.62 (dt, 2 H, J = 9.0, 7.0 Hz, 2 x OCH*H*CH_2), 3.50 (dt, 2 H, J = 9.0, 6.5 Hz, 2 x OC*H*HCH_2), 3.61 (ddd, 2 H, J = 6.0, 5.0, 3.5 Hz, H-2, H-5), 3.10 (d, 2 H, J = 6.0 Hz, 3-OH, 4-OH), 2.50 (br s, 2 H, 1-OH, 6-OH), 1.60-1.50 (m, 4 H, 2 x $OCH_2CH_2CH_2$), 1.40-1.20 (m, 20 H, 2 x $OCH_2CH_2(CH_2)_5$), 0.90 (t, 6 H, J = 8.0 Hz, 2 x CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 80.9, 71.2, 70.2, 61.5, 32.2, 30.5, 29.8, 29.6, 26.5, 23.0, 14.2; MS (CI, NH_3) *m/z* (relative intensity) 424 (MNH_4^+, 5.0), 407 (MH^+, 37), 185 (27), 157 (19), 110 (26), 71 (74), 57 (100); Anal. Calcd for $C_{22}H_{46}O_6$: C, 64.99; H, 11.40. Found: C, 65.04; H, 11.41.



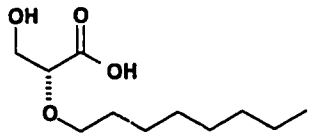
(3'*R*)-2,5-Di-*O*-(3',7'-dimethyl-octyl)-D-mannitol (98). A suspension of 5 % palladium on carbon (0.1 g) in acetic acid (5 mL) was stirred under a hydrogen atmosphere for 20

min. Compound **95** (850 mg, 1.34 mmol) in acetic acid (15 mL) was added and the resulting mixture was stirred under hydrogen at room temperature and atmospheric pressure for 12 h. The mixture was filtered and concentrated *in vacuo* to give an oil. ^{1}H NMR analysis indicated incomplete reaction. Hence, the oil was redissolved in acetic acid (5.0 mL) and stirred under hydrogen in the presence of 10 % palladium on carbon (50 mg) for a further 24 h. The reaction mixture was filtered and concentrated *in vacuo* to give a residue which was subjected to flash chromatography (silica, CH_2Cl_2-MeOH, 60:1) to give tetraol **98** (247 mg, 40 %) as a waxy solid: $[\alpha]_D$ -20.7° (c, 0.98, $CHCl_3$); IR ($CHCl_3$ cast) 3374 (br), 2953, 2926, 1464, 1093, 1031 cm^{-1}; ^{1}H NMR (CD_2Cl_2 + trace of D_2O, 400 MHz) δ 3.86 (d, 2 H, *J* = 6.5 Hz, H-3, H-4), 3.78 (dd, 2 H, *J* = 11.5, 5.0 Hz, H-1a, H-6a), 3.72 (dd, 2 H, *J* = 11.5, 3.5 Hz, H-1b, H-6b), 3.64 (ddd, 2 H, *J* = 9.0, 7.0, 6.5 Hz, 2 x OC*H*HCH$_2$), 3.55 (ddd, 2 H, *J* = 9.0, 7.5, 5.5 Hz, 2 x OCH*H*CH$_2$), 3.45 (ddd, 2 H, *J* = 6.5, 5.0, 3.5 Hz, H-2, H-5), 1.65-1.10 (m, 20 H, 8 x C*H*$_2$, 4 x C*H*), 0.95-0.85 (m, 18 H, 6 x C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 463 (MH^+, 100), 213 (19); Anal. Calcd for $C_{26}H_{54}O_6$: C, 67.49; H, 11.76. Found: C, 67.45; H, 12.13.



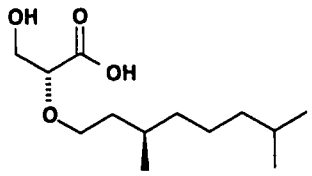
(3'*S*)-2,5-Di-*O*-(3',7'-dimethyl-octyl)-D-mannitol (99). The procedure used to prepare **98** was followed. Thus, hydrogenation of **96** (1.12 g, 1.77 mmol) in the presence of 5 % palladium on carbon (0.1 g) in acetic acid (5 mL) for 12 h gave an oil which was purified by flash chromatography (silica, CH_2Cl_2-MeOH, 60:1) to give **99** (396 mg, 48 %) as a waxy solid; IR ($CHCl_3$ cast) 3456 (br), 3376 (br), 2954, 2927, 1467, 1406, 1107, 1096 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 3.88 (t, 2 H, *J* = 6.0 Hz, H-3, H-4), 3.84-3.65 (m,

6 H, H-1a, H-1b, H-6a, H-6b, 2 x OC*H*HCH$_2$), 3.53 (dt, 2 H, *J* = 10.0, 7.0 Hz, 2 x OCH*H*CH$_2$), 3.45 (ddd, 2 H, *J* = 6.0, 5.0, 3.0 Hz, H-2, H-5), 3.05 (d, 2 H, *J* = 6.0 Hz, 3-OH, 4-OH), 2.45 (dd, 2 H, *J* = 7.5, 4.5 Hz, 1-OH, 6-OH), 1.65-1.10 (m, 20 H, 8 x C*H*$_2$, 4 x C*H*), 0.85-0.95 (m, 2 d, 18 H, *J* = 6.0, 6.0 Hz, 6 x C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 81.0, 70.2, 69.5, 61.4, 39.7, 37.8, 37.5, 30.2, 28.4, 25.1, 22.8, 22.7, 19.7; MS (CI, NH_3) *m/z* (relative intensity) 480 (MNH_4^+,19), 463 (MH^+, 100); Anal. Calcd for $C_{26}H_{54}O_6$: C, 67.47; H, 11.76. Found: C, 67.34; H, 11.84.

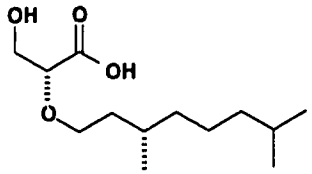


(*R*)-3-Hydroxy-2-octyloxypropanoic Acid (100). A solution of sodium periodate (127 mg, 0.66 mmol) in water (1 mL) was added to a stirred solution of **97** (225 mg, 0.555 mmol) in THF (3 mL). The resulting mixture was stirred at 60 °C for 1 h. The white precipitate was filtered and washed with THF (4 mL). Silver (I) oxide (257 mg, 1.11 mmol) and NaOH (44.0 mg, 1.11 mmol) were added to the filtrate. The resulting mixture was stirred at room temperature for 6 h. The mixture was filtered, and the filtrate was concentrated to remove THF. A solution of sodium hydroxide (10 mg) in water (2 mL) was added to the remaining aqueous solution and the resulting mixture was extracted twice with CH_2Cl_2. The aqueous layer was then acidified to pH 1 with conc HCl and extracted with CH_2Cl_2. The organic extracts of the acidic solution were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to give **100** (206 mg, 85 %) as an oil: IR (CH_2Cl_2 cast) 3429-3024 (br), 2955, 2926, 2856, 1733, 1466, 1458, 1125, 1052; cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.20–6.20 (br s, 2 H, 2 x O*H*), 4.0 (dd, 1 H, *J* = 5.0, 4.0 Hz, H-2), 3.91 (dd, 1 H, *J* = 12.0, 3.5 Hz, H-3a), 3.85 (dd, 1 H, *J* = 12.0, 3.5 Hz, H-3b), 3.68 (dt, 1 H, *J* = 9.5, 6.5 Hz, OC*H*HCH$_2$), 3.51 (dt, 1 H, *J* = 9.5, 9.5 Hz, OC*H*HCH$_2$), 1.70-1.50 (m, 2 H, OCH$_2$C*H*2CH2), 1.10-1.40 (m, 10 H,

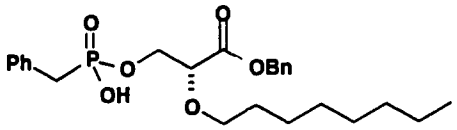
$OCH_2CH_2(CH_2)_5$), 0.85 (t, 3 H, J = 8.0 Hz, CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 174.6, 79.7, 71.9, 63.2, 32.2, 30.0, 29.7, 29.6, 26.3, 23.0, 14.2; MS (CI, NH_3) *m/z* (relative intensity) 236 (MNH_4^+, 100), 218 (MH^+, 1).



(2*R*, 3'*R*)-3-Hydroxy-2-(3',7'-dimethyloctyloxy)propanoic Acid (101). The procedure used to prepare the corresponding octyl derivative **100** was modified. Thus, **98** (230 mg, 0.497 mmol) was treated with sodium periodate (116 mg, 0.571 mmol) in THF-H_2O (9:1 v/v, 5 mL) at 50 °C for 1 h. Filtration of the reaction mixture and evaporation of the solvent from the filtrate gave a colorless oil. This was then treated with silver (I) oxide (246 mg, 0.924 mmol) and NaOH (42.0 mg, 1.06 mmol) in THF-H_2O (5:1 v/v, 6 mL) at room temperature for 18 h. A further portion of sodium hydroxide (42.0 mg, 1.06 mmol) in water (1.0 mL) was then added, and the mixture was filtered. The filtrate was then concentrated *in vacuo* to remove the THF, and the remaining aqueous solution was extracted with petroleum ether. The aqueous layer was then acidified to pH 1 with concd HCl and extracted with petroleum ether. The organic extracts of the acidic solution were washed with brine and dried ($MgSO_4$). Solvent removal *in vacuo* gave the acid **101** (215 mg, 94 %) as a pale yellow oil: IR ($CHCl_3$ cast) 3400 (br), 2954, 2927, 2869, 1728, 1126; cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.50-7.20 (br, 2 H, 2 x O*H*), 4.00-3.60 (m, 4 H, H-2, H-3a, H-3b, OC*H*HCH_2), 3.55-3.45 (m, 1 H, J = 9.5, 9.5 Hz, OC*H*HCH_2), 1.85-1.00 (m, 10 H, 4 x CH_2, 2 x C*H*), 1.00, 0.70 (2 x s, 9 H, 3 x CH_3); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 264 (MNH_4^+, 100).

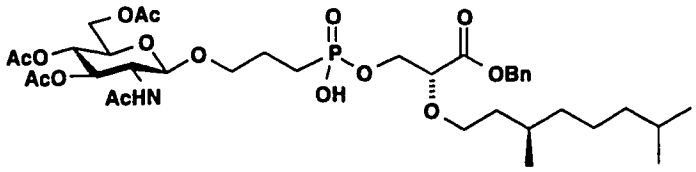


(2*R*, 3'*S*)-3-Hydroxy-2-(3',7'-dimethyloctyloxy)propanoic Acid (102). A procedure analogous to that used for preparation of **101** was followed. Thus, reaction of **99** (356 mg, 0.769 mmol) with sodium periodate (181 mg, 0.864 mmol) in THF (9:1 v/v, 8 mL) at 50 °C for 1 h gave the intermediate aldehyde as a colorless oil. Oxidation with silver (I) oxide (410 mg, 1.77 mmol) and NaOH (71.0 mg, 1.77 mmol) at room temperature for 24 h afforded acid **102** (320 mg, 85 %) as an oil: IR ($CHCl_3$ cast) 3400 (br), 2954, 2927, 1727, 1127, 1068, 1052 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 4.00 (dd, 1 H, *J* = 5.0, 4.0 Hz, H-2), 3.90 (dd, 1 H, *J* = 11.5, 4.0 Hz, H-3a), 3.85 (dd, 1 H, *J* = 11.5, 5.0 Hz, H-3b), 3.70 (ddd, 1 H, *J* = 9.0, 8.0, 7.0 Hz, OC*H*HCH_2), 3.60 (ddd, 1 H, *J* = 9.0, 8.0, 5.5 Hz, OC*H*HCH_2), 1.70-1.10 (m, 10 H, 4 x CH_2, 2 x C*H*), 0.90, 0.85 (m, 9 H, 3 x CH_3); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 173.6, 79.7, 70.3, 63.0, 39.6, 37.7, 37.0, 30.2, 28.4, 25.0, 22.6, 22.7, 19.7; MS (CI, NH_3) *m/z* (relative intensity) 264 (MNH_4^+, 65), 246 (MH^+, 42), 235 (13), 35 (100).



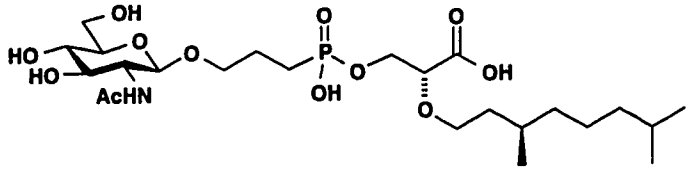
Benzyl (*R*)-3-(Benzylphosphinato)-2-octyloxypropanoate (104). Trichloroacetonitrile (1.5 mL) was added dropwise to a solution of alcohol **90** (70.0 mg, 0.227 mmol) and benzylphosphonic acid (**89**) (39.0 mg, 0.227 mmol) in dry pyridine (4.0 mL) at 70 °C under an argon atmosphere. The resulting mixture was stirred at 70 °C for 48 h, and then the solvent was evaporated *in vacuo*. The residue was then diluted and concentrated several times from toluene to remove pyridine. The residue was dissolved in CH_2Cl_2, washed with H_2O, and then concentrated *in vacuo* to give **104** (103 mg, 98 %) as a

glassy solid. Portions of **104** were further purified by elution through a short silica column (2 x 4 cm) (CH_2Cl_2-MeOH, 4:1), and an AG1-X8 (100-200 mesh, formate form) ion exchange column (MeOH): IR ($CHCl_3$ cast) 3400 (br), 2926, 2856, 1746, 1603, 1455, 1253, 1207, 1191, 1135, 1056 cm^{-1}; ^1H NMR (CD_2Cl_2 + CD_3OD + C_5D_5N, 400 MHz) δ 7.35-7.00 (m, 10 H, Ar*H*), 5.12 (ABq, 2 H, *J* = 11.5 Hz, PhCH_2O), 4.25-4.10 (m, 3 H, H-1a, H-1b, H-2), 3.58 (dt, 1 H, *J* = 15.0, 6.0 Hz, H-1'a), 3.42 (dt, 1 H, *J* = 15.0 , 6.0 Hz, H-1'b), 3.05 (d, 2 H, *J* = 20.5 Hz, PCH_2), 1.52 (dd, 2 H, *J* = 6.0, 6.0 Hz, 2 x H-2), 1.35-1.15 (m, 10 H, 5 x octyl CH_2), 0.85 (t, 3 H, *J* = 6.5 Hz, CH_3); ^{13}C NMR (CD_2Cl_2 + trace of CD_3OD, 100 MHz) δ 171.4, 136.1, 135.8 (d, *J* = 8.0 Hz), 130.2 (d, *J* = 6.0 Hz), 129.0, 128.9, 128.7, 128.5, 126.3, 79.5 (d, *J* = 7.0 Hz), 71.9, 67.4, 65.2 (d, *J* = 4.0 Hz), 35.2 (d, *J* = 134.8 Hz), 32.3, 30.0, 29.9, 29.7, 26.4, 23.1, 14.1; ^{31}P NMR (CD_2Cl_2 + trace of CD_3OD, 162 MHz) δ 18.9; MS (CI, NH_3) *m/z* (relative intensity) 553 (MNH_4^+, 3), 463 (MH^+, 14), 416 (5), 326 (100), 280 (16), 263 (13).



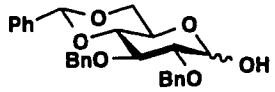
Benzyl (3'-*R* , 2 -*R*)-3-[(3-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-gluco-pyranosyl)propylphosphinato]-2-(3',7'-dimethyloctyloxy)propanoate (105). Trichloroacetonitrile (2.0 mL) was added dropwise to a solution of phosphonic acid **77** (89.1 mg, 0.190 mmol) and alcohol **91** (75.0 mg, 0.222 mmol) in anhydrous pyridine (3.0 mL), and the resulting solution was heated at 70 °C for 42 h under an argon atmosphere. The brown reaction mixture was then concentrated *in vacuo*, and the resulting residue was extracted with petroleum ether to remove excess **91**. The remaining residue was then extracted with toluene, and the toluene extracts were evaporated *in vacuo* to give **105** (138 mg, 93 %) as a glassy solid: IR (CH_2Cl_2 cast) 3279 (br), 2954,

2929, 1747, 1665, 1368, 1231, 1044 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of CD_3OD, 400 MHz) δ 7.40-7.30 (m, 5 H, Ar*H*), 5.20-5.12 (m, 3 H, H-3, PhC*H*O_2), 5.00 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-4), 4.50 (d, 1 H, *J* = 8.5 Hz, H-1), 4.28-4.20 (m, 3 H, H-6a, POC*H*$_2$CH), 4.15-4.06 (m, 2 H, H-6b, POCH$_2$C*H*), 3.80-3.65 (m, 4 H, H-2, H-5, OC*H*H(CH$_2$)$_2$P, OC*H*HCH$_2$CH), 3.53-3.40 (m, 2 H, OCH*H*(CH$_2$)$_2$P, OCH*H*CH$_2$CH), 2.04, 1.99, 1.98, 1.90 (4 x s, 12 H, 4 x C*H*$_3$CO), 1.85-1.05 (m, 14 H, PC*H*$_2$C*H*$_2$, 4 x C*H*$_2$, 2 x C*H*), 0.84, 0.86 (2 x d, *J* = 7.0 Hz, 3 x C*H*$_3$); ^{13}C NMR (CD_2Cl_2 + trace of CD_3OD, 100 MHz) δ 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, 69.2, 69.9 (d, *J* = 14.6), 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; ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 34.5; MS (FAB, Cleland) *m/z* (relative intensity) 811 (MNa^+, 0.5), 789 (MH^+, 1.4), 747 (0.1), 460 (0.9), 119 (100).



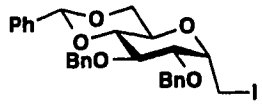
(*2R,3'R*)-3-[(3-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-propylphosphinato]-2-(3',7'-dimethyloctyloxy)propanoic Acid (106). A solution of **105** (27 mg, 0.0343 mmol) in 95 % EtOH (2 mL) was stirred under hydrogen in the presence of 10 % palladium on carbon (15 mg) for 4 h. The mixture was filtered through a bed of Celite and then concentrated *in vacuo*. The resulting residue was dissolved in anhydrous MeOH (1.8 mL) and was cooled to 0 °C. Sodium methoxide (0.7 mL of a 0.2 M solution in methanol, 0.14 mmol) was then added dropwise over a period of 20 min. The resulting solution was stirred at 0 °C for 40 minutes and then at room temperature for 1.5 h. An excess amount of AG50W-X8 (H^+) ion exchange resin was added to quench the reaction. Filtration followed by concentration *in vacuo* afforded a

residue which was precipitated from acetone to give **106** (18.8 mg, 96 %) as a white powder: IR (CH_2Cl_2 cast) 3425 (br), 2925, 2853, 1717, 1384, 1050 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD, 4:1, 400 MHz) δ 4.30-4.15 (m, 7 H, H-1, 5 x O*H*, N*H*), 4.08-4.12 (br m, 2 H, POC*HH*CH), 3.88-3.84 (br m, 1 H, OC*H*H$(CH_2)_2$P), 3.75-3.65 (m, 2 H, H-2, OC*H*HCH_2), 3.65-3.45 (m, 3 H, OCH*H*$(CH_2)_2$P, OCH*H*CH_2, POCH_2C*H*), 3.50-3.10 (m, 5 H, H-3, H-4, H-5, H-6a, H-6b), 1.90 (br s, 3 H, CH_3CO), 1.75-1.55 (br m, PCH_2CH_2), 1.50-0.90 (m, 10 H, 4 x CH_2, 2 x C*H*), 0.70 (t, 9 H, J = 6.5 Hz, 3 x CH_3); ^{13}C NMR (CD_2Cl_2 + CD_3OD, 4:1, 100 MHz) δ 173.3, 172.1, 100.5, 77.7 (d, J = 7.0 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; ^{31}P NMR (CD_2Cl_2-CD_3OD, 4:1, 162 MHz) δ 32.2; MS (FAB, Cleland) *m/z* (relative intensity) 595 (MNa^+, 2), 219 (12), 217 (19), 135 (58), 103 (100).



2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (107). A mixture of **119** (674 mg, 1.38 mmol) and potassium *t*-butoxide (186 mg, 1.65 mmol) in dry DMSO (4 mL) was heated at 100 °C for 2 h. The resulting black solution was cooled to room temperature and concentrated *in vacuo* overnight. The remaining solution was poured into ice water and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a white solid. This was dissolved in acetone : water (10 : 1 ; 44 mL) and yellow mercuric oxide (357 mg, 1.65 mmol) was added followed by dropwise addition of a solution of mercuric chloride (448 mg, 1.65 mmol) in acetone : water (10 : 1, 8 mL). The resulting mixture was stirred for an additional 20 min, and was then filtered through Celite. The colorless filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous KI solution (100 mL) followed by 10 % aqueous sodium sulfite. The organic layer was

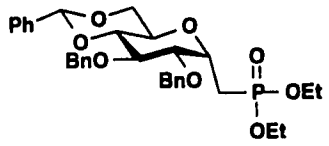
dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica, petroleum ether-EtOAc, gradient, 5 :1 to 3 : 1) of the crude product provided **107** (535 mg, 86 %) as a 1.1 : 1 mixture of α- and β-anomers: mp 168.5-169.5 °C (lit.[119] mp 160-162 °C); $[\alpha]_D$ -26.3° (c 1.20, $CHCl_3$); IR ($CHCl_3$ cast) 3402 (br), 1451, 1386, 1366, 1090, 1071, 1028, 1007, 693 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace D_2O, 400 MHz, 1.1 : 1 mixture of α-, β-anomers) δ 7.25-7.55 (m, 15 H, Ar*H*), 5.60 (s, 1 H, PhC*H*O_2), 5.24 (d, 0.5 H, J = 4.0 Hz, H-1α), 4.68-4.95 (m, 4.5 H, 2 x PhCH_2O, H-1β), 4.25-4.35 (dd, 1 H, J = 10.0, 5.0 Hz, H-6e of α- and β-anomers), 3.98-4.05 (m, 1 H), 3.60-3.80 (m, 3 H), 3.35-3.50 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 100 MHz, 1.1 : 1 mixture of α-, β-anomers) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 466 (MNH_4^+, 64), 449 (MH^+, 65), 431 (7), 360 (38), 357 (18), 342 (6), 91 (65), 35 (100); Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.50; H, 6.36.



(2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methyl Iodide (108). A solution of (2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methyl mercury chloride (**121**) (1.81 g, 2.66 mmol) in dry CH_2Cl_2 (100 mL) was treated with iodine (2.16 g, 8.51 mmol) at room temperature. After stirring for 4 h, the mixture was treated with 10 % aqueous sodium sulfite solution (50 mL), and stirred at room temperature for 20 min. The organic layer was separated and washed successively with 5 % aqueous KI and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (silica, petroleum ether-ethyl acetate, 15:1) of the residue gave a 4.3 : 1 mixture (determined by ^1H-NMR) of α- and β-anomers (1.22 g, 80 %) as a waxy solid. The α-isomer **108** was

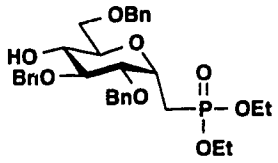
separated from the β-anomer by further flash column chromatography (silica, petroleum ether-ethyl acetate, 20:1).

For **108**: IR ($CHCl_3$ cast) 1453, 1367, 1141, 1097, 1063 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.25-7.50 (m, 15, Ar*H*), 5.58 (s, 1 H, PhC*H*O_2), 4.90 (d, 1 H, *J* =11.5 Hz, PhCH*H*O), 4.76 (d, 2 H, *J* = 11.5 Hz, 2 x PhCH*H*O), 4.65 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.30 (dd, 1 H, *J* = 10.0, 5.0, Hz, H-7e), 4.16 (ddd, 1 H, *J* = 11.5, 4.5, 4.5 Hz, H-2), 3.82 (dd, 1 H, *J* = 9.0, 8.5 Hz, H-4), 3.79 (dd, 1 H, *J* =8.5, 4.5 Hz, H-3), 3.71(dd, 1 H, *J* = 10.0, 10.0, H-7a), 3.68 (dd, 1 H, *J* = 10.0, 9.0 Hz, H-5), 3.62 (dd, 1 H, *J* = 11.5, 4.5 Hz, H-1a), 3.54 (ddd, 1 H, *J* = 10.0, 10.0, 5.0 Hz, H-6), 3.47 (dd, 1 H, *J* = 11.5, 11.5 Hz, H-1b); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 590 (MNH_4^+, 30), 573 (MH^+, 52), 481 (6), 464 (19), 447 (14), 417 (18), 416 (73), 402 (90), 398 (16), 384 (14), 357 (22.), 35 (100); Anal. Calcd for $C_{28}H_{29}IO_5$: C, 58.75; H, 5.11. Found: C, 58.55; H, 5.12.



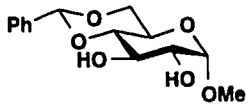
Diethyl (2,3-*O*-Dibenzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylphosphonate (109). A solution of **108** (20.0 mg, 0.0349 mmol) and freshly distilled triethyl phosphite (4 mL) was heated at reflux for 24 h under an argon atmosphere. The reaction mixture was then concentrated under high vacuum, and the residue was purified by elution through a short silica column (2 x 5 cm, ethyl acetate) to give **109** (7.6 mg, 37 %) as a syrup: IR (CH_2Cl_2 cast) 2925, 1726, 1273, 1097, 1069, 1050, 1027 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.25 (m, 15 H, Ar*H*), 5.60 (s, 1 H, PhC*H*O_2), 4.90 (d, 1 H, *J* = 11.0 Hz, PhC*H*HO), 4.80 (d, 1 H, *J* = 11.0 Hz, PhC*H*HO), 4.75 (d, 1 H, *J* = 11.0 Hz,

PhCH*H*O), 4.68 (d, 1 H, J = 11.0 Hz, PhCH*H*O), 4.55-4.45 (m, 1 H, H-2), 4.25-4.00 (m, 5 H, H-7e, 2 x OC*H*$_2$CH$_3$), 3.80-3.65 (m, 5 H, H-3, H-4, H-5, H-6, H-7a), 2.35 (ddd, 1 H, J = 16.5, 11.0, 11.0 Hz, H-1a), 2.25 (ddd, 1 H, J = 20.0, 16.5, 3.5 Hz, H-1b), 1.30 (t, 6 H, J = 7.0 Hz, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 139.2, 138.5, 138.1, 129.2, 128.9, 128.7, 128.6, 128.5, 128.3, 128.22, 128.16, 127.9, 126.4, 101.6, 82.8, 79.4 (d, J = 13.0 Hz), 78.8, 74.9, 74.0, 71.4 (d, J = 4.9 Hz), 69.6, 64.5, 62.1, (d, J = 6.0 Hz), 61.9 (d, J = 6.5 Hz), 23.6 (d, J = 143.9 Hz), 16.7 (d, J = 7.0 Hz), 16.6 (d, J = 6.0 Hz); MS (CI, NH_3) *m/z* (relative intensity) 636 (MNH_4^+, 26), 576 (5), 427 (3), 391 (2), 335 (3), 300 (4), 35 (100).

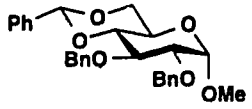


Diethyl (2,3,6-Tri-*O*-benzyl-α-D-glucopyranosyl)methylphosphonate (110). A solution of **126a** (152 mg, 0.265 mmol) in freshly distilled triethyl phosphite (2 mL) was heated at 150 °C for 7 h. Further triethyl phosphite (1 mL) was added and the heating was continued at 150 °C for 2.5 h. The reaction mixture was warmed to 200 °C over 10 min and was then cooled to room temperature. Concentration under high vacuum gave a colorless oil which was purified by flash chromatography (silica, CH_2Cl_2-MeOH, 100:1) to provide **110** (82 mg, 53 %) as a colorless syrup: IR (CH_2Cl_2 cast) 3355 (br), 3063, 3033, 2906, 1453, 1367, 1247, 1224, 1096, 1052, 1027, 965, 698 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.25-7.40 (m, 15 H, Ar*H*), 4.82 (d, 1 H, J =12.5 Hz, PhCH*H*O), 4.72 (d, 1 H, J = 12.5 Hz, PhCH*H*O), 4.68 (d, 1 H, J = 12.5 Hz, PhCH*H*O), 4.64 (d, 1 H, J = 12.5 Hz, PhCH*H*O), 4.57 (d, 1 H, J = 12.5 Hz, PhCH*H*O), 4.52 (d, 1 H, J = 12.5 Hz, PhCH*H*O), 4.48 (dddd, 1 H, J =11.0, 10.0, 5.0, 4.5 Hz, H-2), 4.05 (dq, 4 H, J = 7.5, 7.5 Hz, 2 x POC*H*$_2$), 3.71-3.80 (m, 2 H, H-3, H-4), 3.62-3.70 (m, 3 H, H-5, H-6, H-7e),

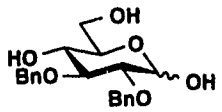
3.58 (dd, 1 H, J =9.0, 9.0 Hz, H-7a), 2.23 (ddd, 1 H, J = 17.5, 17.5, 10.0 Hz, H-1a), 2.15 (ddd, 1 H, J = 17.5, 17.5, 4.5 Hz, H-1b), 1.29 (t, 3 H, J = 7.5 Hz, OCH_2CH_3), 1.26 (t, 3 H, J = 7.5 Hz, OCH_2CH_3); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 139.2, 138.7, 138.4, 128.8, 128.75, 128.7, 128.4, 128.24, 128.20, 128.1, 128.02, 127.99, 79.8, 78.62 (d, J = 10.8 Hz), 74.7, 73.9, 73.3, 71.1, 70.3, 69.05 (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), 16.64 (d, J = 5.4 Hz); MS (CI, NH_3) m/z (relative intensity) 585 (MH^+, 100), 91 (49); Anal. Calcd for $C_{32}H_{41}O_8P$: C, 65.74; H, 7.07. Found: C, 66.05; H, 7.20.



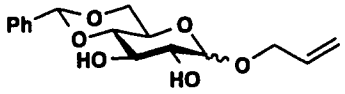
Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (113). A procedure analogous to that used for the preparation of **15** was followed. Thus, a mixture of methyl α-D-glucopyranoside (15.0 g, 77.3 mmol), benzaldehyde (41.0 g, 386 mmol), and $ZnCl_2$ (10.0 g) was stirred at room temperature for 2 days. After work-up and recrystallisation (CH_2Cl_2-hexane), **113** (9.8 g, 45 %) was obtained as a colorless crystalline solid: mp 167-168 °C (lit.[151] mp 166-167 °C); IR (CH_2Cl_2 cast) 3257 (br), 3063, 3001, 2939, 2913, 1452, 1372, 1076, 1062, 1040, 1028, 999 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.52-7.30 (m, 5 H, Ar*H*), 5.50 (s, 1 H, PhC*H*O_2), 4.72 (d, 1 H, J = 4.0 Hz, H-1), 4.25 (dd, 1 H, J = 9.0, 3.0 Hz, H-6e), 3.85 (ddd, 1 H, J = 10.0, 9.0, 2.5 Hz, H-3), 3.80-3.65 (m, 2 H, H-4, H-5), 3.50 (ddd, 1 H, J = 9.5, 9.0, 4.0 Hz, H-2), 3.44 (dd, 1 H, J = 9.0, 9.0 Hz, H-6a), 3.42 (s, 3 H, OCH_3), 3.20 (d, 1 H, J = 2.5 Hz, 3-O*H*), 2.65 (d, 1 H, J = 9.5 Hz, 2-O*H*); MS (CI, NH_3) m/z (relative intensity) 300 (MNH_4^+, 17.1), 283 (MH^+, 100); Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.61; H, 6.43.



Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside (114). A 60 % suspension of sodium hydride in oil (1.56 g, 39.0 mmol) was washed with petroleum ether and was then added portionwise to a solution of **113** (4.80 g, 17.0 mmol) in dry DMF (50 mL) under argon. The resulting mixture was stirred at 80 °C for 30 min and then benzyl chloride (9.90 g, 78.0 mmol) was added dropwise at room temperature. The reaction mixture was stirred at 60 °C for 3 h and then a further portion of NaH (3.10 g, 60 % dispersion in oil, 77.0 mmol) was added. The reaction mixture was maintained at 60 °C overnight and then quenched by the addition of MeOH (40 mL). The resulting mixture was concentrated *in vacuo*, and the remaining solution was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (EtOAc-hexane, 7:1) on silica gave **114** (7.48 g, 95 %) as a white crystalline solid: mp 96-97 °C (lit.[152] mp 93 °C); IR ($CHCl_3$ cast) 3032, 2911, 1453, 1372, 1151, 1134, 1106, 1089, 1077, 1054, 1029 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 7.55-7.25 (m, 15 H, Ar*H*), 5.58 (s, 1 H, PhC*H*O_2), 4.90 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.82 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.80 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.74 (d, 1 H, *J* = 3.5 Hz, H-1), 4.66 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.26 (dd, 1 H, *J* = 9.0, 3.5 Hz, H-6e), 3.98 (dd, 1 H, *J* = 9.5, 9.0 Hz, H-3), 3.90-3.72 (m, 2 H, H-4, H-5), 3.61 (dd, 1 H, *J* = 9.5, 9.0 Hz, H-6a), 3.58 (dd, 1 H, *J* = 9.5, 3.5 Hz, H-2), 3.40 (s, 3 H, OC*H*$_3$); MS (CI, NH_3) *m/z* (relative intensity) 480 (MNH_4^+, 16.9), 463 (MH^+, 51), 371 (11), 91 (100); Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.36; H, 6.48.



2,3-Di-*O*-benzyl-D-glucopyranose (115). A mixture of **114** (2.85 g, 6.17 mmol), acetic acid (60 mL), and 2 N H_2SO_4 (46 mL) was heated at 85 °C for 6 days. After cooling to room temperature, the mixture was diluted with acetone (100 mL). $BaCO_3$ (20 g) was added and the resulting mixture was stirred for 5 h. The solid which formed was removed by filtration, and the filtrate was stirred with Na_2CO_3 (10 g) overnight. Filtration and concentration *in vacuo* afforded a syrup which was purified by flash chromatography (silica, CH_2Cl_2-MeOH, 20:1) to yield the known[153] reducing sugar **115** (0.46 g, 21 %) as a mixture of α- and β-anomers in a 3:1 ratio, respectively (by ^1H NMR): IR ($CHCl_3$ cast) 3380 (br), 1454, 1143, 1110, 1056, 1028, 697 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 7.40-7.30 (m, 10 H, Ar*H*), 5.00-4.65 (m, 5 H, H-1, 2 x PhC*H*$_2$O), 3.85-3.20 (m, 6 H, H-2, H-3, H-4, H-5, H-6a, H-6b); MS (CI, NH_3) *m/z* (relative intensity) 379 (MNH_4^+, 100), 361 (NH^+, 99), 91 (93); Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.14; H, 6.70.



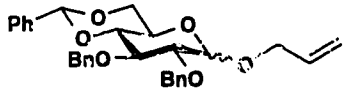
Allyl 4,6-*O*-Benzylidene-D-glucopyranoside (118). AG50W-X8 (H^+) ion exchange resin (5.0 g, 50-100 mesh) was dried at 56 °C *in vacuo* for 1 day and was then added to a suspension of D-glucose (9.00 g, 50 mmol) in anhydrous allyl alcohol (60 mL). After stirring at 100 °C for 3 h, the mixture was filtered to remove the black residue. The filtrate was concentrated *in vacuo* to a constant weight. To this yellowish residue, zinc chloride (7.0 g) and freshly distilled benzaldehyde (50 mL) were added, and the mixture was stirred at room temperature under argon for 2 days to give a brown solution. After extraction with petroleum ether (5 x 100 mL), the mixture solidified. The solid was

dissolved in CH_2Cl_2, washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, petroleum ether-EtOAc, 1:1) to give **118** (11.2 g, 72 %) as a mixture of α- and β-anomers as well as some fractions containing pure α- and β-anomers.

For the α-**anomer**: $[\alpha]_D$ +93.8° (c 1.256, $CHCl_3$); IR (CH_2Cl_2 cast) 3543 (br), 3280 (br), 3065, 2009, 2866, 1451, 1385, 1372, 1150, 1075, 1044, 1015, 995, 968, 935, 746 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.35-7.50 (m, 5 H, Ar*H*), 5.95 (dddd, 1 H, *J* = 17.0, 10.5, 5.0, 5.0 Hz, CH_2=C*H*CH_2O), 5.51 (s, 1 H, PhC*H*O_2), 5.32 (dddd, 1 H, *J* = 17.0, 1.5, 1.5, 1.5 Hz, C*H*H=$CHCH_2O$), 5.23 (dddd, 1 H, *J* = 10.5, 1.5, 1.5, 1.5 Hz, CH*H*=$CHCH_2O$), 4.91 (d, 1 H, *J* = 4.0 Hz, H-1), 4.25 (dd, 1 H, *J* = 10.0, 4.5 Hz, H-6e), 4.24 (dddd, 1 H, *J* = 13.0, 6.0, 1.5, 1.5 Hz, CH_2=CHCH*H*O), 4.05 (dddd, 1 H, *J* = 13.0, 6.0, 1.5, 1.5 Hz, CH_2=CHC*H*HO), 3.89 (dd, 1 H, *J* = 9.5, 9.5 Hz, H-3), 3.82 (ddd, 1 H, *J* = 10.0, 10.0, 5.0 Hz, H-5), 3.70 (dd, 1 H, *J* = 10.0, 10.0 Hz, H-6a), 3.57 (dd, 1 H, *J* = 9.0, 4.0 Hz, H-2), 3.46 (dd, 1 H, *J* = 9.5, 9.5 Hz, H-4), 3.20 (br, 1 H, 3-O*H*), 2.60 (br, 1 H, 2-O*H*); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 326 (MNH_4^+, 27.8), 309 (MH^+, 100), 251 (15); Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.22; H, 6.70.

For the β-**anomer**: mp 144-145 °C; $[\alpha]_D$ -47.3° (c 1.30, $CHCl_3$); IR (CH_2Cl_2 cast) 3510 (br), 3218 (br), 3076, 2924, 2846, 1452, 1402, 1373, 1351, 1267, 1171, 1105, 1187, 1044, 1031, 1003, 748, 697; cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.35-7.50 (m, 5 H, Ar*H*), 5.95 (dddd, 1 H, *J* = 17.5, 10.5, 5.5, 5.5 Hz, CH_2=C*H*CH_2O), 5.53 (s, 1 H, PhC*H*O_2), 5.32 (dddd, 1 H, *J* = 17.5, 1.5, 1.5, 1.5 Hz, CH*H*=CHCH2O), 5.22 (dddd, 1 H, *J* = 10.5, 1.5, 1.5, 1.5 Hz, C*H*H=$CHCH_2O$), 4.42 (d, 1 H, *J* = 8.0 Hz, H-1), 4.35 (dddd, 1-H, *J* = 12.5, 5.5, 1.5, 1.5 Hz, CH_2=CHCH*H*O), 4.31 (dd, 1 H, J = 10.5, 5.0 Hz, H-6e), 4.12 (dddd, 1 H, *J* = 12.5, 5.5, 1.5, 1.5 Hz, CH_2=CHC*H*HO), 3.76 (dd, 1 H, *J* = 10.5,

10.5 Hz, H-6a), 3.75 (ddd, 1 H, J = 9.5, 9.5, 2.5 Hz, H-3), 3.51 (dd, 1 H, J = 9.5, 9.5 Hz, H-4), 3.49-3.39 (m, 2 H, H-2, H-5), 3.30 (d, 1 H, J = 2.5 Hz, 3-O*H*), 2.94 (d, 1 H, J = 3.0-Hz, 2-O*H*); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 326 (MNH_4^+, 12.9), 309 (MH^+, 100), 251 (6); Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.07; H, 6.39.

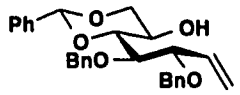


Allyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside (119). A 60 % suspension of sodium hydride in oil (71.0 mg, 1.77 mmol) was washed with petroleum ether and then added to a solution of **118** (mixture of α- and β-anomers, 219.0 mg, 0.71 mmol) in dry DMF (10 mL) at room temperature. The reaction mixture was stirred for 20 min and then benzyl chloride (537.0 mg, 4.44 mmol) was added dropwise. The resulting mixture was heated at 75 °C for 24 h. It was then was poured into ice water and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in *vacuo*. The residue was purified by flash chromatography (silica, petroleum ether - ethyl acetate, 20 : 1) to give **119** (278 mg, 80 %) as a mixture of α, β-anomers as well as fractions containing pure α- and β-anomers.

For **α-anomer**: mp 78-79 °C; $[\alpha]_D$ -3.75° (c 1.12, $CHCl_3$); IR ($CHCl_3$ cast) 2913, 2866, 1452, 1367, 1153, 1109, 1089, 1051, 1028, 745, 695 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.25-7.50 (m, 15 H, Ar*H*), 5.98 (dddd, 1 H, J = 17.5, 10.5, 5.0, 5.0 Hz, CH_2=C*H*CH_2O), 5.59 (s, 1 H, PhC*H*O_2), 5.36 (dddd, 1 H, J = 17.5, 1.5, 1.5, 1.5 Hz, CH*H*=$CHCH_2O$), 5.24 (dddd, 1 H, J = 10.5, 1.5, 1.5, 1.5 Hz, C*H*H=$CHCH_2O$), 4.90 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.89 (d, 1 H, J = 3.4 Hz, H-1), 4.82 (d, 1 H, J = 11.5 Hz, PhC*H*HO), 4.79 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.67 (d, 1 H, J = 11.5 Hz, PhC*H*HO), 4.25 (dd, 1 H, J = 10.0, 5.0 Hz, H-6e), 4.21 (dddd, 1 H, J = 13.0, 5.0, 1.5, 1.5 Hz,

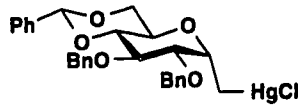
CH_2=CHC*H*HO), 4.01 (dddd,1 H, *J* = 13.0, 5.0, 1.5, 1.5 Hz, CH_2=CHCH*H*O), 4.01 (dd, 1 H, *J* = 9.5, 9.5 Hz, H-3), 3.89 (ddd, 1 H, *J* = 10.0, 10.0, 5.0 Hz, H-5), 3.74 (dd, 1 H, *J* = 10.0, 10.0 Hz, H-6a), 3.62 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-4), 3.59 (dd, 1 H, *J* = 9.5, 3.4 Hz, H-2); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 506 (MNH_4^+, 13), 489 (MH^+, 42), 431 (8), 397 (7), 181 (12), 91 (100); Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.88; H, 6.69.

For β-**anomer**: $[\alpha]_D$ -33.7° (c 1.33, $CHCl_3$); IR ($CHCl_3$ cast) 2875, 1452, 1365, 1130, 1126, 1090, 1076, 1029, 1006, 744, 693 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.20-7.50 (m, 15 H, Ar*H*), 5.95 (dddd, 1 H, *J* = 17.0, 11.0, 5.5, 5.5 Hz, CH_2=C*H*CH_2O), 5.51 (s, 1 H, PhC*H*O_2), 5.35 (dddd, 1 H, *J* = 17.0, 1.5, 1.5, 1.5, 1.5 Hz, CH*H*=CHCH_2O), 5.21 (dddd, 1 H, *J* = 11.0, 1.5, 1.5, 1.5 Hz, C*H*H=CHCH_2O), 4.90 (d, 2 H, *J* = 11.0, 2 x PhCH*H*O), 4.80 (d, 1 H, *J* = 11.0 Hz, PhC*H*HO), 4.78 (d, 1 H, *J* = 11.0 Hz, PhC*H*HO), 4.55 (d, 1 H, *J* = 7.5 Hz, H-1), 4.40 (dddd, 1 H, *J* = 13.0, 5.5, 1.5, 1.5 Hz, CH_2=CHC*H*HO), 4.35 (dd, 1 H, *J* = 10.5, 5.0 Hz, H-6e), 4.15 (dddd, 1 H, *J* = 13.0, 5.5, 1.5, 1.5 Hz, CH_2=CHCH*H*O), 3.79 (dd, 1 H, *J* = 10.5, 10.5 Hz, H-6a), 3.74 (dd, 1 H, *J* = 8.5, 8.5 Hz, H-3), 3.69 (dd, 1 H, *J* = 8.5, 8.5 Hz, H-4), 3.49 (dd, 1 H, *J* = 8.5, 8.5 Hz, H-2), 3.40 (ddd, 1 H, *J* = 10.5, 8.5, 5.0 Hz, H-5); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (CI, NH_3) *m/z* (relative intensity) 506 (M^++18, 15), 489 (M^++1, 21), 431 (10), 397 (9), 342 (9), 181 (13), 91 (100); Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60; O, 19.65. Found: C, 73.77, 6.69.



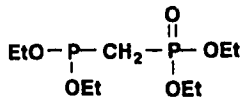
3,4-Di-*O*-benzyl-5,7-*O*-benzylidene-1,2-dideoxy-D-glucohept-1-enitol (120). *n*-Butyllithium (12.1 mL of a 1.6 M solution in hexanes, 19.4 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (6.93 g, 19.4 mmol) in dry DME (70 mL) at -78 °C under an argon atmosphere. The mixture was allowed to warm to room temperature and the stirring was continued for 30 min to give a bright yellow suspension of the ylide. *n*-Butyllithium (4.18 mL of a 1.6 M solution in hexanes, 6.69 mmol) was added to a suspension of **107** (3.00 g, 6.69 mmol) in dry DME (90 mL) at -78 °C over a period of 10 min under argon. The cooling bath was removed and the mixture was stirred at room temperature 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, at which point no starting material could be detected by TLC. Acetone (40 mL) was then added to decompose the excess ylide, and the resulting solution was stirred for an additional 2 h. The solvents were evaporated *in vacuo*, and the yellowish residue was suspended in brine and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellowish solid. Flash chromatography (silica, petroleum ether-ethyl acetate gradient, 6:1 to 4:1) afforded **120** (2.35 g, 79 %) as a white crystalline solid: mp 94-95 °C; $[\alpha]_D$ -10.7° (c 1.20, $CHCl_3$), IR ($CHCl_3$ cast) 3430 (br), 1453, 1398, 1154, 1074, 1027, 697 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.45-7.25 (m, 15 H, Ar*H*), 5.90 (ddd, 1 H, *J* = 18.0, 10.0, 7.0, H-2), 5.39 (dd, 1 H, *J* = 18.0, 1.0 Hz H-1a), 5.35 (dd, 1 H, *J* = 10.0, 1.0 Hz, H-1b), 5.33 (s, 1 H, PhC*H*O_2), 4.86 (d, 1 H, *J* = 12.0 Hz, PhCH*H*O), 4.79 (d, 1 H, *J* = 12.0 Hz, PhC*H*HO), 4.65 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.47 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.29 (dd, 1 H, *J* = 7.0, 7.0 Hz, H-3), 4.21 (dd, 1 H, *J* = 10.0, 5.0 Hz, H-7e), 3.86 (ddd, 1 H, *J* = 10.0, 10.0, 5.0 Hz, H-6), 3.76 (dd, 1 H, *J* = 7.0,

3.5 Hz, H-4), 3.62 (dd, 1 H, J = 10.0, 3.5 Hz, H-5), 3.49 (dd, 2 H, J = 10.0, 10.0 Hz, H-7a), 1.85(br, 1 H, O*H*); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; MS (NH_3, CI), *m/z* (relative intensity) 464 (MNH_4^+, 8), 181 (2), 179 (1), 108 (12), 91 (100); Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.22; H, 6.85.

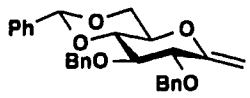


(2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)methylmercuric Chloride (121). A solution of **120** (98.4 mg, 0.221 mmol) and mercuric trifluroacetate (123 mg, 0.234 mmol) in dry THF (7 mL) was stirred at room temperature overnight. A solution of potassium chloride (115 mg, 1.55 mmol) in H_2O (2 mL) was then added, and the mixture was stirred at room temperature for a further 5 h. THF was removed *in vacuo* and the remaining aqueous solution was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. Flash chromatography (petroleum ether-ethyl acetate, 8:1) of the residue afforded a mixture of α- and β-anomers of **121** (145 mg, 96 % yield) as a white foam. ^{1}H-NMR showed that the α : β ratio was 4.3 : 1, respectively. The major α-anomer could be separated from β-anomer by further flash column chromatography (silica, petroleum ether-ethyl acetate, 12:1). For the α-anomer: $[\alpha]_D$ -19.7° (c 1.17, $CHCl_3$); IR ($CHCl_3$ cast) 1453, 1368, 1086, 1075, 1027, 749 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.30-7.50 (m, 15 H, Ar*H*), 5.58 (s, 1 H, PhC*H*O_2), 4.92 (d, 1 H, J =11.5 Hz, PhCH*H*O), 4.90 (d, 1 H, J =11.5 Hz, PhCH*H*O), 4.80 (d, 1 H, J =11.5 Hz, PhCH*H*O), 4.70 (d, 1 H, J =11.5 Hz, PhCH*H*O), 4.23 (m, 2 H, H-2, H-7e), 3.85 (dd, 1 H, J =8.5, 8.5 Hz, H-4), 3.75 (m, 2 H, H-3, H-7a), 3.66 (m, 2 H, H-5, H-6), 2.15 (dd, 1 H, J =12.0, 10.0, H-1a), 1.90 (dd, 1 H, J =12.0, 6.0,

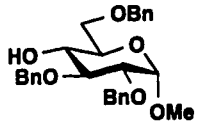
H-1b); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 139.1, 138.0, 137.8, 129.2, 129.07, 128.97, 128.6, 128.5, 128.4, 128.3, 128.0, 126.4, 101.6, 83.3, 78.7, 75.1, 74.9, 74.8, 70.0, 63.6, 26.9; MS (CI, NH_3) *m/z* (relative intensity) 700 (MNH_4^+, 0.2), 683 (MH^+, 0.5), 464 (70), 447 (16), 416 (22), 402 (37), 384 (7), 358 (16), 341 (14), 339 (10.2), 91 (85), 35 (100); Anal. Calcd for $C_{28}H_{29}ClHgO_5$: C, 49.34; H, 4.29. Found: C, 49.39; H, 4.23.



Diethyl [(Diethoxyphosphino)methyl]phosphonate (123). Due to the possible toxicity and extreme sensitivity of the product toward oxidation, all of the operations described below were performed in a hood under an argon atmosphere. *n*-Butyllithium (12.5 mL of a 1.6 M solution in hexanes, 20.0 mmol) was added dropwise to a vigorously stirred solution of diethyl methylphosphonate (2.50 g, 20.0 mmol) in THF (5 mL) at -78 °C. The resulting cloudy mixture was stirred at -78 °C for 1 h and was then added to a solution of diethyl phosphorochloridite (6.0 g, 38.3 mmol) in anhydrous pentane (30 mL). The resulting mixture was allowed to warm to room temperature and was stirred for 12 h. Dry pentane (30 mL) was added to the reaction mixture and the stirring was stopped to allow the lithium salt to settle. The supernatant was then transferred to another reaction vessel *via* cannula and the pentane was evaporated by passing a flow of argon through the solution. The remaining liquid was distilled at atmospheric pressure and then under vacuum to give **123** (1.62 g, 30 %) as a colorless liquid: 80-120 °C (0.7-1.0 torr) (lit.[127] bp 90 °C (0.02 torr)); IR ($CHCl_3$ cast) 2983, 2908, 1257, 1098, 1029, 971, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.08-3.92 (m, 4 H, 2 x OCH_2CH_3), 3.85-3.69 (m, 4 H. 2 x OCH_2CH_3), 2.10 (dd, 2 H, J = 20.0, 4.5 Hz, PCH_2P), 1.17 (2 t, 18 H, J = 7.0, 12 Hz, 6 x OCH_2CH_3); ^{31}P NMR, ($CDCl_3$, 162 MHz) δ 164.3 (d, J = 40.5 Hz), 23.5 (d, J = 40.5 Hz); HRMS Calcd for $C_9H_{22}O_6P_2$ (M^+): (oxidized product): 288.0891. Found: 288.0890.



2,6-Anhydro-3,4-di-*O*-benzyl-5,7-*O*-benzylidene-1,2-dideoxy-D-*gluco*-hept-1-enitol (124). A solution of **123** (0.46 g, 1.69 mmol) in pentane (4.0 mL) was added to iodide **108** (71.0 mg, 0.124 mmol) under an argon atmosphere. The resulting mixture was heated to 170 °C and the pentane was allowed to evaporate. After 2 h of heating, a further portion of **123** (0.92 g, 3.38 mmol) was added and the reaction mixture was kept at 170 °C for an additional 3 h. The reaction mixture was then cooled to room temperature and concentrated under high vacuum to give a viscous oil. Purification by flash chromatography (silica, petroleum ether-ethyl acetate, 15:1) gave **124** (22.3 mg, 41 %) as a white crystalline solid: mp 80-82 °C; IR ($CHCl_3$ cast) 2861, 1659, 1453, 1371, 1095, 1072 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.50-7.40 (m, 15 H, Ar*H*), 5.58 (s, 1 H, PhC*H*O_2), 4.76 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.74 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.71 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.69 (s, 1 H, H-1a), 4.59 (dd, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.51 (s, 1 H, H-1b), 4.40 (dd, 1 H, *J* = 10.2, 5.0 Hz, H-7e), 4.00-3.93 (m, 2 H, H-3, H-6a), 3.87-3.80 (m, 2 H, H-4, H-5), 3.75 (dd,1 H, *J* = 10.2, 10.0 Hz, H-7a); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 155.3, 138.71, 138.34, 137.9, 129.3, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 126.5, 101.7, 94.9, 82.0, 81.7, 79.3, 73.4, 72.0, 69.5, 67.7; MS (CI, NH_3) *m/z* (relative intensity) 462 (MNH_4^+, 3), 445 (MH^+, 27), 35 (100); Anal. Calcd for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35. Found: C, 75.24; H, 6.08.



Methyl 2,3,6-Tri-*O*-benzyl-α-D-glucopyranoside (125). A mixture of benzylidene derivative **114** (462 mg, 1.00 mmol), powdered 3 Å molecular sieves (0.1 g), and sodium cyanoborohydride (785 mg, 12.5 mmol) was stirred at 0 °C for 20 min, then ethereal

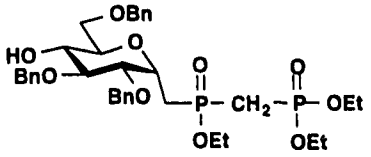
hydrogen chloride (ca. 6 mL) was added dropwise until gas evolution ceased. The cooling bath was removed and the stirring was continued for a further 10 minutes, at which time no starting material was visible by TLC. The reaction mixture was poured into water (40 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with brine and saturated $NaHCO_3$, and then dried (Na_2SO_4). Evaporation of the solvent *in vacuo* followed by flash chromatography (silica, hexane-ethyl acetate, 5:1) gave the known compound[154] **125** (393 mg, 85 %) as a syrup: IR ($CHCl_3$ cast) 2911, 1453, 1156, 1093, 1080, 1055, 1028 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.40-7.25 (m, 15 H, Ar*H*), 4.98 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.76-4.63 (m, 4 H, 3 x PhC*H*HO, H-1), 4.55 (ABq, 2 H, *J* = 11.5 Hz, PhC*HH*O), 3.76-3.65 (m, 4 H, H-3, H-5, H-6a, H-6b), 3.56 (ddd, 1 H, *J* = 10.0, 9.5, 2.5 Hz, H-4), 3.52 (dd,1 H, *J* = 9.5, 3.5 Hz, H-2), 3.36 (s, 3 H, OC*H*$_3$), 2.48 (d, 1 H, *J* = 2.5 Hz, 4-O*H*); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 139.2, 138.9, 138.8, 128.72, 128.68, 128.3, 128.2, 128.1, 128.0, 127.9, 98.3, 81.6, 80.3, 75.4, 73.8, 73.1, 71.4, 70.3, 55.4; MS (CI, NH_3) *m/z* (relative intensity) 482 (MNH_4^+, 30), 253 (12), 108 (12), 91 (100); Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.29; H, 6.90.

(2,3,6-Tri-*O*-benzyl-α-D-glucopyranosyl)methyl Iodide (126a) and (2,3,4-Tri-*O*-benzyl-α-D-glucopyranosyl)methyl Iodide (126b). Diethyl ether saturated with hydrogen chloride gas was added in small portions to a mixture of benzylidene derivative **108** (250 mg, 0.437 mmol), sodium cyanoborohydride (300 mg, 4.77 mmol), and powered 3 Å molecular sieves (0.1 g) in anhydrous THF (12 mL) at 0 °C until gas evolution ceased. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 20 min. The reaction was quenched with brine and extracted with ether.

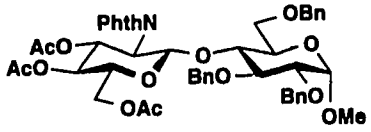
The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica, petroleum ether-ethyl acetate gradient, 10:1 to 7.5:1) of the residue gave **126a** (161 mg, 64 %) as a waxy solid. The corresponding 6-OH isomer **126b** (27 mg, 11 %) also could be isolated as the minor product.

For **126a**: IR ($CHCl_3$ cast) 3340 (br), 3030, 2905, 2869, 1496, 1453, 1365, 1096, 1048, 1027, 737, 697 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.25-7.40 (m, 15 H, Ar*H*), 4.80 (d, 1 H, *J* =11.5 Hz, PhCH*H*O), 4.70 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.69 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.60 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.58 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.52 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.12 (ddd, 1 H, *J* = 10.5, 4.5, 4.5 Hz, H-2), 3.60-3.80 (m, 6 H, H-3, H-4, H-5, H-6, H-7a, H-7e), 3.51 (dd, 1 H, *J* =10.0, 4.5, H-1a), 3.41(dd, 1 H, *J* =10.5, 10.0, H-1b), 2.87 (d, 1 H, *J* = 4.0 Hz, 5-O*H*); ^{13}C NMR (CD_2Cl_2, 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; MS (CI, NH_3) *m/z* (relative intensity) 592 (MNH_4^+, 42), 502 (12), 412 (11), 91 (100); Anal. Calcd for $C_{28}H_{31}IO_5$: C, 58.54; H, 5.44. Found: C, 58.35; H, 5.41.

For **126b:** IR (CH_2Cl_2 cast) 3450 (br), 3063, 3030, 2904, 2867, 1453, 1360, 1210, 1125, 1091, 1027 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.40-7.35 (m, 15 H, Ar*H*), 4.92 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.90 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.86 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.75 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.80 (ABq, 2 H, *J* = 11.5 Hz, PhC*HH*O), 3.78-3.70 (m, 2 H, H-3, H-4), 3.68-3.48 (m, 4 H, H-7a, H-2, H-1a, H-1b), 3.42-3.35 (m, 2 H, H-5, H-7b), 3.12 (ddd, 1 H, *J* = 9.0, 5.5, 2.5 Hz, H-6), 2.60 (br s, 7-OH); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 139.2, 138.6, 128.81, 128.75, 128.7, 128.3, 128.22, 128.17, 128.11, 128.08, 128.00, 86.4, 81.7, 78.4, 77.8, 75.5, 75.4, 73.9, 72.6, 70.6, 8.00; MS (CI, NH_3) *m/z* (relative intensity) 592 (MNH_4^+, 100), 483 (11); Anal. Calcd for $C_{28}H_{31}IO_5$: C, 58.54; H, 5.44. Found: C, 58.58; H, 5.39.

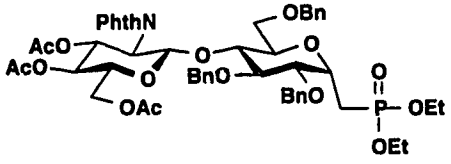


Triethyl [(2,3,6-Tri-*O*-benzyl-α-D-glucopyranosyl)hydroxyphosphinyl]methylphosphonate (127). A solution of iodide **126a** (20.0 mg, 0.0347 mmol) in **123** (0.20 g, 0.74 mmol) was heated at 130°C for 3 h, followed by 150 °C for 6 h, and was then concentrated under high vacuum. Purification of the oily residue by flash chromotography (silica, CH_2Cl_2-MeOH, gradient, 100:1 to 50:1) gave **127** (2.5 mg, 10 %): ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.45-7.25 (m, 15 H, Ar*H*), 4.90-4.50 (m, 5 H, PhC*H*O_2, 2 x PhCH_2O), 4.35-4.22 (m, 1 H, H-2), 4.20-3.60 (m, 12 H, H-2, H-3, H-4, H-5, H-6a, H-6b, 3 x OCH_2CH$_3$), 2.70-2.25 (m, 4 H, CH_2P(O)CH_2P), 1.45-1.20 (m, 9 H, 3 x OCH$_2$CH_3)); MS (CI, NH_3) *m/z* (relative intensity) 691 (MH^+, 6), 593 (3), 492 (3), 341 (4), 132 (100).



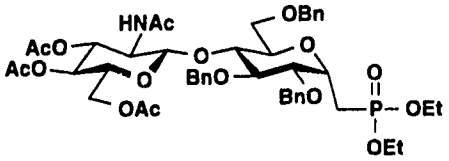
Methyl 4-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (128). A mixture of **125** (30.0 mg, 6.84 μmol), silver trifluoromethanesulfonate (17.6 mg, 68.4 μmol), collidine (90 μL, 68.4 μmol), and powdered 4 Å molecular sieves (90 mg) in dry nitromethane (1.5 mL) was stirred at -30 °C for 10 min. To this mixture, 3,4,6-*tri*-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (**58**) (29.3 mg, 64.6 μmol) in dry nitromethane (1.0 mL) was added dropwise over a period of 20 min. The resulting mixture was stirred at -30 °C for 1 h and was then allowed to warm to room temperature. After a further 2 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a pad of Celite. The filtrate was washed with H_2O, 1 N HCl, saturated $NaHCO_3$, and brine. Evaporation of

the solvent *in vacuo* followed by flash chromatography (silica, petroleum ether-ethyl acetate, gradient, 4:1 to 3:1) on silica afforded the disaccharide **128** (30.3 mg, 53 %) as a solid: IR ($CHCl_3$ cast) 1777, 1748, 1718, 1386, 1240, 1227, 1097, 1047 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.90-7.80 (m, 4 H, Ar*H*), 7.45-7.22 (m, 15 H, Ar*H*), 5.72 (dd, 1 H, *J* = 10.5, 9.0 Hz, H-4'), 5.60 (d, 1 H, *J* = 8.2 Hz, H-1'), 5.10 (dd, 1 H, *J* = 10.0, 9.0 Hz, H-3'), 4.98 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.85 (d, 1 H, *J* = 11.5 Hz, PhC*H*HO), 4.64 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.60 (d, 1 H, *J* = 3.8 Hz, H-1), 4.55 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.38 (ABq, 2 H, *J* = 11.5 Hz, PhC*HH*O), 4.25 (dd, 1 H, *J* = 10.6, 8.7 Hz, H-4), 4.11 (dd, 1 H, *J* = 12.5 , 3.8 Hz, H-6'a), 3.99 (dd, 1 H, *J* = 10.0, 8.2 Hz, H-2'). 3.88 (dd, 1 H, *J* = 12.5, 2.5 Hz, H-6'b), 3.79 (dd, 1 H, *J* = 9.0, 8.7 Hz, H-3), 3.55-3.42 (m, 5 H, H-5', H-5, H-6a, H-6b, H-2), 3.25 (s, 3 H, OCH_3), 1.96 (s, 6 H, 2 x CH_3CO), 1.80 (s, 3 H, CH_3CO); ^{13}C NMR (CD_2Cl_2, 50 MHz) δ 170.8, 170.4, 169.8, 168.3, 140.17, 139.1, 134.8, 132.0, 128.7, 128.6, 128.3, 128.1, 127.8, 127.7, 127.5, 123.9, 98.5, 97.7, 80.3, 76.1, 74.9, 73.5, 73.3., 72.3, 71.2, 70.1, 69.5, 69.0, 62.3, 55.9, 55.5, 20.8, 20.6; MS (FAB, Cleland) *m/z* (relative intensity) 882 (MH^+, 1), 880 (2), 742 (0.6), 418 (7), 298 (100).



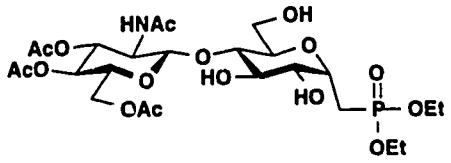
Diethyl [4-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]methylphosphonate (129). A mixture of **110** (0.84 g, 1.46 mmol) and silver trifluoromethanesulfonate (0.57 mg, 2.22 mmol) was dried overnight *in vacuo* over P_2O_5 in the dark. Collidine (300 μL, 2.22 mmol), powered 4 Å molecular sieves (0.1 g), and anhydrous CH_2Cl_2 (14 mL) were then added, and the resulting mixture was stirred at -78 °C for 30 min. A solution of pyranosyl chloride **58**

(1.01 g, 2.22 mmol) in anhydrous CH_2Cl_2 (6 mL) was then added. The reaction mixture was stirred at -30 °C for 1 h, and was then allowed to warm to room temperature. After stirring for 24 h, the reaction mixture was diluted with CH_2Cl_2 and filtered to remove the silver salts and molecular sieves. The filtrate was washed with water, 1N HCl, $NaHCO_3$, and brine. The organic solution was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The resulting residue was subjected to flash chromatography (silica, CH_2Cl_2 : MeOH gradient, 12.5:1 to 10:1) to give the disaccharide **129** (1.22 g, 83 %) as a white foam: IR ($CHCl_3$ cast) 1750, 1718, 1386, 1366, 1240, 1227, 1077, 1029 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.70-7.85 (m, 4 H, Ar*H*), 7.20-7.40 (m, 15 H, Ar*H*), 5.72 (dd, 1 H, *J* = 10.5, 9.0, H-3'), 5.60 (d, 1 H, *J* = 8.0 Hz, H-1'), 5.11 (dd, 1 H, *J* = 10.0, 9.0 Hz, H-4'), 4.92 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.76 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.61 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.51 (d, 1 H, *J* = 11.5 Hz, PhCH*H*O), 4.32-4.42 (m, 3 H, PhCH_2O and H-2), 4.27 (dd, 1 H, *J* = 10.5, 8.0 Hz, H-2'), 4.12 (dd, 1 H, *J* = 12.0, 4.5 Hz, H-6'), 4.03 (dd, 1 H, *J* = 9.0, 7.5 Hz, H-5), 3.89-3.99 (m, 5 H, H-6', 2 x POCH_2), 3.69 (dd, 1 H, *J* = 7.5, 7.5 Hz, H-4,), 3.62 (ddd, 1 H, *J* = 7.5, 5.0, 1.5 Hz, H-3), 3.54-3.48 (m, 2 H, H-5', H-6), 3.45-3.30 (m, 2 H, H-7a, H-7e), 1.93-2.09 (m, 2 H, H-1a, H-1b), 1.99 (s, 3 H, CH_3CO), 1.97 (s, 3 H, CH_3CO), 1.81 (s, 3 H, CH_3CO), 1.16 (dt, 6 H, *J* = 18.0, 7.5 Hz, 2 x $POCH_2CH_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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 Hz), 69.2, 68.7, 62.0, 61.98 (d, *J* = 5.0 Hz) 61.7 (d, *J* = 5.0 Hz), 55.6, 23.7 (d, *J* = 143.6 Hz), 20.84, 20.80, 20.6, 16.5 (d, *J* = 4.0 Hz); ^{31}P NMR (CH_2Cl_2, 162 MHz) δ 28.7; MS (FAB, Cleland) *m/z* (relative intensity) 1002.20 (MH^+, 34), 585.06 (55), 495.15 (14), 297.79 (90), 255.87 (79), 154.78 (64), 119.08 (100); Anal. Calcd for $C_{52}H_{60}NO_{17}P$: C, 62.33; H, 6.04; N, 1.40. Found: C, 62.39; H, 6.15; N, 1.38.

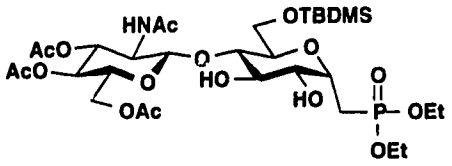


Diethyl [4-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]methylphosphonate (130). Hydrazine hydrate (58 μL of an 85 % aqueous solution, 57 mmol) was added to a solution of phthalimido derivative **129** (43.0 mg, 0.0429 mmol) in 95 % ethanol (2 mL), and the resulting mixture was heated at 80 °C for 1.5 h. The solvents were removed *in vacuo* and the residue was dried under high vacuum for 4 h. The resulting solid was treated with pyridine (3 mL) and acetic anhydride (3 mL) for 12 h. The excess acetic anhydride was decomposed by addition of 95 % ethanol. Evaporation *in vacuo* followed by flash chromatography (silica, MeOH:CH_2Cl_2, gradient, 100:1 to 30:1) of the residue afforded **130** (34.5 mg, 88 %) as a white foam: IR ($CHCl_3$ cast) 1747, 1367, 1241, 1230, 1164, 1106, 1073, 1043 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) 7.20-7.50 (m, 15 H, Ar*H*), 5.02-4.98 (m, 2 H, H-3', N*H*), 4.96 (dd, 1 H, J = 10.0, 10.0 Hz, H-4'), 4.95 (d, 1 H, J = 12.0 Hz, PhCH*H*O), 4.71 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.69 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.63 (d, 1 H, J = 8.5 Hz, H-1'), 4.62 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.54 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.44 (d, 1 H, J = 11.5 Hz, PhCH*H*O), 4.44-4.40 (m, 1 H, H-2), 4.11 (dd, 1 H, J = 12.0, 4.5 Hz, H-6'), 4.00-4.09 (m, 4 H, 2 x POC*H*$_2$CH$_3$), 3.87-3.92 (m, 2 H, H-6', H-5), 3.75 (ddd, 1 H, J = 10.0, 10.0, 9.0 Hz, H-2',), 3.60-3.70 (m, 4 H, H-3, H-4, H-6, H-7a), 3.60-3.57 (m, 1 H, H-7b), 3.49 (ddd, 1 H, J = 10.0, 4.0, 2.0 Hz, H-5'), 2.05-2.21 (m, 2 H, H-1a, H-1b), 2.00 (s, 3 H, C*H*$_3$CO), 1.99 (s, 3 H, C*H*$_3$CO), 1.90 (s, 3 H, C*H*$_3$CO), 1.71 (s, 3 H, C*H*$_3$CO), 1.30 (dt, 6 H, J = 13.0, 6.5 Hz, 2 x POCH$_2$C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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,

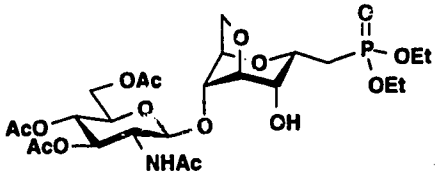
78.5 (d, J = 12.1 Hz), 77.6, 74.6, 73.9, 73.4, 73.0, 72.1, 71.9, 69.6 (d, J = 4.0 Hz), 68.9, 68.7, 62.3, 62.05 (d, J = 5.0 Hz), 61.76 (d, J = 6.0 Hz), 55.2, 23.6 (d, J = 132.8 Hz), 23.3, 20.8, 16.6 (d, J = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 28.8. MS (FAB, Cleland) *m/z* (relative intensity) 936.4 (MNa^+, 1.4), 914.2 (MH^+, 18), 585.2 (64), 495.3 (19), 375.3 (1.2), 330.0 (34), 210.2 (30), 181.1 (6.2), 92.1 (100); Anal. Calcd for $C_{46}H_{60}NO_{16}P$: C, 60.45; H, 6.62 N, 1.53. Found: C, 60.74; H, 6.33; N, 1.60.



Diethyl [4-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]methylphosphonate (131). A solution of the tribenzyl derivative **130** (200 mg, 0.219 mmol) in 95 % ethanol-acetic acid (8 mL, 3:1, v/v) was hydrogenated in the presence of 10 % palladium on carbon (100 mg) for 20 hours. The reaction mixture was filtered though a pad of Celite and the filtrate was evaporated *in vacuo* to give **131** (142 mg, 99 %) as a glassy solid: IR(CH_2Cl_2 cast) 3388 (br), 2923, 2853, 1735, 1651, 1378, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$-CD_3O-D_2O, 200 MHz) δ 5.20 (dd, 1 H, J = 10.5, 9.5 Hz, H-3'), 5.00 (dd, 1 H, J = 9.5, 9.5 Hz, H-4'), 4.80-4.60 (m, 5 H, H-1', 3 x O*H*, N*H*), 4.40-4.25 (m, 1 H, H-2), 4.25-3.90 (m, 8 H, H-5, H-2', H-6'a, H-6', 2 x OCH_2CH_3), 3.70-3.50 (m, 6 H, H-3, H-4, H-6, H-7a, H-7b, H-5'), 2.30-2.10 (m, 2 H, H-1a, H-1b), 2.10, 2.05, 2.01, 1.95 (4 x s, 12 H, 4 x CH_3CO), 1.30 (dt, 6 H, J = 7.0, 2.5 Hz, 2 x OCH_2CH_3); MS (CI, NH_3) *m/z* (relative intensity) 635.5 (M^+-18, 0.6), 580 (0.3), 204 (17), 35 (100).

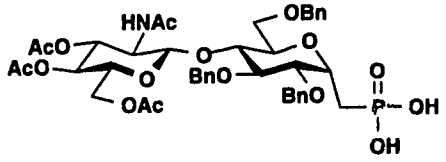


Diethyl [4-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-6-*tert*-butyldimethylsilyl-α-D-glucopyranosyl]methylphosphonate (133). Tetraol **131** (70 mg, 0.109 mmol) was treated with *t*-butyldimethylsilyl chloride (30.4 mg, 0.109 mmol) and imidazole (18.5 mg, 0.272 mmol) in DMF (1.0 mL) at room temperature for 18 h. Evaporation of the reaction mixture *in vacuo* afforded a residue which was purified by flash chromatography (silica, CH_2Cl_2-MeOH, gradient, 30:1 to 20:1) to give the silyl ether **133** (28 mg, 34 %) as a glassy solid: IR ($CHCl_3$ cast) 3277 (br), 2955, 2929, 2855, 1751, 1676, 1664, 1369, 1230, 1162, 1111, 1079, 1044 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 5.75 (d, 1 H, J = 9.0 Hz, N*H*), 5.15 (dd, 1 H, J = 10.0, 9.0 Hz, H-3'), 5.01 (dd, 1 H, J = 9.5, 9.0 Hz, H-4'), 4.60 (d, 1 H, J = 8.5 Hz, H-1'), 4.38-4.34 (m, 1 H, H-2), 4.30-3.50 (m, 10 H, H-3, H-4, H-5, H-6, H-7a, H-7b, H-2', H-5', H-6'a, H-6'b), 2.30-1.90 (m, 14 H, H-1a, H-1b, 4 x C*H*$_3$CO), 1.30 (t, 6 H, J = 7.0 Hz, 2 x OCH$_2$C*H*$_3$), 0.90 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.10 (s, 6 H, Si(C*H*$_3$)$_2$); MS (FAB, Cleland) *m/z* (relative intensity) 780.6 (MNa^+, 3.2), 758.5 (MH^+, 27), 700 (10), 429 (100).



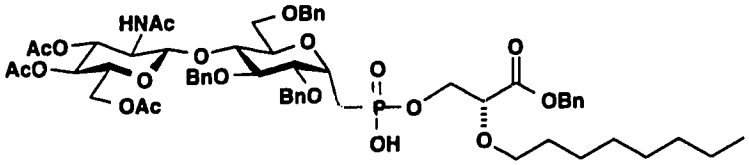
Diethyl [4-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3,6-anhydro-α-D-glucopyranosyl]methylphosphonate (134). A solution of triol **131** (59.0 mg, 0.0917 mmol), benzoic acid (12.5 mg 0.103 mmol), and triphenylphosphine (29.3 mg, 0.112 mmol) in THF (0.8 mL) was cooled to -78 °C. Diethyl azodicarboxylate (18.0 μL, 0.112 mmol) in THF (0.3 mL) was added dropwise to this solution, and the

reaction mixture was allowed to warm to room temperature slowly overnight. Solvent removal *in vacuo* followed by flash chromatography (silica, CH_2Cl_2-MeOH, gradient, 25:1 to 20:1) gave **134** (41.0 mg, 71 %) as a clear syrup: IR (CH_2Cl_2 cast) 3507 (br), 3278 (br), 3077, 2981, 1750, 1666, 1433, 1370, 1230, 1047 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 6.65 (d, 1 H, J = 8.0 Hz, NH), 5.20 (dd, 1 H, *J* = 10.5, 10.0 Hz, H-3'), 5.08 (dd, 1 H, *J* = 10.0, 9.5 Hz, H-4'), 4.72 (d, 1 H, *J* = 8.5 Hz, H-1'), 4.42-4.38 (m, 1 H, H-2), 4.35-3.95 (m, 12 H, H-4, H-5, H-6, H-7a, H-7b, H-5', H-6'a, H-6'b, 2 x OCH_2CH_3), 3.72-3.68 (m, 1 H, H-2'), 3.50 (br m, 2 H, H-3, 3-OH), 2.09-2.20 (m, 2 H, H-1a, H-1b), 2.05, 2.02, 2.00, 1.95 (4 x s, 12 H, 4 x CH_3CO), 1.30 (dt, 6 H, *J* = 7.0, 7.0 Hz, 2 x OCH_2CH_3); ^{13}C NMR (CD_2Cl_2 + trace of D_2O, 100 MHz) δ 171.6, 171.2, 170.9, 169.7, 99.5, 75.9, 72.6, 72.4, 72.1, 71.2 (d, *J* = 10.9 Hz), 69.8, 69.1, 68.9, 62.4 (d, *J* = 6.9 Hz), 62.3, 62.2 (d, *J* = 7.3 Hz), 54.1, 27.6 (d, *J* = 143.9 Hz), 23.3, 20.8, 20.78, 16.5 (d, *J* = 4.5 Hz); MS (FAB, Cleland) *m/z* (relative intensity) 648 (MNa^+, 12), 626 (MH^+, 15), 329.8 (80), 297 (100).



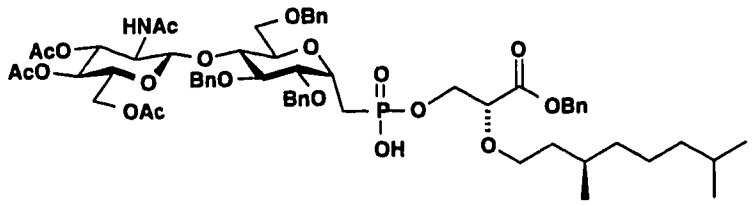
[4-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]methylphosphonic Acid (135). Bromotrimethylsilane (50 μL, 0.346 mmol) was added dropwise to a solution of **134** (30.8 mg, 0.0337 mmol) in dry CH_2Cl_2 (0.4 mL) at room temperature. The mixture was stirred for 2 h and then concentrated to dryness *in vacuo*. Acetone (1.5 mL) and water (10 μL) were added to the residue, and the mixture was stirred for 20 min. Evaporation of the solvents *in vacuo* afforded an off-white residue which was precipitated from CH_2Cl_2 : acetone : petroleum ether to give **135** (26.3 mg, 91 %) as a white solid: IR (CH_2Cl_2 + MeOH cast) 3290 (br), 17445, 1661, 1549, 1375, 1251, 1228, 1117, 1050, 1032, 975, 751, 697 cm^{-1}; ^1H NMR

($CDCl_3$ + DMSO-d_6, 400 MHz) δ 7.15-7.35 (m, 15 H, Ar*H*), 5.50 (br, 3 H, 2 x O*H*, N*H*), 5.11 (dd, 1 H, *J* = 10.0, 10.0, H-3'), 4.86-4.78 (m, 3 H, H-4', 2 x PhC*H*HO), 4.68-4.45 (m, 5 H, H-1', 4 x PhC*H*HO), 4.42-4.38 (m, 1 H, H-2), 3.88-3.75 (m, 3 H, H-5, H-2', H-6'), 3.75-3.55 (m, 5 H, H-3, H-4, H-6, H-7a, H-7b), 3.38 (m, 1 H, H-5'), 1.85-2.05 (m, 8 H, H-1a, H-1b, 2 x CH_3CO), 1.70 (s, 3 H, CH_3CO), 1.80 (s, 3 H, CH_3CO); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz) δ 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; ^{31}P NMR ($CDCl_3$ + DMSO-d_6, 162 MHz) δ 23.6. MS (FAB, Cleland) *m/z* (relative intensity) 879.8 (MNa^+, 5), 857.8 (M^+, 2), 790 (2), 529.0 (2), 154.7 (57), 149.8 (56), 134.9 (47), 119.0 (100).



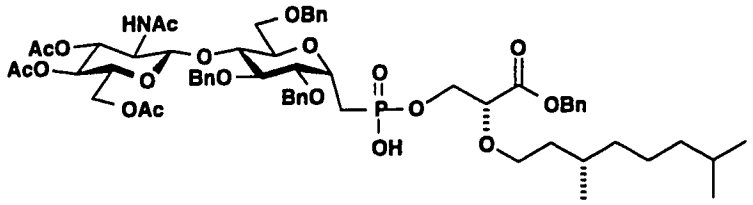
Benzyl (*R*)-3-{[4-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]methylphosphinato}-2-octyloxypropanoate (136). A solution of **135** (93.5 mg, 0.109 mmol), trichloroacetonitrile (1.6 mL) and **90** (55 mg, 0.178 mmol) in anhydrous pyridine (3 mL) was stirred at 70 °C for 42 h under argon. The resulting brown solution was concentrated *in vacuo*, and the residue was extracted with petroleum ether to remove excess **90**. The residue was extracted with toluene, and the extracts were concentrated *in vacuo*. The residue was applied to an AG1-X8 (100-200 mesh, formate form) ion exchange column and eluted with MeOH to give **136** (96.0 mg, 78 %) as a glassy solid: IR (CH_2Cl_2 cast) 3284 (br), 2953, 2927, 2856, 1747, 1666, 1454, 1367, 1231, 1087, 1070, 1045 cm^{-1}; ^1H NMR (CD_2Cl_2 + CD_3OD, 400 MHz) δ 7.45-7.20 (m, 15 H, Ar*H*), 5.20-5.05 (m, 3 H, H-3', 2 x PhC*H*HO), 5.00-4.85 (m, 2 H, H-4', PhC*H*HO), 4.70-4.40 (m, 6 H, H-1', 5 x PhC*H*HO), 4.40-3.35

(m, 16 H, H-2, H-3, H-4, H-5, H-6, H-7a, H-7b, H-2', H-5', H-6'a, H-6'b, POC*H*$_2$CH, POCH$_2$C*H*, OC*H*$_2$CH$_2$), 1.90-2.10 (m, 8 H, H-1a, H-1b, 2 x C*H*$_3$CO), 1.80 (s, 3 H, C*H*$_3$CO), 1.90 (s, 3 H, C*H*$_3$CO), 1.55 (m, 2 H), 1.60-1.45 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$), 1.40-1.15 (m, 10 H, 2 x OCH$_2$CH$_2$(C*H*$_2$)$_5$), 0.80 (t, 3 H, J = 8 Hz, C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 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, 22.83, 20.69, 20.66, 20.6, 14.1; ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 30.2; MS (FAB, Cleland) *m/z* (relative intensity) 1171.5 (MH^++Na^+, 23), 1170.5 (MNa^+, 35), 1080.6 (3).



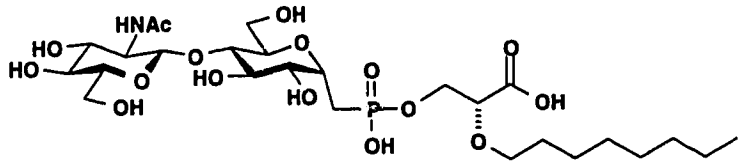
Benzyl (2*R*,3'*R*)-3-{[4-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]methylphosphinato}-2-(3',7'-dimethyloctyl-oxy)propanoate (137). A procedure analogous to that used for the preparation of **136** was followed. Thus, a solution of **135** (93.5 mg, 0.109 mmol), trichloroacetonitrile (1.6 mL), and alcohol **91** (55.0 mg, 0.163 mmol) in anhydrous pyridine (4.0 mL) was stirred at 70 °C under argon for 48 h. After work-up and purification, phosphonate **137** (126 mg, 98 %) was obtained as a glassy solid: IR ($CHCl_3$ cast) 3380 (br), 2990, 2980, 1750, 1663, 1455, 1367, 1230, 1073, 1044 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 7.50-7.30 (m, 20 H, ArH), 5.52 (d, 1 H, J = 8.5 Hz, N*H*), 5.18 (ABq, 2 H, J = 11.5 Hz, PhC*HH*O), 5.06 (dd, 1 H, J = 10.0, 9.0 Hz, H-3'), 4.97 (dd, 1 H, J = 9.0, 9.0 Hz, H-4'), 4.94 (d, 1 H, J = 11.5 Hz, PhC*HH*O), 4.72-4.64 (m, 3 H, H-1', 2 x PhC*HH*O), 4.58 (ABq, 2 H, J = 11.5 Hz, PhC*HH*O), 4.52-4.42 (m, 2 H, H-2, PhCH*H*O), 4.32-4.23 (m,

2 H, POC*H*$_2$CH), 4.15-4.05 (m, 2 H, H-6'a, POCH$_2$C*H*), 3.94-3.87 (m, 2 H, H-5, H-6'b), 3.80 (dd, 1 H, J = 10.0, 10.0 Hz, H-2'), 3.75-3.55 (m, 6 H, H-3, H-4, H-6, H-7a, H-7b, OC*H*HCH$_2$), 3.50-3.40 (m, 2 H, H-5', OCH*H*CH$_2$), 2.40-1.00 (m, 10 H, 4 x C*H*$_2$, 2 x C*H*), 2.00, 1.99, 1.90, 1.75 (4 x s, 12 H, 4 x C*H*$_3$CO), 0.90-0.80 (m, 9 H, 3 x C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 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; ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 30.9; MS (FAB, Cleland) *m/z* (relative intensity) 1198 (MNa^+, 0.6), 1176 (MH^+, 1.0).



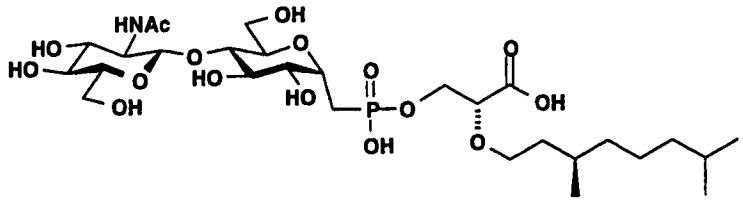
Benzyl (*2R,3'S*)-3-{[4-*O*-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl]methylphosphinato}-2-(3',7'-dimethyloctyl-oxy)propanoate (138). A procedure analogous to that used for the preparation of **136** was followed. Thus, phosphonic acid **135** (93.5 mg, 0.109 mmol), trichloroacetonitrile (1.6 mL), alcohol **92** (55.0 mg, 0.163 mmol), and anhydrous pyridine (3.0 mL) were stirred at 70 °C under argon for 48 h. After work-up and purification, **138** (122 mg, 95 %) was obtained as a glassy solid: IR ($CHCl_3$ cast) 3400 (br), 2950, 2925, 2875, 1750, 1650, 1542, 1454, 1367, 1231, 1114, 1073, 1043 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.50-7.30 (m, 20 H, Ar*H*), 5.40 (d, 1 H, J = 8.5 Hz, N*H*), 5.19 (ABq, 1 H, J = 11.5 Hz, PhC*H*H*O*), 5.07 (t, J = 10.0, 10.0 Hz, H-3'), 5.02-4.90 (m, 2 H, H-4', PhC*H*HO), 4.75-4.65 (m, 3 H, H-1', 2 x PhC*H*HO), 4.56 (ABq, 2 H, J = 11.5 Hz, PhCH*H*O), 4.52-4.42 (m, 1 H, H-2), 4.40 (d, 1 H, J = 11.5 Hz,

PhCH*H*O), 4.35-4.25 (m, 2 H, POCH_2CH), 4.15-4.07 (m, 2 H, H-6'a, POCH$_2$C*H*), 3.93-3.85 (m, 2 H, H-5, H-6'b), 3.78 (dd, 1 H, J = 10.0, 9.0 Hz, H-2'), 3.76-3.58 (m, 6 H, H-3, H-4, H-6, H-7a, H-7b, OC*H*HCH$_2$), 3.52-3.42 (m, 2 H, H-5', OCH*H*CH$_2$), 2.40-1.00 (m, 10 H, 2 x CH_2, 2 x C*H*), 2.10, 2.00, 1.95, 1.75 (4 x s, 12 H, 4 x CH_3CO), 0.90-0.80 (m, 9 H, 3 x CH$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 170.7, 170.5, 170.1, 169.8, 139.6, 138.4, 136.0, 129.1, 128.93, 128.89, 128.70, 128.66, 128.56, 128.48, 128.50, 128.0, 127.64, 127.58, 100.9, 79.5, 78.7 (d, J = 7.5 Hz), 78.2 (d, J = 12.8 Hz), 77.4, 74.6, 73.9, 73.2, 73.0, 72.1, 71.9, 70.2, 69.4 (d, J = 3.7 Hz), 69.0, 68.9, 67.2, 65.3 (d, J = 5.3 Hz), 62.3, 55.3, 39.6, 37.8, 37.0, 30.2, 28.3, 25.0, 23.4, 22.8, 22.7, 20.8, 19.6; ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 31.4; MS (FAB, Cleland) *m/z* (relative intensity) 1198 (MNa^+, 12), 1176 (MH^+, 2).



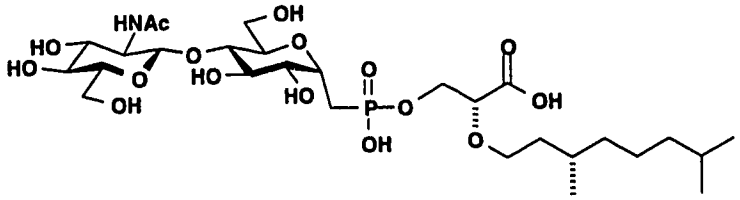
(*R*)-3-{[4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]methyl-phosphinato}-2-octyloxypropanoic Acid (139). A suspension of 10 % palladium on carbon (90 mg) in 95 % ethanol-acetic acid (1:1 v/v, 4 mL) was stirred under hydrogen for 30 min and then **136** (96.0 mg, 0.0836 mmol) was added. After stirring at room temperature for 28 h, the mixture was diluted with MeOH (10 mL) and filtered. Evaporation of the solvents *in vacuo* yielded a glassy solid which was dissolved in dry MeOH (2 mL) and cooled to 0 °C. A solution of sodium methoxide (22.7 mg, 0.406 mmol) in MeOH (2 mL) was added, and the resulting solution was stirred at 0 °C for 20 min and then at room temperature for 1 h to yield a cloudy solution. To this solution, excess AG50W-X8 (H^+) was added and the solution gradually cleared. After stirring at room temperature for 15 min, the resin was removed by filtration, and the filtrate was

concentrated *in vacuo*. Precipitation of the crude product from MeOH-acetone gave **139** (51.6 mg, 96 %) as a glassy solid: IR (CH_2Cl_2 cast) 3333 (br), 2924, 2854, 1736, 1462, 1378, 1212, 1202, 1086, 1067, 1055; ^{1}H NMR (CD_3OD, 300 MHz) δ 4.90 (br s, 9 H, 8 x O*H*, N*H*), 4.50-4.00 (m, 5 H, H-1', H-2, POCH_2CH, POCH$_2$C*H*), 4.00-3.35 (m, 14 H, H-3, H-4, H-5, H-6, H-7a, H-7b, H-2', H-3', H-4', H-5', H-6'a, H-6'b, OCH_2CH$_2$), 2.20-2.35 (m, 2 H, H-1a, H-1b), 2.00 (s, 3 H, CH_3CO), 1.65-1.55 (m, 2 H, OCH$_2$CH_2CH$_2$), 1.45-1.20 (m, 10 H, 2 x OCH$_2$CH$_2$(CH_2)$_5$), 0.90 (t, 3 H, *J* = 8 Hz, CH_3); ^{13}C NMR (CD_3OD, 75 MHz) 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_3OD 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; ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 29.8; MS (FAB, glycerol) *m/z* (relative intensity) 662.3 (MH^+, 0.6).

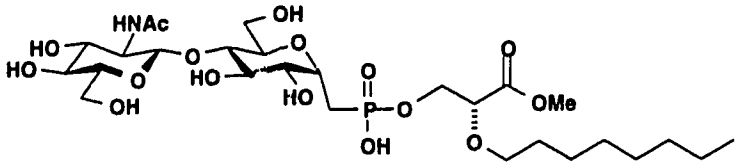


(2*R*,3'*R*)-3-{[4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]-methylphosphinato}-2-(3',7'-dimethyloctyloxy)propanoic Acid (140). Compound **140** was prepared by the same procedure used for **139.** Thus, **137** (117 mg, 99.5 μmol) in 95 % ethanol-acetic acid (3:1 v/v 10 mL) was hydrogenated in the presence of 10 % palladium on carbon (80 mg) for 26 h. Deacetylation in anhydrous MeOH (2.0 mL) by treatment with sodium methoxide (1.94 ml of a 0.2 M solution in MeOH, 0.389 mmol) gave, after work-up and precipitation (MeOH-acetone), **140** (51 mg, 95 %) as a glassy solid: IR (CH_2Cl_2 + MeOH cast) 3363 (br) 2926, 1736, 1652, 1561, 1384, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$-CD_3OD-D_2O, 3:3:1, 400 MHz) δ 4.25 (d, 1 H, *J* = 8.5 Hz, H-1'),

4.15 (br s, 10 H, 8 x O*H*, N*H*, H-2), 4.10-4.00 (m, 2 H, POC*HH*CH), 3.89-3.86 (m, 1 H, $POCH_2CH$), 3.72-3.68 (br m, 1 H, $OCHHCH_2$), 3.50-3.15 (m, 13 H, H-3, H-4, H-5, H-6, H-7a, H-7b, H-2', H-3', H-4', H-5' H-6'a, H-6'b, $OCHHCH_2$), 2.10-1.95 (m, 2 H, H-1a, H-1b), 1.82 (s, 3 H, CH_3CO), 1.50-0.90 (m, 10 H, 4 x CH_2, 2 x C*H*), 0.68 (2 d, 9 H, J = 7.0 Hz, 3 x CH_3); ^{31}P NMR ($CDCl_3$-CD_3OD-D_2O, 3:3:1) δ 29.6; MS (FAB, Cleland) *m/z* (relative intensity) 712 (MNa^+, 2).



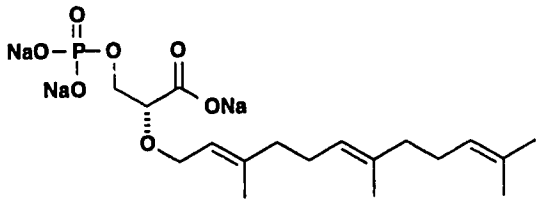
(2*R*,3'*S*)-3-{[4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]-methylphosphinato}-2-(3',7'-dimethyloctyloxy)propanoic Acid (141). Compound **141** was prepared by the same procedure used for **139**. Thus **138** (120 mg, 0.102 mmol) in 95 % ethanol-acetic acid (3:1 v/v, 10 mL) was hydrogenated in the presence of 10 % palladium on carbon (80 mg) for 20 h, and then deacetylated in anhydrous MeOH (2.0 mL) by treatment with sodium methoxide (2.4 ml of a 0.2 M solution in MeOH, 0.480 mmol) to give, after work-up and precipitation (MeOH-acetone), **141** (64 mg, 92 %) as a glassy solid: IR (CH_2Cl_2 + MeOH cast) 3344 (br), 2954, 2927, 2871, 1733, 1652, 1554, 1383, 1203, 1071 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 4.50-3.85 (m, 6 H, H-1', $POCH_2CH_2$, $POCH_2CH$, OCH_2CH_2), 3.80-3.40 (m, 13 H, H-2, H-3, H-4, H-5, H-6, H-7a, H-7b, H-2', H-3', H-4', H-5', H-6'a, H-6'b), 2.25-2.10 (m, 2 H, H-1a, H-1b), 2.00 (s, 3 H, CH_3CO), 1.70-1.10 (m, 10 H, 4 x CH_2, 2 x C*H*), 0.95-0.85 (m, 9 H, 3 x CH_3); MS (FAB, Cleland) *m/z* (relative intensity) 712 (MNa^+, 1.8).



Methyl (*R*)-3-{[4-O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranosyl]methylphosphinato}-2-octyloxypropanoate (142). A solution of sodium methoxide (8.0 mg, 0.148 mmol) in MeOH (1 mL) was added to a stirred solution of **136** (23.0 mg, 20.0 μmol) in CH_2Cl_2 : MeOH (1:2, v/v, 3 mL). The resulting solution was stirred at room temperature for 3 h. Excess AG50W-X8 (H^+) was added to the reaction mixture and stirring was continued for 30 min. The resin was removed by filtration, and the filtrate was concentrated *in vacuo* to yield a syrup (16.0 mg, 85 %), which was identified as methyl (*R*)-3-{[4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranos-yl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl]methylphosphinato}-2-octyloxy-propanoate: IR ($CHCl_3$ cast) 3268 (br), 2927, 2856 1742, 1659, 1453, 1436, 1074, 1028 cm^{-1}; ^1H NMR (CD_2Cl_2+ CD_3OD, 400 MHz) δ 7.20-7.45 (m, 15 H, Ar*H*), 4.90 (d, 1H, *J* =11.0 Hz, PhC*H*HO), 4.49-4.70 (m, 6 H, 5 x PhC*H*HO), 4.00-4.25 (m, 10 H), 3.80-3.85 (m, 2 H), 3.10-3.80 (m, 14 H), 2.05-2.35 (m, 2 H, H-1a, H-1b), 1.90 (s, 3 H, CH_3CO), 1.60-1.50 (m, 2 H, $OCH_2CH_2CH_2$), 1.15-1.35 [m, 10 H, 2 x $OCH_2CH_2(CH_2)_5$], 0.80 (t, 3 H, *J* = 8 Hz, CH_3); ^{13}C NMR (CD_2Cl_2 + CD_3OD, 100 MHz) δ 171.0, 138.6, 138.3, 138.1,129.0, 128.8, 128.7, 128.4, 128.3, 128.2, 100.6, 78.6, 76.2, 75.6, 75.3, 74.0, 73.3, 72.6, 71.8, 71.7, 69.4, 69.2, 65.3, 62.2, 57.34, 52.5, 32.2, 30.0, 29.9, 29.7, 29.6, 26.2, 23.0, 14.14; ^{31}P NMR (CD_2Cl_2 + CD_3OD, 162 MHz) δ 28.7. MS (FAB, Cleland) *m/z* (relative intensity) 968.5 (MNa^+, 0.9), 946.5 (MH^+, 0.1).

A suspension of methyl (*R*)-3-{[4-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2,3,6-tri-O-benzyl-α-D-glucopyranosyl]methylphosphinato}-2-octyloxypropanoate (15.0 mg, 0.0159 mmol) and palladium on carbon (8 mg) in 95 % ethanol-acetic acid (1:1, v/v, 4 mL) was stirred under hydrogen atmosphere (1 atm) for 42 h. The reaction mixture was

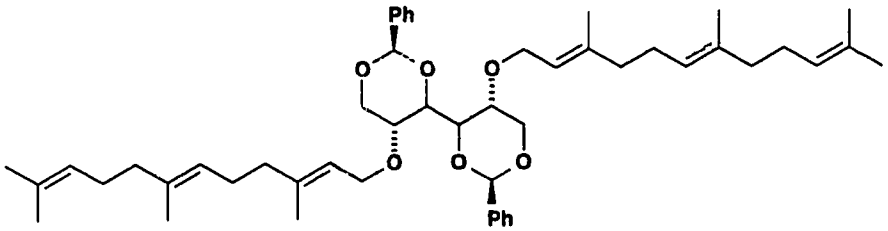
diluted with MeOH (5 mL) and filtered. Evaporation of the solvent *in vacuo* provided pure **142** as a white solid (10.4 mg, 97 %): IR (CH_2Cl_2-MeOH cast) 3408 (br), 2922, 1652, 1600, 1384, 1271, 1026 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 4.90-4.70 (br s, 8 H, 7 x O*H*, N*H*), 4.50-3.80 (m, 5 H, H-1', H-2, POC*H*$_2$CH, POCH$_2$C*H*), 3.70-3.18 (m, 17 H, H-3, H-4, H-5, H-6, H-7a, H-7b, H-2', H-3', H-4', H-5', H-6''a, H-6'b, OC*H*$_3$, OC*H*$_2$CH$_2$), 1.90-2.01 (m, 5 H, H-1a, H-1b, C*H*$_3$CO), 1.60-1.45 (m, 2 H, OCH$_2$C*H*$_2$CH$_2$), 1.15-1.35 (m, 10 H, 2 x OCH$_2$CH$_2$(C*H*$_2$)$_5$), 0.80 (t, 3 H, J = 8 Hz, C*H*$_3$); MS (FAB, glycerol) *m/z* (relative intensity) 1372.8 ($2MNa^+$, 0.1), 698.5 (MNa^+, 1.4), 676.4 (MH^+, 0.17).



(*R*)-3-*O*-Phosphoryl-2-*O*-farnesylpropanoic Acid Trisodium Salt (143). Sodium periodate (22 mg, 0.10 mmol) was added to a solution of diol **146** (79 mg, 0.0916 mmol) in THF-H_2O (9:1, v/v, 2 mL), and the solution was stirred at 50 °C for 3 h. The solvent was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The combined extracts were evaporated *in vacuo*. The resulting oil was dissolved in THF-H_2O (12:1, v/v, 3 mL) and treated with silver (I) oxide (49 mg, 0.210 mmol) and NaOH (7.3 mg, 0.183 mmol) for 20 h. The THF was evaporated *in vacuo* and the remaining aqueous solution was washed with petroleum ether. The aqueous layer was then concentrated to dryness *in vacuo* and extracted with MeOH. The organic extracts were evaporated *in vacuo* to give the sodium salt carboxylate **147** (51 mg, 60 %), which was not purified further.

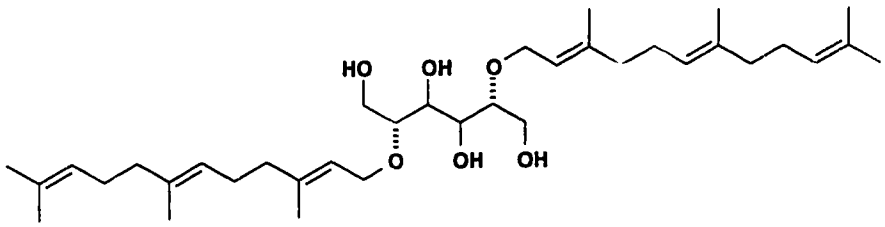
Trimethylsilyl bromide (75 mg, 0.491 mmol) was added to a solution of the sodium salt **147** (41 mg, 0.0982 mmol) and *s*-collidine (36 mg, 0.295 mmol) in dry

CH_2Cl_2 (1.0 mL). The resulting mixture was stirred at room temperature for 16 h. The cloudy white reaction mixture was evaporated *in vacuo* and dried under high vacuum for 12 h to give a white solid, which was treated with a solution of NaOH (15.7 mg, 0.393 mmol) in H_2O (0.5 mL) for 1 h. Evaporation *in vacuo* yielded a solid, which was extracted with MeOH. The organic extracts were evaporated to afford the trisodium salt of **143** (36 mg, 80 %) as a solid: IR (KBr disk) 3432 (br), 1632, 1375, 824 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) d 5.40-5.35 (m, 1 H, H-2'), 5.12-5.02 (m, 2 H, H-6', H-10'), 4.18 (dd, J = 12.0, 6.0 Hz, H-1'a), 4.05 (dd, J =12.0, 7.5 Hz, H-1'b), 3.82-3.75 (m, 3 H, H-2, H-3a, H-3b), 2.15-1.20 (m, 20 H, 4 x CH_2, 4 x CH_3); ^{13}C NMR (CD_3OD, 100 MHz) d 178.7, 141.5, 136.2, 132.1, [illegible] 25.1, 122.1, 81.6, 67.0, 64.1, 40.8 (d, J = 4.0 Hz), 27.8, 27.4, 25.9, 17.8, 16.6, [illegible] AB, Cleland) *m/z* (relative intensity) 479 (MNa^+, 1.4), 457 (MH^+, 1.0), 435 ($M-Na^+$, 1.0), 411 ($M-2Na^+ + H^+$, 1.4), 389 ($M-3Na^+ + 2H^+$, 5.1), 387 (M-3 x Na^+, 2.7).



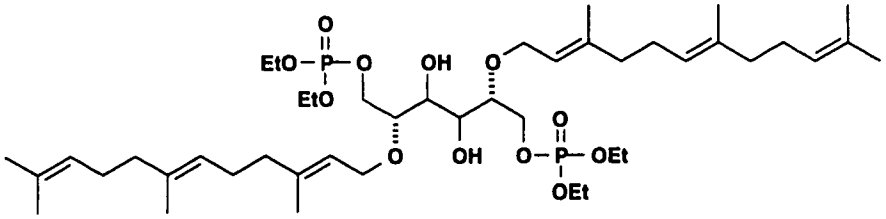
1:4,6-Di-*O*-benzylidene-2,5-di-*O*-farnesyl-D-mannitol (144). A 60 % suspension of [illegible]um hydride in oil (0.90 g, 60 % dispersion in oil, 22.3 mmol) was washed with [illegible]oleum ether and was then added portionwise to a stirred solution of **93** (1.99 g, 5.58 mmol) in dry DMF (15 mL) under argon. The resulting slurry was warmed to 70 °C and stirring was continued for a further 1 h. Farnesyl bromide (4.00 g, 14.0 mmol) in DMF (6 mL) was then added and the reaction mixture was heated at 70 °C for 2 h and 45 °C overnight. After cooling to room temperature, the mixture was treated with MeOH (5 mL) to decompose the excess NaH. The mixture was then poured into water

and extracted with ethyl acetate. The combined organic extracts were washed with water, and dried ($MgSO_4$). Evaporation *in vacuo* followed by flash chromatography (petroleum ether-EtOAc, 40:1) on silica gave **144** (2.66 g, 62 %) as a colorless oil; IR (CH_2Cl_2 cast) 3035, 2967, 2923, 2854, 1453, 1376, 1311, 1218, 1102, 1074, 1030, 980 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 7.50-7.45 (m, 10 H, Ar*H*), 5.41 (s, 2 H, 2 x PhC*H*O_2), 5.40-5.30 (m, 2 H, 2 x H-2'), 5.15-5.05 (m, 4 H, 2 x H-6', 2 x H-10'), 4.45 (dd, 2 H, J = 10.5, 5.0 Hz, 2 x H-1e), 4.20-4.05 (m, 4 H, 2 x H-1'a, 2 x H-1'b), 3.99 (d, 2 H, *J* = 9.5 Hz, 2 x H-3), 3.82 (ddd, 2 H, *J* = 10.0, 9.5, 5.0 Hz, 2 x H-2), 3.64 (dd, 2 H, *J* = 10.5, 10.5 Hz, 2 x H-1a), 2.15-1.95 (m, 16 H, 8 x CH_2), 1.70-1.58 (4 s, 24 H, 8 x C*H*$_3$); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 141.1, 138.4, 135.7, 131.6, 129.1, 128.5, 126.5, 124.7, 124.2, 121.2, 101.4, 77.9, 70.3, 67.4, 66.8, 40.1, 39.9, 27.1, 26.7, 25.8, 17.8, 16.6, 16.1; MS (CI, NH_3) *m/z* (relative intensity) 444 (8), 427 (18), 376 (42), 359 (66), 35 (100); (FAB, Cleland) *m/z* (relative intensity 359 (1.8), 137 (26.7), 105 (100); Anal. Calcd for $C_{50}H_{70}O_6$: C, 78.29; H, 9.20. Found: C, 78.17; H, 9.34.



2,5-Di-*O*-farnesyl-D-mannitol (145). A solution of **144** (0.85 g, 1.10 mmol) in dry THF (10 mL) was added to a mixture of liquid ammonia (40 mL, distilled over sodium) and *tert*-butanol (0.9 mL) at -78 °C. Small pieces of sodium (0.22 g, 9.63 mmol) were added over a period of 1 h to give a blue solution which was stirred for a further 30 minutes, and then quenched by the addition of 10 % aqueous ammonium chloride solution (2 mL). The liquid ammonia was allowed to evaporate slowly and the remaining solution was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with brine.

The organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography to give **145** (303 mg, 46 %) as a waxy solid; IR (CH_2Cl_2 cast) 3466 (br), 3365 (br), 2924, 1448, 1381, 1096, 1045 cm^{-1}; ^1H NMR (CD_2Cl_2 + trace of D_2O, 400 MHz) δ 5.40-5.30 (m, 2 H, 2 x H-2'), 5.15-5.05 (m, 4 H, 2 x H-6', 2 x H-10') 4.15 (dd, 2 H, J = 11.5, 7.5 Hz, H-1a, H-6a), 4.08 (dd, 2 H, J = 11.5, 7.5 Hz, H-1b, H-6b), 3.85 (d, 2 H, J = 6.5 Hz, H-3, H-4), 3.78 (dd, 2 H, J = 12.0, 3.8 Hz, 2 x H-1'a,), 3.70 (dd, 2 H, J = 12.0, 3.8 Hz, 2 x H-1'b), 3.55-3.45 (m, 2 H, H-2, H-5), 2.15-1.95 (m, 16 H, 8 x CH_2), 1.55, 1.70 (2 x s, 24 H, 8 x CH_3); ^{13}C NMR (CD_2Cl_2 + trace of D_2O, 100 MHz) δ 141.5, 135.8, 131.6, 124.9, 120.9, 79.9, 70.1, 67.2, 61.5, 40.0, 30.1, 27.1, 26.7, 25.8, 17.7, 16.6, 16.0; MS (CI, NH_3) *m/z* (relative intensity) 609 (MNH_4^+, 11), 410 (20), 200 (100); Anal. Calcd for $C_{36}H_{62}O_6$: C, 73.18; H, 10.58. Found: C, 73.34; H, 10.54.



1,6-Di-*O*-(diethylphosphoryl)-2,4-di-*O*-farnesyl-D-manitol (146). Diethyl chlorophosphate (120 mg, 0.697 mmol) was added dropwise to a solution of tetraol **145** (187 mg, 0.317 mmol) and triethylamine (80 mg, 0.792 mmol) in anhydrous THF (2 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 3 days. The cloudy white reaction mixture was then diluted with brine and evaporated *in vacuo* to remove the organic solvents. The remaining aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (silica, CH_2Cl_2-MeOH, 50 :1) of the resulting oil gave **146** (218 mg, 80 %) as a colorless oil; IR(CH_2Cl_2 cast) 3854 (br), 3384 (br), 2967, 2924, 2855, 1734, 1668, 1446, 1255, 1104, 1034, 980 cm^{-1}; ^1H NMR (CD_2Cl_2, 400

MHz) δ 5.36-5.28 (m, 2 H, 2 x H-2'), 5.14-5.08 (m, 4 H, 2 x H-6', 2 x H-10'), 4.30-4.00 (m, 12 H, 2 x H-1b, 2 x H-1a, 2 x H-2, 4 x OCH_2CH_3), 3.80-3.40 (m, 6 H, 2 x H-1a, 2 x H-1b, 2 x OH), 2.15-1.90 (m, 16 H, 8 x CH_2), 1.65, 1.60, (2 x s, 24 H, 8 x CH_3), 1.35-1.25 (m, 12 H, 4 x OCH_2CH_3); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ 0.501, 0.452; MS (FAB, Cleland) *m/z* (relative intensity) 885.7 (MNa^+, 0.1), 863.7 (MH^+, 0.1).

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