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Synthesis of Derivatives of Muramic Acid and C-1 Homologated α-D-Glucose as Potential Inhibitors of Bacterial Transglycosylase

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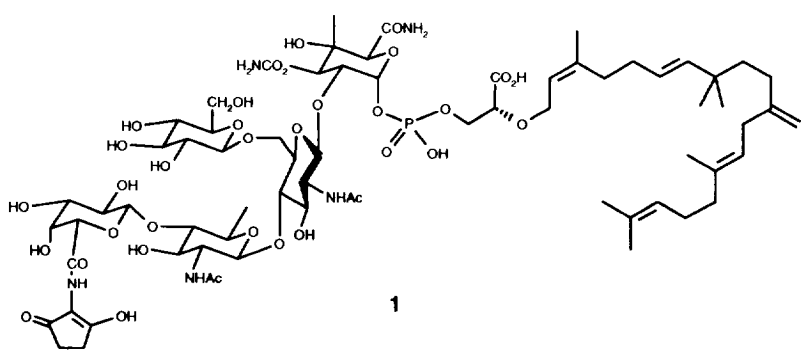
Abstract: Phosphate derivatives of muramic acid, incorporating a lipid-like group, have been synthesised as potential inhibitors of bacterial transglycosylase. The Lewis acid catalysed addition of unsaturated alkyl silanes to methyl α-D-glucopyranoside, followed by an oxidative cleavage, has been used to provide a route to C-1 homologues of glucose. Conversion of α-D-glucose methanephosphonic acid to esters derived from lipid-like groups is also described.

The natural product moenomycin A **1** is an antibacterial agent which has been known for many years[1] although the final detail of its structure was elucidated only recently by Welzel[2] and co-workers. In its mechanism of action moenomycin A is unusual in that it interferes with the transglycosylase enzymes which take as substrate the disaccharide **2** in the biosynthesis of bacterial peptidoglycan.

While there has been considerable research interest in targeting other enzymes involved in peptidoglycan biosynthesis, particularly the transpeptidases, transglycosylase has received little attention. The structures of the enzymes and their mechanism of action are not known but it has been established that in *E. coli* a domain of the cell wall penicillin-binding protein 1b is associated with transglycosylase activity[3].

In addition to his comprehensive and elegant studies of the structure of moenomycin A, Welzel has carried out synthetic studies of close analogues of the natural product and defined some strict requirements for biological activity[4]. Other groups[5,6] have described the synthesis of hybrid structures based on moenomycin **1** and the natural substrate **2**.



1

It has been reported that the monosaccharide degradation product **3** of moenomycin retains some of

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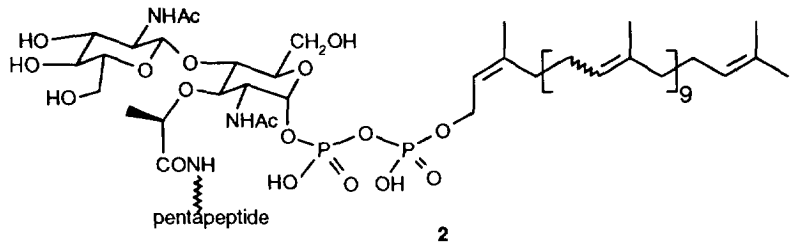
the biological activity of the natural product in an enzyme assay and in antibacterial testing[7]. This encouraged us to investigate the hypothesis that the enzyme could be inhibited by monosaccharides such as muramic acid or even glucose, linked by a phosphate or diphosphate surrogate to a lipid-like component. It was considered that an n-hexadecyl group would provide a simple substitute for the lipid-like functions found in the natural products and that the phosphoglyceric acid found in moenomycin offered a natural choice of linking group which would act as a diphosphate surrogate. Thus compounds such as **4a** could retain recognition elements required by the enzyme and have similar properties to the natural inhibitor.



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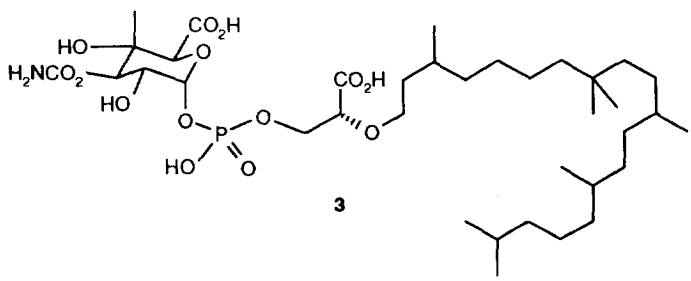

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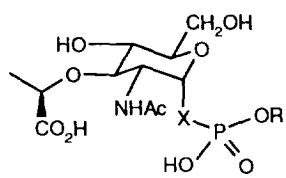
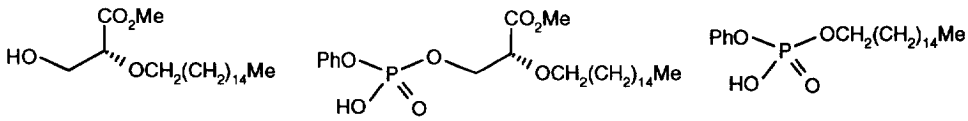


4a X= O R= alkyl, glyceric acid ether

4b X= CH_2, CH_2CH_2O R= alkyl, glyceric acid ether

A second objective was to provide derivatives such as **4b** in which a carbon-carbon bond has replaced the cleavable bond between phosphate and sugar. It was intended to prepare such derivatives of glucose and of muramic acid but in the event, the latter proved inaccessible.

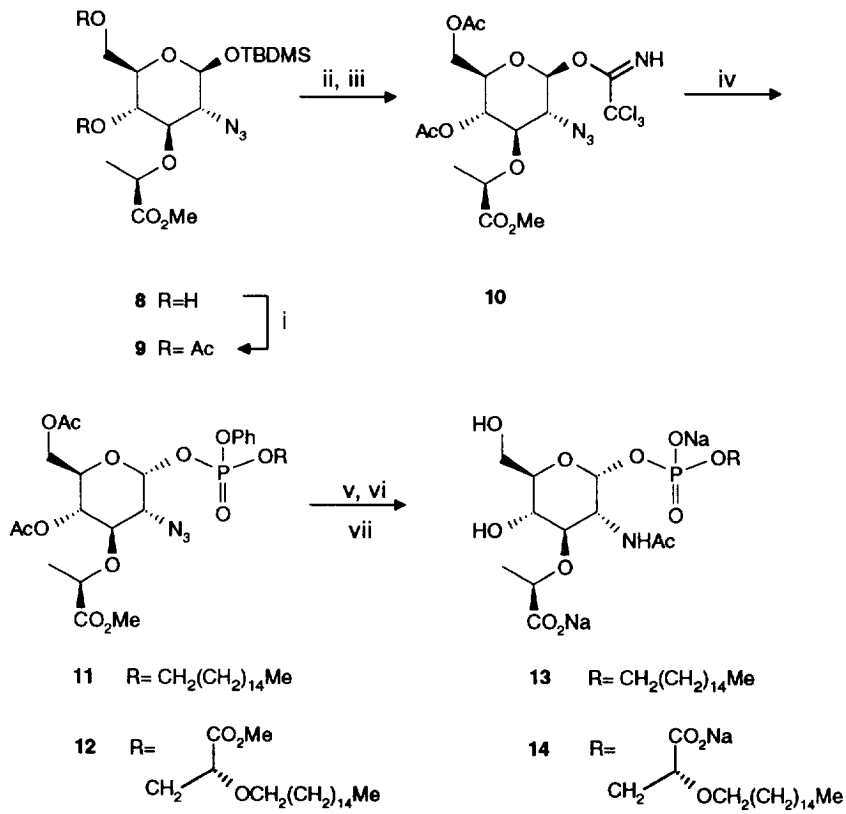
In our synthetic strategy we sought to utilize the imidate methodology of Schmidt[8] in order to introduce the phosphate functionality at C-1 of a suitable monosaccharide with desired α stereochemistry. Our experience had shown that phosphate diesters reacted smoothly with glucosyl imidates giving good stereocontrol and that phenyl esters offered an efficient protection for phosphate groups.



5 6 7

The glyceric acid hexadecyl ether **5** was accessible from D-mannitol using a route developed by Welzel[9]. Conversion to the phosphate derivative **6** was brought about by reaction with phenyl dichlorophosphate followed by triethylamine-aqueous acetone. In similar fashion, n-hexadecanol was converted to n-hexadecyl phenylphosphate **7**.

Scheme 1

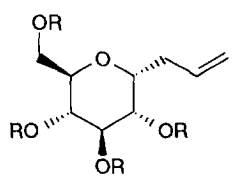


Reagents: i Ac_2O/pyridine ii TBAF/HOAc/THF iii $K_2CO_3/Cl_3CCN/CH_2Cl_2$
iv reaction with (7) or (6) v H_2-Pd/C-Ac_2O vi H_2/PtO_2 vii NaOH/THF/MeOH

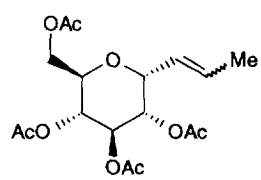
The monosaccharide **8** was synthesised from D-glucal by an established route[10]. Its conversion to the desired phosphate derivatives **11** and **12** is outlined in Scheme 1. Thus compound **8** was protected as the diacetate **9**, desilylated and then reacted with trichloroacetonitrile to give the desired β–imidate **10**. The

reaction of this intermediate with the phosphate diesters **7** and **6** gave good yields of the desired products **11** and **12** with C-1 α stereochemistry. No β–anomers were detected in these reactions.

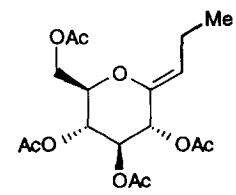
The deprotection of the intermediates **11** and **12** was brought about by a combination of reductive and hydrolytic methods. Thus, hydrogenation of both compounds using palladium on carbon in the presence of acetic anhydride converted azide to acetamide. It is worth noting that the phosphate phenyl ester appeared to be completely stable to these conditions. Further reduction using hydrogen/platinum oxide, in the presence of acid, brought about efficient cleavage of the phosphate phenyl esters and base hydrolysis gave the fully deprotected muramic acid derivatives **13** and **14**.



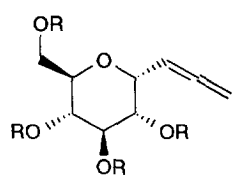
15 R= H
16 R= Ac



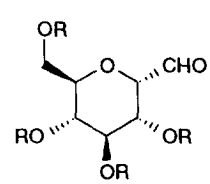
17



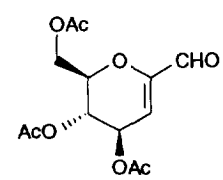
18



19 R= Bn
20 R= Ac



21 R= Bn
22 R= Ac



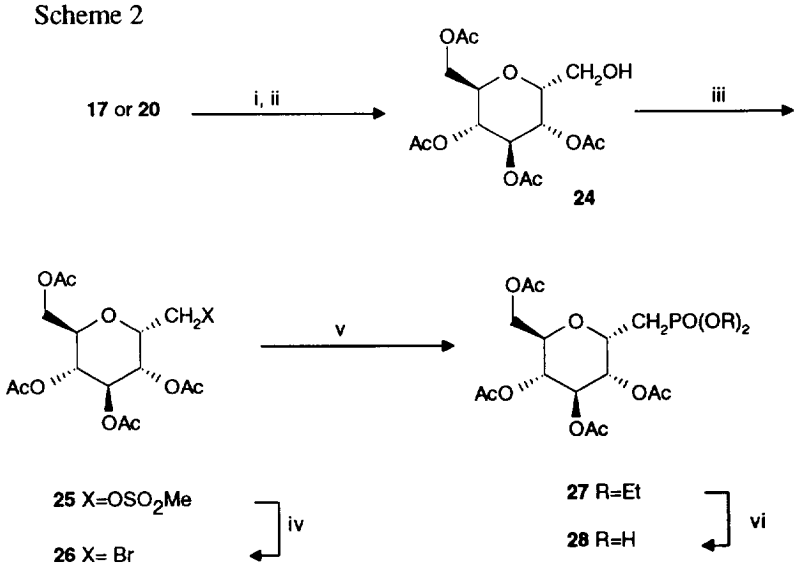
23

For the preparation of analogues with a non-cleavable C-C bond at the site of transglycosylation we first sought to prepare derivatives of glucose. The preparation of 1-deoxy-α-D-glucose methanephosphonic acid has been described by Nicotra et al[11] but in our hands this route was unsatisfactory. The bromination of an intermediate chloromercurio compound proved troublesome and our attention turned to an alternative method for the preparation of a suitably functionalised C-glucoside.

The allyl C-glucoside **15** was readily prepared from methyl α-D-glucopyranoside by a Lewis acid catalysed reaction with allyltrimethylsilane[12]. The reaction proceeded with good stereoselectivity and the desired diastereoisomer with C-1 α stereochemistry was the major product (>9:1). After peracetylation to give **16**, treatment with bis(benzonitrile)palladium (II) chloride in refluxing toluene[13] brought about migration of the double bond to give, as the major product, the propenyl C-glucoside **17** as a mixture of E and Z isomers. Small amounts (up to 3%) of a single propenylidene isomer **18** were also isolated from this reaction after careful column chromatography. NMR studies, in particular an nOe between protons on the double bond and on C-2, supported the stereochemistry shown for this product. The propenyl C-glucoside **17** appeared to be stable once formed, none of the propenylidene derivative **18** being generated during prolonged heating of a pure sample with further portions of bis(benzonitrile)palladium (II) chloride.

Bednarski[14] has described the allenyl C-glucoside **19** as a suitable precursor for conversion to the aldehyde **21**. Using a similar approach, the crystalline allenyl C-glucoside **20** was obtained in 45% yield overall from methyl α-D-glucoside by treatment with propargyltrimethylsilane followed by peracetylation. Only the single diastereoisomer **20** was isolated from this reaction and the C-1 stereochemistry shown for this and subsequent derivatives is consistent with the characteristic coupling constant[15] observed (5.7 Hz) between protons on C-1 and C-2 (sugar numbering).

Scheme 2

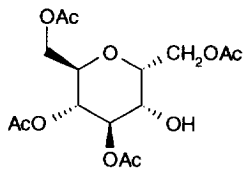


Reagents: i $O_3/CH_2Cl_2/-70^o$ ii $NaAcOBH_3$ iii $MeSO_2Cl$/ pyridine
iv $Bu_4N^+Br^-$ v $PO(OEt)_3/180^o$ vi $TMSBr/CH_2Cl_2$ then H_2O

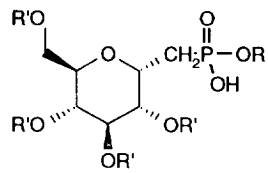
Some difficulty was experienced in carrying out ozonolysis reactions on the derivatives **17** and **20**, both of which should have been converted to the aldehyde **22**. Despite some variation in the reaction conditions and the reductive work-up, pure samples of the aldehyde **22** could not be obtained. One of the problems identified was the ready elimination of acetate to give the α,β–unsaturated aldehyde **23**. Indeed when worked up with triphenylphosphine, the ozonolysis of **20** gave up to 60% yield of the undesired aldehyde **23**. Eventually, modest yields of the C-1 homologue **24** were obtained by using sodium acetoxyborohydride to reduce the crude ozonolysis products obtained from compounds **17** and **20** (see Scheme 2).

Subsequent attempts to prepare the key bromo intermediate **26** by reaction of homoglucose **24** with thionyl bromide or with phosphorus tribromide were completely unsuccessful. When compound **24** was treated with carbon tetrabromide-triphenylphosphine or with bromotrimethylsilane, the only product isolated was the rearrangement product **29**. The ease of migration of acetate from secondary to primary hydroxyl in such systems is known and has been utilised synthetically by others[16]. Eventually the bromo compound **26**

was synthesised by conversion to an intermediate methanesulphonate **25** followed by displacement with tetrabutylammonium bromide. Heating **26** with neat triethyl phosphite purged by argon, gave the desired homoglucose phosphonate **27** which was converted to phosphonic acid **28** by means of bromotrimethylsilane followed by water.

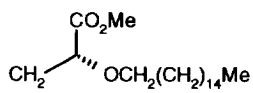


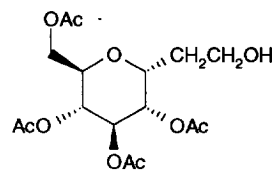
29



30 R' = Ac, R = $CH_2(CH_2)_{14}Me$

31 R' = H, R = $CH_2(CH_2)_{14}Me$

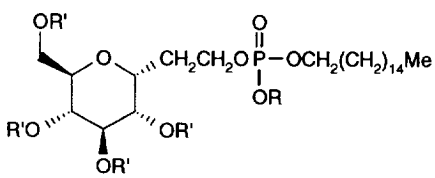
32 R' = Ac, R = 



33

The conversion of phosphonic acid **28** to derivatives bearing lipid-like functionality was pursued by coupling with n-hexadecanol and with glyceric acid hexadecyl ether **5** using trichloroacetonitrile. Removal of acetate from the resulting phosphonate esters **30** and **32** was carried out using aqueous sodium hydroxide. The desired phosphonate **31** (isolated as a sodium salt) was obtained successfully by this method but phosphonate **32** was cleaved to phosphonic acid under these conditions.

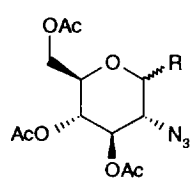
In order to investigate the isosteric replacement of ethyl for phosphate, the bis-homoglucose derivative **33** was readily prepared from the allyl C-glucoside **15** in three steps using the method of Broxterman et al[17]. In this instance compound **33** was converted to the phosphate triester **34** by coupling to phosphate **7** with 1-(mesitylene-2-sulphonyl)-3-nitro-1,2,4-triazole. Successive hydrogenolysis of the phenyl ester and saponification of acetates in **35** gave the deprotected derivative **36**.



34 R' = Ac R = Ph

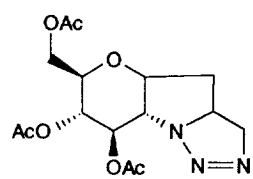
35 R' = Ac R = H

36 R' = H R = Na



37 R = OAc

38 R = allyl



39

Although it has been reported that allyltrimethylsilane does not react with a number of derivatives of α-D-glucosamine[12b] it was hoped that reaction with 2-deoxy-2-azidoglucopyranoside **37** would provide a

route to C-1 homologated derivatives of D-glucosamine and muramic acid. Unfortunately, the reaction gave only a low yield of product identified as a mixture of diastereomers **38** on the basis of its ^1H nmr spectrum. Not only was the low stereoselectivity of this reaction a disappointment but the stability of the product was also poor. Spectroscopic evidence suggested conversion to the tricyclic compound **39**. The formation of a similar tricyclic compound from an O-benzyl pyranoside was reported while our work was in progress[18].

Once it had been established that the stereoselectivity of the reaction of 2-deoxy-2-azidoglucopyranoside **37** with propargyltrimethylsilane was equally poor, this approach to C-1 homologated derivatives of muramic acid was abandoned.

When evaluated in an assay for transglycosylase activity[19], at concentrations of 100μg/ml, compounds **13** and **14** showed very weak (ca 20%) inhibition of peptidoglycan synthesis. Compounds **31** and **36** showed no inhibition. No significant antibacterial activity was shown by any of the compounds and it may be concluded that the requirements for enzyme inhibition cannot be met by simple monosaccharides.

EXPERIMENTAL

IR spectra were recorded using a Perkin Elmer 197. ^1H NMR spectra were recorded on Bruker WM250 or WM400 instruments and referenced to tetramethylsilane. ^{31}P NMR spectra were referenced to 85% phosphoric acid. Mass spectra were recorded using a VG-7070, VG ZAB or VG TRIO-2 instruments. Melting points were determined using a Kofler hot-stage and are uncorrected. Merck silica gel 60 (AA 7729) was used for column chromatography. Organic extracts were dried over anhydrous magnesium sulphate. THF refers to tetrahydrofuran.

2,5-Di-O-n-hexadecyl-D-mannitol

1,3:4,6-Di-O-benzylidene-D-mannitol[20] (7.16 g) was treated with n-hexyl bromide using the method described by Welzel[9]. Acid hydrolysis gave the *title compound* as a white solid, 7.4 g, mp 90-91 °C, $[\alpha]_D^{35}$ -15.2 (c 1, $CHCl_3$); ν_{max}(nujol)/cm^{-1} 3450, 3300; δ_H (400 MHz; $CDCl_3$ -D_2O) 0.88 (3H, t, J 7), 1.20-1.30 (26H, br), 1.52-1.60 (2H, m), 3.49 (1H, ddd, J 6.2, 5.3, 3.8), 3.52 (1H, m), 3.64 (1H, dt, J 9, 6.6), 3.76 (1H dd, J 11.8, 3.8), 3.82 (1H, dd, J 11.8, 5.3), 3.90 (1H, d, J 6.2). Found: C, 72.24; H, 12.47. $C_{38}H_{78}O_6$ requires C, 72.33; H, 12.46%

Methyl (2R)-3-Hydroxy-2-(n-hexadecyloxy)propionate (**5**)

2,5-Di-O-n-hexadecyl-D-mannitol (1.89 g) was dissolved in redistilled THF (50 ml) and a solution of sodium metaperiodate (1.92 g) in water (20 ml) was added dropwise with stirring. After 10 min the mixture was cooled in an ice bath while bromine (0.61 ml) was added dropwise. The resulting mixture was stirred at ca 0 °C for 1.5 h and then diluted with 2N sulphuric acid and extracted with ethyl acetate. The extract was washed with water and with brine, dried and evaporated to a gum which was then suspended in 10% HCl/methanol (50 ml). The mixture was boiled under reflux for 24 h, cooled, concentrated under vacuum, poured onto ice and extracted with ethyl acetate. The extract was washed with water, aq. sodium bicarbonate and with brine. Drying, evaporation and chromatography, eluting with ethyl acetate/ n-hexane (1:2) gave the *title compound* as a white solid, 1.55 g (75%), $[\alpha]_D^{26}$ +32.4 (*c* 1.0, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3600, 2930, 2850, 1740; δ_H (250 MHz; $CDCl_3$-D_2O) 0.88 (3H, t, J 6.5), 1.20-1.40 (26H, m), 1.57-1.68 (2H, m, OCH_2-CH_2), 3.38-3.48 (1H, m), 3.68-3.74 (1H, m), 3.78 (3H, s, OMe), 3.78 (1H, dd, J 11.6, 6.1), 3.88

(1H, dd, J 11.6, 3.6), 3.99 (1H, dd, J 6.1, 3.6); MS m/z (%) 345 (20, MH^+), 314 (80) [MH^+ - OMe]. Found: m/z 345.3006. $C_{20}H_{41}O_4$ requires 345.3005 $[MH]^+$.

(2R)-2-Methoxycarbonyl-2-(n-hexadecyloxy)ethyl Phenyl Hydrogen Phosphate (**6**)

A solution of the propionate **5** (344 mg, 1 mmol) and quinoline (0.13 ml, 1.1 mmol) in dichloromethane (5 ml) was added to a stirred solution of phenyl dichlorophosphate (0.15 ml, 1 mmol) in dichloromethane which was cooled to -10 °C. The mixture was allowed to warm to room temperature and then concentrated by evaporation under reduced pressure. After a further 1h at room temperature, the mixture was diluted with ethyl acetate and washed with 0.5N HCl and with brine. Drying and evaporation gave a gum which was redissolved in acetone (10 ml) to which was added water (1.3 ml) and triethylamine (0.27 ml). After 1.5 h at room temperature, this mixture was concentrated and then diluted with ethyl acetate. The organic phase was washed with 0.5N HCl and with brine. Drying and evaporation gave a crude product which was purified by chromatography eluting with chloroform/ 20% methanol. The *title compound* (6) was obtained as a white foam, 400 mg (80%), $[\alpha]_D^{20}$ +10.9 (c, 1.15, $CHCl_3$), $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2850,1735, 1595; λ_{max} (dioxan) 270nm (760), 262 (930); δ_H (250 MHz; $CDCl_3$ trace CD_3OD) 0.89 (3H, t, J 6.5), 1.25 (26H, brs), 1.4 -1.6 (2H, m), 3.25-3.55 (2H, m), 3.62 (3H, s), 4.01 (1H, t, J 4.6), 4.1- 4.3 (2H, m), 6.95-7.05 (1H, m), 7.15-7.3 (4H, m); FABMS (3-NOBA/Na) m/z (%) 545 (100, $[MNa+Na-H]^+$), 523 (30, $[MNa]^+$); FABMS (thioglycerol) m/z (%) 501 (30, $[MH]^+$).

Hexadecyl Phenyl Hydrogen Phosphate (**7**)

Hexadecanol and phenyl dichlorophosphate were reacted as described above to give the product **7** as a white solid, $\nu_{max}(CHCl_3)/cm^{-1}$ 2940, 2860, 1595, 1485; δ_H (90 MHz; $CDCl_3$) 0.8-1.0 (3H, m), 1.1-1.5 (26H, br s), 1.5 -1.8 (2H, m), 4.04 (2H, q, J 7), 7.0-7.4 (5H,m).

tert-*Butyldimethylsilyl 4,6-di-O-acetyl-2-azido-2-deoxy-3-O-[(R)-1'-(methoxycarbonyl)ethyl]-β-D-glucopyranoside* (**9**)

tert-Butyldimethylsilyl 2-azido-2-deoxy-3-O-[(R)-1-(methoxycarbonyl)ethyl]-β-D-glucopyranoside[10] **8** (1.87g, 4.62 mmol) was dissolved in pyridine (10 ml) and treated with acetic anhydride (1.8 ml). The mixture was stirred overnight at room temperature, diluted with ethyl acetate and washed with 1N HCl, with brine and with aqueous sodium bicarbonate. Drying, evaporation and chromatography, eluting with ethyl acetate/n-hexane gave the *title compound* as a gum, 2.25 g (99%), $[\alpha]_D^{20}$ +2 (c 1.6, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2120, 1745; δ_H (250 MHz; $CDCl_3$) 0.15 (6H, s), 0.93 (9H, s), 1.33 (3H, d, J 6.8), 2.06 and 2.10 (two 3H, two s), 3.2-3.4 (2H, m), 3.45-3.6 (1H, m), 3.79 (3H, s), 4.0- 4.2 (3H, m), 4.49 (1H, d, J 7.3) , 4.96 (1H, dd, J 10, 8.8); FABMS (3-NOBA/Na) m/z (%) 512 (100, $[MNa]^+$).

Desilylation of compound **9**.

tert-Butyldimethylsilyl 4,6-di-O-acetyl-2-azido-2-deoxy-3-O-[(R)-1'-(methoxycarbonyl)ethyl]-β-D-glucopyranoside **9** (489 mg, 1 mmol) was dissolved in THF (5 ml) and acetic acid (0.18 ml). A solution of tetrabutylammonium fluoride in THF (1M, 2ml, 2 mmol) was added and the solution stirred at room temperature for 2h before it was diluted with ethyl acetate, washed with aq. sodium bicarbonate and with brine, dried and evaporated. Chromatography, (ethyl acetate/n-hexane (1:1 > 3:2) gave a quantitative yield of

the intermediate, as a mixture of anomers, $[\alpha]_D^{20}$ +42 (c 1.1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3450(br), 2120, 1745; δ_H (250 MHz; $CDCl_3$) *inter alia* 4.61 (0.4 H, d J 7.6, H-1 beta), 5.35 (0.6H, d J 3.4, H-1 alpha).

O-{4,6-Diacetoxy-2-azido-2-deoxy-3-O-[(R)-1'-(methoxycarbonyl)ethyl]-β-D-glucopyranosyl}-trichloroacetimidate (**10**).

The mixture of anomers obtained above (350 mg, 0.93 mmol) was dissolved in dichloromethane (4.6 ml) and treated with powdered potassium carbonate (0.62 g) and trichloroacetonitrile (0.37 ml). The mixture was stirred at room temperature for 5 h and filtered through Celite. Evaporation of solvent gave a crude product which was purified by chromatography, eluting with ethyl acetate/ n-hexane (ratio 1:3 > 3:2).

The first eluted isomer was the alpha imidate, obtained as a gum, 170 mg (35%), $[\alpha]_D^{20}$ +82 (c 1.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3325, 2120, 1745, 1675; δ_H (250 MHz; $CDCl_3$) 1.39 (3H, d, J 6.8), 2.07 and 2.13 (each 3H, two s), 3.7-3.8 (4H, m, including 3H, s at 3.78), 3.9-4.1 (3H, m), 4.1-4.3 (2H, m), 5.17 (1H, t, J 9.5), 6.47 (1H, d, J 3.5), 8.78 (1H, s).

The second eluted isomer was the *beta imidate* **10**, obtained as a white solid, 274 mg (56%), mp 110-130 °C; $[\alpha]_D^{20}$ +4.9 (c 0.9, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3345, 2120, 1745, 1675; δ_H (250 MHz; $CDCl_3$) 1.37 (3H, d, J 6.8), 2.08 and 2.12 (each 3H, two s), 3.49 (1H, t, J 9.3), 3.65-3.85 (6H, m, including 3H, s at 3.80), 4.10 (1H, dd, J 12.4, 2.4), 4.15-4.35 (2H, m), 5.13 (1H, t, J 9.5), 5.61 (1H, d, J 8.4), 8.76 (1H, s). Found: C, 37.2; H, 4.1; N, 10.8; Cl, 20.1. $C_{16}H_{21}Cl_3N_4O_9$ requires C, 37.0; H, 4.0; N, 10.8; Cl 20.5%.

4,6-Di-O-acetyl-2-azido-2-deoxy-3-O-[(R)-1'-(methoxycarbonyl)ethyl]-α-D-glucopyranosyl n-Hexadecyl Phenyl Phosphate (**11**)

n-Hexadecyl phenyl hydrogen phosphate **7** (50 mg, 0.125 mmol) and the beta imidate **10** (52 mg, 0.1 mmol) were dissolved in toluene (1.5 ml) and stirred at room temperature for 1h. The mixture was chromatographed, eluting with ethyl acetate/n-hexane to give two diastereoisomers (at phosphorus) of *the product* as a gum, 50 mg (66%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2850, 2120,1735, 1590; δ_H (250 MHz; $CDCl_3$) 0.88 (3H, t, J 6.8), 1.26 (26H, brs), 1.37 and 1.38 (3H, two d, J 6.8), 1.65-1.8 (2H, br m), 2.00, 2.05, 2.10 and 2.11 (together 6H, four s), 3.63 and 3.67 (1H, two dt, J 3.3, 1.4), 3.77 and 3.78 (3H, two s), 3.8- 4.4 (7H, m), 5.05-5.2 (1H, m), 5.83 and 5.87 (1H, two dd, J 6.5, 3.3), 7.15-7.4 (5H, m); MS (NH_3DCI) m/z (%) 773 (15, $[MNH_4]^+$), 756 (2, $[MH]^+$).

Disodium 2-Acetamido-2-deoxy-3-O-[(R)-1'-carboxyethyl]-α-D-glucopyranosyl n-Hexadecyl Phosphate (**13**)

Phosphate **11** (40 mg) was dissolved in THF (4 ml) containing acetic anhydride (0.15 ml) and 5% Pd/C (40 mg). The mixture was shaken in an atmosphere of hydrogen for 4 h, the catalyst was filtered off and the filtrate was evaporated to dryness and taken up in toluene. Washing with aq. sodium bicarbonate, drying and evaporation gave a crude product which was purified by chromatography, eluting with ethyl acetate/ n-hexane (1:1 > 4:1). The intermediate acetamide was obtained as a gum, 32 mg (78%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3340, 2930, 2855, 1730, 1670, 1595, which was dissolved in acetic acid (3 ml) containing platinum oxide (Adams catalyst; 32 mg) and shaken in an atmosphere of hydrogen for 3h. Filtration of catalyst and chromatography, eluting with chloroform/ methanol, gave the intermediate hydrogen phosphate, 28 mg, $[\alpha]_D^{20}$ +54 (c 0.7, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3320, 2930, 2850, 1740, 1650, 1560 br; λ_{max} (dioxan)

273 nm (427); δ_H (250 MHz; $CDCl_3$ / CD_3OD) 0.89 (3H, t, J 6.5), 1.27 (26H, brs), 1.39 (3H, d, J 7), 1.5-1.7 (2H, br m), 2.09 (6H, s), 2.15 (3H, s), 3.7-4.1 (9H, m, including 3H, s at 3.81), 4.2- 4.35 (2H, m), 5.14 (1H, t, J 9), 6.08 (1H, dd, J 8.3, 2.8), 8.59 (1H, d, J 3.3); FABMS (-ve ion glycerol) m/z (%) 694 (100, $[M-H]^-$).

Finally the hydrogen phosphate (25 mg, 0.036 mmol) was dissolved in THF (1.5ml) and methanol (0.5 ml) and treated with 0.1N sodium hydroxide (1.6 ml, 0.16 mmol) over a period of 1.5 h. After a further 1 h the solution was filtered through glass fibre, diluted with water, partly evaporated to remove methanol and then purified by passage through a column of HP20ss resin, eluted with water then with 40% acetone/ water. Fractions containing the desired sodium salt were identified by tlc (silica gel, butanol/ ethanol/ water), combined and freeze-dried to give the *title compound*, as a white solid 17 mg (74%), $[\alpha]_D^{20}$ +59 (c 0.33, water); ν_{max}(KBr)/cm^{-1} 3400, 1650, 1590; δ_H (250 MHz; D_2O) 0.84 (3H, t, J 6.5), 1.26 (26H, brs), 1.34 (3H, d, J 6.7), 1.45-1.65 (2H, br m), 2.01 (3H, s), 3.55-3.9 (8H, m), 4.30 (1H, br q, J 6.7), 5.58 (1H, br d, J 5.8, H-1); FABMS (-ve ion thioglycerol) m/z (%) 618 (40, $[M-Na]^-$), 596 (75, $[M-2Na+H]^-$).

4,6-Di-O-acetyl-2-azido-2-deoxy-3-O-[(R)-1'-(methoxycarbonyl)ethyl]-α-D-glucopyranosyl (2"R)-2"-Methoxycarbonyl-2"-(n-hexadecyloxy)ethyl Phenyl Phosphate (**12**)

(2R)-2-Methoxycarbonyl-2-(n-hexadecyloxy)ethyl phenyl hydrogen phosphate **6** (90 mg) was dissolved in toluene (2 ml) and treated with the beta imidate **10** (90 mg) and stirred for 1 h at room temperature. The mixture was then passed through a column of silica gel eluting with ethyl acetate/ n-hexane, giving two diastereoisomers (at phosphorus) of the *title compound* as a gum, 80 mg (50%), $[\alpha]_D^{20}$ +50 (c 1, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2920, 2850, 2110, 1740, 1690; λ_{max} (dioxan) 266nm (257), 260 (337), 254 (282); δ_H (250 MHz; $CDCl_3$) 0.88 (3H, t, J 6.5), 1.26 (26H, brs), 1.37 and 1.38 (3H, two d, J 6.8), 1.5 -1.7 (2H, br m), 2.01, 2.05, 2.11, 2.12 (6H, four s), 3.35-3.55 (1H, m), 3.6-4.6 (16H, m), 5.12 and 5.14 (1H, two t, J 9.6), 5.86 and 5.90 (1H, two dd, J 6.4, 3.3), 7.1-7.4 (5H, m); ^{31}P nmr (162 MHz) -7.2 (d, J 5.3), -7.6 (d, J 5.5) both reduced to s when broad band decoupled; FABMS (3-NOBA/Na) m/z (%) 880 (100, $[MNa]^+$).

Trisodium 2-Acetamido-2-deoxy-3-O-[(R)-1'-carboxyethyl]-α-D-glucopyranosyl (2"R)-2"-Carboxy-2"-(n-hexadecyloxy)ethyl Phosphate (**14**)

4,6-Di-O-acetyl-2-azido-2-deoxy-3-O-[(R)-1'-(methoxycarbonyl)ethyl]-α-D-glucopyranosyl (2"R)-2"-methoxycarbonyl-2"-(hexadecyloxy)ethyl phenyl phosphate **12** (75 mg) was treated as described for the preparation of compound **13** to give the intermediate acetamide, 56 mg (72%), ν_{max}($CHCl_3$)/cm^{-1} 3340, 2920, 2850, 1740, 1675, 1590, 1525.

The acetamide (48 mg) was hydrogenolysed to give the hydrogen phosphate as a gum, 44 mg (quantitative), $[\alpha]_D^{20}$ +57 (c 1.05, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3320, 2930, 2850, 1740, 1645, 1560, 1520; λ_{max} (dioxan) 268nm (100); δ_H (250 MHz; $CDCl_3$ trace CD_3OD) 0.89 (3H, t, J 6.2), 1.26 (26H, brs), 1.37 (3H, d, J 7), 1.5-1.7 (2H, br m), 2.09 (6H, s), 2.13 (3H, s), 3.35-3.65 (2H, m), 3.7-3.9 (8H, m), 3.95- 4.15 (5H, m), 4.2-4.3 (2H, m), 5.13 (1H, t, J 9.5), 6.10 (1H, dd, J 8.2, 2.6), 8.48 (1H, d, J 3.0); ^{31}P nmr (162 MHz, $CDCl_3$ /CD_3OD) -3.9 (br s); FABMS (3-NOBA/Na) m/z (%) 842 (50, $[MNa+Na-H]^+$).

Treatment of the hydrogen phosphate (35 mg, 0.044 mmol) with 0.1N NaOH (2.42 ml, 0.242 mmol) over 1.5 h as described above for compound **13**, gave the *title compound*, as a freeze-dried solid, 26 mg (79%), $[\alpha]_D^{20}$ +71 (c 0.6, water); ν_{max}(KBr)/cm^{-1} 3410, 2940, 2860, 1610 br; δ_H (250 MHz; D_2O) 0.83 (3H, t, J 6.5), 1.25 (26H, brs), 1.33 (3H, d, J 6.9), 1.5-1.65 (2H, br m), 2.03 (3H, s), 3.3-4.1 (11H, m),

4.32 (1H, q, J 6.9), 5.60 (1H, dd, J 6.9, 2.4, H-1); ^{31}P nmr (D_2O) 1.85 (s on broad band decoupling); FABMS (-ve ion glycerol) m/z (%) 750 (20, $[M-H]^-$), 728 (100, $[M-Na]^-$).

1-(2',3',4',6'-Tetra-O-acetyl-α-D-glucopyranosyl)prop-1-ene [21] (**17**)

1-(2',3',4',6'-Tetra-O-acetyl-α-D-glucopyranosyl)prop-2-ene [22] (9.6 g) was dissolved in benzene (1.4 litres) containing bis(benzonitrile)palladium (II) chloride (1 g) and the mixture boiled under reflux in an atmosphere of argon for 48 h, filtered, evaporated and chromatographed (ethyl acetate/ n-hexane (1:2)).

The first eluted product was the propenylidene compound **18,** 10 mg, tlc Rf 0.31; $[\alpha]_D^{20}$ +54 (c 0.9, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1754; δ_H (400 MHz; $CDCl_3$) 0.96 (3H, t, J 7.6), 2.04 (6H, s), 2.05-2.20 (8H, m, CH_3CH_2 and OAc), 3.76 (1H, ddd, J 9.6, 4.9, 2.3, H-5'), 4.20 (1H, dd, J 12.4, 2.4), 4.29 (1H, dd, J 12.4, 4.9), 4.91 (1H, dt, J 7, 1.2, vinylic H), 5.11 (1H, dd, J 8.5, 8.5, H-3'), 5.18 (1H, dd, J 9.4, 8.5, H-4'), 5.40 (1H, dd, J 8.5, ca 1, H-2'); MS (NH_3DCI) m/z (%) 373 (10, $[MH]^+$), 390 (100, $[MNH_4]^+$).

The second eluted product was the *title compound* obtained as a mixture of E and Z isomers, 6.8 g (70%), tlc Rf 0.27; δ_H (250 MHz; $CDCl_3$) 1.72 (0.6H, dd, J 7, 1.5), 1.80 (2.4H, d, J 6.5), 2.0 (9H, br s), 2.1 (3H, s), 3.85-4.0 (1H, m), 4.07 (1H, dd, J 12.3, 2.3), 4.22 (1H, dd J 12.3, 4.5), 4.7 (1H, m), 5.0-5.1 (2H, m), 5.35 (1H, dd, J 9, 9), 5.65 (1H, m), 5.85-6.0 (1H, m); MS (NH_3DCI) m/z (%) 373 (10, $[MH]^+$), 390 (100, $[MNH_4]^+$). Repeated chromatography of this product yielded *the E-isomer*, mp 87-89 °C; $[\alpha]_D^{20}$ +115 (c 0.5, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1750; δ_H (400 MHz; $CDCl_3$) 1.80 (3H, d, J 6.5), 2.0 (9H, s), 2.10 (3H, s), 3.96 (1H, ddd, J 7, 4.5, 2.3, H-5'), 4.07 (1H, dd, J 12.3, 2.3), 4.22 (1H, dd, J 12.3, 4.5), 4.70 (1H, t, J ca 6, H-1'), 5.0-5.1 (2H, m), 5.35 (1H, dd, J 9, 9), 5.69 (1H, dd, J 15, 6.6), 5.90 (1H, dd, J 15, ca 7); FABMS (glycerol) m/z (%) 373 (100, $[MH]^+$). Found: m/z 373.1484 $C_{17}H_{25}O_9$ requires 373.1499 $[MH]^+$.

1-(2',3',4',6'-Tetra-O-acetyl-α-D-glucopyranosyl)allene (20)

Methyl α-D-glucopyranoside (1.36 g, 7 mmol) was suspended in acetonitrile (1.4 ml) and bis(trimethylsilyl)trifluoroacetamide (5.5 ml) added. The mixture was stirred and heated at 60-70 °C under argon for 3h. After cooling to room temperature, propargyltrimethylsilane (5.25 ml, 35 mmol) was added followed by trimethylsilyl triflate (6.75 ml, 35 mmol).

The solution was left overnight and worked up using the method of Bennek[22]. Chromatography of the crude product, eluting with ethyl acetate/ n-hexane (1:2) gave the *product* as a white solid, 1.17 g (55%), mp 87-89 °C (from ethyl acetate/ n-hexane); $[\alpha]_D^{26}$ +142 (c 1, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1955, 1750; δ_H (250 MHz; $CDCl_3$) 2.0-2.05 (9H, br), 2.09 (3H, s), 4.04 (1H, ddd, J 10, 5, 2.2, H-5'), 4.10 (1H, dd, J 12, 2.2, H-6'), 4.21 (1H, dd, J 12, 5, H-6'), 4.85-4.95 (1H, m, H-1'), 4.92-4.98 (2H, m, allenyl), 5.04 (1H, dd, J 10, 9.5, H-4'), 5.10 (1H, dd, J 10, 5.7, H-2'), 5.30 (1H, dt, J 6.7, 6, allenyl), 5.43 (1H, dd, J 10, 9.5, H-3'); MS (NH_3DCI) m/z 388 $[MNH_4]^+$. Found: C, 55.1; H, 5.85. $C_{17}H_{22}O_9$ requires C, 55.1; H, 6.0%.

(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)methanol [21] *(24)*

a) by ozonolysis of olefin **17** and reduction.

1-(2',3',4',6'-Tetra-O-acetyl-α-D-glucopyranosyl)prop-1-ene **17** (2.3 g) was dissolved in dry dichloromethane (100 ml), cooled to -60 °C and ozone was bubbled through for ca 1.5 h when the solution became saturated with the gas. Excess ozone was then removed by purging with argon. Dimethyl sulphide was added and the solution left overnight at room temperature. Evaporation under reduced pressure gave a

crude product which was redissolved in THF (20 ml) and added to a mixture of sodium borohydride (0.243 g 6.4 mmol) and acetic acid (0.35 ml, 6.4 mmol) in THF (20 ml). The mixture was left overnight, diluted with brine and extracted with ethyl acetate. The extract was dried, evaporated and chromatographed, eluting with ethyl acetate/n-hexane (1:1) to give the *title compound* as an oil which slowly crystallized to a white solid, 1.1 g (48%); $[\alpha]_D^{26}$ +55.8 (c 0.48, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 br, 1750; δ_H (400 MHz; $CDCl_3$) 2.0 (1H, br, OH), 2.03 (6H, s, two OAc), 2.08 (3H, s, OAc), 2.10 (3H, s, OAc), 3.77 (1H, ddd, J 12, 7, 4, CHH-OH), 3.96 (1H, ddd, J 12, 7.5, 4, CHH-OH), 4.13 (1H, ddd, J 8, 5, 3, H-5), 4.14 (1H, dd, J 11.5, 3), 4.24 (1H, ddd, J 7.5, 5.6, 4, H-1), 4.29 (1H, dd, J 11.5, 5), 5.01 (1H, dd, J 8.5, 8), 5.15 (1H, dd, J 8.5, 5.6, H-2), 5.39 (1H, dd, J 8.5, 8.5); MS (NH_3DCI) m/z (%) 363 (5, $[MH]^+$), 380 (100, $[MNH_4]^+$).

b) by ozonolysis of allene **20** and reduction.

The allene **20** was treated with ozone as described above to give a 46% yield of the C-1 homo sugar **24**, identical in all respects to that described above. A sample recrystallized from ethyl acetate/ n-hexane had mp 93-94 °C. Found: C, 49.8; H, 6.1. $C_{15}H_{22}O_{10}$ requires C, 49.7; H, 6.1%.

3,4,6-Tri-O-acetyl-1-formyl-D-glucal (**23**)

The allene **20** (180 mg, 0.5 mmol) was treated with ozone in dichloromethane (8ml) as described above. After removal of excess ozone, triphenylphosphine (263 mg, 1 mmol) was added and the mixture left overnight at room temperature. Evaporation of solvent and chromatography gave the *title compound* (23) as a colourless oil, 90 mg (60%), $[\alpha]_D^{20}$ -55 (c 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750, 1720, 1650 w; δ_H (250 MHz; $CDCl_3$) 2.10 (9H, br s), 4.18-4.28 (1H, m), 4.4-4.5 (2H, m), 5.30 (1H, dd, J 7, 5.5), 5.55 (1H, dd, J 5.5, 3.5), 5.85 (1H, d, J 3.5), 9.28 (1H, s); MS (NH_3DCI) m/z (%) 318 (100, $[MNH_4]^+$); FABMS (3-NOBA/Na) m/z (%) 323 (30, $[MNa]^+$).

(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)methyl methanesulphonate (25)

The C-1 homo sugar **24** (1.6 g, 4.4 mmol) was dissolved in pyridine (10 ml) containing 4-dimethylaminopyridine (cat) and cooled in an ice bath. Redistilled methane sulphonyl chloride (0.4 ml, 5 mmol) was added and the mixture stored at 4 °C overnight. The mixture was diluted with dichloromethane and 2N sulphuric acid and the organic layer was washed with aq. sodium bicarbonate and with brine. Drying, evaporation and chromatography, eluting with ethyl acetate/ n-hexane (1:1) gave the *title compound* as an oil, 1g (50%), $\nu_{max}(CHCl_3)/cm^{-1}$ 1750, 1370, 1180; δ_H (400 MHz; $CDCl_3$) 2.1 (12H, br s), 3.1 (3H, s, OSO_2Me), 4.08 (1H, ddd, J 8.5, 5, 2.7), 4.16 (1H, dd, J 12.3, 2.7), 4.26 (1H, dd, J 12.3, 5), 4.32 (1H, dd, J 11.7, 3.2, $CHHOSO_2Me$), 4.46 (1H, ddd, J 8, 5.6, 3.2, H-1), 4.61 (1H, dd, J 11.7, 8, $CHHOSO_2Me$), 5.01 (1H, dd, J 8.5, 8.5), 5.18 (1H, dd, J 8.5, 5.6, H-2), 5.3 (1H, dd, J 8.5, 8.5); MS (NH_3DCI) m/z (%) 458 (100, $[MNH_4]^+$). Found: m/e 441.1072. $C_{16}H_{25}O_{12}S$ requires 441.1067 $[MH]^+$.

(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)bromomethane (26)

The methanesulphonate **25** (270 mg) was dissolved in toluene (17 ml) containing tetrabutylammonium bromide (475 mg; 2.5 eq) and the mixture heated at 80 °C for 17 h. The mixture was partitioned between water and ethyl acetate and the organic layer washed with aq. sodium bicarbonate and with brine. Drying and evaporation gave the *title compound* as a white solid, 225 mg (88%), mp 122-125 °C;

$[\alpha]_D^{25}$ +73 (c 0.75, $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 2.03, 2.08 and 2.10 (together 12H, three s), 3.50 (1H, dd, J 11.7, 5, CHHBr), 3.65 (1H, dd, J 11.7, 10, CHHBr), 3.85-3.90 (1H, m), 4.15 (1H, dd, J 12.2, 2.8), 4.30 (1H, dd, 12.2, 5.5), 4.45 (1H, ddd, J 10, 5.4, 5, H-1), 5.00 (1H, dd, J 8.8, 8.1), 5.18 (1H, dd, J 9, 5.3, H-2), 5.30 (1H, dd, J 9, 8); MS (NH_3DCI) m/z (%) 442 (60, $[MNH_4]^+$). Found: C, 42.5; H, 5.1; Br, 18.1. $C_{15}H_{21}BrO_9$ requires C, 42.4; H, 5.0; Br, 18.8%.

Diethyl (2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)methanephosphonate (27)

The bromide **26** (480 mg) was dissolved in triethyl phosphite (redistilled; 10 ml) and heated in an oil bath to 180 °C while purging the solution with argon. After 24 h the solution was cooled and triethyl phosphite was removed by evaporation under reduced pressure. Chromatography, eluting with ethanol/chloroform (1:20), gave the *phosphonate* **27** as an oil, 374 mg (68%), $[\alpha]_D^{20}$ +62.6 (c 1.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1755; δ_H (250 MHz; $CDCl_3$) 1.3-1.4 (6H, m, $POCH_2CH_3$), 2.0-2.1 (ca 13H, br s), 2.31 (1H, ddd, J 16.6, 16, 11, CHHP), 3.98 (1H, ddd J 9, 3.5, 3, H-5), 4.05-4.20 (5H, m, $POCH_2CH_3$ and H-6), 4.30 (1H, dd, J 12, 4), 4.50-4.65 (1H, m, H-1), 5.05 (1H, dd, J 9, 9), 5.10 (1H, ddd, J, 9, 5.5, 2), 5.25 (1H, dd, J 9, 9); ^{13}C nmr (100 MHz; $CDCl_3$) 23.7 (d, J_{P-C} 144Hz); MS (NH_3DCI) m/z (%) 483 (100, $[MH]^+$), 500 (10, $[MNH_4]^+$). Found: m/z 483.1629. $C_{19}H_{32}O_{12}P$ requires 483.1631 $[MH]^+$.

(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)methanephosphonic acid [21] (28)

The phosphonate ester **27** (142 mg, 0.29 mmol) was dissolved in dry dichloromethane (10 ml) under argon and bromotrimethylsilane (0.78 ml, 6 mmol) added dropwise. The clear solution was left overnight at room temperature and then evaporated to dryness. The resulting foam was redissolved in THF (2 ml) and water (0.025 ml) added. After 1 h the solution was evaporated to dryness and dried in vacuo over phosphorus pentoxide. The *phosphonic acid* was obtained as a white foam, 140 mg (quantitative), $\nu_{max}(CHCl_3)/cm^{-1}$ 2100-3500,1755; δ_H (400 MHz; CD_3OD) 2.00-2.07 (13H, m), 2.36 (1H, ddd, J17.2, 15.8, 9), 4.02 (1H,ddd, J 9.5, 4.5, 2.5, H-5), 4.14 (1H ,dd, J 12.2, 2.5), 4.29 (1H, dd, J 12.2, 4.5), 4.58 (1H, ddt, J 9, 5.7, 3.8, H-1), 5.00 (1H, dd, J 9.5, 9), 5.04 (1H, ddd , J 9.5, 5.7, 1.7, H-2), 5.33 (1H, dd, J 9.5, 9); MS (NH_3DCI) m/z 427 $[MH]^+$, 444 $[MNH_4]^+$.

(3,4,6-Tri-O-acetyl-α-D-glucopyranosyl)methyl acetate (**29**)

The C-1 homo sugar **24** (45 mg) in acetonitrile (5 ml) was treated with bromotrimethylsilane (0.03 ml) at room temperature for 3 h. Evaporation of solvent and chromatography, eluting with ethyl acetate/ n-hexane (2:1) gave *the product* (**29**) as an oil, 35 mg (77%), $[\alpha]_D^{20}$ +63 (c 0.8, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1745; δ_H (400 MHz; d6 benzene) 1.71, 1.73 and 1.74 (together 12H, three s), 3.0 (1H, brs, OH), 3.82 (1H, dd, J 8.5, 5.7, H-2), 4.10 (1H , ddd J 8.5, 5, 2.7, H-5), 4.11 (1H, dd, J 11.5, 2.7, H-6), 4.21 (1H, ddd, J 8.5, 5.7, 3.2, H-1), 4.30 (1H, dd, J 12.5, 3.2), 4.39 (1H, dd, J 11.5, 5, H-6), 4.64 (1H, dd, J 12.5, 8.5), 5.12 (1H, dd, J 8.5, 8.5, H-4), 5.32 (1H, dd, J 8.5, 8.5, H-3); MS (NH_3DCI) m/z (%) 363 (30, $[MH]^+$), 380 (100, $[MNH_4]^+$). Found: 363.1296 $C_{15}H_{23}O_{10}$ requires 363.1291 $[MH]^+$.

n-Hexadecyl Hydrogen (2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)methanephosphonate (30)

The phosphonic acid **28** (90 mg, 0.21 mmol) and n-hexadecanol (48 mg, 0.2 mmol) were dissolved in dry pyridine (1ml) and trichloroacetonitrile (0.067 ml, 0.67 mmol) added. The mixture was stirred and heated

at 80 °C under argon overnight and then evaporated to dryness. The residue was taken up in water and insoluble material separated by centrifugation. Evaporation of the aqueous phase gave a crude solid which was purified by chromatography on silica gel eluting with ethyl acetate/ ethanol/ water (7:2:1). The *title compound* was obtained as a gum, 46 mg (34%), $[\alpha]_D^{20}$ +31 (c, 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2940, 2860, 1755; δ_H (400 MHz; CD_3OD) 0.89 (3H, t, J 7), ca. 1.3 (26H, brs), 1.61 (2H, m), 1.83 (1H, ddd, J 19.6, 16, 4, CHHP), 1.97-2.07 (12H, m), 2.20 (1H, ddd, J 16, 16, 10.7, CHHP), 3.86 (2H, dt, J 6.5, 6.5), 4.05 (1H, ddd, J 9.2, 3.6, 3), 4.14 (1H, dd, J 12.2, 3), 4.35 (1H, dd, J 12.2, 3.6), 4.57 (1H, ddt, J 9, 5.7, 3.8, H-1), 5.01 (1H, dd, J 9, 9), 5.04 (1H, ddd , J 9, 5.7, 1.5, H-2), 5.32 (1H, dd, J 9, 9); FABMS (3-NOBA/Na) m/z 651 $[MH]^+$, 673 $[MNa]^+$.

n-Hexadecyl Sodium (α-D-glucopyranosyl)methanephosphonate (**31**)

The hexadecyl phosphonate **30** (28 mg, 0.043 mmol) was dissolved in THF (3 ml) and water (1 ml). Aqueous sodium hydroxide (1N, 0.215 ml, 0.215 mmol) was added. After 3.5 h, solvent was removed under reduced pressure and the resulting solid purified by passage through a column of HP20ss resin eluting with water and then with acetone-water (6:4). *The product* (31) was obtained as a white, freeze-dried solid, 14.5 mg (66%), tlc Rf 0.1 (ethyl acetate/ethanol/ water (7:2:1)); δ_H (250 MHz; D_2O) 0.85 (3H, br t), 1.3 (26H, br), 1.6 (2H, br), 1.9-2.1 (2H, m), 3.35-3.45 (2H, m), 3.5-3.9 (6H, m), 4.3- 4.4 (1H, m, H-1), 6.95-7.05 (1H, m), 7.15-7.3 (4H,m); FABMS (glycerol) m/z 505 $[MH]^+$, 527 $[MNa]^+$. Found: m/z 505.2929. $C_{23}H_{47}O_8NaP$ requires 505.2906 $[MH]^+$.

(2"R)-2"-Methoxycarbonyl-2"-(n-hexadecyloxy)ethyl Hydrogen (2',3',4',6'-Tetra-O-acetyl-α - D-glucopyranosyl)methanephosphonate (**32**)

The phosphonic acid **28** (90 mg, 0.21 mmol) and propionate **5** (69 mg, 0.2 mmol) were dissolved in dry pyridine (1.5 ml) and treated with trichloroacetonitrile (0.09 ml, 0.9 mmol) as described above for the preparation of compound **30**. Work up as before gave the *title compound* as a gum, 51 mg (32%), $[\alpha]_D^{29}$ +34 (c, 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2950, 2860,1755; δ_H (400 MHz; CD_3OD) 0.89 (3H, t, J 7), ca 1.3 (26H, m), 1.6 (2H, m), 1.85 (1H , ddd, J 19.6, 16, 3.5, H-1), 2.00, 2.01, 2.05 (together 12H, four s), 2.20 (1H, ddd, J 16, 16, 11.2, H-1), 3.48 (1H, dt, J 9, 6.5), 3.63 (H , dt, J 9, 6.5), 3.76 (3H, s), 4.05-4.15 (3H, m, H-1" and H-2"), 4.15 (1H, dd, J 12.5, 2.5), 4.35 (1H, dd, J 12.5, 3.3), 4.58 (1H, m, H-1'), 5.01 (1H, ddd, J 9.6, 5.7, 1.7, H-2'), 5.03 (1H, dd, J 9.5, 9), 5.31 (1H, dd, J 9.6, 9.5); MS (NH_3DCI) m/z 753 $[MH]^+$.

n-Hexadecyl Phenyl 2-(2',3',4',6'-Tetra-O-acetyl-α-D-glucopyranosyl)ethyl Phosphate (**34**)

A solution of (2',3',4',6'-Tetra-O-acetyl-α-D-glucopyranosyl)ethanol[17] (100 mg) and n-hexadecyl phenyl hydrogen phosphate **7** (126 mg) in dry toluene (20 ml) was evaporated and the residue dried under high vacuum for 1 h. The resulting gum was stirred in dry pyridine (3 ml) under argon and 1-(mesitylene-2-sulphonyl)-3-nitro-1,2,4-triazole (156 mg) was added. The reaction mixture was stirred at room temperature for 2 h and then evaporated to dryness. The residue was chromatographed, eluting with ethyl acetate/hexane (4:6 > 1:1) to give the *phosphate* as a colourless gum, 129 mg (64%) that was a mixture of diastereoisomers about phosphorus; $[\alpha]_D^{21}$ +39 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2860, 1755, 1600; δ_H (250 MHz; $CDCl_3$) 0.88 (3 H, t, J 6.5, CH_3), 1.26 (26 H, br s, CH_2s), 1.68 (2 H, br pent, J 6.8, $OCCH_2$), 1.88 - 2.24 (2 H, m), 2.04, 2.04, 2.05, 2.06, 2.07 and 2.08 (12 H, 6 s, $COCH_3$s), 3.79 - 3.90 (1 H, m, H-5'), 4.04 - 4.38 (7H,

m), 4.98 (1H, t, J 8.8, H-4'), 5.09 and 5.10 (1H, 2 dd, J 8.8 and 5.6, H-2'), 5.26 and 5.27 (1 H, 2 t, J 8.8, H-3'), 7.16 - 7.39 (5 H, m, Ar-H); MS m/z 757 $[MH]^+$.

2-(α-D-Glucopyranosyl)ethyl n-Hexadecyl Hydrogen Phosphate [21] (**35**)

Adams platinum oxide catalyst (100 mg) was added to a solution of the phospho triester **34** (126 mg) in glacial acetic acid (10 ml) and the mixture hydrogenated at atmospheric pressure for 3 h. The resulting solution was filtered from the catalyst, evaporated to dryness and re-evaporated several times from toluene. Chromatography of the residue using chloroform/ethanol (3:1 > 1:1) as eluant gave the *phosphoric acid* as a gum, 109 mg (96%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 br, 2930, 2860, 1755; δ_H (250 MHz; $CDCl_3$ + CD_3OD) 0.88 (3 H, t, J 6.5, CH_3), 1.26 (26 H, br s, CH_2s), 1.61 (2 H, br pent, J 6.9, $OCC\underline{H}_2$), 1.78 - 1.97 (1H, m), 2.05 (6H, s, two $COCH_3$), 2.07 and 2.11 (6H, 2 s, two $COCH_3$), 2.10 - 2.35 (1H, m), 3.80 - 4.03 (5H, m), 4.11 (1H, dd, J 12.2, 2.6), 4.27 (1H, dd, J 12.2, 4.7), 4.35 (1H, ddd, J 11.0, 5.7, 3.6, H-1'), 5.01 (1H, t, J 9.1), 5.09 (1H, dd, J 9.1, 5.7, H-2'), 5.30 (1H, t, J 9.1). FABMS (3NOBA/Na) m/z 703 $[MNa]^+$.

Sodium 2-(α-D-Glucopyranosyl)ethyl n-Hexadecyl Phosphate (**36**)

A solution of the tetra-acetate **35** (108 mg) in methanol (16 ml) was treated with 880 aqueous ammonia (1.6 ml) and stirred at room temperature for 18 h. The resulting solution was evaporated and the residue redissolved in water and converted to the sodium salt by passage through a column of Amberlite IR-120 (Na form) ion-exchange resin using water as eluant. Fractions containing the phosphate were combined and evaporated and then chromatographed using ethyl acetate/ethanol/water (7:2:0.5 > 7:2:1 > 3:2:1) as eluant. Fractions containing the required product were freeze-dried to give the *phosphate* as a colourless solid, 84 mg (99%); $[\alpha]_D^{21}$ +17 (*c* 1.0, methanol); $\nu_{max}(KBr)/cm^{-1}$ 3399 br, 2918, 2850, 1466, 1383, 1230, 1081; δ_H (250 MHz; CD_3OD) 0.90 (3H, t, J 6.5, CH_3), 1.28 (26H, br s, CH_2s), 1.62 (2H, pent, J 6.7, $OCC\underline{H}_2$), 1.92 - 2.05 (2H, m), 3.25 (1H, t, J 9.1), 3.47 (1H, ddd, J 9.1, 5.8, 2.7, H-5'), 3.52 (1H, t, J 9.1, H-3'), 3.63 (1H, dd, J 9.1, 5.8, H-2'), 3.68 (1H, dd, J 11.8, 5.8), 3.83 (1H, dd, J 11.8, 2.7), 3.86 (2H, q, J 6.3, OCH_2), 3.93 - 4.06 (2H, m), 4.16 - 4.27 (1H, m, H-1); FABMS (glycerol) m/z, 535 $[MH]^+$, 557 $[MNa]^+$.

Reaction of 2-azidoglucose acetate (**37**) *with allyltrimethylsilane.*

1,3,4,5-Tetra-O-acetyl-2-deoxy-2-azidoglucose (74 mg, 0.2 mmol) was dissolved in dry acetonitrile (1 ml) and allyltrimethylsilane (0.16 ml, 1 mmol) added, followed by boron trifluoride-etherate (0.197 ml, 1.6 mmol). The solution was heated at 60 °C under argon for 2 h, cooled and diluted with aq. sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the extract washed with brine, dried, evaporated and chromatographed (ethyl acetate/ hexane (1:2)) to give the product **38** as a gum 8.5 mg (12%), $\nu_{max}(CHCl_3)/cm^{-1}$ 2110, 1750; δ_H (400 MHz; $CDCl_3$) *inter alia* 2.43-2.6 (2H, $C\underline{H}_2CH{=}CH_2$), 3.42 (1/3 H, dd, J 10, 9, H-2 beta isomer), 3.89 (2/3 H, dd, J 10, 6, H-2 alpha isomer), 5.7-5.9 (1H, m, vinylic H). FAB MS (3-NOBA/Na) m/z (%) 378 (80, $[MNa]^+$).

Heating the azide in acetonitrile at 60 °C for 2h led to loss of the infra red absorption at 2110 cm^{-1}. Similarly the nmr signals at 2.3-2.6 δ and 5.7-5.9 δ disappeared.

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    1,3,4,5-Tetra-O-acetyl-2,6-anhydro-7,8,9-trideoxy-D-glycero-L-gulo-non-7-enitol (**17**); *1,3,4,5-Tetra-O-acetyl-2,6-anhydro-D-glycero-L-gulo-heptitol* (**24**); *1,3,4,5-Tetra-O-acetyl-2,6-anhydro-7-deoxy-7-(phosphono)-D-glycero-L-gulo-heptitol* (**28**); *n-Hexadecyl Hydrogen 1,3,4,5-Tetra-O-acetyl-2,6-anhydro-7-deoxy-D-glycero-L-gulo-octit-8-yl Phosphate* (**35**)
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