Novel sugar phosphorus ylides: Their synthesis, structure and reactivity. Synthesis of a series of sugar-derived phosphorus ylides from protected sugar derivatives and beta-oxo ylides as a route to novel alkynes and trioxo compounds.

Novel Sugar Phosphorus Ylides: Their Synthesis, Structure and Reactivity

Synthesis of a series of sugar-derived phosphorus ylides from protected sugar derivatives and beta-oxo ylides as a route to novel alkynes and trioxo compounds

Nina Carole Sahabo,

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Abstract

Higher carbon chain sugars have gained increased interest recently; they are important building blocks of natural and unnatural products with biological properties. The synthesis of these higher sugar skeletons is commonly known to be achieved with the Wittig methodology which exploits phosphorus ylide chemistry. This method has been successfully used for the synthesis of the higher carbon sugars. The aim of this project was to synthesise β,β'-dioxo sugar-derived phosphorus ylides, a new class of ylides, as versatile intermediates to valuable higher carbon sugar derivatives and carbohydrate mimics.

Model reactions were initially conducted; tetrahydro-2-furoic acid and tetrahydro-2*H*-pyran-4-carboxylic acid, compounds which are structurally similar to the precursor sugars, were identified as suitable model compounds. These compounds were converted to acyl chlorides and then converted to β,β'-dioxo phosphorus ylides precursors by acylation. The methodology proved successful and 8 examples were isolated. However, low yields were obtained due to the inevitable formation of triphenylphosphine oxide.

The method was then extended to sugar derivatives, prepared using standard protecting group chemistry. It was found that acylation could be achieved using the simple acyl chloride route or peptide coupling methodology for sugar derivatives which were acid sensitive. β,β'-dioxo sugar-derived phosphorus ylides (16 examples) were successfully isolated in low yields.

The oxidation and thermal reactivity of the β,β'-dioxo ylides were studied. Oxidation resulted in the successful synthesis of vicinal tricarbonyls, isolated as a mixture with the gem-diols (hydrates). The thermal decomposition of the ylides gave alkynes in moderate yields.

Acknowledgements

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Contents

List of figures

List of tables

Abbreviations

BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BSA	*N*,*O*-bis-(trimethylsilyl)acetamide
$CDCl_3$	Deuterated chloroform
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DMAD	Dimethyl acetylenedicarboxylate
DMAP	Dimethylaminopyridine
DMF	Dimethyl formamide
EDCI-HCl	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
ESI-MS	Electro-spray Ionisation- Mass Spectrometry
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HBTU	*O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HCTU	*O*-(6-Chlorobenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
Hr	Hours
IR	Infrared
J	Spin- spin coupling constant in Herz

KBr	Potassium bromide
Lit.	Literature
M	Molar
min	Minutes
ml	Milliliters
mg	Milligrams
mmol	Millimoles
m.p.	Melting point
NaCl	Sodium chloride
NMR	Nuclear magnetic resonance
PNB	Propylene glycol *n*-butyl ether
PyBOP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RT	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromtography
TOTU	*O*-[(Ethoxycarbonyl)cyanomethylenamino]-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate

1. Introduction

1.1 Organophosphorus compounds

Organophosphorus chemistry began in the nineteenth century and since then it has been a lively and stimulating field of research. Organophosphorus compounds have been used in various areas: agricultural chemicals, medicinal compounds (anticancer, antiviral and antibacterial agents), and catalyst systems based on metal-coordinated tertiary phosphines used for many industrial processes, flame retardants for fabrics and plastics and many more.[1]

The oxidation states of phosphorus range from -3 to +5 and examples of compounds are displayed in Table 1.1.

Table 1.1: Oxidation states of phosphorus and examples of compounds[2]

Oxidation	**Example**
-3	PH_3 (phosphine); R_3P (trialkyl phosphines); $R_3P^{+}-CH_2R'$ (tetraalkyl phosphonium)
-1	$R_3P{=}O$ (phosphine oxides)
0	P elemental
+1	$HO-\overset{\overset{O}{\|}}{P}R_2$ (phosphenic acid)
+3	$HO-\overset{\overset{O}{\|}}{\underset{\underset{OH}{\|}}{P}}-R$ (phosphonic acid); $(RO)_3P$ (phosphite esters)
+5	$(RO)_3P{=}O$ (phosphate esters); Phosphorus pentoxide

Organophosphorus compounds are extremely useful tools in organic and inorganic synthesis. They are involved in biological systems (e.g. metabolic pathways, nucleic structures), in medicine (e.g. anticancer agents), in agricultural applications (e.g.

insecticides), in nonbiological commercial applications (e.g. flame retardants for fabrics and plastics) and as reagents in organic synthesis (e.g. Wittig synthesis alkenes, reducing agents and ester formation with the Mitsunobu reaction). The usefulness of organophosphorus reagents in organic synthesis derives from phosphorus' ability to progress from the lowest to the highest coordination number.[1]

The key factors in this are:

a) The high nucleophilicity of the tervalent phosphorus reagents towards a wide range of electrophiles;

b) The strong bonds that phosphorus forms with oxygen, nitrogen, sulphur, the halogens and carbon;

c) The capability of phosphorus to stabilize adjacent anions.[2]

The most useful organophosphorus compounds are the phosphines; they may be primary, secondary or tertiary. The most common ones are the tertiary phosphines, e.g. triphenylphosphine and tri-*n*-butylphosphine. They carry lone pairs of electrons which provide basicity and nucleophilicity on the molecule. These characteristics influence the chemistry of phosphines when used in organic and organometallic synthesis.

Tertiary phosphines, such as trialkylphosphines, are powerful nucleophiles but the strength decreases in the secondary and the primary phosphines as fewer electrons are donated by the alkyl group. Phenyl substitution also decreases the nucleophilicity; nevertheless, triphenylphosphine is the phosphine of choice for the synthesis of phosphorus ylides. Triphenylphosphine is a solid (79-81°C.), safe to handle, commercially available, stable to air oxidation and it is of right nucleophilicity for quaternization. It also has the advantage of not having hydrogen atoms adjacent to the phosphorus atom that could compete in any deprotonation step. The nucleophilicity

allows trivalent phosphines to react rapidly with alkyl halides and produce phosphonium salts. This in turn is used to prepare one of the most important reagents, an ylide (Wittig reagent), which is used in Wittig reactions.[3]

1.2 Phosphonium ylides

Michaelis and Gimborn prepared the first ylide, however they were unsuccessful in understanding its structure.[4] It is now known that an ylide is defined as a substance in which a carbanion is attached directly to a heteroatom, carrying a substantial degree of positive charge, i.e. the phosphorus atom.[3] Phosphonium ylides function as carbanions effecting both substitution and addition reactions. This allows the ylides to produce new carbon-carbon single bonds by using ylides as nucleophiles, and new carbon-carbon double bonds, using ylides in the reaction with carbonyl compounds (Wittig reaction).

Phosphorus ylide chemistry has evolved tremendously since they were first reported in the 19th century. The development of phosphonium ylides chemistry is associated with eminent chemists; for example, Staudinger, Nobel prize laureate 1953, conducted research on phosphonium ylides and iminophosphoranes. Disregarding developments in Wittig chemistry, researchers have been able to explore numerous methods of generating phosphorus ylides and to enhance their reactivity. Ylides have been recognised as important reagents in the synthesis of a wide range of substances, such as olefins, acetylenes, cyclic and heterocyclic compounds, naturally occurring compounds (pheromones, steroids and carotenoids) and pharmaceutically and biologically active compounds (antibiotics and prostaglandins).[5]

A review by Taillefer and Cristau,[6] which is an update on the 1999 comprehensive review of 'Phosphorus Ylide, Chemistry and Application in Organic Synthesis',[5] summarises recent studies. The focus has been on the chemistry of cumulene ylides, the preparation and reactivity of stabilized ylides and the chemistry of phosphorus ylides α-C-substituted by metals, metalloids and non-metals.[6] The chemistry of phosphonium ylides substituted at the α-carbon atom with the different elements of the periodic table has been studied There is the exception of the inert gases and the unstable radioactive elements.[2,7]

The synthesis, bond properties and bond activation of bis-ylides have also been of great interest lately. Bis-ylides are attractive because of their additional stabilization and their importance as a C-donor ligands in organometallic chemistry as well as transition metal complexes.[8, 9] These ylides and derivatives have been used in different biological applications such as fungicides and antiparasitics. The chemistry of phosphorus ylides has inspired the investigation of the nature of the ylidic bond using energy decomposition analysis (EDA) and the domain-averaged Fermi hole (DAFH) analysis. These analyses have shown that the features of the ylidic bond can be understood in terms of donor and acceptor interactions between close-shell fragments.[10]

1.2.1 Structure

Phosphonium ylides are stable carbanions where their stability is attributed to the presence of secondary interaction between the carbanionic centre and the positive phosphorus, making the P-C bond short and strong.[2] The structure of a typical phosphonium ylide is shown in Figure 1. This structure was analysed by X-ray photoelectron spectroscopy which clarified the dπ-pπ interaction in the P-C bond and by combustion heat which confirmed the stability of the ylide, attributed to the contribution

of the polar bond structure.[11] Other analytical characterisations, such as NMR and IR spectroscopy, were also used but mainly to complement the X-ray and combustion heat studies.

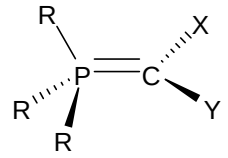
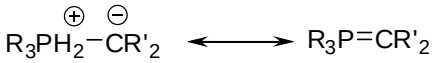


Figure 1.1: Structure of a phosphonium ylide

The good P-C stability, present in most chemical reactions, will allow the ylides to survive experimental conditions, including many acid and base hydrolysis and oxidising conditions.

The chemical properties of the C-substituted ylides will be determined according to the substituent attached to the carbon atom.[7, 12] The properties are divided into two classes:

1. Substituents (such as lead, tin and nitrogen) that increase electron density hence increase the reagent activity; these are also known as the nonstabilised ylides. The substituents on the ylidic carbon cannot conjugate with the P=C double bond as illustrated in Figure 1.2.



1a **1b**

Figure 1.2: Non-stabilised ylides

2. Subtituents (such as germanium and silicon atoms and transition metals) that decrease electron density are able to stabilise the ylide carbanion. This then reduces the ylide nucleophilicity. These substituents on the ylidic carbon can either delocalise the carbanion charge **2c** or conjugate with the P=C π bond **2a** (Figure 3). These properties have helped to emerge new and useful synthetic developments. β-Keto yildes **2** are an example of stabilised ylides.

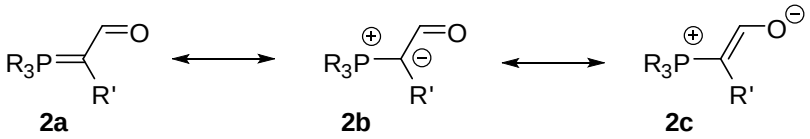


Figure 1.3: Structure of β-oxo ylides

1.2.2 Other types of ylides

Sulphur, oxygen and nitrogen ylides are also known. These are generated as unstable and highly reactive intermediates from mild and efficient methods. Their rich chemistry has allowed rapid preparation of highly functionalised compounds from relatively simple components, e.g. by rearrangement, epoxidation, olifenation, cyclopropanation and aziridination.[13, 14] The chemistry of these ylides has been reviewed by Dai and co-workers.

1.3 β-Oxo ylides

Phosphonium ylides, with their strong nucleophilicity, have the potential to react with electrophiles. This type of reaction is used to convert simple ylides into more complex ones, by attaching particular substituents at a specific point on a target molecule. This reaction will be used in this research for the synthesis of complex ylides derived from sugars.

1.3.1 Synthesis of phosphonium ylides

There are various methods of preparing phosphonium ylides. The general method is the synthesis of a phosphonium salt. Phosphonium salts are synthesised from S_N2 quaternization reactions, involving the nucleophilic attack of trialkyl- or triarylphosphines on alkyl halides. The reaction employs a variety of solvents, chosen

with the condition that the phosphonium salt will be obtained as a precipitate and considering their electrophilicity, polarity and polarisability effects.

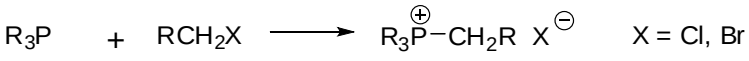


Figure 1.4: Synthesis of phosphonium salts

Phosphonium ylides are then prepared by deprotonation of the phosphonium salts. The latter is reacted with a strong base capable of shifting the acid-base equilibrium fully to the phosphonium ylide side. When choosing the base, it is important to consider the acidity of the phosphonium salt, which includes the nature of the phosphorus substituents and that of the carbon substituents. For instance, non-stabilised ylides will need a strong base (e.g. *n*-butyllithium) under inert conditions; while stabilised ylides will need a weak base (e.g. aqueous sodium hydroxide). The base should not react with other functional groups in the molecule or irreversibly alter the ylide.

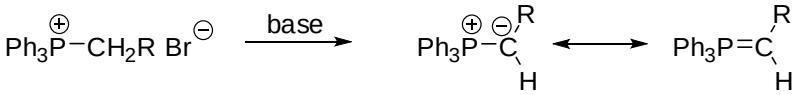


Figure 1.5: Synthesis of a phosphonium ylide

There have been few reports on the development of new methodology. Balema and co-workers reported on a solid-state and solvent-free procedure for generating phosphorus ylides. The method involved ball-milling the phosphonium salt with excess potassium carbonate under helium for a range of reaction times (3-20 hr) depending on the salt. The procedure was successful, generating the ylide in good to excellent yield. The products were analysed by ^{31}P NMR spectroscopy, X-ray diffraction and differential thermal analysis to investigate the possibility of reactants melting during milling.[15]

1.3.2 Acylation of phosphonium ylides

Acylation of phosphonium ylides is a reaction generally used for constructing carbon frameworks. It is an accessible method for the preparation of carbonyl stabilised ylides.[4] Numerous established methods are available involving the acylation of phosphonium ylides with carboxylic acid derivatives.

1.3.2.1 Acylation by acyl halides

β-Keto ylides are usually synthesised by acylation reactions. The general method is transylidation which requires a 2:1 ratio of ylide **1** to an acyl chloride in order to obtain **3**. The reaction of the ylide with the acyl chloride produces the phosphonium salt **2**. This in turn, can be deprotonated by the starting ylide **1** to give the acylated ylide **3** (transylidation).

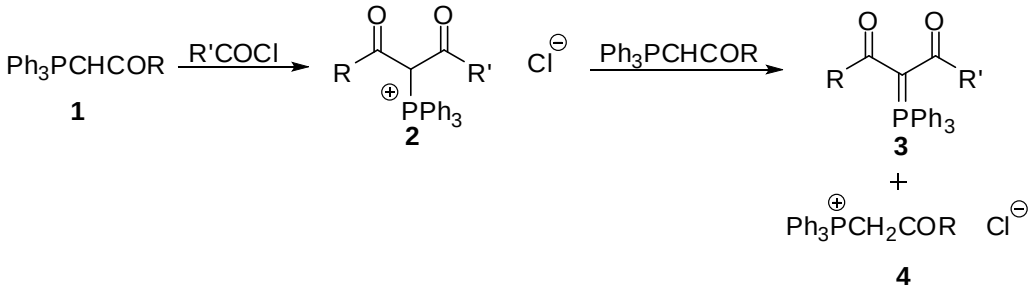


Figure 1.6: Transylidation reaction

The disadvantage of this method is that transylidation is wasteful, 50% of the starting ylide gets lost. A more efficient alternative exists, which requires the presence of triethylamine at ratio 1:1 with the starting ylide (Figure 1.7). This method counteracts the 50% loss and produces good yields.[16]

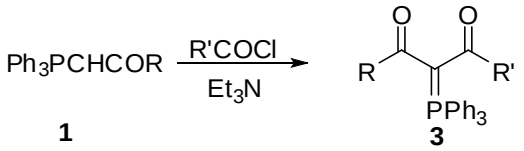


Figure 1.7: Alternative method to the transylidation method

Acyl halides are the most reliable and powerful acylating reagents. Acylation with acyl chloride can occur at the ylide carbon or at the β-carbonyl, depending on the reaction conditions used. Ester stabilised ylides can undergo ***C***-acylation and also ***O***-acylation but at a lower temperature. For example, ethyl 2-(triphenylphosphoranylidene) propionate **5** reacted with acetyl chloride at -10°C to produce the enol-ester-ether **6** which undergoes rearrangement to give **7** (Figure 1.8).[17]

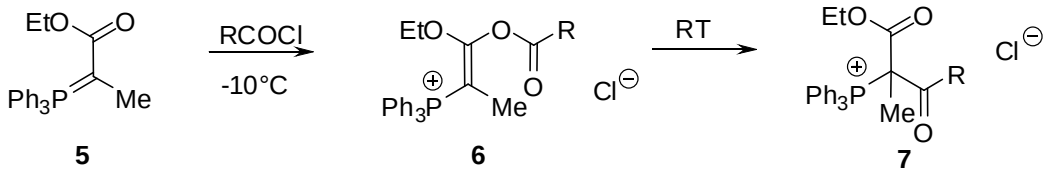


Figure 1.8: Acylation of ethyl 2-(triphenylphosphoranylidene)propionate by acetyl chloride

1.3.2.2 Acylation by acid anhydrides

The use of acid anhydrides in acylating phosphonium ylides has been effective and uncomplicated. Stabilised ylides such as **8** have been reacted with numerous linear anhydrides to produce the phosphonium salts **9**. The latter are either heated or treated with aqueous sodium hydroxide to afford the acylated ylide **10**.[18]

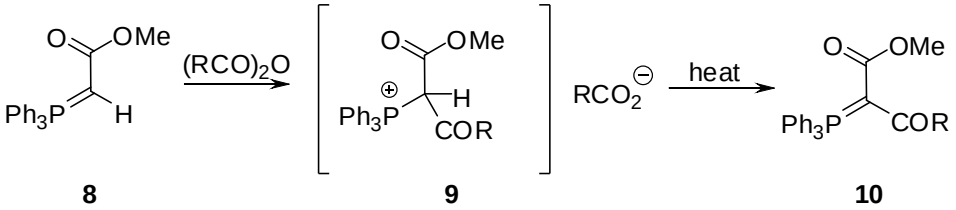


Figure 1.9: Acylation of phosphonium ylide **8** by acid anhydride

The reaction of cyclic anhydrides with phosphonium ylides, however, is different from that of linear anhydrides with the ylides. The reaction produces lactones. Nevertheless, this reaction is still of interest.[19]

1.3.2.3 Acylation by esters

While acyl halides have been the reagent of choice as the acylating reagent, esters are also known to be a good acylating reagent. Esters react with phosphonium ylides by following one of the two routes. The first step of the reaction in both routes involves the attack of the ylide carbanion on the ester carbonyl producing an intermediate such as **12**. The intermediate will in turn produce the substituted ylide **13** or alkene **14** depending on the substituents and the reaction conditions.

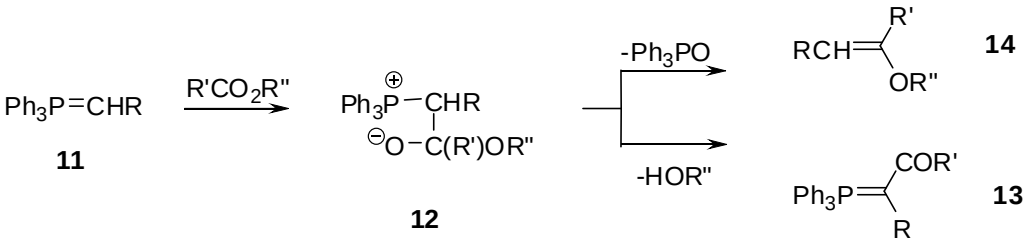
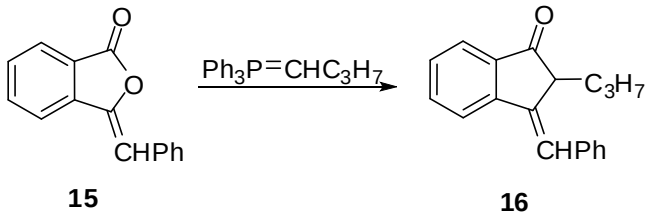


Figure 1.10: Acylation of phosphonium ylide **11** by esters

The formation of the β-oxo ylide will depend on the R" groups attached to the ester. It has been possible to improve the yields of β-oxo ylides, by performing the reactions under salt free conditions and using butyl lithium.[11]

1.3.2.4 Acylation by lactones

It was found that enol γ-lactones reacted with ylides by attacking the carbonyl group to produce an acylated ylide intermediate, which then undergoes intramolecular reaction. The overall result is the replacement of oxygen of **15** by the ylide alkyl group to afford **16**.[4]

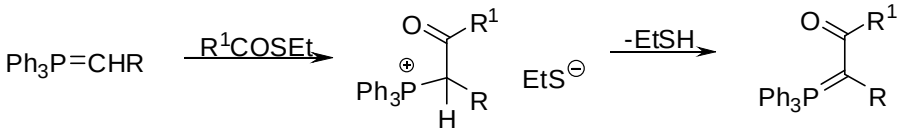


15 **16**

Figure 1.11: Acylation of phosphonium ylide by lactone

1.3.2.5 Acylation by thioesters

Bestmann and Arnason found that the use of thioesters was a good mean of improving the acylation of ylides. The success of the reaction depends on the basicity of the thiolate anion formed in the first step of the reaction, which converts the salt **17** to the corresponding ylide **18**.[20]

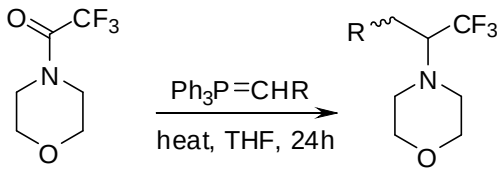


17 **18**

Figure 1.12: Acylation of phosphonium ylide by thioester

1.3.2.6 Acylation by amides

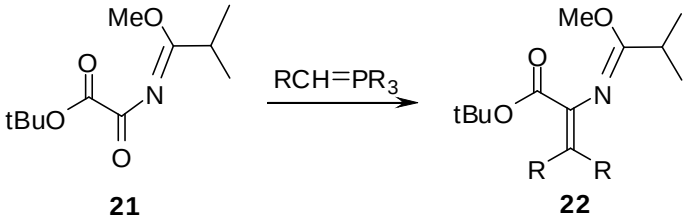
Few amides are known to be reactive towards ylides. A reaction with fluorinated amides has been reported to have worked but was limited to the use of trifluoroacetamides **19**.[11]



19 **20**

Figure 1.13: Acylation of trifluoroacetamides 19 with amides

An alternative to the acylation reaction was the formation of azadienes **22** from the reaction of *t*-butyl oxalyl imidates **21** with stabilised ylides.

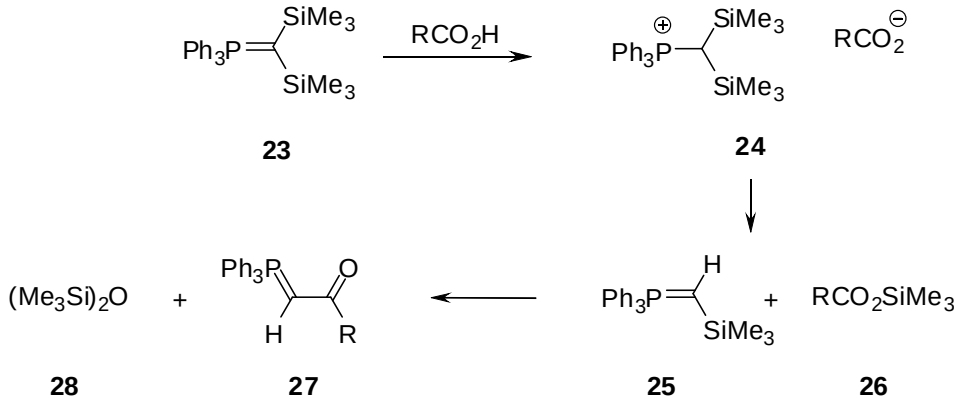


21 **22**

Figure 1.14: Reaction of imidates **21** with stabilised ylides to give azadienes **22**

1.3.2.7 Acylation by carboxylic acids

This method was explored to overcome the limitations described in Section 1.3.2.1. The procedure uses free carboxylic acids as acylating reagents. Bis-(trimethylsilyl) methylenetriphenylphosphorane **23**, a deprotonating reagent**,** was treated with the carboxylic acid to produce a β-oxo ylide **27** as well as hexamethyldisiloxane. The advantage of this technique is that the reaction allows the substitution of the OH group of the carboxylic acid by the ylide function in a one-pot procedure. Bestmann's group achieved good results and successfully applied the method to dicarboxylic acids and free amino acids to make bisacyl ylides and α-aminoacyl ylides respectively, in good yields.[21] It is important to note that in presence of water the reagent gets destroyed.



23 **24** **28** **27** **25** **26**

Figure 1.15: Acylation of bis-(trimethylsilyl)methylenetriphenylphosphorane **23** with acid

The alternative method by Wassermann uses peptide coupling reagents such as DCC and EDCI to form the β-oxo ylide **27**.[22] Amino acids are known to use peptide reagents, EDCI in presence of DMAP, to couple with ylides to form keto phosphoranes.[23-25] It is important to note that any functional groups, such as NH_2, OH, CO_2H, present on the substrate which may react with the coupling reagents must be protected prior to coupling.

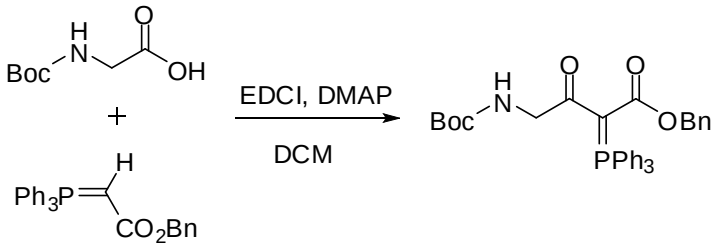


Figure 1.16: Peptide coupling reaction and subsequent oxidation

A number of other coupling agents have been developed such as BOP, PyBOP, HOBt and HOBt-based coupling reagents such as HBTU, HCTU and HATU for peptide synthesis and other acylation reactions. For decades, HOBt has been the most commonly used coupling enhancing reagent. However, HOBt monohydrate was recently reclassified by the United Nation as a desensitised explosive.[26] An alternative reagent, ethyl 2-cyano-2-(hydroxyimino)acetate, also known as Oxyma Pure, has been reported. Subiros Funosas *et al*. have proven this reagent to be safer, more efficient and to give lower racemisation than HOBt in carbodiimide-mediated coupling reactions. Two coupling reagents based on Oxyma Pure have been developed: COMU and TOTU.

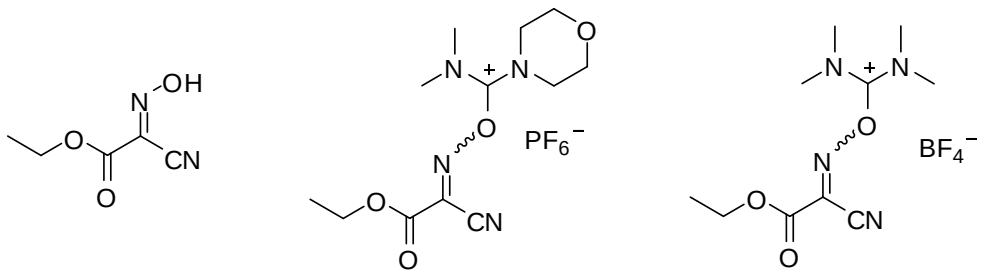
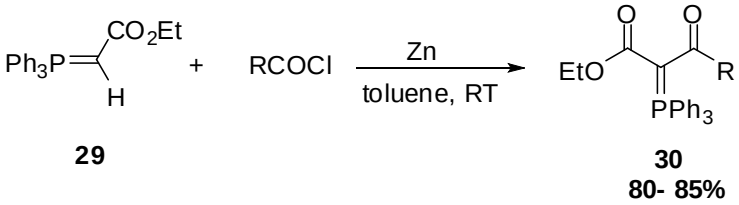


Figure 1.17: New coupling reagents

1.3.2.8 Metal mediated acylation

Most of the acylation methods have had disadvantages. Recently, Yadav and co-workers developed metal catalysed reactions which have been shown to improve the acylation of ylides. Among all metals, zinc catalysis was the most efficient because of its ability to coordinate with polar groups.[27] This property increases the electrophilicity of the acyl groups. However limitations of this method have not yet been reported.



29 **30**
80- 85%

Figure 1.18: Zinc catalysed acylation

1.4 Sugar-derived ylides

Phosphorus ylides have been used in sugar chemistry for many decades. They have been involved in synthesis of terminal acetylenic sugar derivatives, in the search for anti-viral nucleosides analogues and diverse sugar derivatives.[28, 29]

A great deal of effort has been channelled in the production of both natural and unnatural carbohydrates and their mimics. In the past two decades, chemists have been

interested in the preparation of higher carbon sugars with more than 10 carbon atoms in the chain. They are important components of antibiotics, e.g. tunicamine, and have potential use as non-metabolised analogues of disaccharides.[30-32]

Elongation of carbon chain of sugars started with the addition of one carbon atom. An example of this type of reaction is the classical Kiliani-Fischer synthesis (Figure 1.19). This method involves the synthesis of a cyanohydrin followed by its reduction. This methodology has been limited by the use of toxic reagents and the low yields. Other traditional methods include chain-lengthening by nitromethane and preparation of ketoses *via* the aldonic acid chloride and diazomethane.

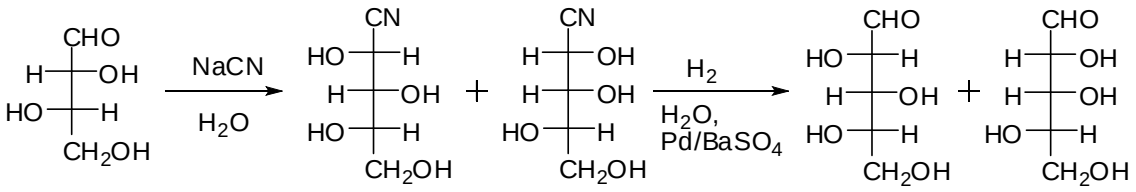


Figure 1.19: Kiliani-Fischer synthesis

Methodologies which exploit phosphorus ylide chemistry have been developed. However, only three methods based on sugars have been developed. These three methods, two based on the coupling of sugar-derived phosphorus ylide and a third on alkyne addition to a carbonyl group, have the widest application in the synthesis of higher sugar skeleton.

The Wittig methodology involves the coupling of two sugar sub-units, one of which is a sugar-derived stabilized phosphorus ylide (Figure 1.20).

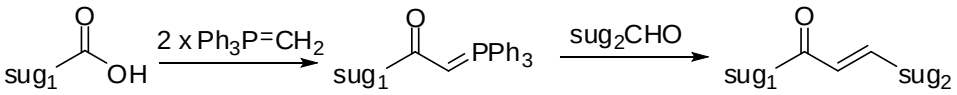


Figure 1.20: Wittig methodology using a sugar-derived stabilised phosphorane.

The reaction was accomplished with sugar-derived stabilized phosphorus ylides (Figure 1. 21) to give their corresponding enones in moderate to good yields.[33]

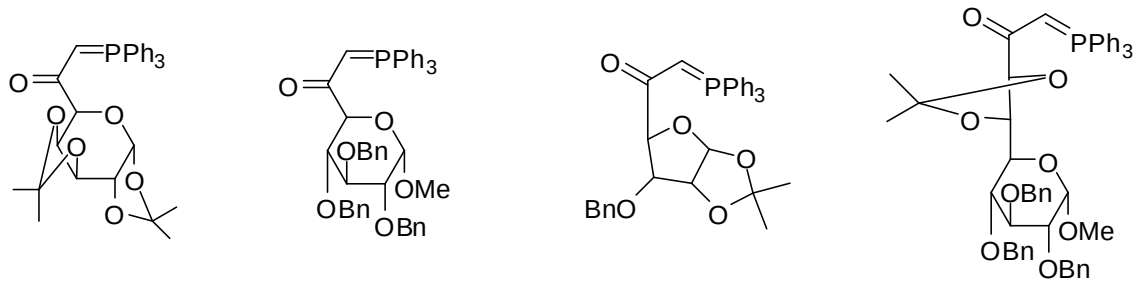


Figure 1.21: sugar-derived stabilised phosphorus ylides

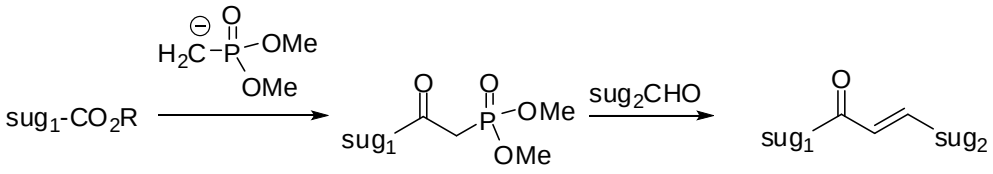


Figure 1.22: Horner-Emmons methodology using a sugar-derived phosphonate.

The Horner-Emmons methodology (Figure 1.22) was used as an alternative procedure to the Wittig methodology. This would overcome the low yields obtained from converting uronic acid into the stabilized phosphorus ylide (phosphorane), as illustrated in Figure 1.23. Hence the phosphorane was replaced by the phosphonate which is more nucleophilic. The conversion of the uronic acid **31** into the phosphorus ylide **32** was achieved at only 50% yield, making the overall yield of the final product **35** low (route a). The alternative intermediate, phosphonate **33**, was produced in very good yield (91%) from the methyl ester of the uronic acid **31**. Subsequently the final product **35** was

obtained in very good yield (90%) (route b). Compound **35** is a precursor to higher sugar (C_{12} and C_{13}) dialdose.[30]

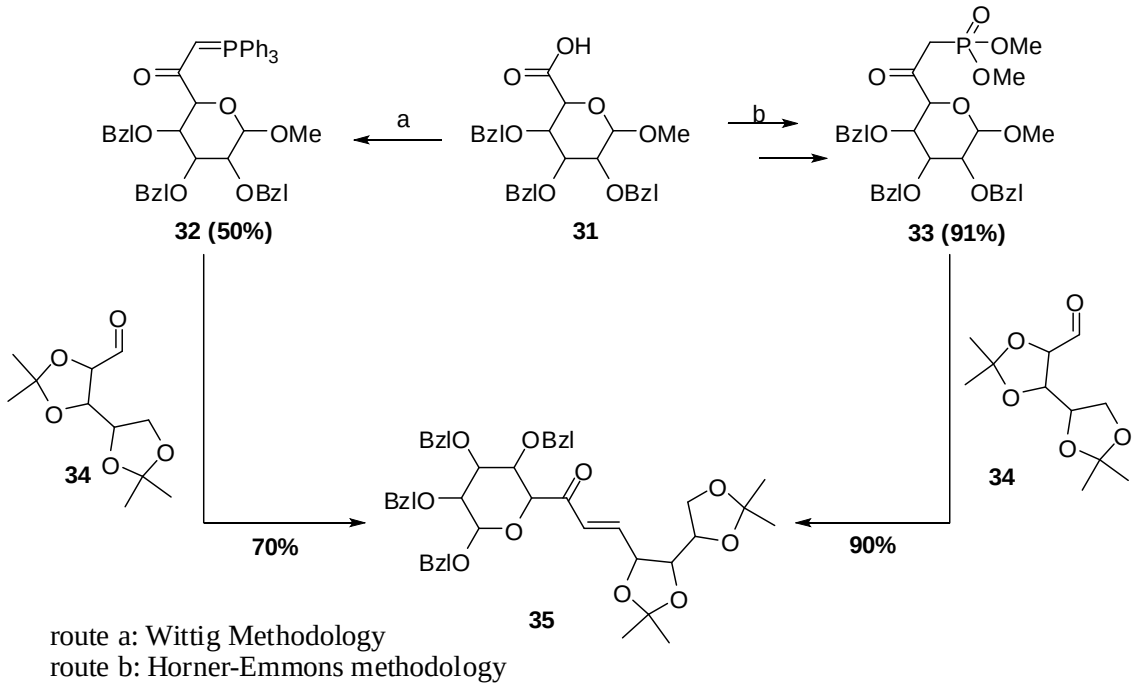


Figure 1.23: Comparison of the Wittig and Horner-Emmons methodologies

The third method exploits carbonyl chemistry and involves the addition of an alkyne to a carbonyl group.

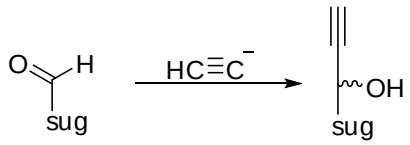


Figure 1.24: Conversion of aldehydo-sugar into sugar alkyne

The sugar alkynes, also known as sugar acetylenes, are also synthesised by a method called *C*-glycosidation (alkynylation), which was designed to introduce carbon chains onto sugars.[34] This methodology has been used to synthesise natural products such as ciguatoxin and tautomycin.[34] There are only a few methods which are available for the preparation of this class of compounds.

Figure 1.25: *C*-glycosidation

Rollin *et al* have reported the application of the Wittig approach to synthesise carbohydrate-derived vinyl sulphides. They are known to be useful intermediates for the synthesis of various carbohydrate mimics to natural substances.[35]

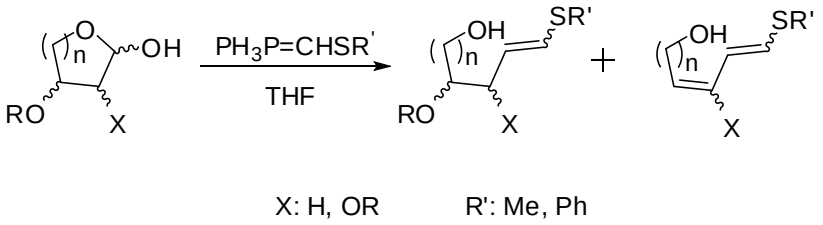


Figure 1.26: Application of Wittig method to synthesise sugar-derived vinyl sulphides

1.5 Oxidation of β-oxo ylides

Vicinal tricarbonyls have been known since diphenyl triketone was reported in 1890 by de Neufville and von Pechmann.[27] Since then, there has been a growing interest in how many carbonyl groups can be juxtaposed. Towards the end of the 20th century, vicinal polycarbonyl compounds started receiving greater attention as reagents in organic synthesis. Vicinal tricarbonyl compounds have become an important class of substrates due to the central carbonyl being strongly electrophilic which explains the fact that tricarbonyls are hydrates at this position.

The first cyclic vicinal polyketones to be documented were croconic acid and rhodizonic acid (Figure 1.27) with more than two carbonyl groups, and their structures were established much later. The first linear vicinal polyketones to be reported were diphenyl triketone, diphenyl tetraketone and dimethyl triketone.

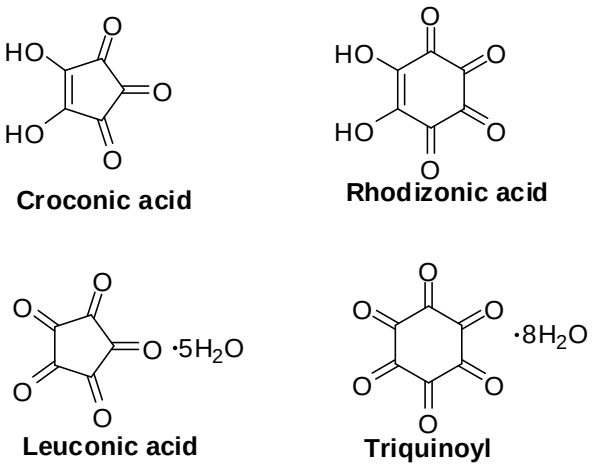


Figure 1.27: The first cyclic vicinal polyketones[36]

There has been a considerable variety of reported procedures for the preparation of tricarbonyl compounds. For many of those, β-dicarbonyl compounds have been starting materials due to their ready availability and reactivity at the α-position which could have different functional groups at that position, as illustrated in Figure 1.28.

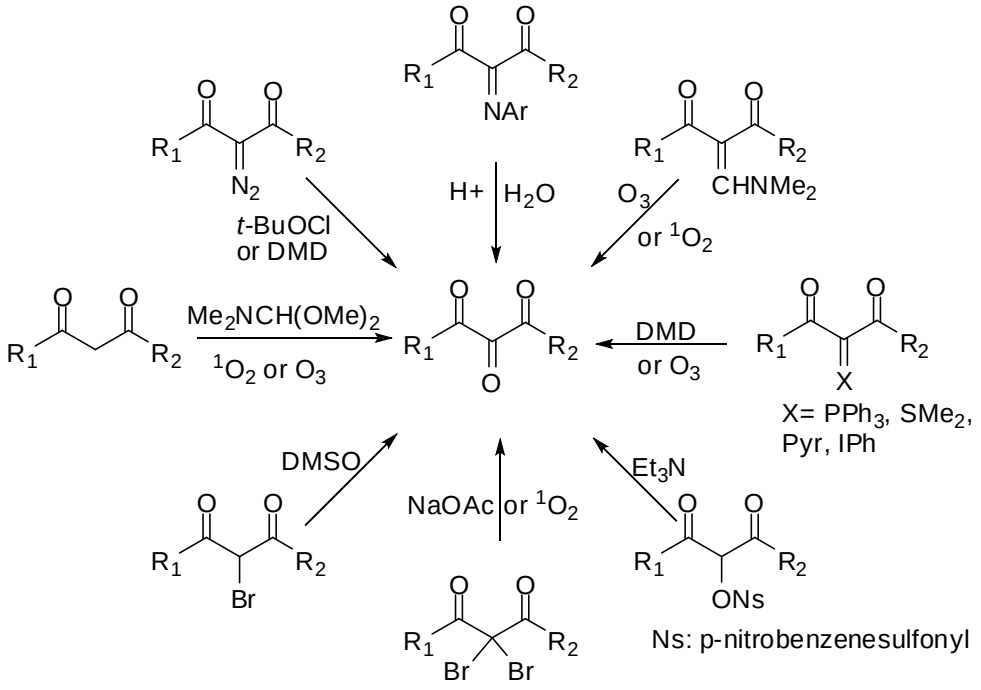
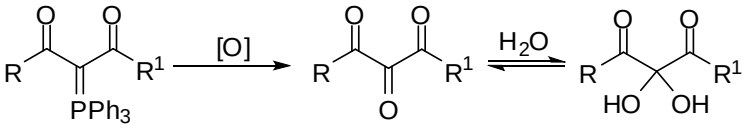


Figure 1.28: The major synthetic reactions for the preparation of tricarbonyls from β-dicarbonyl precursors[37]

Lately, the most attractive methods have been those reported by Wasserman and co-workers, which focus on the formation of the vicinal tricarbonyls from carboxylic acids. This method involves the coupling of a carboxylic acid or acid chloride with stabilized phosphorus ylides. β-Dicarbonyl compounds no longer become the starting materials. The resulting ylide intermediate **3**, i.e. tricarbonyl precursor, is then converted to the tricarbonyl hydrate by oxidising agents such as singlet oxygen,[38] Oxone®,[39] ozone [40] or dimethyl dioxirane [41] (Figure 1.29).



3 **36** **37**

Figure 1.29: General method for the synthesis of vicinal tricarbonyls from β,β'-dioxo ylides

The β,β'-dioxo ylide is stable and may be considered as a protecting group for the tricarbonyls. The C=P bond masks the electrophilic C=O groups which is activated by oxidative cleavage of the C=P bond. This has been the case for the synthesis of diketoamides and peptidyl diketoesters.[42]

From these oxidative procedures, hydrates are produced in equilibrium with the parent tricarbonyls in solution (Figure 1.29). The resultant hydrates can be converted to tricarbonyl compounds by sublimation, distillation, crystallisation or treatment with dehydrating agents such as molecular sieves or phosphorus pentoxide.[37]

The structures of the hydrates were assumed to be that of the gem-diols. Spectroscopic methods (NMR) and X-ray studies confirmed that the hydration occurs at the central carbonyl group. The steric and electronic effects play an important role in determining the position of the hydration equilibrium.

As previously mentioned, the central carbonyl of the tricarbonyl unit is highly electrophilic, providing great potential for its application in organic synthesis. Early studies have focused on addition reactions of the tricarbonyls with a variety of nucleophiles, using donor reagents such as alcohols, amines, water and mercaptans.

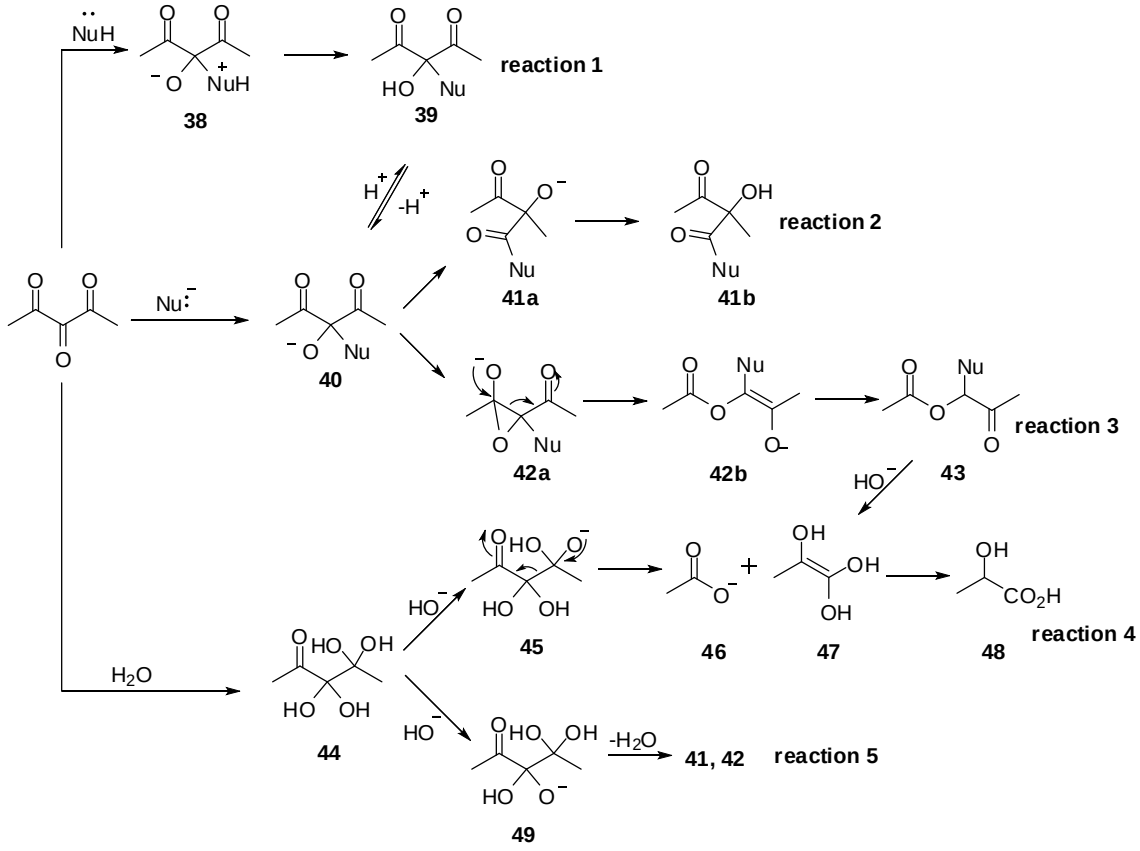


Figure 1.30: Nucleophilic addition reaction at central carbonyl[37]

A review by Rubin and Gleiter summarised the interaction of tricarbonyls with nucleophiles; a simplified scheme is illustrated in Figure 1.30. Reaction 1 is a reversible addition reaction of neutral nucleophiles at the central carbonyl of the tricarbonyl to provide the zwitterion **38** followed by proton transfer to provide **39**. This reaction becomes a hydration reaction when Nu is OH. When the Nu is anionic, oxyanion **40** is produced which may protonate to give **39**. The oxyanion **40** can also react in two different ways: (i) to produce **41** by acyl migration, an exchange in positions of the Nu

and the end group of **40** in reaction 2 and (ii) to produce ketolester **43** (reaction 3) by an initial attack on the carbon atom adjacent to a carbonyl group to form the epoxy intermediate **42** which rebonds and protonates to form **43**. These rearrangement reactions observed in reaction sequences 2 and 3 depend on the structural constraints and the steric requirements of subsequent steps.[37] Rearrangement does not take place in reaction 1 due to mild reaction conditions or to the rapid proton transfer to neutral species after initial addition.

Reaction 4 and 5 are results of tricarbonyls subjected to aqueous systems to form dihydrate intermediates **44**, followed by reaction with strong base to give two possible oxyanions, **45** and **49**. The oxyanion **45** (reaction 4) undergoes a reverse aldol reaction to give fragmentation products, carboxylic acid **46** and enetriol **47**. The latter is in turn converted to an α-hydroxy acid. It is also possible to produce **47** from ketolester **43** by hydrolysis. In reaction 5, oxyanion **49** undergoes the same type of rearrangement sequences as described in reaction 2.

Other reactions that have been attempted on polycarbonyls are thermolysis, cycloaddition, ene reactions, keto-enol tautomerism, reduction and photochemical reactions. These reactions have been reported to have worked, producing a mixture of products varying from low to good yields. Thermolysis of polycarbonyls has been limited to sublimation, crystallisation and heating under vacuum, these methods are used for purification procedures, because their thermal stability has not been efficiently examined.

Wasserman and Parr were interested in a different reaction pattern: intramolecular addition reactions as shown in Figure 1.31.

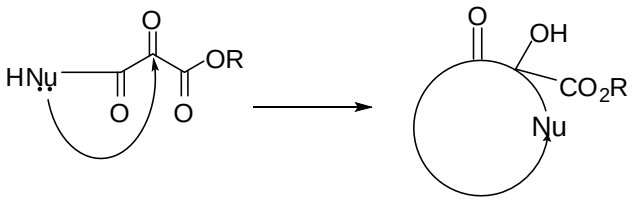


Figure 1.31: Intramolecular nucleophilic addition at central carbonyl[42]

It was possible to synthesise an intermediate to the preparation of the natural product, bicyclomycin **54**. The diamide **50** was converted to the ylide **51**, which was subsequently transformed to the diacyl ylide **52**. Oxidation of **52** with ozone yielded the key intermediate to the natural product **53** (Figure 1.32).

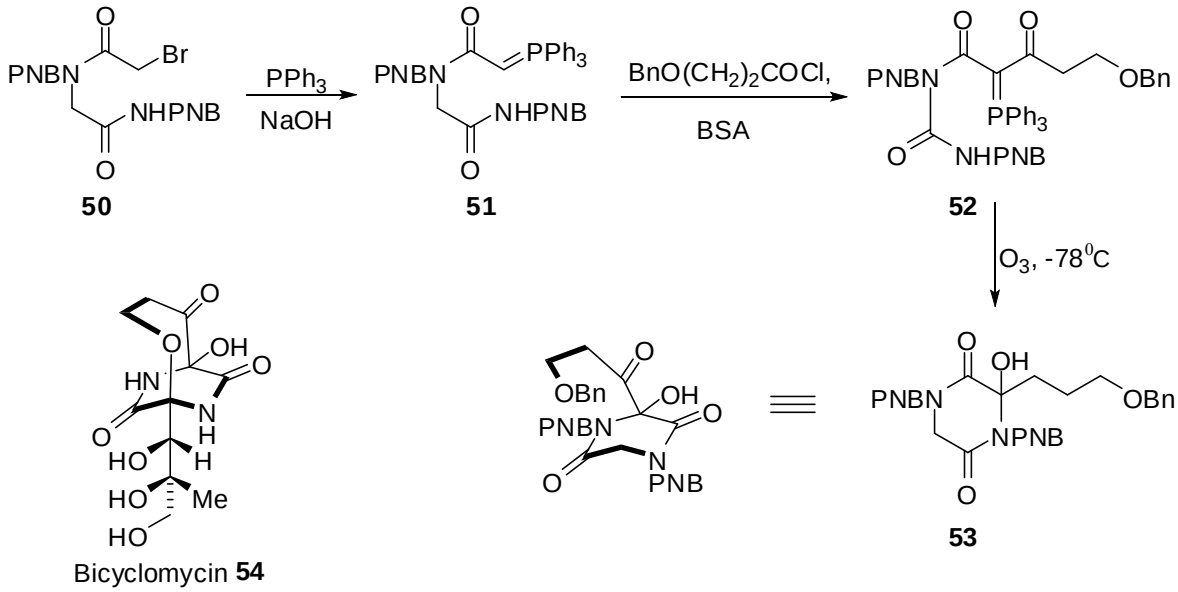


Figure 1.32: Preparation of bicyclomycin intermediate **53**

Reactions involving this procedure/mechanism have led to the synthesis of novel compounds such as isoquinoline alkaloids, papaveraldine, hydrastine and Cordrastine.[42] The substitution of the vicinal tricarbonyl unit with a neighbouring electrophilic group, for example an olefinic, an acetylenic, a carbonyl or an epoxide group, has generated novel polyelectrophiles. This reaction has been used in pyrrole formation (Figure 1.33), for example, for the preparation of bacterial metabolites such as prodigiosin **55**.[42]

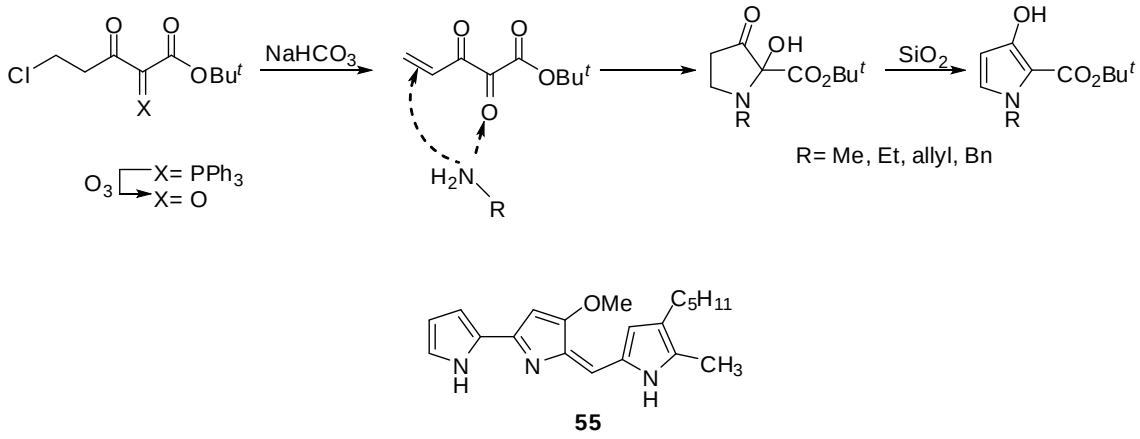


Figure 1.33: Synthesis of pyrroles

The study of electrophilic reactions of the vicinal tricarbonyls was extended to the preparation of enzyme inhibitors containing α-keto amides.[42] The procedure for the preparation of those inhibitors, involved the coupling of protected peptide carboxylic acid **56** with ylide **57** in the presence of EDCI, a coupling reagent. The produced diacyl ylide **58** was oxidised with ozone yielding the peptidyl tricarbonyl **59**.

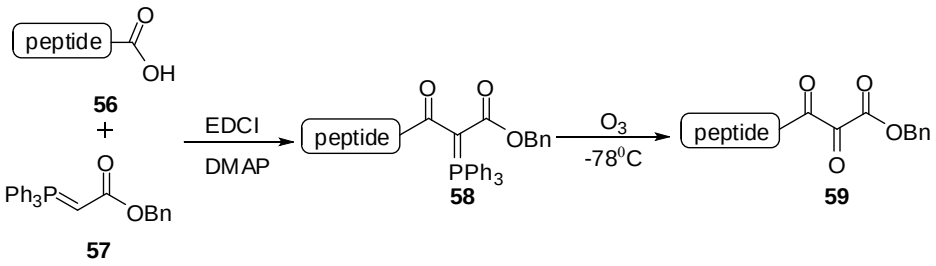


Figure 1.34: Synthesis of peptidyl tricarbonyls

This methodology was used to extend the chemistry of vicinal tricarbonyls in the isolation of biologically active natural products such as FK-506 (Figure 1.35), rapamycin and related immunosuppressant, protease inhibitors YM-47141 and YM-47142 (Figure 1.35).

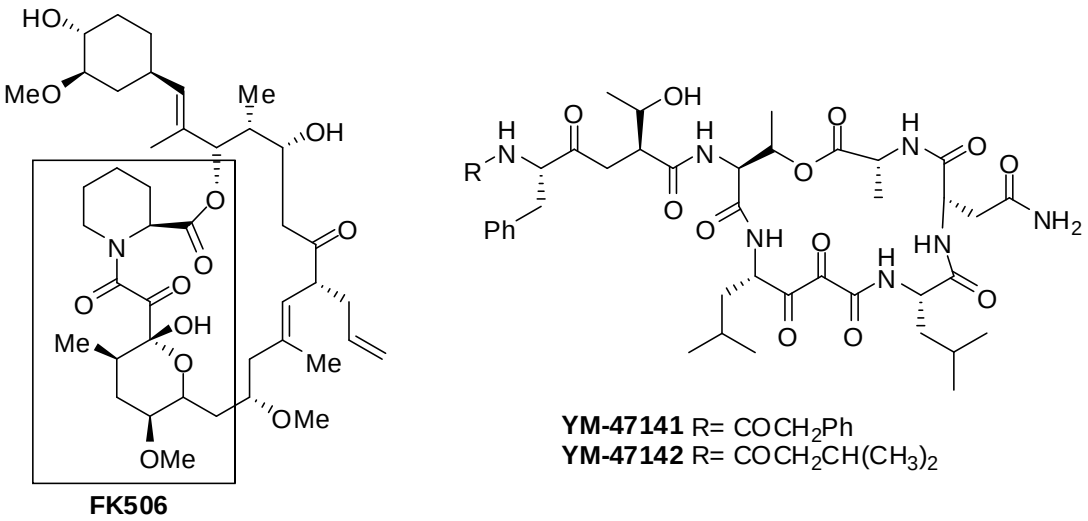


Figure 1.35: Examples of vicinal tricarbonyl natural products

Vicinal tricarbonyl compounds have also been involved in the formation of highly substituted furan derivatives by reaction with isocyanide- DMAD zwitterion (Figure 1.36).[43]

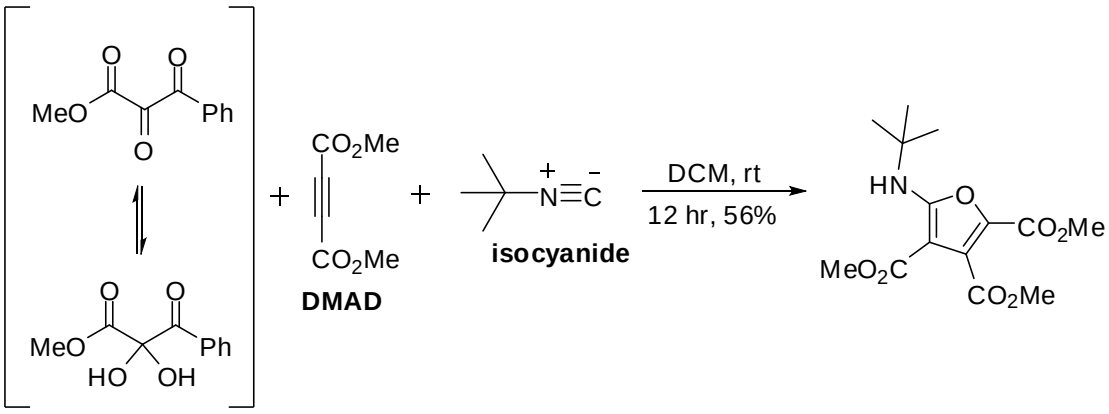


Figure 1.36: Isocyanide-DMAD zwitterions reaction[43]

More recently Schofield and co-workers reported the cleavage of the C-C bonds in vicinal tricarbonyl compounds with aqueous ferric ions at room temperature and in the absence of added ligands (Figure 1.37).[44] This reaction was used for the detection of amino acids by ninhydrin and for the metabolism of vitamin C.[44]

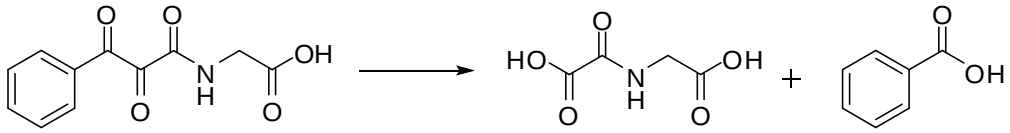


Figure 1.37: Iron-mediated C-C bond cleavage

Tetra-, penta- and hexaketones have also been synthesised. Tetraketones and pentaketones have been synthesised as open chain compounds. Tetraketones can also be obtained as a cyclic compound. Their synthesis is illustrated in Figure 1.38. The synthesis of higher polyketones has been attempted but it is still a challenge.

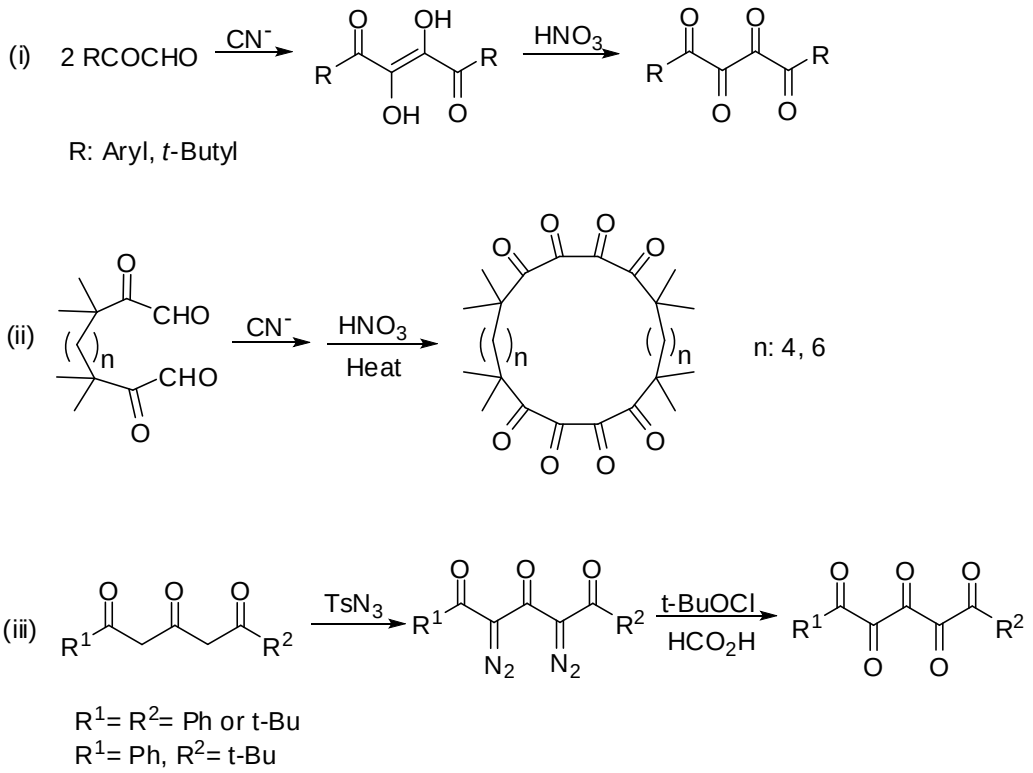


Figure 1.38: Synthesis of (i) Open chain and (ii) cyclic tetracarbonyls and (iii) open chain pentacarbonyl

These polycarbonyls can undergo the same reactions as the tricarbonyls. Cyclic polyketones have been observed to be more reactive than the open chains.

1.6 Thermolysis of β-Oxo Ylides

β-Oxo ylides are the one category of phosphonium ylides that is predictably liable to thermal decomposition.[45] This thermal decomposition of β-oxo ylides has lead to extrusion of triphenylphosphine oxide to produce alkynes. When thermal extrusion was first discovered in 1959, α-benzoylbenzylidene was heated at 300˚C for 0.5 hr , in the absence of solvent, to produce quantitative amount of diphenylacetylene and triphenylphosphine oxide.[46]

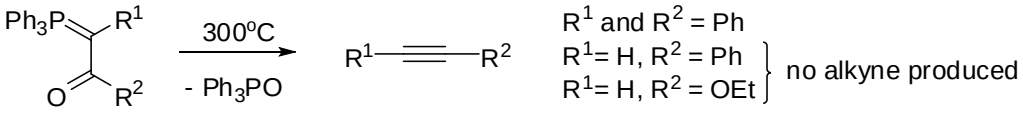
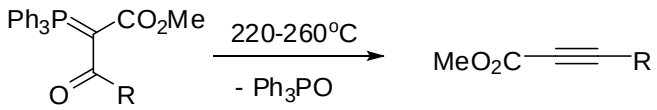


Figure 1.39: Thermal decomposition at 300°C

This procedure was extended to ylides with R^1= CN and CO_2Et. Later on, Märkl illustrated the conversion of methoxycarbonyl ylides **60** by heating at 220-260˚C under vacuum to produce acetylenic esters **61** in 65-80% yield.[16] It was noted that this reaction had already been used, 40 years earlier, for the formation of benzonitrile from a phosphinimine, Ph_3P=N-COPh.



60 **61**

Figure 1.40: Pyrolysis of dioxo phosphorus ylides

Conventional pyrolysis has helped to gain access to the synthesis of a variety of acetylenic esters, bis-acetylenic esters and intermediates in natural product synthesis and other functionalized examples with R^1= aryl, CO_2R, CN, COSMe, Br or Cl, SR, SeAr, OAr and $PO(OPh)_2$.[16] This important and useful method has been regarded as an intramolecular Witting reaction.

The method presented some disadvantages. Pyrolysis of β-oxo alkylidenetriphenylphosphorane would only produce alkynes if a) neither R^1 nor R^2 is hydrogen or alkyl and b) R^1 or R^2 is an electron withdrawing group, i.e. carbonyl or phenyl group. Hence the desired aliphatic and terminal alkynes could not be synthesized. Instead side reactions were produced which included partial extrusion of thriphenylphosphine and isomerisation of the alkynes to allenes. These limitations were overcome by the development of flash vacuum pyrolysis (FVP), which employs a flow-system that combines low pressure (10^{-1}-10^{-6} torr) and high temperatures (350- >1000˚C) and letting each substrate spend a short time in contact with the hot zone. The use of FVP provided the access to a variety of aliphatic and terminal alkynes, in multigram quantities, where conventional pyrolysis failed. Another advantage to this method is that the products are obtained in pure form, free of solvents, reagents, or by products.[4]

The first examples of ylides subjected to FVP, showed no change at temperatures up to 600˚C. However they underwent complete reaction at 750˚C at a pressure of 10^{-2} torr, to give triphenylphosphine oxide and alkynes where R^1 is a hydrogen or primary alkyl and R^2 is a primary, secondary, tertiary, or cycloalkyl, alkenyl or phenyl.[45] After the successful application of flash vacuum pyrolysis, temperature change was used as a tool to control thermal transformation. For example, α-ethoxycarbonyl-β-oxo ylides **62**, with R^2 as aryl, substituted aryl or heteroaryl, were exposed to FVP at 500˚C, triphenylphosphine oxide was eliminated and acetylenic esters **63** were produced. When temperature was raised to 750˚C, terminal alkynes **64** were obtained in moderate yields (16-66%) due to a rearrangement caused by the loss of the ethoxycarbonyl group.[45]

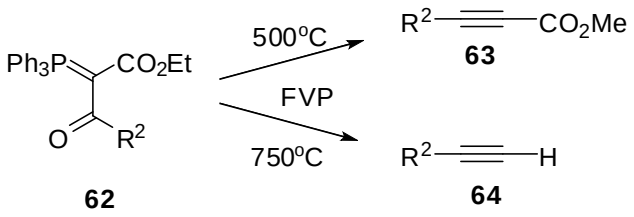


Figure 1.41: Temperature as a mean to control thermal transformation

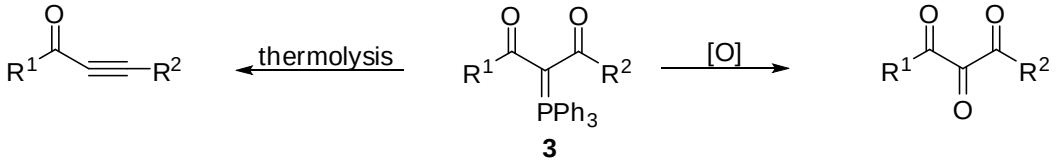
From these new developments, a number of functionalised compounds were prepared, which included benzofurans *via* 2-methoxyphenylalkynes and benzothiophenes *via* 2-methylthiophenylalkynes, diacylalkynes, terminal 1,3-diynes, and unsymmetrical 1,3-diynes, 1,3-enynes, pyrroloisoindolediones, styrylalkynes, substituted napthalenes, and protected acetylenic amino acids.[45]

Flash vacuum pyrolysis has since been extended to the pyrolysis of tetraoxo ylides and hexaoxo bis-ylides, stabilized phosphoranes containing heteroatoms (S, Se) attached to the ylide and stabilized halophosphoranes.[45]

Alkynes can undergo further reactions such as electrophilic and nucleophilic addition and reduction. They become precursors to new compounds due to the carbon-carbon triple bond.

2. Programme of research

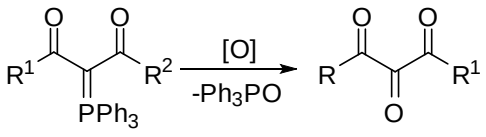
β-oxo ylides are important precursors in a number of synthetic reactions, such as Wittig reaction, oxidation, hydrolysis and pyrolysis. The main focus of this project is the synthesis of vicinal polycarbonyls and the study of thermal stability of the ylides as potential precursors of alkynes. The β,β'-dioxo ylides **3** are susceptible to thermal decomposition[4543] and triphenylphosphine oxides are eliminated to afford alkynes.



3

Figure 2.1: The different reactions that β,β'-dioxo ylides can undergo

β,β'-dioxo ylides have been important in the synthesis of vicinal polycarbonyls by oxidation achieved with a number of oxidising agents and resulting in the elimination of triphenylphosphine oxides as an extra carbonyl group is formed. The oxidative cleavage of the C=P bond unmasks the electrophilic C=O groups.



3 **36**

Figure 2.2: Oxidation of β,β'-dioxo ylides

Sugar derivatives containing carbonyl and alkyne functionalities are valuable synthons for the preparation of biologically relevant molecules and therefore access to them is of importance. A methodology based on phosphorus ylide chemistry is attractive.

The focus of this research is:

- Model studies using simple heterocycles as sugar mimics for the acylation methodologies.
- Modification of sugars using protecting group strategies for the synthesis of β,β'-dioxo ylides.
- The preparation and characterisation by ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy and mass spectrometry of novel β,β'-dioxo sugar-derived phosphonium ylides.
- Reactivity of the sugar derived phosphonium ylides: it is the oxidation and thermolysis reactions which were the main focus of the thesis.

3. Results and Discussion

3.1 Synthesis of Phosphorus Ylides

The synthesis of sugar derived ylides involved, initially, the preparation of the precursors phosphonium salts and ylides. These compounds were prepared by various modification of the method reported by Michaelis and Gimborn.[4]

The method involved reaction of triphenylphosphine with a halo-ketone or halo-ester in dry toluene. The mixture was heated under reflux for two hours and left to stir at room temperature overnight (Figure 3.1). The precipitate which formed was filtered, washed with dry ether and dried to give phosphonium salts, **66a-d**, in good yields and high purity (Table 2.1).

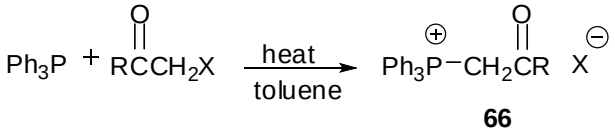


Figure 3.1: Synthesis of phosphonium salts **66**

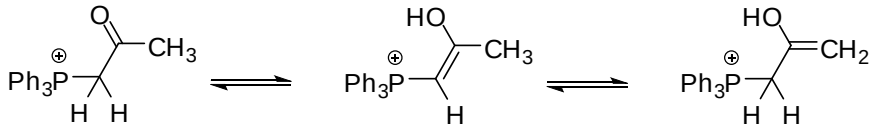
Table 2.1: Phosphonium salts $Ph_3P^+CH_2COR\ X^-$ synthesised

Compound	R	Yield (%)	^{31}P (ppm)	mp (°C)	Lit. mp.(°C)
66a	OEt	90	+21.5	156-157	155-158[47]
66b	Ph	95	+22.5	266-267	265-266[48]
66c	*t*-Bu	89	+22.8	216-217	216-217[49]
66d	CH_3	57	+14.0, +20.4	235-236	233-234[50]

The phosphonium salts were characterised by ^{31}P, ^{1}H, ^{13}C NMR and IR. ^{31}P NMR spectroscopy was initially used to analyse the purity of the products. Analysis of these compounds by ^{31}P NMR is possible due to two properties of phosphorus: the element only has one naturally occurring isotope (i.e. 100% abundance) and its spin quantum

number is ½ hence ensuring that phosphorus has only two spin states and therefore it is NMR active.[1] Its frequency relative to ^{1}H at 100 MHz is 40.480742 MHz.[1] The Chemical shifts of known phosphorus compounds are spread over a wide range (-300 to 500 ppm); there no definitive compilation of the range. All the phosphorus species present in a mixture may be readily identified.

The likely impurities were therefore easily identified; the signals of the starting material (triphenylphosphine) and triphenylphosphine oxide occurred at -5 and +30 ppm respectively. The signals of the phosphonium salts appeared in the range of +20.4 to +22.8 ppm. Interestingly the spectrum of (acetylmethyl)tripenylphosphonium chloride showed two signals at +20.4 ppm and +14.0, in the ratio of 2:1, indicating the presence of two forms of the phosphonium salt. Those signals suggested the presence of the enol and keto forms of the compound. The tautomers are therefore structures (I) and (II), and structure (III), which is unlikely, was not observed.[51] This observation was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The IR spectrum also confirmed the presence of both a carbonyl and a hydroxyl stretch.



(I) **(II)** **(III)**

+20.4 ppm +14.0 ppm

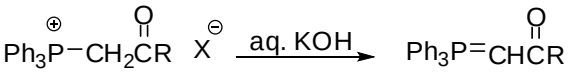
Figure 3.2: Tautomerism in (acetylmethyl)tripenylphosphonium chloride **66d**

The ^{1}H NMR spectra of compounds **66a-d** showed the expected signals of the phenyl rings in the range of 7.23 to 7.84 ppm. The ^{1}H-^{31}P coupling was seen most clearly from the methylene protons; these appeared as doublets. ^{1}H-^{31}P couplings were also observed for the R group protons of the phosphonium salts **66a** and **66d**. The couplings become smaller for protons further away from the phosphorus atom. The α-carbon protons of

(acetylmethyl)tripenylphosphonium chloride **66d** appeared as doublets at 4.45 ppm and 6.04 ppm, representing the keto and enol forms, respectively.

The ^{13}C NMR spectra also showed the expected signals for the phenyl groups in the range of 118.0 to 135.3 ppm. ^{13}C-^{31}P couplings were greatest for the α-carbon and the C-1 phenyl carbons, with values for C-2 and C-3 being similar, as illustrated in Figure 3.4. The ^{13}C NMR spectrum of **66d** provided additional information to the ^{1}H NMR spectrum, with the peaks at 40.4 ppm and 70.1 ppm corresponding to the keto form (I) and enol form (II) respectively. These signals represented $P^{+}–CH_2$ and P–CH=C respectively hence confirming the structures of the tautomers of phosphonium salt **66d**. The IR spectra showed the expected bands which confirmed the presence of the hydroxyl and carbonyl functional groups.

The synthesis of the phosphorus ylides is efficient and involves the reaction of phosphonium salts with base. The method[22] chosen is easy and produced good yields of the desired ylides are produced. The phosphonium salts **66a-d** were used to synthesise the stabilised phosphonium ylides **67a-d**. This involved the deprotonation of the phosphonium salts using dilute aqueous sodium hydroxide (Figure 3.3). The ylides were isolated in good yields (Table 2.2). This is a straight forward reaction, however it was important to not expose the phosphonium salts to the base for too long. The base is capable of hydrolysing the ylides to give triphenylphosphine oxide and the corresponding alkyl compound.



66 **67**

Figure 3.3: Synthesis of ylides **67a-d**

Table 2.2: Ylides Ph_3P=CHCOR synthesised

Compound	**R**	**Yield (%)**	**^{31}P (ppm)**	**mp (°C)**	**Lit. mp.(°C)**
67a	OEt	72	+18.2	162-164	162-163[52]
67b	Ph	74	+17.4	174-176	178-180[52]
67c	*t*-Bu	75	+16.8	172-173	172-173[53]
67d	Me	79	+14.9	177-178	176-178[47]

The phosphonium ylides were characterised by ^{31}P, ^{1}H, ^{13}C NMR and IR spectroscopy. Similar to the phosphonium salts, ^{31}P NMR spectroscopy was initially used to determine the purity of the products. The chemical shifts were obtained in the range of +14.9 to +18.2 ppm. These signals are present at lower chemical shift values compared to those of the phosphonium salts. This is attributed to the decrease in positive charge on the phosphorus atom in the ylide.[11]

The ^{1}H NMR spectra showed the expected signals of the phenyl protons in the range of 7.18 to 7.64 ppm. The ^{1}H-^{31}P coupling was mostly seen, as doublets, for the methine protons of phosphonium ylides **67b** and **67d**. It was noticed that methine protons signals appeared at higher chemical shift than the methylene signals. This may be due to the higher electron densities on the methylene carbon.[11] In addition to this, the chemical shifts of both methylenes and methines are due to the electron releasing character of the substituents adjacent to the carbonyl group.

The ^{13}C NMR signals for each of the phenyl carbons in the phosphonium salts and ylides have appeared at a specific chemical shift range (Figure 3.4). It was observed that all signals appeared as doublets, with the exception of C-4. Occasionally C-4 signals do appear as doublets but with a coupling value of less than 3 Hz; hence these signals can be easily assigned as singlets. With the increase of positive charge on the phosphorus,

C-4 is shielded while C-1 is deshielded. C-2 and C-3 have small variations. The shifts at C-1 and C-4 are due to reduction and enhancement, respectively, of the electron density at those carbons.[54] This is illustrated in Figure 45.

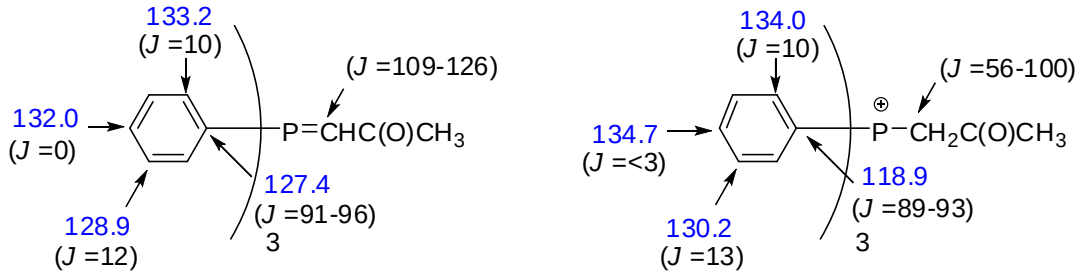


Figure 3.4: The effect of the positive charge on the phosphorus

3.2 Modification of Sugars

Carbohydrates play a vital role in the control of many key biological processes by acting as reciprocating compounds with proteins in molecular recognition events.[55] This is one of the reasons for incorporating sugars into potentially biologically active molecules. The Organic Chemist exploits sugars because they are multifunctional and can be exploited as precursors for a wide range of target compounds. It has also been recognised that the functionality and stereochemistry of carbohydrates can be manipulated to produce starting materials for the synthesis of complex organic compounds, non-sugar compounds, and many polymeric, oligomeric and monomeric products which are important in the different industries. The chemistry of carbohydrates has allowed significant research in medicinal development; examples include the synthesis of antibiotic methymycin **68** and galactan **69** (Figure 3.5).

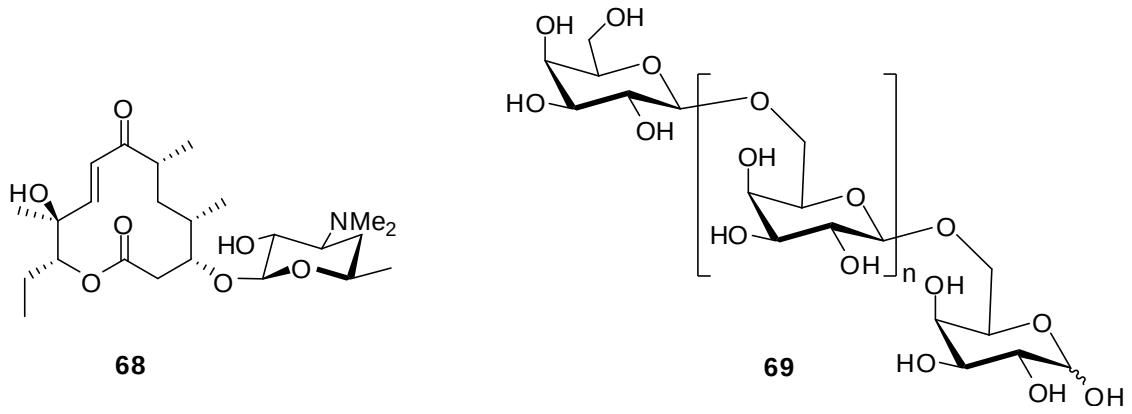


Figure 3.5: Examples of sugar-derived compounds: Methymycin **68** and β-D-(1, 6)-Galactan **69**

Sugars are highly polar and polyhydroxylated and complex strategies are required to achieve any synthetic transformations. In most cases, when a selective chemical manipulation needs to be performed, protecting groups must be introduced to block most of the hydroxyls and these must be easily removed after reaction. The choice of protecting groups is one of the decisive factors in the successful synthesis of a complex target compound from a sugar.[48]

The reactivity pattern of the hydroxyl groups is known. If the anomeric hydroxyl group is disregarded, the primary hydroxyl group is more reactive than secondary groups. Therefore, selective protection can be effected. This is particularly so if space-demanding reagents are involved. Regarding the secondary hydroxyl groups, the equatorial secondary hydroxyl groups of pyranoid compounds tend to react more readily than secondary axial and the C-2 of glucopyranosides is the most reactive and C-4 least reactive of secondary hydroxyl groups. While this is the general trend, the reactivity of the hydroxyl groups is also dependent on reaction conditions.[56]

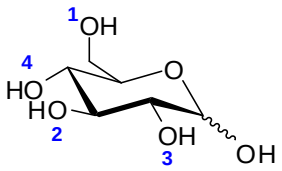


Figure 3.6: Reactivity of hydroxyl groups

A wide range of protecting groups has been developed for hydroxyl functionalities. These include ethers, esters, carbonates and acetals.[57] The choice of the protecting group must fulfil a number of requirements, which include stability under reaction conditions.

In this study four monosaccharides starting materials, D-glucose **70**, sodium D-glucuronate **71**, D-mannitol **72** and methyl-α-D-glucopyranoside **73**, were selected due to their ready availability. The modification of each of the sugars is discussed separately.

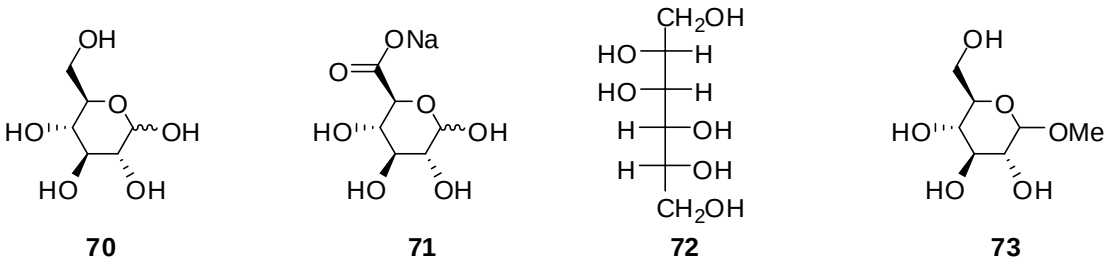


Figure 3.7: Structure of D-glucose **70**, sodium D-glucuronate **71**, D-mannitol **72**, methyl-α-D-glucopyranoside **73**

3.2.1 D-Glucose

Glucose is abundantly found in nature and plays a central role in biochemistry. It is commonly used in organic synthesis because it is extremely economical and it is regarded as the parent compound of the sugar family.

It is important to note that in solution, glucose undergoes intramolecular reaction to yield cyclic hemiacetals. There are two 5-membered rings (furanose forms) and two 6-membered rings (pyranose forms) which are favoured. D-Glucose preferentially forms the 6-membered rings. The ratio of the two anomers depends on the reaction conditions. In water, the sugars are represented in the cyclic form (Figure 3.8).

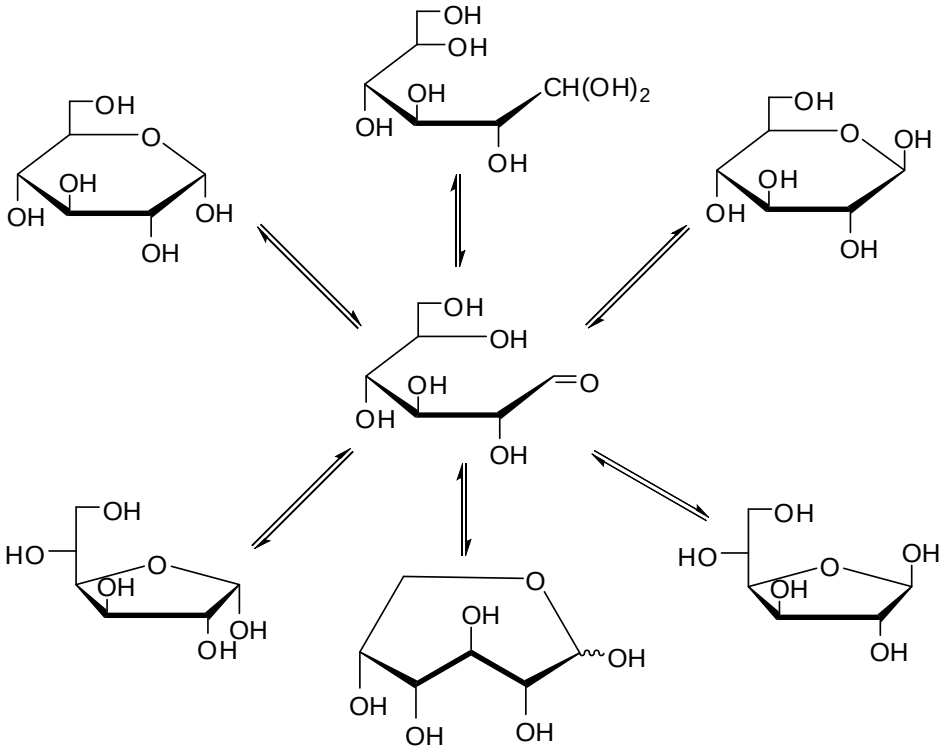


Figure 3.8: Cyclisation of D-glucose

The sugar starting materials required for reaction with the phosphorus ylides **67a-d** (Section 3.1) need to possess a carboxylic acid functionality. Therefore the strategies employed have focused on the creation of this group. D-Glucose required initial protection of the primary hydroxyl group and this was followed by protection of the secondary hydroxyl groups. The next stage required unblocking the primary hydroxyl to effect conversion to the carboxylic acid (Figure 3.9).

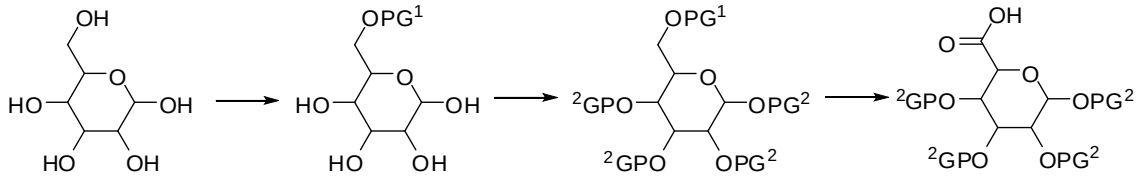
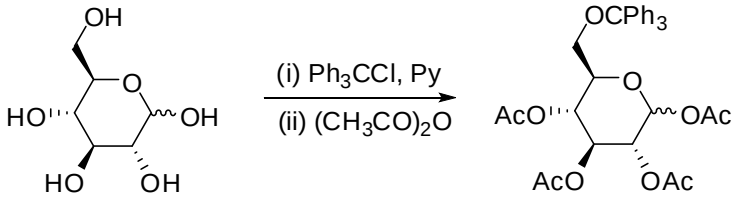


Figure 3.9: Synthetic Scheme

3.2.1.1 Synthesis of 1, 2, 3, 4-tetra-*O*-acetyl-β-D-glucose

In order to protect the primary hydroxyl group at C-6 selectively, the triphenylmethyl (trityl) group was selected. This is a bulky space demanding group which is very selective to primary hydroxyl groups. It is easily incorporated and removed under mild conditions.



70 **74**

Figure 3.10: Tritylation and acetylation of D-glucose

D-glucose and trityl chloride were dissolved in anhydrous pyridine by warming. The mixture was stirred until all the starting materials had fully dissolved. The trityl protected derivative was not isolated but reacted subsequently with acetic anhydride. After 12 hr of stirring at room temperature, the reaction was quenched by pouring it as a thin stream into a mixture of ice, water and acetic acid. The crude product was isolated from this mixture as an off-white precipitate.

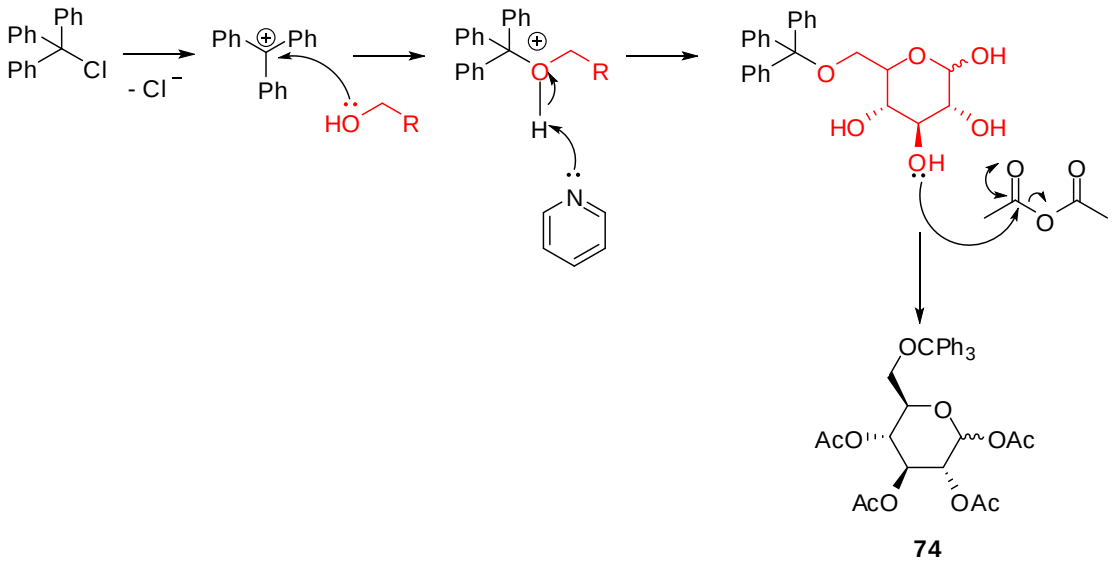


Figure 3.11: Proposed mechanisms of tritylation and esterification

The α- and β-anomers of the protected glucose were both present in the crude product. The anomers were separated by preferential solubilisation. The mixture of anomers was introduced into diethyl ether which resulted in some of the precipitate dissolving. The undissolved solid was recovered by filtration and recrystallised from 95% ethanol before removing the trityl protecting group.

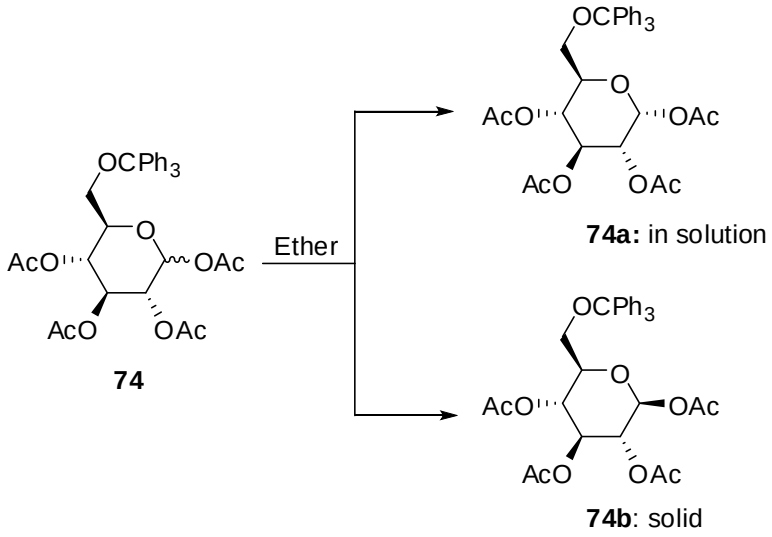
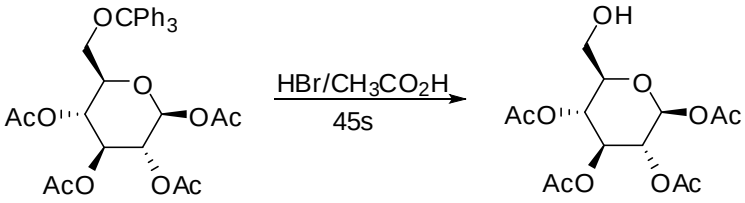


Figure 3.12: Separation of α- and β-anomers

Characterisation of the fully protected sugar by NMR and IR spectroscopy confirmed the structure of the compound. The ^{1}H NMR and IR spectra clearly showed that the OH

had reacted since the OH signals were absent in the spectra. The position of the anomeric proton helped in differentiating between the α- and β-isomer which were observed at 5.71 and 6.45 and ppm, respectively. The methylene protons at position C-6 appeared at 3.03 and 3.32 ppm, the CH_3 groups were observed as singlets at 1.72, 1.99, 2.03 and 2.15 ppm and the aromatic signals corresponding to fifteen hydrogens appeared in the region 7.20-7.60 ppm. ^{13}C NMR spectroscopy confirmed the formation of the esters, with carbonyl signals at 19.3, 19.8, 20.5 and 20.8 ppm. In addition, the signals for the phenyl rings were in the expected region as four peaks.



74b **75**, 25%

Figure 3.13: Synthesis of tetraacetate **75**

Removal of the trityl group can be accomplished by several reagents and choice of reagents depends on the presence of the other protecting groups on the secondary hydroxyl functionalities. In this case deprotection at C-6 was achieved by using 50% hydrogen bromide in glacial acetic acid to produce trityl bromide as a precipitate. The filtrate was then poured into ice water and glucose tetraacetate **75** was extracted with dichloromethane, washed with water, dried and concentrated. Crystals (25%) were formed on addition of anhydrous of diethyl ether.

β-Glucose tetraacetate **75** was characterised by ^1H NMR spectroscopy. The success of the deprotection was confirmed by the absence of the signals corresponding to the phenyl groups. However, impurities were still present and these were difficult to remove.

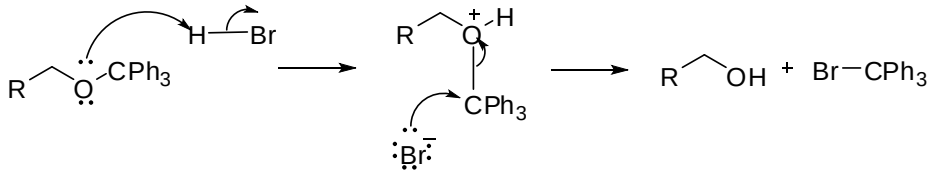
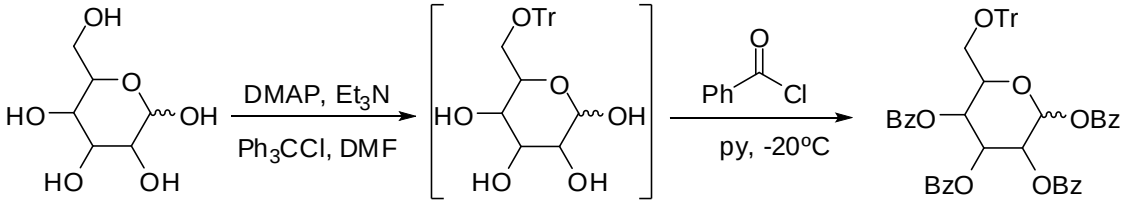


Figure 3.14: Proposed mechanism of deprotection

3.2.1.2 Synthesis of 1,2,3,4-tetra-*O*-benzoyl-6-*O*-triphenylmethyl-α and β-D-glucopyranoses



70 **76** **77**

Figure 3.15: Protection of hydroxyl groups with benzoyl chloride

The one-pot approach of complete protection of the hydroxyl groups was again used. However, modification of the previous method was required in order to improve the yield. The primary hydroxyl group at C-6 was protected with trityl chloride in the presence of DMAP and triethylamine in DMF. The mixture was stirred for 18 hr at room temperature. Subsequently, pyridine was added and the mixture was cooled to -20ºC. Benzoyl chloride was added in portions and the mixture was stirred for 2 hr. The mixture was then poured into ice-water and extracted with dichloromethane. The organic phase was washed sequentially with sulphuric acid and saturated sodium hydrogen carbonate, dried and evaporated. The crude product was purified by column chromatography to give an isomeric mixture. Preparative TLC was then used to separate the isomers to give α-isomer (25%, mp 95°C) and β-isomer (38%, mp 83°C). This modified method was as time-consuming as the original method with yields slightly greater.

The products were characterised by ^{1}H NMR and ^{13}C NMR spectroscopy. The aromatic regions of the spectra were complex due to the presence of the seven phenyl rings from the trityl group and the four benzoyl groups.

3.2.1.3 Synthesis of 3-*O*-benzyl-1, 2-isopropylidene-α-D-glucofuranuronic acid

The synthetic strategy involved initial formation of diacetal followed by protection of the C-3 OH group. Selective deprotection and oxidation give access to acid **82.**

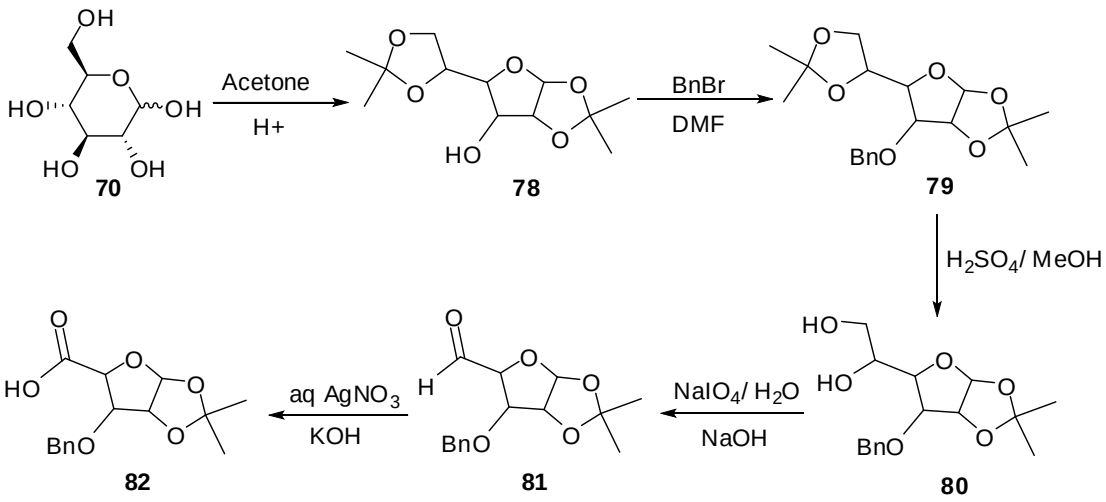


Figure 3.16: Synthesis of 3-*O*-benzyl-1, 2-isopropylidene-α-D-glucopyranoic acid **82**

Reaction of glucose with adjacent *cis* hydroxyl groups results in cyclic ketal and acetal formation. Therefore the reaction of glucose with acetone/ sulphuric acid results in the structure of furanose **78** being formed. This is an ideal method of capturing the furanose form of glucose. Reaction with D-galactose yields diacetal **83** while reaction with D-xylose yields diacetal **84**. Similar treatment with other sugars can be complex.[56]

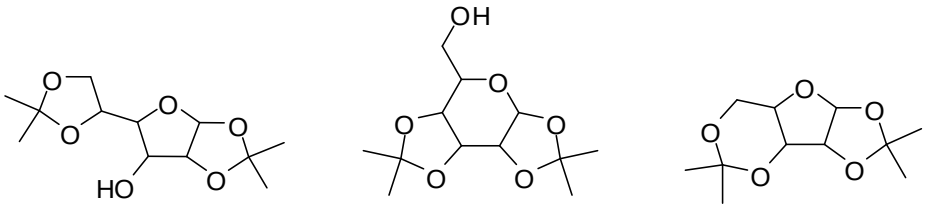


Figure 3.17: Acetal protection

Diacetone-D-glucose **78** provides a great advantage. It contains four hydroxyl groups already protected leading to fewer protecting procedures. This reaction produces mono- and diacetone-D-glucose. Fortunately the monoacetone can be converted to the diacetone in the presence of acetone and 2,2-dimethoxypropane, hence no loss of product occurs. However this adds an extra step to the synthetic scheme.

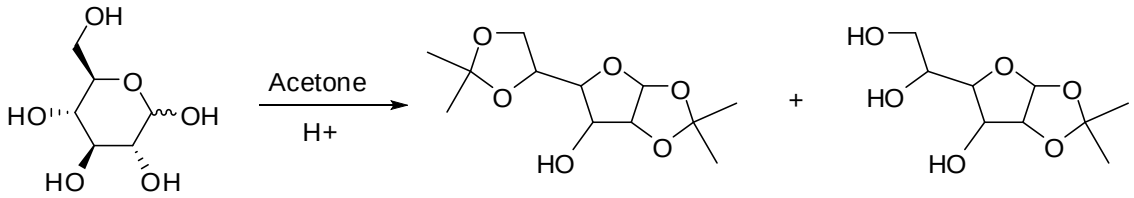


Figure 3.18: Formation of diacetone from D-glucose and monoacetone-D-glucose

D-glucose was stirred vigorously in acetone and the temperature of the solution was cooled with an ice bath. Sulfuric acid was added in small portions to maintain low temperature (5-10^{o}C). After 5 hr at room temperature, the solution was cooled again and aqueous sodium hydroxide was added to neutralise the mixture. Sodium hydrogen carbonate was then added to maintain the pH of the solution overnight, at room temperature. The mixture was filtered, the filtrate concentrated, and the residue dissolved in chloroform and washed with water. The organic phase was dried and evaporated to give the diacetone-D-glucose as a white solid (42%). The aqueous phase was evaporated to give the monoacetone-D-glucose as a brown solid (55%). The melting points matched the literature data.[58]

The structure of diacetone-D-glucose was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum showed four new signals corresponding to 12 protons corresponding to the methyl groups at 1.29, 1.34, 1.41 and 1.47 ppm. Characteristic signals at 25.2 and 26.2 ppm in the ^{13}C NMR spectrum, corresponded to the carbons of the methyl groups; signals at 109.6 and 111.8 ppm corresponded to the quaternary carbons from the acetal protecting groups.

The structure of the monoacetal was also confirmed by ^{1}H NMR spectroscopy. In comparison to the spectrum of the diacetal, only two singlets were observed instead of four, at 1.33 and 1.48 ppm. These were attributed to the methyl groups.

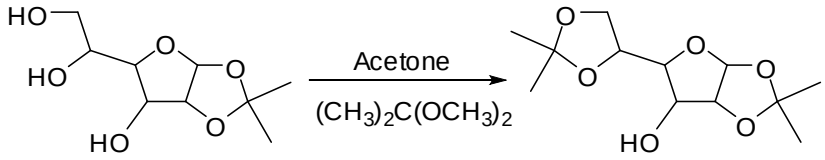
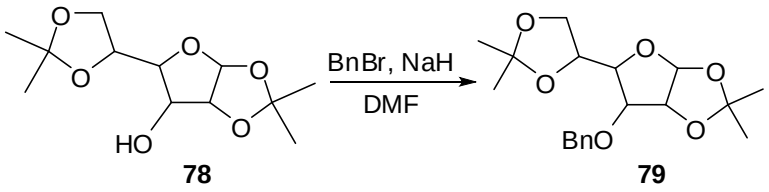


Figure 3.19: Conversion of monoacetal to diacetial

Monoacetone-D-glucose was reacted with acetone, 2,2-dimethoxypropane in the presence of the catalyst toluene-*p*-sulphonic acid for 10 min. The mixture was neutralised and the solvents were evaporated. The residue was dissolved in dichloromethane and washed with water, dried and evaporated. The crude product was crystallised from ethanol to give a white solid (52%) with a melting point of 110ºC which corresponded to the literature.[58]

The structure was confirmed by comparing the ^{1}H NMR spectra of the diacetal obtained by the two methods.

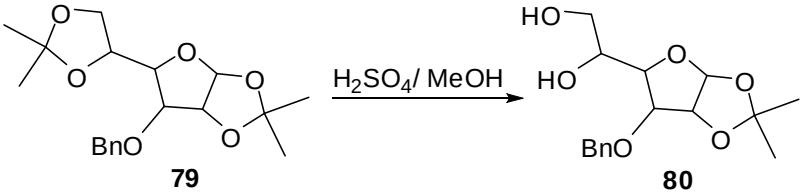


78 **79**

Figure 3.20: Protection of the hydroxyl group at C-3

The next step was the protection of the hydroxyl group at C-3. This involved the reaction of diacetone-D-glucose **78** with benzyl bromide in the presence of sodium hydride in DMF to give **79** as a pale-yellow oil in good yield (68%).

The ^{1}H NMR spectrum showed the presence of new peaks at 4.69 ppm, integrating to two protons, and at 7.36 which integrated to five protons as expected for the aromatic ring. The ^{13}C NMR spectrum also confirmed the structure with signals at 72.5 ppm corresponding to methyl group and the signals at 127.8, 127.9, 128.5 and 137.7 ppm were attributed to the phenyl group.



79 **80**

Figure 3.21: Deprotection at C-5 and C-6

The next step was deprotection at C-5 and C-6. This acetal is linked to a primary carbon and a secondary carbon, which makes it easier to deprotect. The fully protected sugar **79**, dissolved in methanol, was reacted with sulphuric acid (0.8%). The reaction needed frequent monitoring by TLC for completion of the deprotection. Once complete the mixture was neutralised with sodium hydrogen carbonate to give **80** as a yellow oil in satisfactory yield (61%).

^{1}H NMR spectrum showed the absence of 2 singlets at 1.40 and 1.45 ppm associated with the methyl groups from the acetone protecting group on C-5 and C-6. The spectrum also showed new signals at 2.02 and 2.49 ppm representing the diols. The ^{13}C NMR spectrum confirmed the structure; the three carbon peaks at 25.5 and 26.9 ppm corresponding to the methyl groups and at 109.1 ppm corresponding to quaternary carbon were absent.

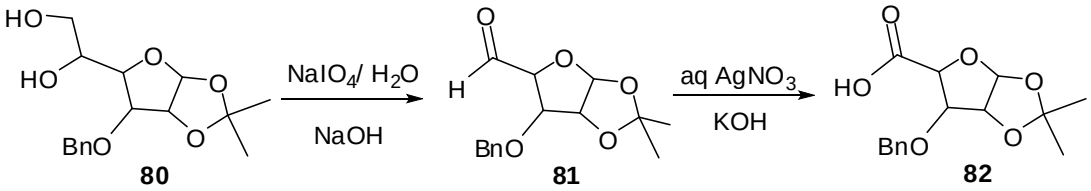


Figure 3.22: Synthesis of carboxylic acid **82**

Once the deprotection was complete, the next two steps were oxidation, from the diols **80** to the aldehyde **81** and finally to the carboxylic acid **82**.

Reaction of sugars containing 1,2-diol groups (*cis*-α-diols) with periodate (as free acid or Na/K salt) leads to preferential C-C cleavage (Figure 64).[59] This is synthetically very useful.

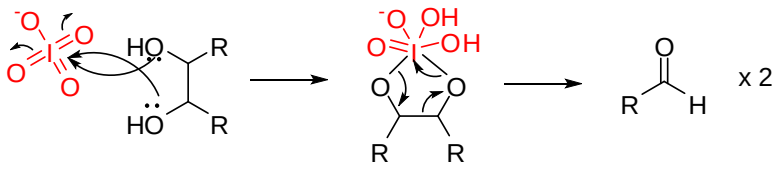


Figure 3.23: Proposed mechanism of cleavage

A mixture of the sugar diols **80** and sodium metaperiodate in water was reacted with sodium hydroxide. Sodium hydroxide allowed the oxidation to take place by adjusting the pH to 7. The resultant sugar aldehyde **81** was obtained as orange oil in very good yield (88%). When the product was analysed by ^{1}H NMR and ^{13}C NMR spectroscopy, the characteristic signal for the aldehyde proton was observed at 9.70 ppm and that of

the carbon at 200.1 ppm. There was also an apparent loss of the two hydroxyl peaks as well as those of the CH_2 and CH groups.

The final oxidation step involved addition of silver nitrate to the aldehyde. This was followed by the addition of aqueous potassium hydroxide which produced a precipitate. The reaction was completed by acidifying the filtrate to pH 2 with hydrochloric acid. After extraction, the carboxylic acid **82** was obtained as a solid in low yield (33%). The structure was confirmed by the disappearance of the distinctive signal of the aldehyde proton from the ^{1}H NMR. As expected the aldehydic carbonyl group at 200.1 ppm disappeared and the corresponding carboxylic carbonyl group appeared at a lower chemical shift (171.1 ppm) in the ^{13}C NMR spectrum. IR spectroscopy confirmed this functional group conversion.

3.2.2. Glucuronic acid

Glucuronic acid and its sodium sodium salt, sodium glucuronate, are commercially available and offer a shorter route to a protected sugar derivative containing an acid functionality. Conversion of the acid to the salt is straight forward. The salt was treated with acetic anhydride to give the tetraacetate at C-1, C-2, C-3 and C-4. This step was repeated several times to improve the yields.

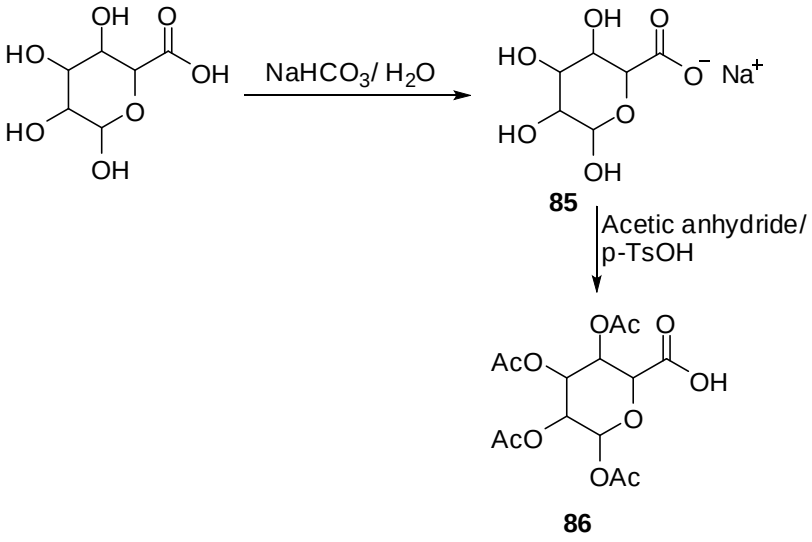


Figure 3.24: Synthesis of tetraacetate **86**

The method involved the addition of sodium-D-glucuronic acid to acetic anhydride in the presence of *p*-toluenesulfonic acid at 0°C with 3 hr of stirring. The product was extracted subsequently with ether and dichloromethane. The combined organic phases were washed with water to remove excess acetic anhydride, and dried and evaporated. This method was repeated three times, producing very low yields (8-11%).

The structure was confirmed by the appearance of the characteristic signals of the methyl group protons and carbons in the ^{1}H NMR and ^{13}C NMR spectra, respectively. Signals arising from the carbonyl groups of the acetate protecting groups were also observed (169.4, 169.9 and 170.2 ppm), as well as the carbonyl group from the carboxylic acid (172.7 ppm) in the ^{13}C NMR spectrum.

3.2.3 D-Mannitol

D-Mannitol contains two primary hydroxyl groups and four secondary hydroxyl groups (Figure 3.25) and it can be obtained by the reduction of D-mannose.

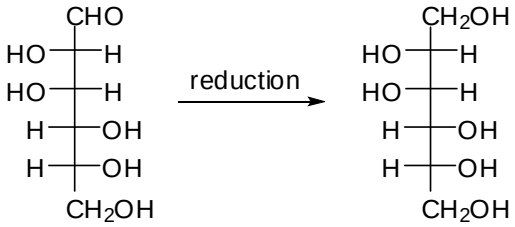


Figure 3.25: D-mannose and D-mannitol

Mannitol has use in a number of medicinal applications such as treatment for intracranial pressure, for cystic fibrosis and bronchiectasis and much more.[60] Mannitol is also used in food (sweetners for diabetics) and in illicit drugs.

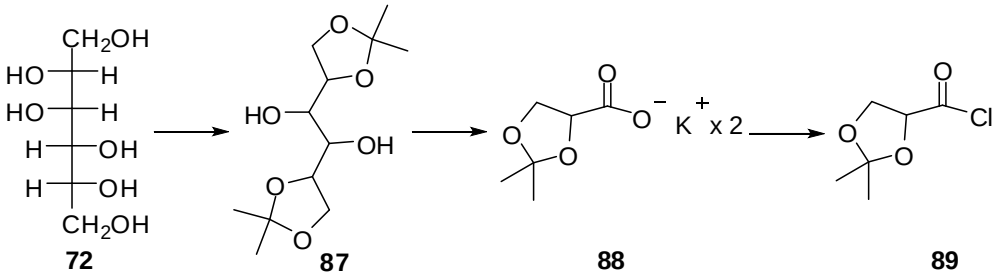


Figure 3.26: Synthesis of 2, 3-isopropylideneglyceryl chloride **89**

The preparation of carboxylic acid salt **88** involved three steps. Mannitol was first protected at C-1, C-2, C-5 and C-6 by reaction with 2, 2-dimethoxypropane and catalysed with stannous chloride to produce diacetone-D-mannitol **87**.

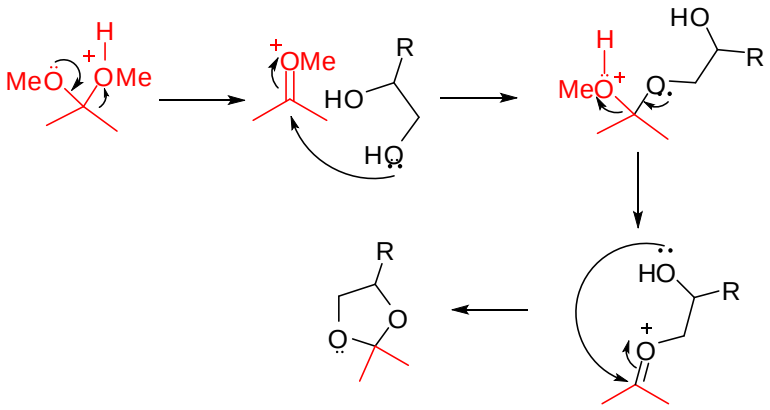


Figure 3.27: Proposed mechanism of *syn*-1,2-diols protection

Acetonides, such as 2,2-dimethoxypropane, selectively react with 1, 2-diols in sugars. While protecting mannitol, there is the possibility of producing mono- **90** or/and tris-acetonide **91** as by-products.

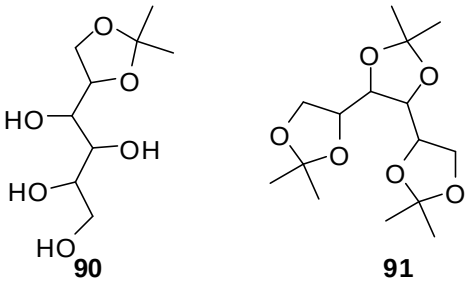


Figure 3.28: mono- **90** and tris-acetonides **91**

Diacetone-D-mannitol **87** was produced as white crystals (63%). The melting point matched that of the literature. The structure was characterised by ^{1}H NMR, ^{13}C NMR and IR. ^{1}H NMR and ^{13}C NMR spectra confirmed the structure with the presence of new signals at 1.23 and 1.28 ppm and 24.3 and 25.8 ppm.

An advantage is that D-mannitol can be easily cleaved between C-3 and C-4 to give (*R*)-2,3-dihydroxypropanoic acid **88** which is widely used as a precursor in synthesis.
In the next step, sodium periodate and potassium permanganate, were used to cleave **87** between C-3 and C-4 to produce potassium 2,3-isopropylideneglycerate **88** in high yield (71%).

Analysis of compound **88** by ^{1}H NMR spectroscopy showed the characteristic singlets at 1.28 and 1.33 ppm corresponding to the methyl groups. The methylene protons appeared as doublet of doublets at 3.80 ppm and the signal at 4.17 ppm also appeared as doublet of doublets corresponding to the CH group. ^{13}C NMR spectrum displayed six signals as expected; the characteristic signal at 176.7 ppm corresponds to the carboxylate group.

The potassium salt **88** was suspended in dry ether and oxalyl chloride was added dropwise. After stirring for 20 hr at room temperature, the solvent was removed by suction to give an off-white solid. Care must be taken in storing the compound under condition that excludes moisture to avoid hydrolysis to the acid.

The structure was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. Both spectra displayed a small difference chemical shift compared to the spectra of compound **88**. The most significant signal is that of the carbonyl group in the ^{13}C NMR spectra which shifted from 176.7 ppm to 173.6 ppm.

A shorter (90 min) alternative method for the synthesis of acyl chloride **89** utilised the Vilsmeir-Haack reagent which was prepared from DMF.

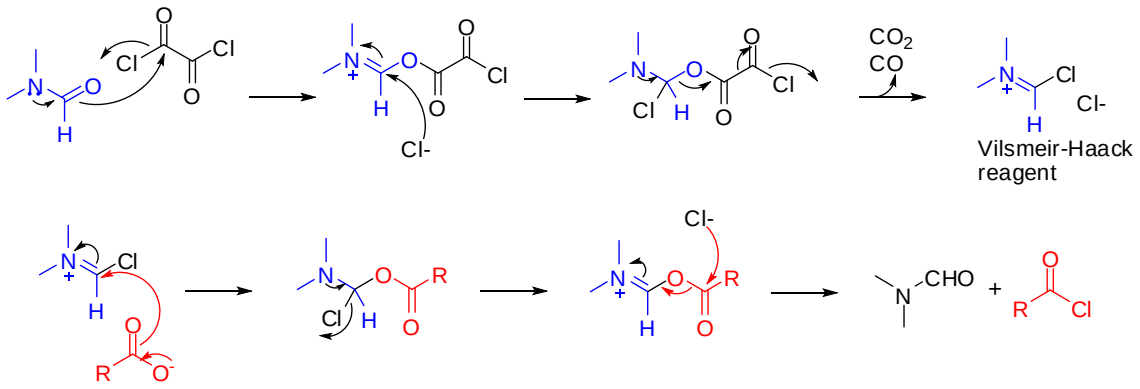


Figure 3.29: Proposed mechanism for acid chloride formation with DMF: Vilsmeir mechanism[59]

Reagents such as oxalyl chloride, thionyl chloride and phosphorus pentachloride can be used for this functional group conversion. Oxalyl chloride was selected as it tends to be a more selective reagent, it can be used under milder reaction conditions and the by-products are gaseous.

3.2.4 Methyl-α-D-glucopyranoside

3.2.4.1 Synthesis of methyl 2, 3, 4-tri-*O*-acetyl-α-D-glucopyranoic acid and methyl 2, 3, 4-tri-*O*-acetyl-α-D-glucopyranoic acid

One of the issues encountered when protecting D-glucose with acetic anhydride, was the formation of both α- and β-anomers; which was unavoidable. This required separation of the anomers and it was time consuming. An alternative approach is to choose a starting sugar in which the stereochemistry at the anomeric centre is already fixed. This was the reason for choosing methyl-α-D-glucopyranoside. The methoxy group at the anomeric carbon prevent ring opening and thus prevents the formation of isomers.

Several methods are available for the synthesis of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoic acid **95** and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoic acid **98**. The method by Bernotas et al,[61] Horning,[62] and Rej et al[63] was used and **95** and **98** were readily prepared from methyl-α-D-glucopyranoside. The advantage of this method was the higher yields and shorter reaction times. The preparation of methyl 2,3,4-tri-*O*-acetyl derivative **95** and the benzyl-α-D-derivative **98** was divided into three steps; protection of the primary alcohol by tritylation followed by acetylation/ benzylation and finally, detritylation (Figures 3.30 and 3.34).

Tritylation of methyl-α-D-glucopyranoside was achieved using pyridine to give **92** as an oil. The structure was confirmed by ^{1}H NMR spectroscopy; the characteristic signal for the phenyl groups at 7.21-7.37 ppm, integrated to 15 hydrogens.

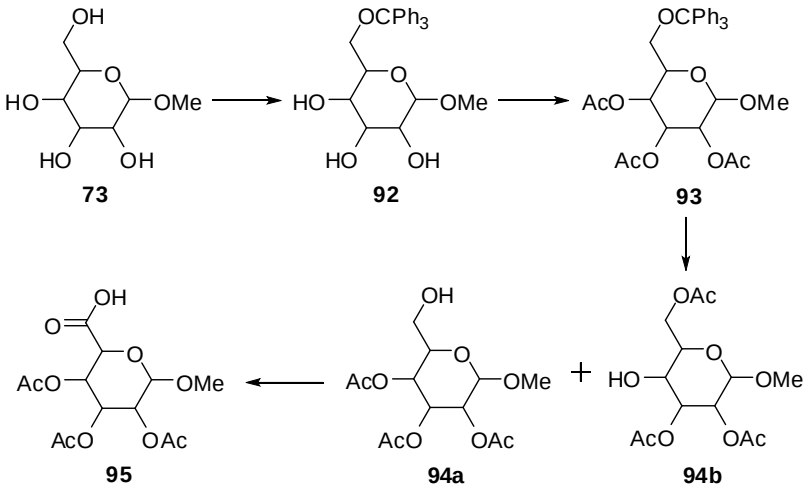
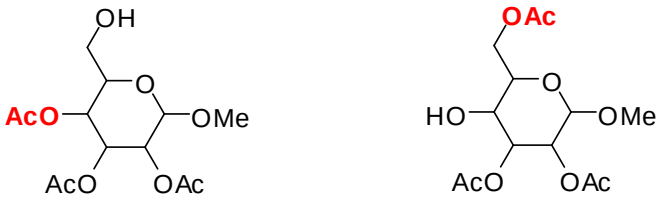


Figure 3.30: Synthesis of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoic acid **95**

The tritylated sugar **92** was used directly in the next step, acetylation. Acetic anhydride was added to a solution to the tritylated sugar in pyridine and stirred for 12 h. The mixture was poured into another mixture of ice water and glacial acetic acid. Simultaneous vigorous stirring resulted in the precipitation of the product. It was filtered and washed with cold water to remove the residual pyridine, and air-dried to give product **93** as a solid. The structure was confirmed using spectroscopy. The ^{1}H NMR spectrum displayed the expected signals for the three protons from the methyl groups at 1.76, 2.01 and 2.11 ppm and signals in the region 7.30- 7.50 ppm corresponded to the aromatic protons. The ^{13}C NMR spectrum displayed characteristic signals at 20.5, 20.7 and 20.8 ppm corresponding to the methyls, signals at 127.0, 127.8, 128.7 and 143.7 ppm were assigned to the aromatic rings and the carbonyl groups from the acetates appeared at 169.3, 170.2 and 170.3 ppm.

The next reaction, detritylation, involved adding a solution of hydrogen bromide in glacial acetic acid to another solution of the fully protected sugar **93** in glacial acetic acid and the mixture was stirred vigourously for 1 min. This procedure was to precipitate out trityl bromide. The filtrate was then poured into ice water and the

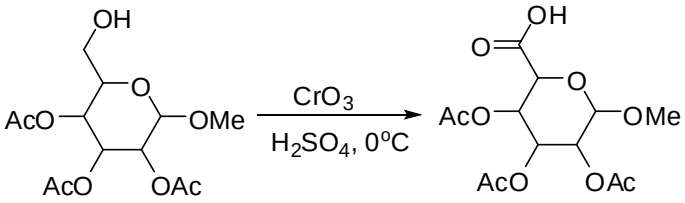
product extracted with chloroform. TLC analysis of the reaction mixture showed two components. The crude product was therefore purified by column chromatography using a mixture of ethyl acetate and hexane; the mobile phase suggested in the literature.[64] Three fractions were obtained from the column; these were identified by NMR spectroscopy as the desired product **94a** (in very low yield, 8%), a by-product **94b** (in low yield, 30%) and a 1:4 mixture of both (62%). Compound **94b** was formed by the migration of the acetyl group to C-6. This is a well known phenomenon. The use of strong acid conditions to cleave the trityl group encourages the formation of **94b** which is produced by hydrolysis of the acetate.



94a **94b**

Figure 3.31: Acetyl migration

Methyl 2,3,4-tri-*O*-acetyl -α-D-glucopyranoside **94a** was characterised by both ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum showed new signals at 2.06, 2.10, and 2.14 ppm corresponding to nine protons from the three acetyl groups. The ^{13}C NMR spectrum confirmed the structure with the presence of three carbonyl peaks at 169.3, 170.3 and 170.4 ppm.



94a **95**

Figure 3.32: Oxidation of alcohol **94a** to carboxylic acid **95**

The next synthetic step was oxidation of the alcohol **94a**. This was achieved by using Jones' reagents. To a solution of the sugar derivative **94a** in acetone, was added a solution of chromium trioxide in sulphuric acid at 0°C. This was stirred for 3 hr and then water was added to dilute the excess chromium. The product was extracted with dichloromethane and washed with 20% aqueous sodium chloride. The sugar acid **95** was obtained as a solid after recrystallisation in excellent yield (86%). The melting point matched the literature data.[65]

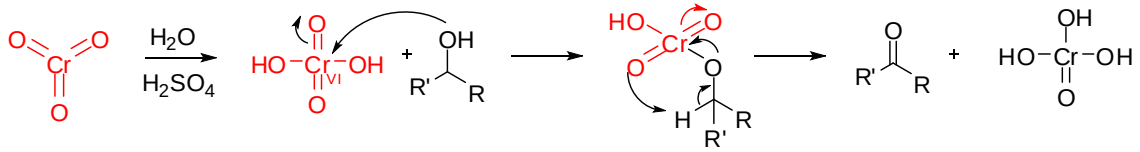


Figure 3.33: Proposed mechanism for the Jones oxidation

The proposed mechanism of the oxidation involves initial formation of chromic acid which undergoes nucleophilic attack by the primary alcohol (Figure 3.33). Subsequent deprotonation and elimation releases the aldehyde.

The structure was confirmed by the disappearance of the two protons from the ^{1}H NMR spectrum, and the absence of the carbon signal at 61.1 ppm and the gain of a new carbonyl signal at 170.2 ppm in the ^{13}C NMR spectrum.

The tritylated sugar **92** was directly converted to the tribenzyl analogue. It was important to remove all the pyridine before proceeding to the benzylation as DMF is

used to facilitate the S_N2 mechanism. Tritylated sugar **92** was dissolved in DMF and deprotonated with sodium hydride at 0 ºC. Benzyl bromide was added after 30 min and the mixture was stirred for 3 hr at RT. An additional amount of DMF was added to the reaction mixture and left to stir overnight. The excess sodium hydride was decomposed by addition of acetic acid. The structure was confirmed by the presence of six protons in the region 4.55-4.80 ppm corresponding to methyl groups in the ^{1}H NMR spectrum. The 30 protons arising from the aromatic rings were observed at 7.30-7.40 ppm. The ^{13}C NMR spectrum also displayed signals corresponding to the expected signals.

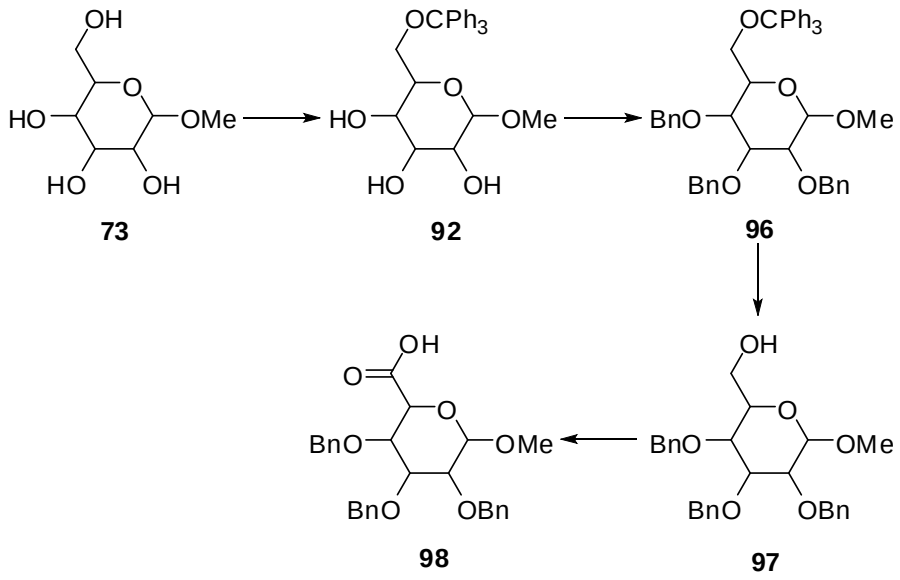


Figure 3.34: Synthesis of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoic acid **98**

The fully protect sugar **96** was deprotected at C-6 directly. The reaction was conducted at room temperature using a solution of concentrated sulphuric acid and methanol. The crude product was purified by column chromatography to give the desired product **97** as an oil in low yield (42%). When the product was analysed, the ^{1}H NMR spectrum showed new signals at 4.71, 4.72, 4.88 and 4.92 ppm representing the six protons from the methylene groups of the benzyl groups and the signals at 7.35-7.40 ppm integrated to 15 protons (3 x Ph) as expected. The ^{13}C NMR spectrum confirmed the structure with

the presence of new carbon signals at 73.4, 75.0 and 75.8 ppm (3 x CH_2), and four new peaks in the region of 127.9 to 138.1 ppm arising from the six aromatic carbons.

The alcohol **97** was also oxidised with Jones' reagents, prepared according to the method by Jones et al, afforded methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoic acid **98** as an oil in moderate yield (55%).

3.3 Synthesis of Novel Heterocyclic β,β'-dioxo Phosphorus Ylides

The presence of a proton on the ylidic carbon has allowed the synthesis of many complex ylides. For the β-oxo ylides, acylation can lead to dioxo and poly-oxo ylides which can act as precursors for multifunctional compounds (Figure 3.35). Acylation has been a successful approach, as described in Section 1.3 of the Introduction. For the synthesis of the desired complex sugar-derived ylides, acylation by acyl chloride, the most commonly used method, was initially explored. The standard approach involved the coupling of one equivalent of the β-oxo ylide and one equivalent of the acyl chloride in dry toluene and in the presence of one equivalent of triethylamine at room temperature.[65]

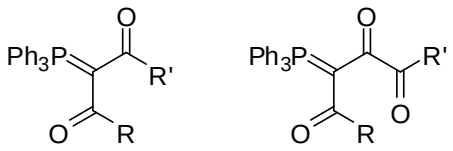
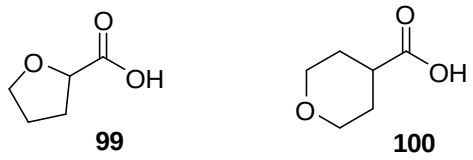


Figure 3.35: Poly-oxo ylides

Before the acylation was performed on the synthesised starting phosphorus ylides **67a-d** and sugar derivatives **82, 88, 95** and **98**, model reactions were carried out. The rationale for this was to gain experience in the Chemistry and to make any modification to the methods if required. The products from these reactions are interesting in their own right as precursors.

3.3.1 Model reactions

Two simple heterocyclic compounds were chosen which were structurally similar to the synthesised sugar derivatives, i.e. consisting of the tetrahydrofuran and tetrahydropyran rings. The tetrahydro-2-furoic acid **99** and tetrahydro-2*H*-pyran-4-carboxylic acid **100** were selected for study and they were used as racemic mixtures (Figure 3.36).



99 **100**

Figure 3.36: Structures of Tetrahydro-2-furoic acid 99 and tetrahydro-2*H*-pyran-4-carboxylic acid **100**

Tetrahydro-2-furoic acid **99** was commercially available and tetrahydro-2*H*-pyran-4-carboxylic acid **100** was not commercially available. However, the methyl ester was readily available. The de-esterification of the ester to the corresponding carboxylic acid **100** was carried under basic conditions (Figure 3.37). The ester was reacted with aqueous sodium hydroxide for 90 mins. Unreacted ester was removed by addition of dichloromethane and the recovered aqueous phase was acidified. The product was extracted with dichloromethane, dried and evaporated to give crystals (60%). The melting point matched the literature value.[66] ^{1}H NMR spectrum confirmed the structure by the absence of signal the methyl group. The spectrum also displayed a broad signal at 11.0 ppm which corresponded to the OH from the carboxylic acid group. This was supported by a strong broad OH absorption observed in the IR spectrum. The structure was also confirmed by ^{13}C NMR spectrum by the absence of the methyl group and signal of the carbonyl group appearing at higher chemical shift.

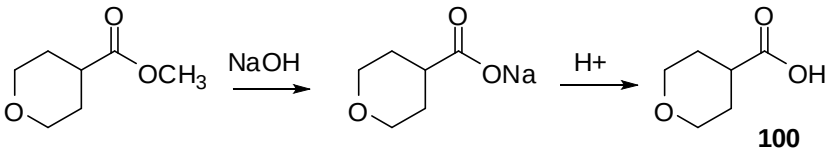


Figure 3.37: De-esterification of tetrahydro-2*H*-pyran-4-carboxylate **100**

Prior to the acylation reaction, both acids were converted to their corresponding acyl chlorides **101** and **102**.

Solutions of the carboxylic acids in dichloromethane were treated with excess oxalyl chloride in the presence of a catalytic amount of DMF (Figure 3.29).[59] The reaction mixtures were stirred for 90 min. The excess oxalyl chloride was removed by high vacuum evaporation.

Figure 3.38: Tetrahydro-2-furoic chloride **101** and tetrahydro-2*H*-pyran-4-carboxylic chloride **102**

Once the formation of the acid chlorides was complete, the products were directly reacted with ylides **67a-d** in dry toluene and in the presence of one equivalent of triethylamine at room temperature and under nitrogen. It was important to work with dry solvents and under an inert atmosphere to avoid the oxidation of the ylide to give triphenylphosphine oxide. As the acid chlorides were added to the solution of ylide **67a-d**, white fumes were observed which was an indication that hydrochloric acid was forming, hence the coupling was proceeding. The colour change from a pale yellow solution to a brown solution was also observed. Purification of the crude products was achieved by column chromatography.

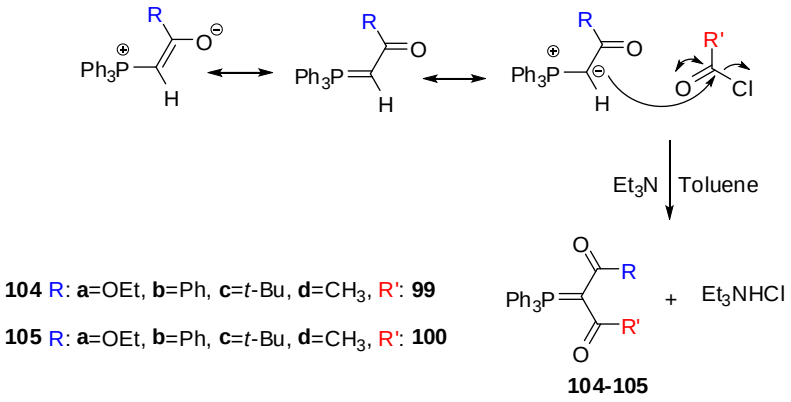


Figure 3.39: Acylation by acyl chlorides **101** and **102**

The initial step of characterisation was by ^{31}P NMR spectroscopy, which would indicate the success and completion of the reaction. Each phosphorus species in the reaction mixture would be represented as a singlet in the spectrum. Therefore the appearance of a new phosphorus peak and the absence of the starting ylide phosphorus peak would confirm that the reactions were successful.

Table 2.3: Preparation of ylides 104a-d and 105a-d; [a]calculated by NMR, [b]contains Ph_3PO

Compound	Yield (%)	δp (ppm)	mp (°C)
104a	3.6	+17.6	oil
104b[a]	35	+17.4	oil[b]
104c	8.9	+16.2	oil
104d	12	+15.6	oil
105a[a]	95	+17.4	oil[b]
105b[a]	50	+14.3	oil[b]
105c[a]	12	+16.0	oil[b]
105d[a]	89	+14.3	oil[b]

For all heterocyclic-ylides **104** and **105**, a new phosphorus peak was observed a few units upfield or downfield from the starting ylide (Table 2.3). However the ^{31}P NMR spectra also showed the presence of triphenylphosphine oxide which is most likely to be

formed during the aqueous work-up stage. This explained the low yields of the dioxo ylides **104** and **105**.

^{1}H NMR analysis showed the absence of the proton from the ylidic carbon while ^{13}C NMR analysis showed a significant chemical shift of the ylidic bond (C=P) bond in comparison to the starting ylides. In addition, a decrease of the coupling constant $J_{\text{P-C ylidic}}$ was observed (Table 2.4).

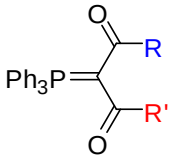


Table 2.4: Comparison of ^{13}C NMR data of ylidic C=P bonds

R	**67 (C=P) δ (^{13}C ppm)**	**104 (C=P) R′ = δ (^{13}C ppm)**	**105 (C=P) R′ = δ (^{13}C ppm)**
a: OEt	30.2 (125.7)	68.9 (109.8)	69.9 (109.8)
b: Ph	50.8 (112.7)	84.6 (101.0)	50.8 (111.2)
c: *t*-Bu	47.3 (109.8)	80.3 (124.4)	72.0 (103.2)
d: CH_3	51.7 (111.3)	86.1 (101.0)	52.8 (105.4)

^{13}C NMR spectra provided new information by showing couplings of both carbonyl carbons with phosphorus. Similar to the starting ylides, $J_{\text{P-C}}$ coupling was observed throughout the aromatic rings, including C-4 of phenyl (Figure 3.40).

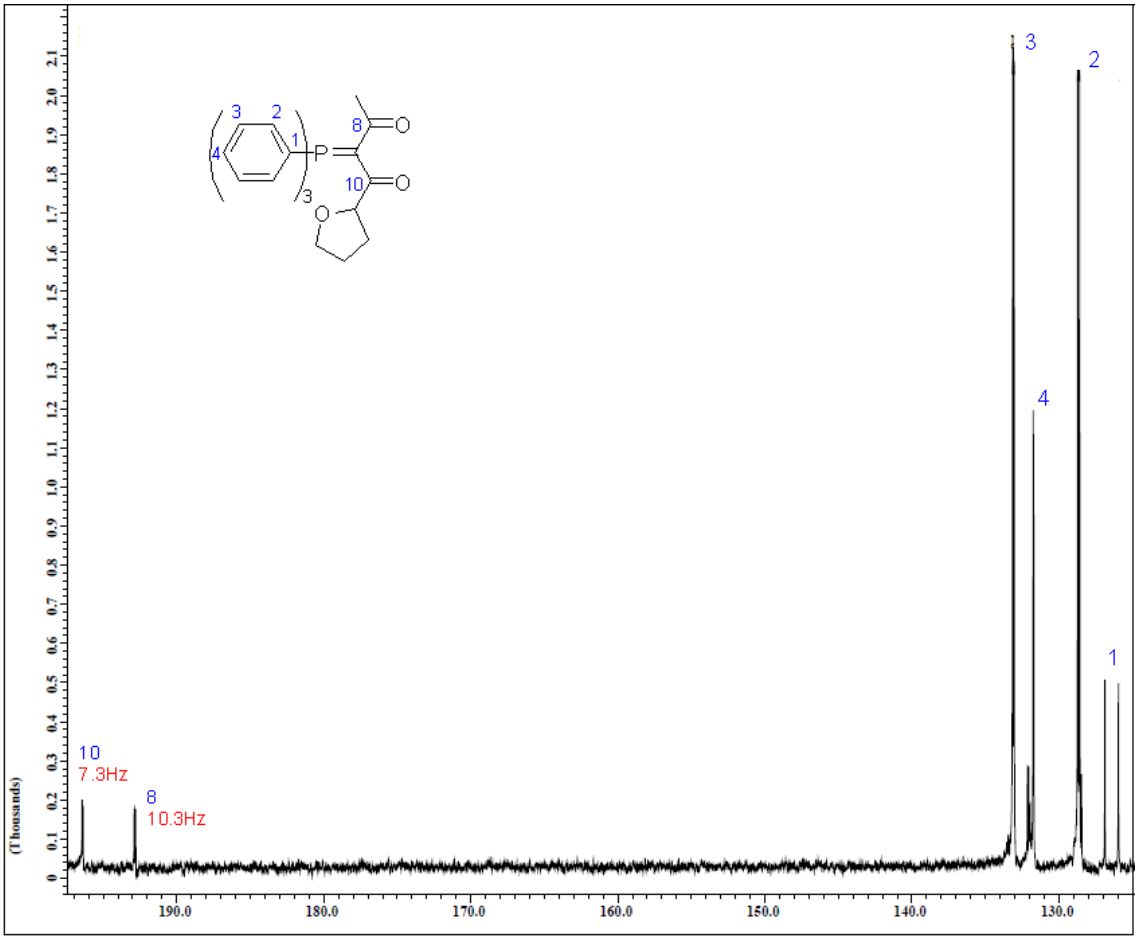
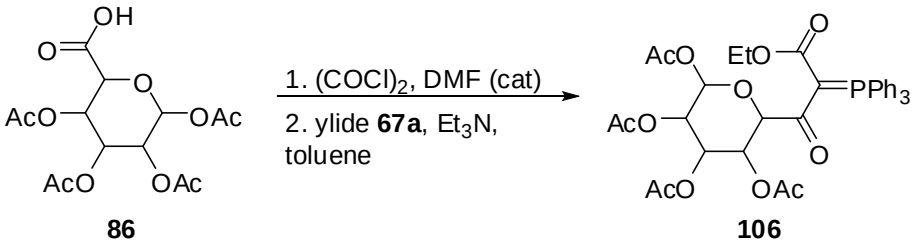


Figure 3.40: ^{13}C NMR spectrum of **104d**

Even though poor yields were obtained, the results proved that the acylation reaction worked (Table 2.3). No signals corresponding to unreacted starting ylides were observed in the ^{31}P NMR spectra. Hence the procedure could be used for the coupling of the ylides and sugar derivative with the aqueous work-up being performed as quickly as possible.

3.3.2 Synthesis of sugar-derived ylides

Attention now turned to the coupling of the synthesised sugar precursors with the β-oxo phosphorus ylides **67a-d**. As described in the model reaction section, the sugar acid chlorides were initially prepared and reacted immediately with the ylides in the presence of triethylamine.



86 **106**

Figure 3.41: Synthesis of sugar derived-ylides

The tetraaceate **86** was readily converted to the acyl chloride according to the method used to prepare **89**. The subsequent reaction with the ethoxycarbonyl ylide **67a** gave a mixture which contained seven signals in the ^{31}P NMR spectrum; two signals corresponded to Ph_3PO (+30 ppm) and unreacted starting material (+18.2 ppm) in 5% and 20%, respectively.

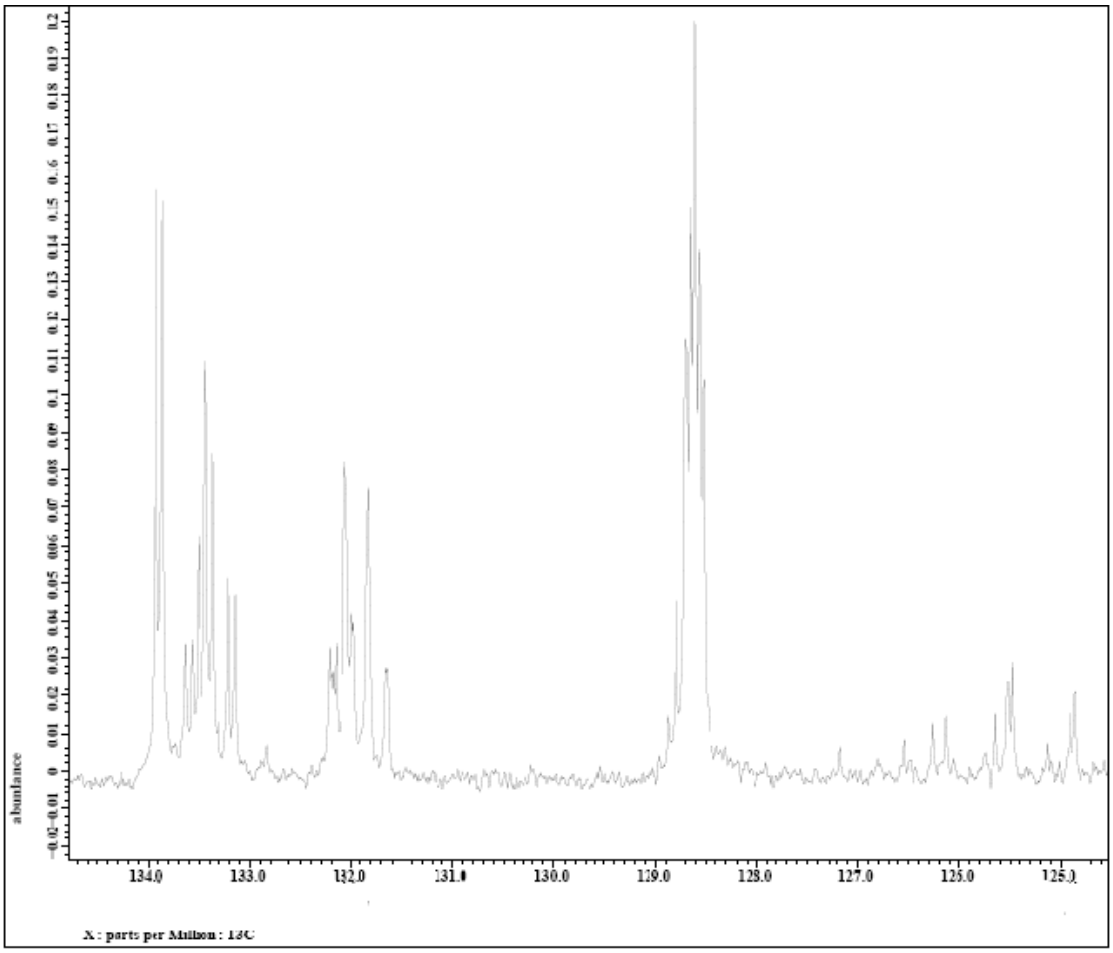


Figure 3.42: Aromatic region of **106**

The ^{13}C NMR spectrum appeared complex. However, characteristic signals were used to give an indication of the possible structures of the five unknown phosphorus compounds. Expansion of the aromatic region (Figure 3.42) showed the presence of five sets of doublets at 124.9-127.2 ppm ($J_{P\text{-}C}$ 93 Hz). These signals are indicative the C-1 of P-phenyl of ylides and one of set matched the signals from the starting ylide. The presence of three sets of doublets at 187.0, 187.4 and 187.7 ppm corresponding to β,β′ carbonyl groups suggest that the sugar has linked to the starting ylide. An OH stretch in the IR spectrum, together with signals corresponding to carbonyl functionalities, alludes to structures in Figure 3.43 being present in this mixture.

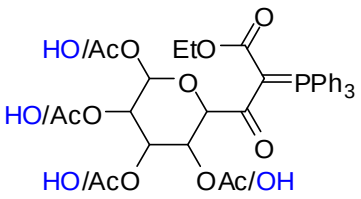
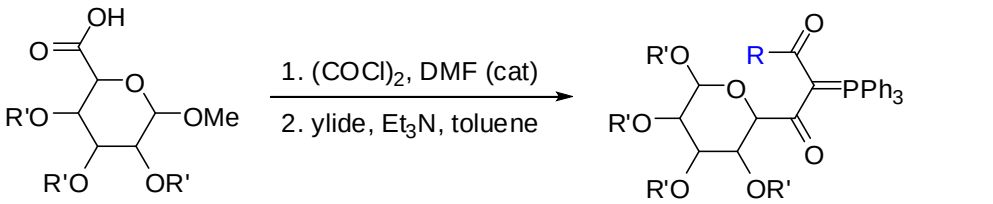


Figure 3.43: Proposed products

Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoic acid **95** and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoic acid **98** were reacted with oxalyl chloride under standard conditions and subsequently reacted with β-oxo ylides **67a-d** (Figure 3.44) to give the desired compounds in low yields after chromatography on silica gel (Table 2.5).

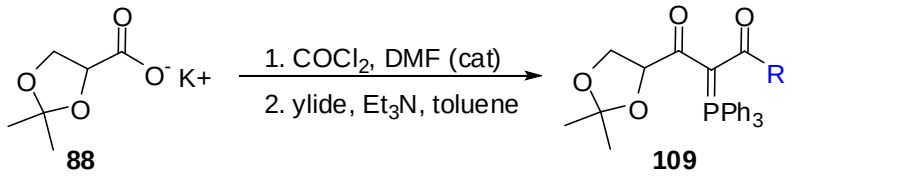


95 R'= Ac, **98** R'= Bn

107 R'= Ac, R= OEt, Ph, *t*-Bu, CH_3
108 R'= Bn, R= OEt, Ph, *t*-Bu, CH_3

Figure 3.44: Acetyl/benzyl pyranoside-derived ylides **107** and **108**

2,3-Isopropylideneglycerate **87** was also reacted with oxalyl chloride under standard conditions and subsequently with β-keto ylides **67a-d** to give the desired products as oils, in low yields (Table 2.5).



88 **109**

109 R: **a**= OEt, **b**= Ph, **c**= *t*-Bu, **d**= CH_3

Figure 3.45: 2,3-Isopropylideneglycerate derived ylides **109**

^{31}P NMR spectrum of **109a** displayed 13 signals including the signal corresponding to triphenylphosphine oxide (+30 ppm). The crude was purified by column chromatography on silica gel to give four fractions. In three of the fractions, ^{31}P NMR spectra displayed more than one phosphorus peak. The samples were subjected to further purification by column chromatography on silica gel. However their analyses were not clear enough to draw any conclusions. The products **109b** and **109c** were not purified as their ^{31}P NMR spectra showed only two signals corresponding to the desired product and triphenylphosphine oxide. The decision not to purify the ylides was due to loss of product during chromatography and the knowledge that further reactivity of the ylides (oxidation and thermolysis) would produce triphenylphosphine oxide. It was decided that the final products would be purified and fully characterised. Product **109d** was produced in very low yield and it was only analysed by ^{31}P NMR spectroscopy.

As expected, acylation by the acyl chloride method was not compatible with all sugar derivatives; especially those possessing acid-labile protecting groups. Instead, peptide coupling reagents were an alternative route to sugar-derived ylides according to the method developed by Wassermann.[27]

As described in Section 1.3.2.7 (Introduction), the peptide coupling reactions commonly utilise carbodiimides. The purpose of these reagents is to activate the carboxylic acid to give a reactive *O*-acylisourea intermediate **110** which undergoes nucleophilic attack by the ylide to produce an intermediate **111**. Electron rearrangement and elimination of the urea **112** yields the desired dioxo-ylide **113**.

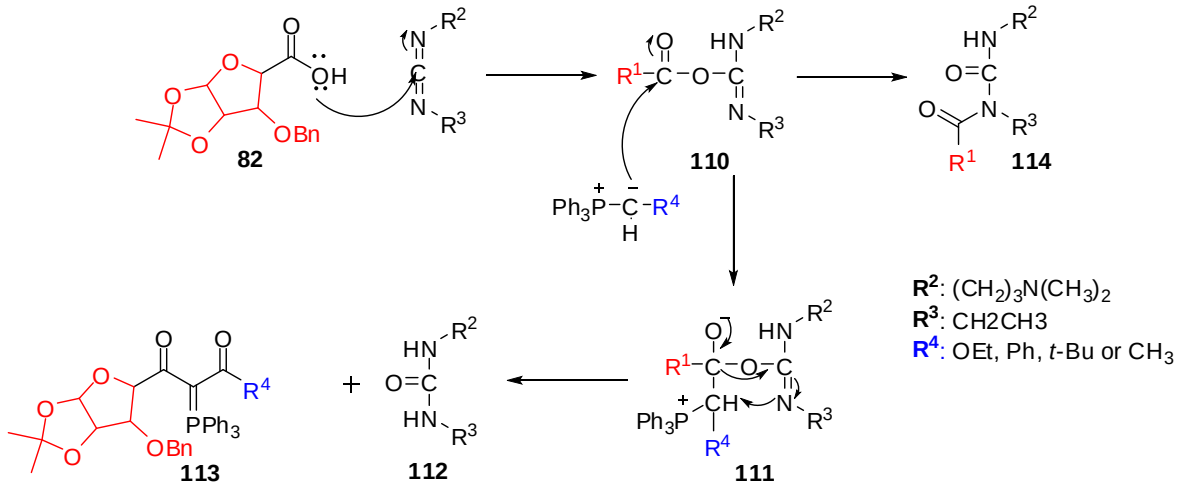


Figure 3.46: Proposed mechanism of acylation mediated by carbodiimide using acid 82 reagents[67]

Problems have been associated with carbodiimide coupling. The *O*-acylisourea intermediate **110** has poor selectivity for specific nucleophiles and can lead to racemisation.[67] It can also undergo rearrangement to form the less reactive *N*-acylurea **114** which results in product contamination and poor yield. These problems could be minimised by the use of dielectric solvents such as dichloromethane or additive such as 1-hydroxybenzotriazole (HOBt).[67]

DCC has been the most popular carbodiimide reagent. However the dicyclohexylurea intermediate causes a problem as it is insoluble in water, making its removal by aqueous extraction difficult. In addition, it is a potent allergen. EDC, mostly used as a

hydrochloride, has provided an advantage over DCC as the urea produced is soluble in water hence easily removed.

Sugar derivative **82**, which is protected with the acetonide protecting group (an acid sensitive), was a candidate for the carbodiimide mediated coupling reaction (Figure 3.46). EDCI mediated coupling of sugar acid **82** with starting ylides **67a-d** was performed under anhydrous and inert conditions. The coupling reagent was added to a solution of the sugar acid and ylide in dry dichloromethane and in the presence of a catalytic amount of DMAP, at 0°C and stirred for 30 min. The reaction was then allowed to stir overnight. Brine was added to the reaction mixture and the product was extracted with dichloromethane, washed with water and the solvent evaporated to give the desired products.

The four expected products **113a-d** were obtained as oils, three in poor yield and one in moderate yield as illustrated in Table 2.5. They were all initially analysed by ^{31}P NMR spectroscopy. The spectra helped monitor the completion of the reaction by the appearance of new phosphorus peaks and disappearance of the starting ylide peaks. ^{1}H NMR analysis confirmed the structures by the absence of the proton from the ylidic carbon. ^{13}C NMR analysis provided new signals for the C=P bond at higher chemical shifts and lower coupling constant compared to the starting ylides. Further conclusive evidence was obtained from the position and coupling constants of the carbonyl groups.

Table 2.5 summarise the yields, melting points and ^{31}P NMR data of the sugar-derived ylides.

Table 2.5: Sugar-derived ylides 107-109 and 113; Method A: acylation using acyl chloride, Method B: acylation using carboxylic acid; [a]calculated by NMR, [b]contains Ph_3PO

Compound	Method(A/B)	Yield (%)	δp (ppm)	mp (°C)
107a	A	13	17.2	oil
107b	A	10	18.8	oil
107c	A	5	17.1	oil
107d	A	4	16.7	oil
108a	A	20	17.0	oil
108b	A	0	0	oil
108c	A	41	17.7	oil
108d	A	15	19.8	oil
109a[a]	A	0	0	oil[b]
109b[a]	A	56	18.2	oil[b]
109c[a]	A	90	16.8	oil[b]
109d[a]	A	9	16.1	oil[b]
113a	B	50	17.5	oil
113b	B	2	17.3	oil
113c	B	2	16.7	oil
113d	B	5	15.6	oil

3.3.3 Characterisation of β,β′-dioxo-ylides

All sugar-derived ylides were characterised by ^{1}H, ^{13}C, ^{31}P NMR, IR spectroscopy and Mass spectrometry.

3.3.3.1 IR spectroscopy

The sugar-derived ylides present similar functional group and their absorptions were observed in their expected regions. However absorptions of the carbonyl groups adjacent to the ylidic carbon at 1751-1650 cm^{-1} were of special interest for these compounds in confirming the structures.

3.3.3.2 ^{31}P NMR spectroscopy

^{31}P NMR was the most efficient and optimum way to monitor the progress of all reactions. The spectra confirmed the completion of the reactions with the presence of a new phosphorus peak at a lower chemical shift to that of the starting ylide.

^{31}P NMR spectra of the crude products displayed single peaks representing the desired products. In some cases, additional peaks were observed which most commonly included triphenylphosphine oxide (+30 ppm). Triphenylphosphine oxide was most likely formed during the aqueous work-up stage by hydrolysis leading to the decomposition of the product. This continued to occur despite precautions being taken to prevent this hydrolysis. This is one area for further method development.

3.3.3.3 ^{1}H NMR spectroscopy

^{1}H NMR was very useful. The proton on the ylidic carbon, from the starting β-keto ylide, allows acylation to take place. Hence the absence of the proton in the spectra indicated that the reactions were successful.

It was observed that the couplings between protons in the sugar structures were affected by the addition of the phosphorus ylides. There was a variation, increase or decrease of coupling constants. The change in coupling constant was also due to peaks changing from doublets to doublet of doublets or vice versa or to triplets; this is illustrated in (Figure 3.47).

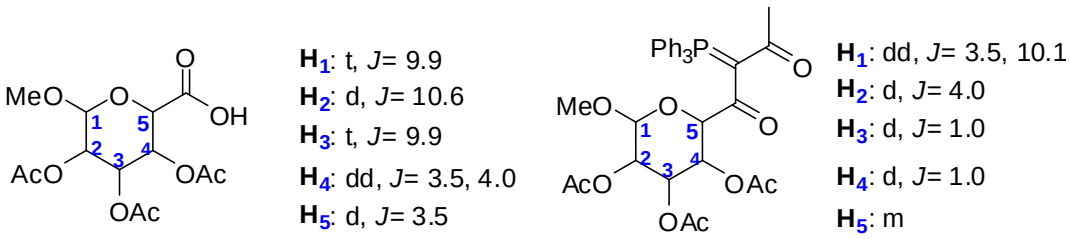


Figure 3.47: The effect of the phosphorus ylide on the protons

3.3.3.4 ^{13}C NMR spectroscopy

^{13}C NMR spectra provided more information about the structures. The observation of the absence of the ylidic proton in the ^{1}H NMR spectra was supported by the data from ^{13}C NMR spectra. Signals corresponding to the C=P bond were present at a significantly higher chemical shift in the region of 60-90 ppm compared to the starting ylides signals which were present in the region of 30-55 ppm. The P-C coupling of the ylidic carbon also altered; the β,β′-dioxoylides exhibited lower coupling compared to the β-oxoylides. A trend was observed between the ester and the keto compounds. The C=P bond from the ester compounds was at a lower chemical shift compared to the C=P bond from the keto compounds (Tables 2.6-2.9).

The spectra showed the interaction between phosphorus and the neighbouring carbonyl groups; the coupling with phosphorus extended up to two bonds in both directions away from the α-carbon. Similar to the starting ylide, coupling to the phosphorus is observed throughout the aromatic rings, extending up to four bonds. The assignment of the aromatic signals was based on the work be Aitken et al; C-3 of phenyl has a higher coupling than C-2 of phenyl (Figure 3.48).

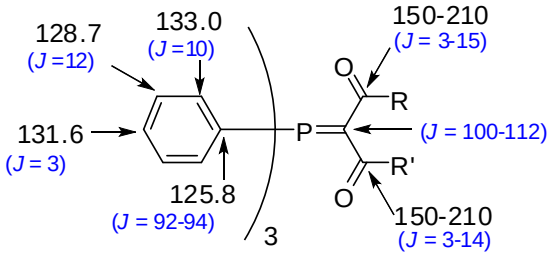


Figure 3.48: Phosphorus interaction with neighbouring carbons

The carbonyl signals appeared as characteristic double doublets in the 150-210 ppm range with *J*=3-15 Hz.

3.3.3.5 Mass spectrometry

The sugar-derived ylides were initially analysed by low resolution mass spectrometry by electrospray ionisation which illustrated the fragmentation pattern of the ylides and also helped to measure molecular weights of the products. The mass spectra of sugar-derived ylide **107c** did not give the full molecular weight of the structure. This was due to the loss of the tertiary butyl group as methylpropene which is a known labile group.

A pattern was observed in the fragmentation of the methyl triacetyl-α-D-glucopyran-β,β'-dioxo ylides **107b-d** and the benzyl isopropylidene-α-D-glucopyran-β,β'-dioxo ylides **113b-d**. The spectra of **107b-d** showed the loss of 60 m/z corresponding to OAc. The spectra of **113b-d** showed a peak at 91 m/z corresponding to the loss of the benzyl group as an ion and a peak at 279 m/z corresponding to the loss of Ph_3PO which fragmented by cleavage of the C-P bond.

The structures of the novel ylides were confirmed by high resolution mass spectrometry. The spectra provided more information, with more fragmentations, than the spectra from the low resolution mass spectrometry. Common fragmentations were also observed.

3.3.4 Method development

Microwave-assisted reactions have been used with a great deal of success in the past few years. Microwave irradiation has been used to simplify and improve standard organic reactions by decreasing reaction times, increasing yields and providing cleaner reactions. Microwave methods have resulted in efficient and safe technology, 'Green Chemistry'.[68]

Microwave irradiation has been used in acylation of amines, alcohols and phenols utilising solid-supported reagents.[69] The developed methodology proved to be efficient particularly in obtaining high yields, pure products, except for the acylation of alcohols, and products without racemisation in acylation of amines.

Microwave-assisted acylation of phosphorus ylide **67a** with **102** was investigated. A mixture of β-oxoylide **67a**, acyl chloride **102** and triethylamine in toluene was exposed to microwave irradiation for 2 min. An orange homogeneous solution was obtained and a portion was analysed by ^{31}P NMR spectroscopy. The spectrum showed signals at +18.2 and +30 ppm. The latter corresponds to tripehylphoslphine oxide and the former corresponds to the unreacted starting ylide. Further experiments were conducted with difference ylides and acyl chlorides and similar results were obtained. Therefore microwave-assisted acylation experiments were discontinued.

Table 2.6: ^{13}C NMR of tetrahydro-2-furan-β,β'-dioxo ylides **104**

	Furan-					**Ylide**						
R	CH_2	CH_2	CH_2	CH	CO	C=P	C-1	C-2	C-3	C-4	CO	R signals
OEt	69.2	25.3	31.0	80.7 (8.8)	196.7 (2.9)	68.9 (109.8)	126.5 (93.7)	133.1 (9.5)	128.5 (11.7)	131.6 (2.9)	167.5 (13.9)	13.7, 58.5
Ph	69.1	25.5	30.2	76.6 (8.8)	196.5 (9.2)	84.6 (101)	125.8 (92.2)	133.3 (10.3)	128.6 (12.4)	131.8 (2.9)	193.2 (8.8)	137.9, 129, 128.2, 130.8
CH_3	68.9	25.4	29.7	81.0	196.4 (7.3)	86.1 (101)	126.4 (92.9)	133.1 (9.5)	128.7 (12.4)	131.7 (2.9)	192.8 (10.3)	30.3
tBu	68.3	25.5	30.1	81.8 (6.6)	207.0	80.3 (124.4)	126.2 (91.5)	133.9 (9.5)	128.4 (13.2)	131.7 (2.9)	174.1	28.2, 45.9 (5.1)

Table 2.7: ^{13}C NMR of tetrahydro-2H-pyran-β,β'-dioxo ylides **105**

	Pyran-						**Ylide**						
R	CH_2	CH_2	CH	CH_2	CH_2	CO	C=P	C-1	C-2	C-3	C-4	CO	R signals
OEt	68.0	29.5	43.3 (6.6)	29.5	68.0	198.9 (2.9)	69.9 (109.8)	126.9 (93.7)	132.9 (10.3)	128.5 (12.4)	131.5 (2.9)	167.5 (14.6)	13.7, 58.3
Ph	66.6	28.1	40.9	28.1	66.6	192.3	50.8 (111.2)	118.8 (92.2)	133.2 (10.3)	128.5 (11.7)	132.0	170.3	137.7, 129, 128.2, 130.6
CH_3	66.7	28.1	41.0	28.1	66.7	190.7 (4.4)	52.8 (105.4)	126.8 (90.7)	133.1 (10.3)	128.9 (12.4)	132.0 (2.9)	177.1	28.2
tBu	66.7	28.0	41.0	30	67.9	206.9	72.0 (103.2)	118.6 (92.2)	132.1 (10.3)	128.5 (11.7)	131.9 (2.2)	204.0	26.8, 44.1

Table 2.8: ^{13}C NMR of sugar-derived ylides **107**

	Sugar									**Ylide**						
		OAc									PPh_3					
R	OMe	CH_3	CO	CH	CH	CH	CH	CH	CO	C=P	C-1	C-2	C-3	C-4	CO	R signals
OEt	55.9	20.6, 20.7	169, 170.1, 170.3	97.2	70.7	71.0	67.8 (9.5)	71.0	187.6 (4.4)	72.9 (108.)	125.7 (93.7)	133.0 (10.3)	128.6 (12.4)	131.8 (2.9)	167.0 (13.9)	13.7, 58.9
Ph	56.7	20.9, 21.1	169.8, 170.0, 184.8	101.9	68.5	68.5	66.4	97.1	192.9 (7.3)	81.7 (103.2)	125.3 (92.2)	133.6 (10.3)	128.8 (13.2)	132.2 (2.9)	151.1 (11.7)	127.9, 128.9, 130.6, 143
CH_3	56.7	20.8	168.9, 170.1, 170.5	97.7	70.7	70.7	70.0 (9.5)	77.3	192.8 (8.1)	89.4 (100.3)	125.8 (92.2)	133.0 (9.5)	128.7 (12.4)	131.9 (2.9)	186.8 (6.6)	30.8
tBu	56.6	20.9, 21.1	169.9, 170.1, 171.1	103.2	69.1	69.1	66.9	97.9	205.9 (4.4)	78.9 (101.7)	125.9 (92.9)	133.7 (9.5)	128.6 (12.4)	131.9 (2.2)	181.2 (8.8)	28.2, 45.3 (5.1)

Table 2.9: ^{13}C NMR of sugar-derived ylides **113**

	Sugar									**Ylide**						
										PPh_3						
R	CH_3	CH	C	CH_2	C-1	C-2	C-3	C-4	CO	C=P	C-1	C-2	C-3	C-4	CO	R signals
OEt	26.8, 27.3	83.3, 83.6 (9.5), 84.0, 105.0	111.7	71.9	138.1	128.3	127.9	127.5	188.9 (3.7)	70.4 (112.0)	126.3 (92.9)	133.2 (9.5)	128.4 (13.2)	131.4 (2.2)	167.1 (14.6)	13.8, 58.6
Ph	26.7, 27.1	82.5 (9.5), 83.1, 84.0, 104.9	111.7	71.9	137.9	128.2	127.8	127.6	192.7 (10.3)	84.5 (102.5)	125.5 (92.9)	133.5 (10.3)	128.5 (12.4)	131.6 (2.9)	187.5 (3.7)	128.3, 128.7, 130.7, 143.6 (5.9)
CH_3	26.8, 27.2	83.0, 84.5, 84.6 (6.6), 105.1	111.9	72.3	138.0	128.4 (5.1)	127.8	127.6	192.5 (13.9)	86.9 (105.4)	126.2 (92.9)	133.4 (9.5)	128.7 (12.4)	131.8 (2.2)	191.3 (7.3)	30.1
tBu	26.5, 26.9	82.3, 83.9 (6.6), 84.0, 105.4	111.9	72.5	138.5	128.3	127.4	127.3	208.2 (6.6)	79.2 (98.1)	126.3 (92.2)	134.0 (9.5)	128.2 (12.4)	131.6 (2.9)	184.9 (5.1)	28.0, 46.2 (5.1)

3.4 Oxidation of β,β′-dioxo phosphorus ylides with oxone

Oxidation was carried out on all successfully synthesised sugar derived ylides. The heterocyclic-derived ylides were the first to undergo each procedure since from the start they were designed to be used as model compounds.

As already mentioned in the Introduction, there are a number of oxidising agents that can be used to produce vicinal tricarbonyl and polycarbonyls compounds which include singlet oxygen, oxone, ozone and dimethyldioxirane. The cleavage can be performed rapidly with ozone; however oxone has been popular as it is a milder and more selective reagent as well as being simple to handle, non-toxic and stable.[14]

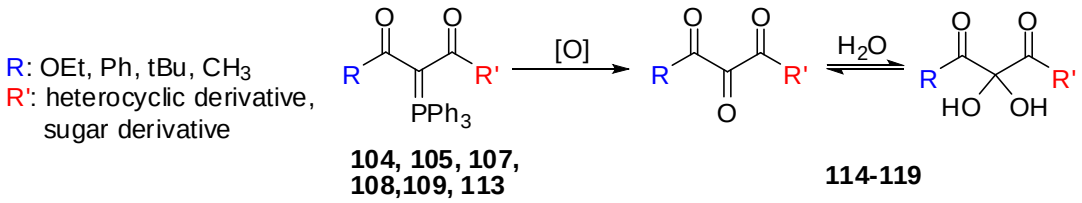


Figure 3.49: Synthesis of vicinal tricarbonyls

Vicinal tricarbonyls were prepared by the oxidation of one equivalent of dioxoylide with 1.5 equivalents of oxone in THF/water solvent system to give the tricarbonyl and its hydrate. The duration of the experiments ranged from one to two days and reactions were monitored by ^{31}P NMR. Colour change of the reaction mixture was observed. The crude products were purified by dissolving the products in cold ether and running the solution through a small plug of silica gel. The products were obtained mostly in the hydrate form and in the form of oils. The products were characterised by ^{31}P NMR, ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

Once it was concluded that the experimental procedure was convenient, the sugar-derived ylides were oxidised sequentially. Unlike in the oxidation reactions of the heterocyclic-derived ylides, most products from sugar-derived ylides were obtained in the tricarbonyl form.

^{31}P NMR was specifically used to monitor the reactions and the completion of the reactions were determined by the consumption of the dioxoylide and the presence of only triphenylphosphine oxide (+30 ppm). ^{1}H NMR analysis was useful in determining whether the product was a tricarbonyl or a hydrate with the absence or presence of a broad OH peak at around 8.9 ppm. This observation was confirmed by IR spectroscopy which displayed a strong peak at around 1700 cm^{-1} and another broad peak at around 3200 cm^{-1} corresponding to the C=O and OH groups, respectively. ^{13}C NMR analysis was also very informative. In comparison to the spectra of the dioxoylides, many changes were observed. These included the presence of a new carbonyl group or a quaternary carbon to which the gem-diols are attached (Figure 3.50). The changes also included the disappearance of the ylidic carbon (C=P) peak in the region of 68-90 ppm.

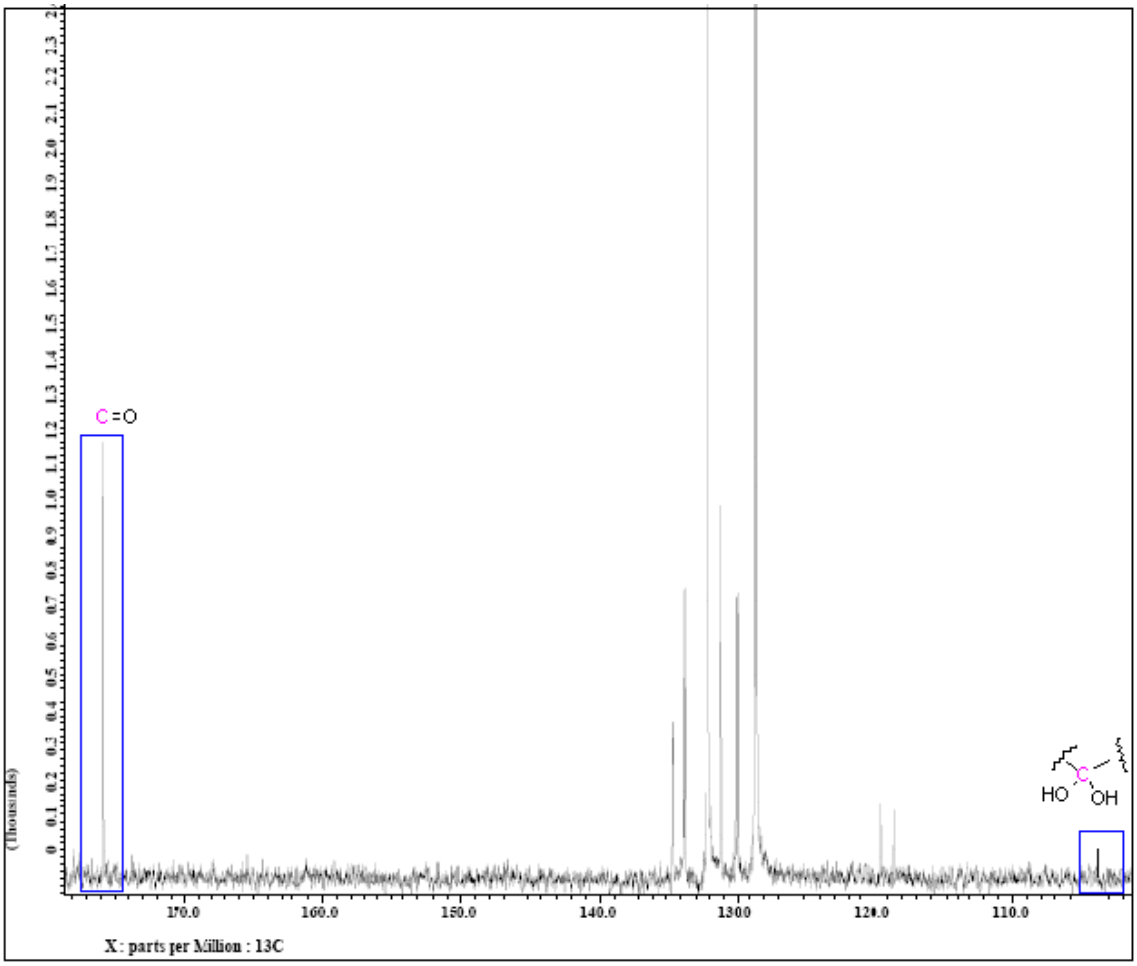


Figure 3.50: ^{13}C NMR spectra of **104c**

3.5 Thermolysis of β,β′-dioxo phosphorus ylides

Research has shown that β,β′-dioxoylides are liable to thermal decomposition. Thermal stability of the synthesised sugar-derived ylides was investigated using thermogravimetric analysis (TGA). This analytical technique measures the weight change of a sample as a function of temperature.

The pyrolysis process subdivides into three stages: (i) evaporation of any present solvent in the sample, (ii) fast thermal decomposition (pyrolysis) and (iii) further cracking/degradation process of residues.

Pyrolysis characteristics of methyl triacetyl-α-D-glucopyranoic-derived ylide **107d,** methyl tribenzyl-α-D-glucopyranoic-derived ylide **108a**, isopropylideneglycerate-derived ylide **109c** and benzyl isopropylidene-α-D-glucopyranoic-derived ylide **113b** were investigated**.** The temperature of the instrument was set to heat up to 600°C and to record the changes at 10°C min^{-1}.

The TGA results are shown in Figure 3.51. The curves show that the samples contained volatile material with a boiling point at about 110°C, attributed to toluene which was used for their synthesis. The curves have also revealed that the best thermal stability was exhibited by **113b** at 180°C. The sequence of the thermal stability was **113b**> **108a**> **107d**> **109c**. TGA has been useful in indicating the temperature at which the dioxoylides can be subjected to pyrolysis.

The results have also provided information on the percentage weight loss during the fast pyrolysis. However this weight loss does not confirm the structures of the volatile products. More experiments, such as TGA-FTIR and TGA-MS analysis, are required to determine the structures of the volatile products and mechanism of the thermal decomposition.

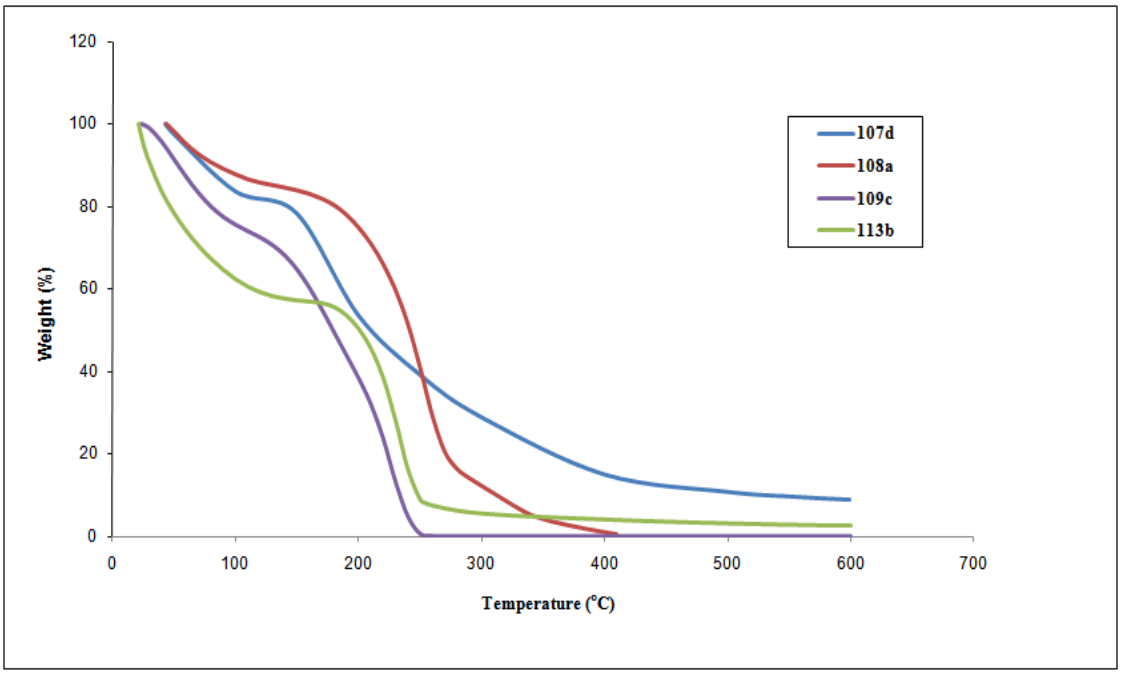


Figure 3.51: TGA results of β,β′-dioxoylides **107d**, **108a**, **109c** and **113b**

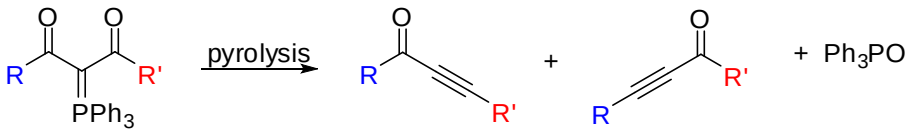
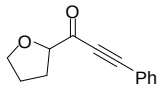
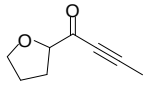
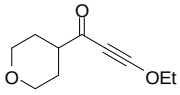
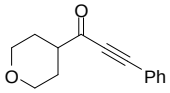
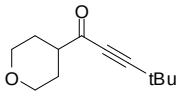
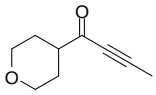
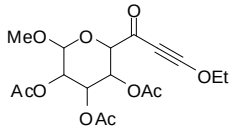
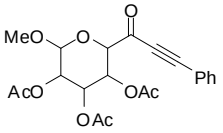
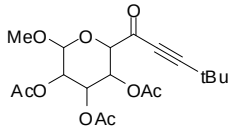
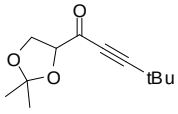
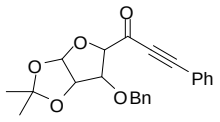
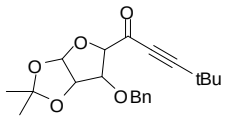
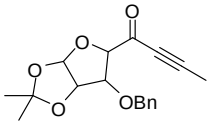


Figure 3.52: Pyrolysis of β,β′-dioxo ylides

Pyrolysis was conducted with Kugelrohr distillation oven. The β,β′-dioxo ylides were gradually heated to 240°C (Figure 3.52). This was expected to result in the formation of alkynes and Ph_3PO. Two fractions were recovered; the residue from the inlet flask and material from the receiver flask. The contents of both flasks were analysed by ^{31}P NMR, ^{1}H NMR, ^{13}C NMR and IR spectroscopy. The inlet flasks contained Ph_3PO and unidentifiable residues while the desired alkyne products were collected in the receiver flasks together with some of the extruded Ph_3PO. For some examples it was not possible to obtain the full analytical data. However, the distinctive signal around 2250 cm^{-1} in the IR spectrum confirmed the presence of the C≡C functionality. The results obtained are summarised in (Table 2.10).

Table 2.10: Alkynes prepared; [a] contains Ph_3PO

Entry	Product		Yield (%)	m.p.
1		**120b**	50	oil[a]
2		**120d**	100	oil[a]
3		**121a**	6	oil[a]
4		**121b**	31	oil[a]
5		**121c**	63	oil[a]
6		**121d**	68	oil[a]
7		**122a**	18	oil[a]
8		**122b**	61	oil[a]
9		**122c**	88	oil[a]
10		**123c**	100	oil[a]
11		**124b**	100	oil[a]
12		**124c**	40	oil[a]
13		**124d**	70	oil[a]

^{31}P NMR analysis was used to confirm that the extrusion of Ph_3PO (+30 ppm) had occurred and ^{1}H NMR analysis was used as a complementary analytical method. ^{13}C NMR spectroscopy was the most informative technique. The spectra showed the presence of two new quaternary carbons corresponding to the alkyne at the characteristic positions and the absence of one carbonyl functional groups provided additional confirmation that the pyrolysis reactions were successful (Figure 3.53).

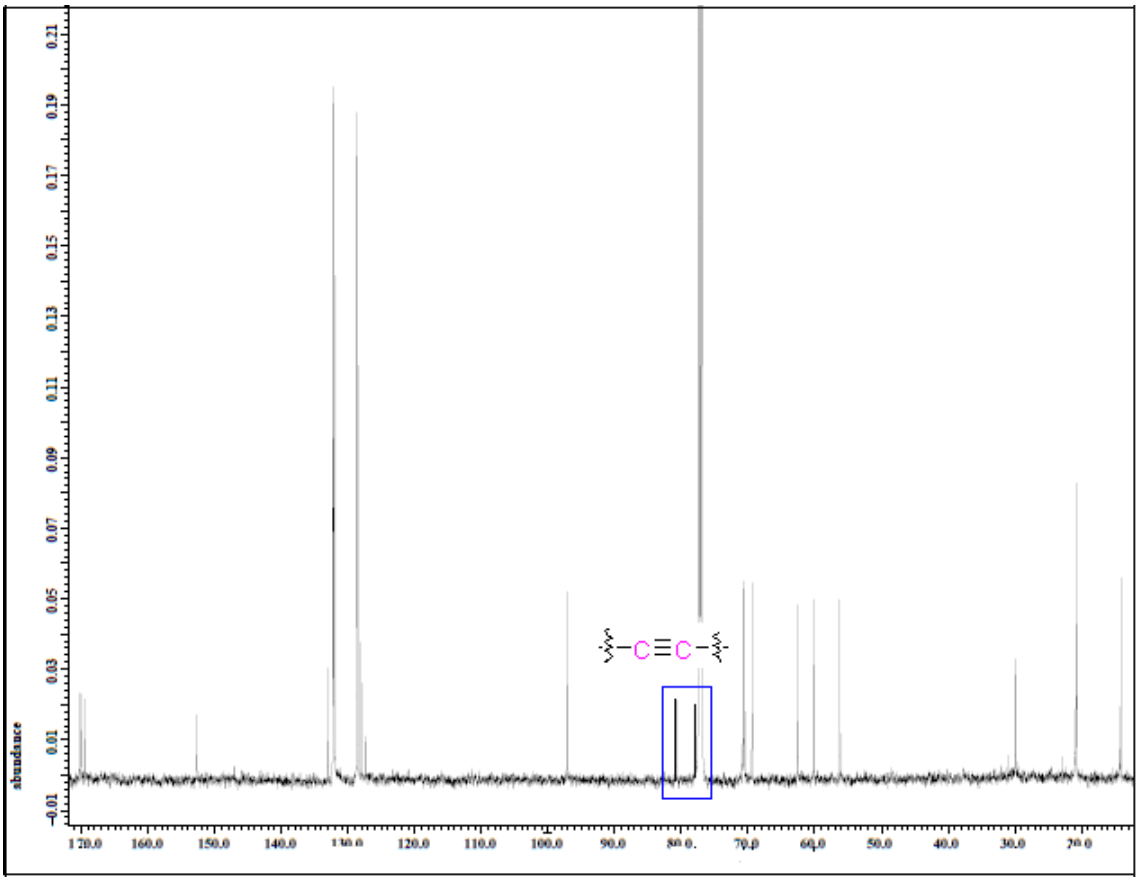


Figure 3.53: ^{13}C NMR spectra of **122a**

4. Experimental

4.1. Reagents

All reagents were purchased from Sigma Aldrich and Alfa Aesar. All solvents were purchased from Fisher Scientific and were of technical grade. Dry diethyl ether and toluene were prepared by storing over sodium wire. Dry dichloromethane was prepared by storing over calcium chloride overnight and distilling. Dry triethylamine was prepared by storing over potassium hydroxide pellets. Distilled water was used to prepare aqueous solutions and during the extraction of products.

All reagents were used as purchased and without further purification.

4.2. General methods and Instrumentation

Thin layer chromatography (TLC) was performed on silica gel or aluminium sheets. The plates were analysed under UV at 254 nm or developed with a solution of sulphuric acid (10% of concentrated H_2SO_4 in methanol (v/v)) sprayed on the plate and heated at 120-140°C for 5 min. The TLC eluent mixtures are reported as v/v ratios.

Preparative layer chromatography was prepared with silica gel ($PF_{254 + 366}$) and distilled water. Flash column chromatography was performed using silica gel (60-200 μm).

^{1}H and ^{13}C NMR spectra were recorded using a JEOL GX270 spectrometer, observing ^{1}H at 270.17 MHz and ^{13}C at 67.80 MHz, and an ECA-GX600 spectrometer observing ^{1}H at 600.17 MHz and ^{13}C at 150.91 MHz. ^{31}P NMR spectra were only recorded using an ECA-GX600 spectrometer at 242.95 MHz. The samples were prepared with $CDCl_3$ or D_2O solutions unless otherwise stated. Chemical Shifts were expressed relative to an

internal standard of tetramethylsilane (TMS). Coupling constants are given in hertz (Hz) and chemical shifts in parts per million (ppm).

IR spectra of solid samples were recorded as KBr discs using 5 mg of dry sample and 35 mg of dry KBr. Spectra for oil samples were recorded as capillary films between NaCl plates. Spectra were recorded on a Digilab Scimitar series spectrophotometer in the range 4000 - 400cm^{-1}.

Low resolution electron ionisation mass spectra were obtained from the Analytical Centre (University of Bradford) using a Micromass Quattro Ultima mass spectrometer. High resolution mass spectra were obtained from the EPSRC National Mass Spectrometry Service Centre, University of Swansea.

Thermal stability measurements were carried out using a TA Instruments Q5000. The TGA system was controlled by Universal Analysis V4.5A software for data acquisition and analysis. In data plots, the weight loss is expressed as a percentage of the initial sample weight and plotted vs. temperature in degree celcius.

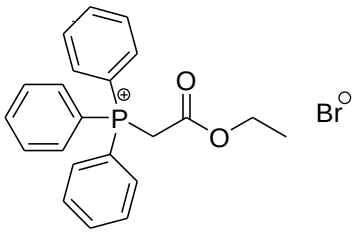
Melting points were determined using a Gallenkamp apparatus and are uncorrected.

4.3. Procedures

4.3.1. Synthesis of phosphonium salts

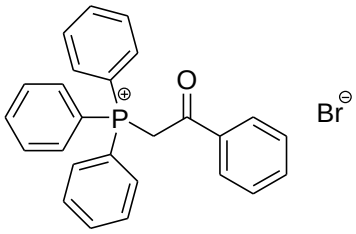
General method 1: Triphenylphosphine (1 equivalent) in dry toluene was added dropwise to ethyl bromoacetate (1 equivalent) in dry toluene. The mixture was heated under reflux for 2 hr and stirred overnight. The precipitate which formed was filtered, washed with dry diethyl ether and dried.

4.3.1.1. (Ethoxycarbonylmethyl)triphenylphosphonium bromide 66a



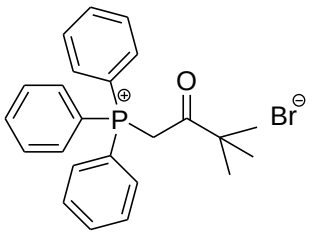
Prepared according to general method 1, using triphenylphosphine (26.3 g, 100 mmol) in dry toluene (150 ml) and ethyl bromoacetate (16.7 g, 100 mmol) in dry toluene (15 ml) to produce **66a** an off-white powder (38.7 g, 90%), m.p. 156-157°C (lit.[70], 155-158 °C); ^{31}P NMR ($CDCl_3$) δ_p +21.5; ^{1}H NMR ($CDCl_3$) δ_H: 0.98 (t, 3H, *J* 7.1, CH_3), 3.96 (q, 2H, *J* 7.1, CH_2), 5.40 (d, 2H, J_{PH} 13.8, P-CH_2), 7.84-7.23 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 13.8 (CH_3), 33.2 (d, *J* 59.2, P^+-CH_2), 62.9 (CH_2), 118.0 (d, *J* 89.6, C-1), 130.4 (d, *J* 13.0, C-3), 134.1 (d, *J* 10.1, C-2), 135.3 (d, *J* 2.89, C-4), 164.5 (C=O).[67] IR ν_{max}/cm^{-1} (KBr) 3000 (C-H, sp^2), 2849 (C-H, sp^3), 1715 (C=O), 1590, 1490, 1420, 1398, 1370 (C-H, bend).

4.3.1.2. (Benzoylmethyl)triphenylphosphonium bromide 66b



Prepared according to general method 1, using triphenylphosphine (15.0g, 57 mmol) in dry toluene (150 ml) and phenacyl bromide (11.4 g, 57 mmol) in dry toluene (15 ml) to produce **66b** as white powder (25.2 g, 95%), m.p. 266-267°C (lit.[71], 265-266°C); ^{31}P NMR ($CDCl_3$) δ_p +22.5; ^{1}H NMR ($CDCl_3$) δ_H 6.34 (d, 2H, J_{PH} 12.03, P-CH_2), 8.34-7.26 (m, 20 H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: 38.9 (d, *J* 61.9, P^+-CH_2), 119.0 (d, *J* 89.6, C-1), 129.1 (C-3, Ph CO), 130.1 (C-4, Ph CO), 130.2 (d, *J* 13.0, C-3), 134.1 (d, *J* 10.1, C-2), 134.8 (C-2, PhCO), 134.8 (d, *J* 2.89, C-4), 135.0 (C-1, PhCO), 192.2 (C=O).[71] IR ν_{max}/cm^{-1} (KBr) 3050 (C-H, sp^2), 2940 (C-H, sp^3), 2564, 1650 (C=O), 1590, 1485, 1450, 1330, 1300.

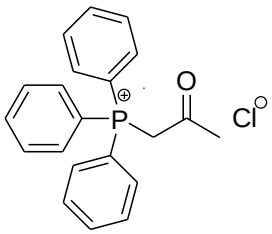
4.3.1.3. (Trimethylacetylmethyl)triphenylphosphonium bromide 66c



Prepared according to general method 1, using triphenylphosphine (20.0 g, 76 mmol) in dry toluene (150 ml) and 1-bromopinacolone (13.7 g, 76 mmol) in dry toluene (15 ml) to produce **66c** as a white powder (29.9 g, 89%), m.p. 216-217°C (lit.[72], 216-217°C); ^{31}P NMR ($CDCl_3$) δ_p +22.8. ^{1}H NMR ($CDCl_3$) δ_H 1.75 (s, 9H, CH_3), 5.84 (d, 2H, J_{PH} 12.0, P-CH_2), 7.84-7.24 (m, 15H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: 28.9 (3 x CH_3), 40.6 (d, *J* 11.6, C), 37.3 (d, *J* 56.4, P^+-CH_2), 119.0 (d, *J* 89.6, C-1), 130.2 (d, *J* 13.0, C-3), 134.1 (d,

J 11.6, C-2), 134.8 (d, *J* 2.89, C-4), 208.7 (C=O).[69] IR ν_{max}/cm^{-1} (KBr): 2960 (C-H, sp^2), 2780 (C-H, sp^3), 1700 (C=O), 1590, 1494, 1450, 1360, 1300.

4.3.1.4. (Acetylmethyl)tripenylphosphonium chloride 66d



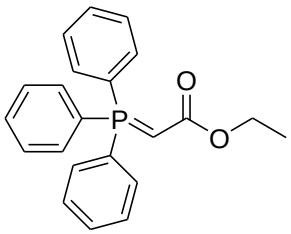
Prepared according to general method 1, using triphenylphosphine (16.4 g, 63 mmol) in dry toluene (150 ml) and chloroacetone (2.4 cm^3, 5.8 g, 63 mmol) in dry toluene (15 ml) to produce **66d** as a white powder (12.7 g, 57%), m.p. 235- 236°C (lit.[73], 233-234°C); ^{31}P NMR ($CDCl_3$) δ_p +14.0, +20.4. ^1H NMR ($CDCl_3$) δ_H 2.49 (d, 6H, J_{PH} 7.2, 2 x CH_3), 4.45 (d, 1H, *J* 19.4, OH), 6.04 (d, 3H, J_{PH} 11.3, P-CH_2, keto; P-CH, enol), 7.81-7.48 (m, 30H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: keto 24.0 (CH_3), 40.4 (d, *J* 57.8, P^+-CH_2), 118.9 (d, *J* 88.1, C-1), 130.0 (d, *J* 13.0, C-3), 134.0 (d, *J* 10.1, C-2), 134.7 (d, *J* 2.89, C-4), 201.3 (d, *J* 7.22, C=O); enol 32.5 (CH_3), 70.1 (d, *J* 99.7, P^+-CH_2), 121.9 (d, *J* 92.5, C-1), 129.9 (d, *J* 13.0, C-3), 133.3 (d, *J* 10.1, C-2), 134.7 (d, *J* 2.89, C-4), 181.6 (C-OH).[70] IR ν_{max}/cm^{-1} (KBr): 3050 (C-H, sp^2), 2760 (C-H, sp^3), 1700 (C=O), 1580, 1480, 1440, 1160.

4.3.2 Synthesis of β-oxo-phosphonium ylides

General method 2: To the salt (1 equivalent) dissolved in dichloromethane was added sodium hydroxide (1 equivalent) in water and the mixture was stirred rapidly. The mixture was transferred to a separating funnel and the organic phase was recovered, then washed with water, dried over magnesium sulphate, filtered and the solvnt

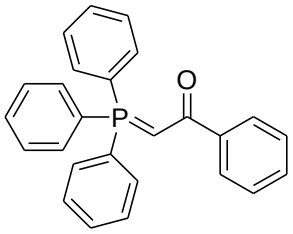
evaporated. The crude product was washed with a small amount of dry ether to remove unreacted starting marterial.

4.3.2.1. (Ethoxycarbonylmethylene)triphenylphosphorane 67a



Prepared according to general method 2, using salt **66a** (10 g, 23 mmol) in dichloromethane (200 ml) and sodium hydroxide (0.9 g, 23 mmol) in water (100 ml) to give **67a** as an off-white powder (7.2g, 72%), m.p. 162-164 °C (lit.[74] 162-163°C); ^{31}P NMR ($CDCl_3$) δ_p +18.2. ^{1}H NMR ($CDCl_3$) δ_H: 1.36 (t, 3H, *J* 7.1, CH_3), 2.87 (s, 1H, CH), 3.95 (q, 2H, *J* 7.1, CH_2), 7.64-7.24 (m, 15H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: 14.9 (CH_3), 30.2 (d, *J* 125.7, P=CH), 128.1 (d, *J* 95.4, C-1), 128.8 (d, *J* 11.6, C-3), 132.0 (C-4), 133.1 (d, *J* 10.1, C-2), 207.1 (C=O).[71] IR ν_{max}/cm^{-1} (KBr): 3056(C-H, sp^2), 2976, 2899, 1608 (C=O), 1520, 1479, 1437, 1372, 1331.

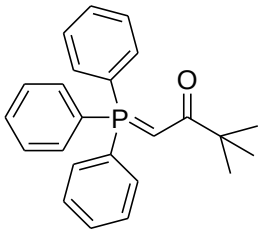
4.3.2.2. (Benzoylmethylene) triphenylphosphorane 67b



Prepared according to general method 2, using salt **66b** (10 g, 22 mmol) in dichloromethane (200 ml) and sodium hydroxide (0.87 g, 22 mmol) in water (100 ml). The ylide **67b** was isolated as a fine yellow powder (7.4g, 74%), m.p. 174-176 °C (lit.[74] 178-180°C); ^{31}P NMR ($CDCl_3$) δ_p +17.4. ^{1}H NMR ($CDCl_3$) δ_H: 4.41 (d, 1H, J_{PC} 22.3,

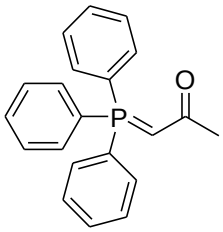
CH), 7.96-7.24 (m, 20H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: 50.8 (d, *J* 112.7, P=CH), 127.0 (d, *J* 23.1, C-1, PhCO), 127.8 (d, *J* 54.9, C-1), 129.0 (d, *J* 11.6, C-3), 129.5 (C-3, PhCO), 132.2 (C-4, C-4 PhCO), 133.2 (C-2, *J* 10.1, PhCO), 133.3 (d, *J* 10.1, C-2), 185.0 (C=O).[71] IR ν_{max}/cm^{-1} (KBr): 3049 (C-H, sp^2), 3010(C-H, sp^3), 1584, 1522 (C=O), 1483, 1436, 1386.

4.3.2.3. (Trimethylacetylmethylene) triphenylphosphorane 67c



Prepared according to general method 2, using salt **66c** (11.1 g, 25 mmol), dichloromethane (200 ml) and sodium hydroxide (1.3 g, 33 mmol) in water (100 ml) to give **67c** as an off-white powder (8.3 g, 75%), m.p. 172-173 °C (lit.[75] 172-173°C); ^{31}P NMR ($CDCl_3$) δ_P +16.8. ^{1}H NMR ($CDCl_3$) δ_H: 1.26 (s, 9H, CH_3), 3.72 (s, 1H, CH), 7.56-7.18 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 28.9 (3 x CH_3), 40.6 (d, *J* 11.6, C), 47.3 (d, *J* 109.8, P=CH), 128.0 (d, *J* 89.6, C-1), 128.8 (d, *J* 11.6, C-3), 131.8 (C-4), 133.1 (d, *J* 10.1, C-2), 200.3 (C=O).[75] IR ν_{max}/cm^{-1} (KBr): 3057 (C-H, sp^2), 2950 (C-H, sp^3), 1574, 1528 (C=O), 1476, 1435, 1391, 1371.

4.3.2.4. (Acetylmethylene) triphenylphosphorane 67d



Prepared according to general method 2, using salt **66d** (10 g, 28 mmol), dichloromethane (200 ml) and sodium hydroxide (1.13 g, 28 mmol) in water (100 ml) to give **67d** as an off-white powder (7.9g, 79%), m.p. 177-178 °C (lit.[70] 176-178°C); ^{31}P NMR ($CDCl_3$) δ_p +14.9; ^{1}H NMR ($CDCl_3$) δ_H: 2.14 (s, 3H, CH_3), 3.68 (d, 1H, J_{PH} 19.42, CH), 7.64-7.24 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 28.6 (d, *J* 17.3, CH_3), 51.7 (d, *J* 111.3, P=CH), 127.4 (d, *J* 91.0, C-1), 128.9 (d, *J* 11.6, C-3), 132.0 (C-4), 133.2 (d, *J* 10.1, C-2), 191.0 (C=O).[67] IR ν_{max}/cm^{-1} (KBr): 3048 (C-H, sp^2), 2986 (C-H, sp^3), 1580, 1537 (C=O), 1479, 1435, 1386.

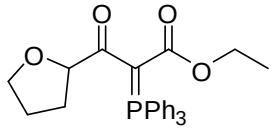
4.3.3. Synthesis of novel dioxo-heterocyclic ylides

General method 3: Acylation by acid chloride.

To a solution of the heterocyclic acid (1 equivalent) in dichloromethane was added oxalyl chloride (2.5 equivalent) and two drops of DMF. This was left to stir for 90 min followed by removal of excess oxalyl chloride under vacuum. The produced acid chloride was dissolved in dry dichloromethane and added dropwise to a solution of ylide (1 equivalent) in dry toluene and triethylamine (1 equivalent) and left to stir overnight at room temperature. The mixture was poured into water and a small amount of dichloromethane, sufficient to distinguish the phases, was added. The organic phase was separated and the aqueous phase extracted once with dichloromethane. The

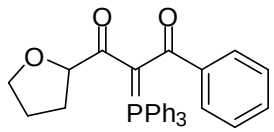
combined organic phases were dried over magnesium sulphate, filtered and the solvent evaporated.

4.3.3.1. Ethyl 3-oxo-3-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)propanoate 104a



Prepared according to method 3, tetrahydro-2-furancarboxylic acid (0.6 ml, 6 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (ethoxycarbonylmethylene)triphenylphosphorane **67a** (2.0 g, 6 mmol) in dry toluene (20 ml) and triethylamine (0.8 ml, 6 mmol). The mixture was poured into water (40 ml). The product was isolated as an oil (0.09 g, 3.6%).[31]P NMR ($CDCl_3$) δ_P +17.6, [1]H NMR ($CDCl_3$) δ_H 0.74 (t, 3H, *J* 7.1, CH_3), 3.71 (q, 2H, *J* 7.1, CH_2), 3.81 (m, 2H, CH_2), 3.92 (q, 2H, *J* 7.6, CH_2), 4.04 (q, 2H, *J* 6.8, CH_2), 5.46 (t, 1H, 6.8, CH), 7.48-7.80 (m, 15H, aromatic). [13]C NMR ($CDCl_3$) δ_C 13.7 (CH_3), 25.3 (CH_2), 31.0 (CH_2), 58.5 (CH_2), 68.9 (d, *J* 109.8, C=P), 80.7 (d, *J* 8.8, CH), 126.5 (d, *J* 93.7, C-1), 128.5 (d, *J* 11.7, C-3), 131.6 (d, *J* 2.9, C-4), 133.1 (d, *J* 9.5, C-2), 167.5 (d, *J* 13.9, CO), 196.7 (d, *J* 2.9, CO).

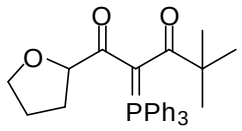
4.3.3.2. 1-Phenyl-3-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)propane- 1,3- dione 104b



Prepared according to method 3, tetrahydro-2-furancarboxylic acid (0.6 ml, 6 mmol) in dichlorormethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry

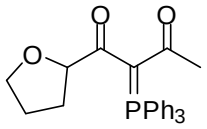
dichloromethane (20 ml), (benzoylmethylene) triphenylphosphorane **67b** (2.0 g, 5 mmol) in dry toluene (20 ml) and triethylamine (0.7 ml, 5 mmol). The mixture was poured into water (40 ml). The product was isolated as an oil and was oxidised without purification. ^{31}P NMR ($CDCl_3$) δ_p +17.4, ^{1}H NMR ($CDCl_3$) δ_H 1.83 (m, 2H, CH_2), 1.94 (q, 2H, *J* 7.1, CH_2), 3.92 (q, 1H, *J* 7.6, CH), 4.04 (q, 1H, *J* 7.3, CH), 4.56 (t, 1H, *J* 6.8, CH), 7.61-7.78 (m, 20H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C 25.5 (CH_2), 30.2 (CH_2), 69.1 (CH_2), 76.6 (d, *J* 8.8, CH), 84.6 (d, *J* 101.0, C=P), 125.8 (d, *J* 92.2, C-1, Ph_3P), 128.2 (C-3, Ph), 128.6 (d, *J* 12.4, C-3, Ph_3P), 129.0 (C-2, Ph), 130.8 (C-4, Ph), 131.8 (d, *J* 2.9, C-4, Ph_3P), 133.3 (d, *J* 10.3, C-2, Ph_3P), 137.9 (C-1, Ph), 193.2 (d, *J* 8.8, CO), 196.5 (d, *J* 9.2, CO).

4.3.3.3. 4,4-dimethyl-1-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)pentane-1,3-dione 104c



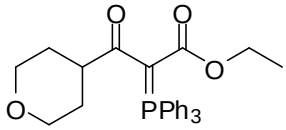
Prepared according to method 3, tetrahydro-2-furancarboxylic acid (0.6 ml, 6 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (trimethylacetylmethylene) triphenylphosphorane **67c** (2.0 g, 6 mmol) in dry toluene (20 ml) and triethylamine (0.8 ml, 6 mmol). The mixture was poured into water (40 ml). The product was isolated as an oil (0.24 g, 8.9%).^{31}P NMR ($CDCl_3$) δ_p +16.2, ^{1}H NMR ($CDCl_3$) δ_H 1.12 (s, 9H, 3 x CH_3), 1.79 (m, 2H, CH_2), 3.75 (m, 2H, CH_2), 3.92 (q, 1H, *J* 7.3, CH), 4.04 (q, 1H, *J* 6.6, CH), 4.42 (m, 1H, CH), 7.46-7.70 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C 25.5 (CH_2), 28.2 (3 x CH_3), 30.1 (CH_2), 45.9 (d, *J* 5.1, C), 68.3 (CH_2), 80.3 (d, *J* 124.4, C=P), 81.8 (d, *J* 6.6, CH), 126.2 (d, *J* 91.5, C-1), 128.4 (d, *J* 13.2, C-2), 131.7 (d, *J* 2.9, C-4), 133.9 (d, *J* 9.5, C-2), 174.1 (CO), 207.0 (CO).

4.3.3.4. 1-(Tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)butane-1,3-dione 104d



Prepared according to method 3, tetrahydro-2-furancarboxylic acid (0.6 ml, 6 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (acetylmethylene) triphenylphosphorane **67d** (2.0 g, 6 mmol) in dry toluene (10 ml) and triethylamine (0.9 ml, 6 mmol). The mixture was poured into water (40 ml). The product was isolated as an oil (0.3g, 12%).^{31}P NMR ($CDCl_3$) δ_p: +15.6, ^{1}H NMR ($CDCl_3$) δ_H 1.79 (q, 2H, *J* 7.1, CH_2), 2.03 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 3.74 (q, 1H, *J* 7.1, CH), 3.86 (q, 1H, *J* 7.1, CH), 4.87 (t, 1H, *J* 6.6, CH), 7.46-7.71 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C 25.4 (CH_2), 29.7 (CH_2), 30.3 (CH_3), 68.9 (CH_2), 81.0 (CH), 86.1 (d, *J* 101.0, C=P), 126.4 (d, *J* 92.9, C-1), 128.7 (d, *J* 12.4, C-3), 131.7 (d, *J* 2.9, C-4), 133.1 (d, *J* 9.5, C-2), 192.8 (d, *J* 10.3, CO), 196.4 (d, *J* 7.3, CO).

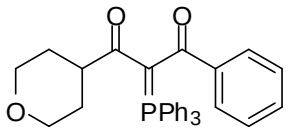
4.3.3.5. Ethyl 3-oxo-3-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene) propanoate 105a



Prepared according to method 1, tetrahydro-2H-pyran-4-carboxylic acid (1.0 g, 8 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (ethoxycarbonylmethylene)triphenylphosphorane **67a** (2.7 g, 8 mmol) in dry toluene (20 ml) and triethylamine (1.1 ml, 8 mmol). The mixture was poured into water (40 ml). The product was isolated as an oil and was oxidised without purification. ^{31}P NMR ($CDCl_3$) δ_p: +17.4, ^{1}H NMR ($CDCl_3$) δ_H 0.64 (t, 3H, *J* 7.07, CH_3),

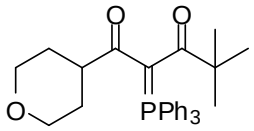
1.72 (m, 4H, 2 x CH_2), 3.54 (dt, 2H, *J* 2.02, J 11.4, CH_2), 3.71 (q, 2H, *J* 7.1, CH_2), 3.82 (m, 1H, CH), 3.97 (d, 2H, *J* 10.6, CH_2), 7.44-7.69 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C 13.7 (CH_3), 29.5 (2 x CH_2), 43.3 (d, *J* 6.6, CH), 58.3 (CH_2-CH_3), 68.0 (2 x CH_2), 69.9 (d, *J* 109.8, C=P), 126.9 (d, *J* 93.7, C-1), 128.5 (d, *J* 12.4, C-3), 131.5 (d, *J* 2.9, C-4), 132.9 (d, *J* 10.3, C-2), 167.5 (d, *J* 14.6, CO), 198.9 (d, *J* 2.9, CO).

4.3.3.6. 1-Phenyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene)propane-1,3-dione 105b



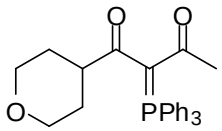
Prepared according to method 3, tetrahydro-2H-pyran-4-carboxylic acid (2.0 g, 15 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (benzoylmethylene) triphenylphosphorane **67b** (5.8 g, 15 mmol) in dry toluene (20 ml) and triethylamine (2.1 ml, 15 mmol). The mixture was poured into water (40 ml). The product was isolated as an oil and was oxidised without purification. ^{31}P NMR ($CDCl_3$) δ_p: +14.3, ^{1}H NMR ($CDCl_3$) δ_H 1.81 (s, 4H, 2 x CH_2), 2.61 (s, 1H, CH), 3.37 (s, 2H, CH_2), 3.92 (d, 2H, *J* 10.6, CH_2), 7.20-7.72 (m, 20H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C 28.1 (2 x CH_2), 40.9 (CH), 50.8 (d, *J* 111.2, C=P), 66.6 (2 x CH_2), 118.8 (d, *J* 92.2, C-1), 128.2 (C-3, Ph), 128.5 (d, *J* 11.7, C-3, Ph_3P), 129.0 (C-2, Ph), 130.6 (C-4, Ph), 132.0 (C-4, Ph_3P), 133.2 (d, *J* 10.3, C-2, Ph_3P), 137.7 (C-1, Ph-CO), 170.3 (CO), 192.3 (CO).

4.3.3.7. 4,4-Dimethyl-1-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene) pentane-1,3-dione 105c



Prepared according to method 3, tetrahydro-2H-pyran-4-carboxylic acid (1.0 ml, 8 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (trimethylacetylmethylene) triphenylphosphorane **67c** (2.8 g, 8 mmol) in dry toluene (20 ml) and triethylamine (1.1 ml, 8 mmol). The mixture was poured into water (40 ml). The product was isolated as oil and was oxidised without purification. ^{31}P NMR ($CDCl_3$) δ_p: +16.0; ^{1}H NMR ($CDCl_3$) δ_H 1.22 (s, 9H, 3 x CH_3), 1.89 (m, 4H, 2 x CH_2), 2.69 (m, 1H, CH), 3.46 (dt, 2H, *J* 3.0, *J* 11.1, CH_2), 4.00 (d, 2H, *J* 11.6, CH_2), 7.46-7.86 (m, 15 aromatic); ^{13}C NMR ($CDCl_3$) δ_C 26.8 (3 x CH_3), 28.0 (CH_2), 30.0 (CH_2), 41.0 (CH), 44.1 (C), 66.7 (CH2), 67.9 (CH_2), 72.0 (d, *J* 103.2, C=P), 118.6 (d, *J* 92.2, C-1), 128.5 (d, *J* 11.7, C-3), 131.9 (d, *J* 2.2, C-4), 132.1 (d, *J* 10.3, C-2), 204.0 (CO), 206.9 (CO).

4.3.3.8. 1-(Tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene)butane-1,3-dione 105d



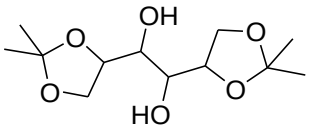
Prepared according to method 3, tetrahydro-2H-pyran-4-carboxylic acid (2.0 g, 15 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (acetylmethylene) triphenylphosphorane **67d** (4.9 g, 15 mmol) in dry toluene (20 ml) and triethylamine (2.1 ml, 15mmol). The mixture was poured into

water (40 ml). The product was isolated as oil and was oxidised without purification. ^{31}P NMR ($CDCl_3$) δ_p: +14.3, ^1H NMR ($CDCl_3$) δ_H: 1.89 (m, 4H, 2 x CH_2), 2.13 (s, 3H, CH_3), 2.69 (m, 1H, CH), 3.46 (dt, 2H, *J* 2.02, *J* 11.2, CH_2), 4.00 (d, 2H, *J* 11.6, CH_2), 7.47-7.69 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 28.1 (2 x CH_2), 28.2 (CH_3), 41.0 (CH), 52.8 (d, *J* 105.4, C=P), 66.7 (2 x CH_2), 126.8 (d, *J* 90.7, C-1), 128.9 (d, *J* 12.4, C-3), 132.0 (d, *J* 2.9, C-4), 133.1 (d, *J* 10.3, C-2), 177.1 (CO), 190.7 (d, *J* 4.4, CO).

4.3.4. Synthesis of sugar derivatives

4.3.4.1. Modification of sugars

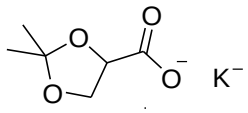
4.3.4.1.1. Synthesis of 1,2:5,6-diisopropylidenemannitol 87



1, 2-Dimethoxyethane (200 ml, 19 mmol) and 2, 2-dimethoxypropane (150 ml, 12 mmol) were added to mannitol (50.1 g, 275 mmol) and vigorously stirred. Tin (II) chloride (0.05 g, 0.3 mmol) was added and the slurry was heated under reflux for 16 hr. The clear solution which formed was left to cool to room temperature and then pyridine (1 ml) was added. The solvent was evaporated in vacuo (80ºC, 20 Torr). A white crude product which formed upon cooling was suspended in hexane and filtrated to collect the insoluble diacetone-D-mannitol. This was dissolved in acetone and evaporated in vacuo and dried under vacuum (0.1 Torr, 16 hr) to produce white crystals (45.3 g, 63%), m.p. 116-118ºC (lit[76] 118-120°C). ^1H NMR ($CDCl_3$) δ_H 1.35 (s, 3H, CH_3), 1.41(s, 3H, CH_3), 2.62 (d, 2H, J_H 6.7, CH_2), 3.74 (t, 1H, J_H 6.3, OH), 3.97(dd, 2H, J_H 8.4, J_H 5.4, CH_2), 4.10-4.20 (m, 4H, CH); ^{13}C NMR ($CDCl_3$) δ_C 25.3 (CH_3), 26.8 (CH_3), 66.8 (CH_2), 71.3

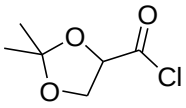
(CH), 76.4 (CH), 109.5 (CO).[73] IR ν_{max}/cm^{-1} (KBr): 3400 (O-H), 3300, 2990 (C-H, sp^3), 2930, 2889, 1380, 1372, 1265, 1215, 1079, 860.

4.3.4.1.2. Synthesis of 2,3-isopropylideneglycerate 88



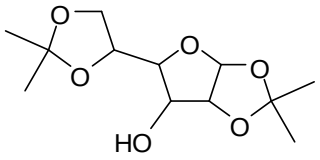
To a mixture of **87** (16.5 g, 63 mmol), dichloromethane (160 ml) and saturated aqueous sodium hydrogen carbonate (6 ml) solution was added sodium metaperiodate (18.9 g, 88 mmol) was added over 20 min with vigorous stirring, maintaining the temperature below 25ºC. This mixture was left to stir for 2 hr. The solution was decanted into another round bottom flask and an additional dichloromethane (100 ml) was added to the remaining solid and stirred for 5 min. This was added to the other solution and the solvent was evaporated. To the crude in water (250 ml) was added a solution of potassium hydroxide (17.4 g, 310 mmol) and potassium permanganate (26.8 g, 170 mmol) in water (400 ml) dropwise. The reaction mixture was stirred at room temperature for 3 hr. The resulting solid was filtered off and the filtrate was evaporated to reduce the volume to about 150 ml. This was acidified with 50% (v/v) sulfuric acid to pH 2-3. The mixture was extracted with ethyl acetate (3 x 100 ml). The inorganic layer was evaporated to give a white solid (11.7 g, 71%), mp: 210-212ºC (lit[77] 244-246ºC); ^{1}H NMR ($CDCl_3$) δ_H 1.28 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.80 (dd, 1H, J_H 6.87, 8.42, CH), 4.17 (dd, 1H, J_H 7.73, 8.42, CH), 4.40 (dd, 1H, J_H 6.70, 7.73, CH); ^{13}C NMR ($CDCl_3$) δ_C 23.8 (CH_3), 24.2 (CH_3), 66.3(CH_2), 74.6 (CH), 109.6(C), 176.7(CO). [74]

4.3.4.1.3. Synthesis of 2,3-isopropylideneglyceryl chloride 89



The reaction was run under nitrogen. **88** (1.9 g, 10 mmol) was suspended in anhydrous diethyl ether (20 ml). Oxalyl chloride (1.4 ml, 17 mmol) was added to the suspension dropwise by syringe over a period of 30 min. The mixture was left to stir for 20 h at room temperature. The solvent was removed by suction and left a white solid (1.8 g, 95%). ^{1}H NMR ($CDCl_3$) δ_H: 1.46 (s, CH_3), 1.47 (s, CH_3), 3.98 (t, 1H, J_H 6.19, CH), 4.12 (q, 1H, J_H 7.22, CH), 4.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ_C: 25.7 (CH_3), 26.0 (CH_3), 67.3 (CH_2), 81.6 (CH), 113.4 (C), 173.6 (CO).[77]

4.3.4.1.4. 1,2: 5,6-di-O-isopropylidene-α-D-glucofuranose 78



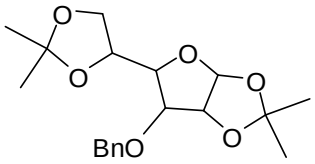
To a stirring solution of D-glucose (5.0 g, 28 mmol) in acetone (100 ml), in an ice bath, was added aqueous sulphuric acid (96%, 4 ml) in small portion at 15 min intervals and keeping the temperature between 5°C and 10°C. The mixture was stirred for 5hr and set aside to allow the temperature to rise room temperature. To the solution, in an ice bath, was slowly added 50% sodium hydroxide solution to near neutrality, followed by a small amount of sodium hydrogen carbonate to maintain the pH of the solution and then left to stand overnight. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in chloroform and washed with water (2 x 50 ml). The combined water solution was in turn washed with chloroform (50 ml) and to the initial chloroform solution. The organic phase was dried with magnesium sulphate and concentrated to give diacetone-D-glucose **78** as white solid (1.5 g, 42%), mp. 108-110°C (lit[58] 110°C).

^{1}H NMR ($CDCl_3$) δ_H: 1.28 (s, 3H, CH_3), 1.33(s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.94 (dd, 1H, *J* 5.4, *J* 2.7, CH), 4.02 (dd, 1H, *J* 2.7, CH), 4.13 (dd, 1H, *J* 5.4, CH), 4.29 (m, 2H, 2 x CH), 4.49 (d, 1H, *J* 3.0, CH). ^{13}C NMR ($CDCl_3$) δ_C: 25.2 (CH_3), 26.2 (CH_3), 26.9 (2 x CH_3), 67.6 (CH_2), 73.2 (CH), 74.9 (CH), 81.3 (CH), 105.3 (CH), 109.6 (C), 111.9 (C).[58]

The inorganic phase was also concentrated to give monoacetone-D-glucose as a brown solid (1.7 g, 55%), mp. 157-159°C (lit[58] 160°C). ^{1}H NMR ($CDCl_3$) δ_H: 1.33(s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.59 (dd, 1H, *J* 5.4, CH), 3.77 (dd, 1H, *J* 5.4, CH), 3.88 (m, 1H, CH), 4.05 (dd, 1H, *J* 2.7, CH), 4.28 (d, 1H, *J* 2.0, CH), 4.66 (d, 1H, *J* 2.7, CH), 5.98 (d, 1H, *J* 2.8, CH).

The product (1.7 g, 8 mmol) in acetone (8 ml), 2,2-dimethoxypropane (4 ml, 33 mmol) and *p*-toluenesulfonic acid (0.1 g, 1 mmol) acid was stirred for 10 min. Aqueous sodium hydrogen carbonate was added to neutralise the mixture. The solution was concentrated. The residue was dissolved in dichlormethane (20 ml), washed with water, dried with magnesium sulphate and evaporated. The crude was crystallised from ethanol to give diacetone-D-glucose as white solid (5.5 g, 52%).

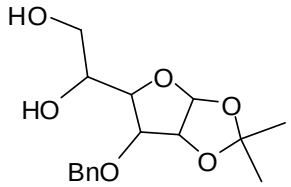
4.3.4.1.5. 3-O-benzyl-1, 2: 5, 6-di-O-isopropylidene-α-D-glucofuranose 79



To a solution of diacetone-D-glucose **78** (10.0 g, 39 mmol) in DMF (80 ml), sodium hydride (4.0 g, 167 mmol) was added in protions and stirred for 30 min. Benzyl bromide (10 ml, 84 mmol) in DMF (10 ml) was added dropwise to the mixture and stirred at room temperature for an extra 2.5 hr. Excess reagents were decomposed by

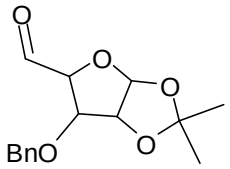
careful adding methanol (15 ml) and the solvents were evaporated. The residue was extracted with chloroform (150 ml), washed with water (3 x 100 ml), dried over magnesium sulphate, filtered and the solvent evaporated to give yellow oil (14.7 g, 68%).[1]H NMR ($CDCl_3$) δ_H 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 4.03 (d, 1H, *J* 2.5, CH), 4.05 (d, 1H, *J* 2.5, CH), 4.15 (m, 2H, CH2), 4.39 (q, 1H, *J* 6.1, CH), 4.61 (d, 1H, *J* 4.0, CH), 4.69 (q, 1H, *J* 11.6, CH_2), 5.92 (d, 1H, *J* 3.5, CH), 7.36 (m, 5H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C 25.5 (CH_3), 26.3 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 67.5 (CH_2), 72.5 (CH_2), 72.6 (CH), 81.4 (CH), 81.8 (CH), 82.7 (CH), 105.4 (CH), 109.1 (C), 111.9 (C), 127.8 (C-3), 127.9 (C-4), 128.5 (C-2), 137.7 (C-1).[78]

4.3.4.1.6. 3-O-benzyl-5, 6-diol-1,2-O-isopropylidene-α-D-glucofuranose 80



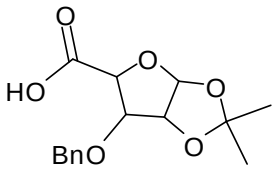
The protected sugar derivative **79** (14.0 g, 40 mmol) in methanol (100 ml) and 0.8% aqueous sulphuric acid (88 ml) was stirred for 12 hr and monitored by TLC (ether/petroleum ether, 1:1) for completion. The reaction mixture was neutralised with sodium hydrogen carbonate and filtered. The filtrate was concentrated to give dark yellow oil (7.65 g, 61%). ^{1}H NMR ($CDCl_3$) δ_H: 1.35 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 2.02 (t,1H, *J* 6.1, OH), 2.49 (d, 1H, *J* 6.1, OH), 3.71 (m, 1H, CH), 3.84 (m, 1H, CH), 4.06 (m, 1H, CH), 4.14 (m, 2H, CH_2), 4.66 (q, 2H, *J* 11.6,CH_2), 4.67 (d, *J* 3.5, CH), 5.97 (d, 1H, *J* 3.5, CH), 7.35-7.42 (m, 5H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: 26.3 (CH_3), 26.8 (CH_3), 64.5 (CH_2), 69.4 (CH2), 72.2 (CH), 80.0 (CH), 82.0 (CH), 82.1 (CH), 105.2 (CH), 112.0 (C), 128.0 (C-3), 128.4 (C-4), 128.8 (C-2), 138.3 (C-1).[79]

4.3.4.1.7. 3-O-benzyl-5-carbaldehyde-1,2-isopropylidene-α-D-glucofuranose 81



Sodium metaperiodate (5.3 g, 25 mmol) was added to a stirring solution of 5, 6-deprotected sugar **80** (7.65 g, 25 mmol) in water (100 ml). Sodium hydroxide (0.1 N) was carefully added to the mixture to adjust the pH to 7, allowing oxidation to take place. The product was extracted with chloroform (4 x 50 ml) and the combined extracts were washed, dried over magnesium sulphate, filtered and the solvent evaporated to give orange oil (6.1 g, 88%). ^{1}H NMR ($CDCl_3$) δ_H: 1.36 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.37 (d, 1H, *J* 3.5, CH), 4.53 (s, 1H, CH), 4.59 (d, 1H, *J* 1.5, CH), 4.62 (s, 1H, CH), 4.67 (d, 1H, *J* 3.5, CH), 6.15 (d, 1H, *J* 3.5, CH), 7.30-7.40 (m, 5H, aromatic), 9.70 (d, 1H, *J* 1.5, CH). ^{13}C NMR ($CDCl_3$) δ_C: 26.5 (CH_3), 27.1 (CH_3), 72.5 (CH_2), 82.3 (CH), 83.8 (CH), 84.7 (CH), 106.3 (CH), 112.7 (C), 127.8 (C-2), 128.3 (C-4), 128.7 (C-3), 136.7 (C-1), 200.1 (CO).[76]

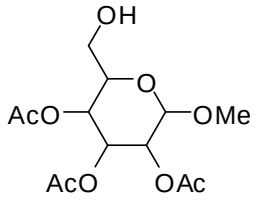
4.3.4.1.8. 3-O-benzyl-1,2-isopropylidene-α-D-glucofuranuronic acid 82



To an emulsion of aqueous solution of silver nitrate (0.588 M, 96 ml) and the aldehyde **81** (6.1 g, 22 mmol) was added aqueous potassium hydroxide (0.91 M, 123 ml) solution to form a dark precipitate. This was stirred for an hour, filtered through a Buchner funnel and the filtrate cooled to 0ºC. The solution was acidified with aqueous hydrochloric acid (6 M) to pH=2, which was then extracted with dichloromethane. The

combined extracts were washed with brine, dried and evaporated to give a white solid (2.1 g, 33%), mp 139-141ºC (lit. 140-141 ºC). ^{1}H NMR ($CDCl_3$) δ_H: 1.34 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.35 (d, 1H, *J* 3.5, CH), 4.63 (q, 2H, *J* 11.6, CH_2), 4.63 (d, 1H, *J* 3.5, CH), 4.89 (d, 1H, *J* 3.5, CH), 6.11 (d, 1H, *J* 3.5, CH), 7.27-7.38 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 26.4 (CH_3), 27.0 (CH_3), 72.8 (CH_2), 79.7 (CH), 82.0 (CH), 82.4 (CH), 105.9 (CH), 112.9 (C), 127.8 (C-3), 128.1 (C-4), 128.5 (C-2), 136.6 (C-1), 171.1 (CO).[80]

4.3.4.1.9. Methyl 2,3,4-tri-O-acetyl-α-D-glucopyranoside 94a and 94b



Step 1

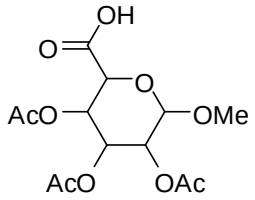
A solution of methyl α-D-glucopyranoside (20.0 g, 103 mmol) and trityl chloride (28.7 g, 103 mmol) in pyridine (150 ml) was heated for 3 hr at 90ºC. The solution was cooled, diluted with sodium carbonate (200 ml) and extracted with dichloromethane (3 x 150 ml). The combined extracts were dried and evaporated to give yellow oil.

The monotrityl derivative was straight away dissolved in pyridine (100 ml) and acetic anhydride (80 ml, 847 mmol) was added in one portion. After 12 hr of stirring, the mixture was slowly poured into a mixture of ice water (1 L) and glacial acetic acid (100 ml) and vigorously stirred for 2 hr. The precipitate was filtered, washed with cold water and left to air-dry. The product was then used directly in step 2.

Step 2

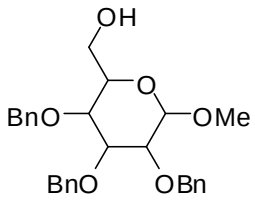
To a solution of the protected sugar in glacial acetic acid (200 ml) was added a saturated solution of hydrogen bromide (20 ml) in glacial acetic acid (20 ml). The mixture was shaken for 1 min to precipitate out trityl bromide. This was filtered by suction and the filtrate poured immediately into ice water. The product was extracted with chloroform (250 ml), which in turn was washed with cold water (3 x 100 ml), dried over magnesium sulphate, filtered and the solvent evaporated. This gave an oil (21.0 g, 64%) which was purified by column chromatography (ethyl acetate/hexane, 1:1) to give C-4 deprotected sugar **94a** (5.0 g, 30%). ^{1}H NMR ($CDCl_3$) δ_H: 2.05 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 4.01 (m, 1H, CH), 4.13 (dd, 1H, *J* 2.3, *J* 2.3, CH), 4.28 (dd, 1H, *J* 4.6, *J* 4.6, CH), 4.92 (dd, 1H, *J* 3.8, *J* 3.8, CH), 4.97 (d, 1H, *J* 3.8, CH), 5.09 (t, 1H, *J* 9.7, CH), 5.50 (t, 1H, *J* 9.9, CH). ^{13}C NMR ($CDCl_3$) δ_C: 21.3 (3 x CH_3), 55.8 (OCH_3), 62.8 (CH_2), 66.3 (CH), 68.1 (CH), 69.6 (CH), 70.9 (CH), 72.3 (CH), 99.6 (CH), 169.5 (CO), 170.6 (CO), 171.0 (CO);[64] C-6 deprotected **94b** (1.3 g, 8%). ^{1}H NMR ($CDCl_3$) δ_H: 2.06 (d, 3H, *J* 16.2, CH_3), 2.10 (d, 3H, *J* 4.6, CH_3), 2.14 (d, 3H, *J* 12.1, CH_3), 2.93 (d, 1H, *J* 5.6, OH), 3.43 (d, 3H, *J* 2.5, CH_3), 3.85 (m, 1H, CH), 4.32 (dd, 1H, *J* 2.5, *J* 2.5, CH), 4.51 (dd, 1H, *J* 4.6, *J* 4.6, CH), 4.89 (m, 1H, CH), 4.93 (d, 1H, *J* 3.5, CH), 5.01 (t, 1H, *J* 9.9, *J* 3.5, CH), 5.32 (t, 1H, *J* 9.6, CH). ^{13}C NMR ($CDCl_3$) δ_C: 20.7 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 55.4 (OCH_3), 61.1 (CH_2), 68.9 (CH), 69.3 (CH), 69.4 (CH), 69.7 (CH), 96.8 (CH), 169.3 (CO), 170.3 (CO), 170.4 (CO);[78] and a mixture of both (10.1 g, 62%).

4.3.4.1.9. Methyl 2,3,4-tri-O-acetyl-α-D-glucopyranoic acid 95



Chromium trioxide (6.6 g, 66 mmol) in sulphuric acid [3.5 M] (8.6 ml, 161 mmol) was added dropwise to a solution of the acetylated sugar (1.3 g, 4 mmol) in acetone (80 ml), at 0ºC. After 3 hr at 0ºC, water (50 ml) was added to dilute the excess chromium. The product was extracted with dichloromethane (3 x 100 ml). The extract was then washed with 20% sodium chloride (50 ml), dried over magnesium sulphate, filtered and the solvent evaporated. The crude was recrystallised with ethyl acetate/hexane (1:1) to give an off white powder (1.2 g, 86%), mp 148°C (lit.[79] 149°C). ^{1}H NMR ($CDCl_3$) δ_H: 2.05 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 4.38 (d, 1H, *J* 10.6, CH), 4.93 (dd, 1H, *J* 3.5, *J* 4.0, CH), 5.09 (d, 1H, *J* 3.5, CH), 5.25 (t, 1H, *J* 9.9, CH), 5.50 (t, 1H, *J* 9.9, CH). ^{13}C NMR ($CDCl_3$) δ_C: 20.6 (3 x CH_3), 56.2 (OCH_3), 67.5 (CH), 69.2 (CH), 69.3 (CH), 70.4 (CH), 97.1 (CH), 169.8 (CO), 169.9 (CO), 170.1 (CO), 170.2 (CO).[81]

4.3.4.1.10. Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside 97



Step 1

Trityl chloride (7.2 g, 26 mmol) was added to methyl α-D-glucopyranoside (5.0 g, 26 mmol) in pyridine (70 ml) and heated for 3 hr at 90ºC. The solution was then allowed to

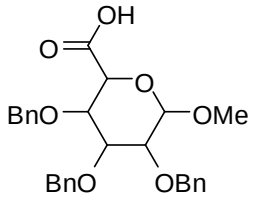
cool and saturated sodium carbonate (70 ml) was added. The product was extracted with dichloromethane (3 x 100 ml), dried and evaporated to give an oily product.

The tritylated sugar in DMF (50 ml) was added to sodium hydride (3.5 g, 146 mmol) in DMF (80 ml) at 0ºC over a 30 min period. Benzyl bromide (20.0 ml, 116 mmol) was then added and left to stir for 3 hr at room temperature. Extra DMF (70 ml) was added and the mixture was left to stir overnight. A sufficient amount of acetic acid was added to the mixture to decompose the excess sodium hydride, followed by water (250 ml). The product was extracted with ether (4 x 200 ml), dried over magnesium sulphate, filtered and the solvent evaporated. The product was then used directly in step 2.

Step 2

The product, fully protected sugar, was dissolved in a mixture of concentrated sulphuric acid (4.3 ml) and methanol (266 ml) and stirred for 90 min at room temperature. This was basified with 10% sodium hydroxide and extracted with dichloromethane (3 x 150 ml), dried over magnesium sulphate, filtered and the solvent evaporated. The crude was purified by column chromatography (ethyl acetate/hexane, 1:4) followed by ethyl acetate to give an oil (4.98 g, 42%). ^{1}H NMR ($CDCl_3$) δ_H: 3.39 (s, 3H, CH_3), 3.53 (m, 2H, CH_2), 4.03 (t, 1H, *J* 9.3, CH), 4.59 (d, 1H, *J* 3.5, CH), 4.68 (d, 1H, *J* 3.0, CH), 4.71 (d, 2H, *J* 3.0, CH_2), 4.72 (d, 2H, *J* 2.0, CH_2), 4.81 (s, 1H, CH), 4.84 (d, 1H, *J* 3.5, CH), 4.88 (d, 1H, *J* 8.0, CH), 4.92 (d, 1H, *J* 2.5, CH), 5.01 (d, 1H, *J* 11.1, CH), 7.35-7.40 (m, 15H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: 55.2 (CH_3), 61.9 (CH_2), 70.7(CH), 73.4 (CH_2), 75.0 (CH_2), 75.8 (CH_2), 77.4 (CH), 80.0 (CH), 82.0 (CH), 98.2 (CH), 127.9 (C-2), 128.1 (C-4), 128.5 (C-3), 138.1 (C-1).[82]

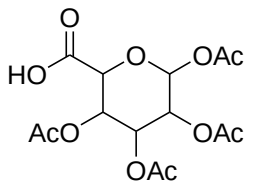
4.3.4.1.11. Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoic acid 98



Chromium trioxide (25.8 g, 258 mmol) in sulphuric acid [3.5 M] (33.6 ml, 343 mmol) was added dropwise to a solution of the benzylated sugar (4.98 g, 11 mmol) in acetone (100 ml), at 0ºC. After 3 hr at 0ºC, water (100 ml) was added to dilute the excess chromium. The product was extracted with dichloromethane (3 x 100 ml). The extract was then washed with 20% sodium chloride (2 x 50 ml), dried over magnesium sulphate, filtered and the solvent evaporated to give a yellow solid (2.8 g, 55%). ^{1}H NMR ($CDCl_3$) δ_H: 3.44 (s, 3H, CH_3), 3.75 (t, 1H, *J* 9.6, CH), 4.05 (t, 1H, *J* 9.3, CH), 4.26 (d, 1H, *J* 10.1, CH), 4.64 (s, 1H, CH), 4.65 (s, 1H, CH), 4.68 (s, 1H, CH), 4.71 (s, 1H, CH), 4.82 (s, 1H, CH), 4.84 (s, 1H, CH), 4.99(s, 1H, CH), 7.49-7.67 (m, 15H, aromatics). ^{13}C NMR ($CDCl_3$) δ_C: 55.7 (CH_3), 69.6 (CH), 73.6(CH_2), 75.2 (CH_2), 76.0 (CH_2), 79.2 (CH), 79.4 (CH), 81.4 (CH), 98.6 (CH), 127.8 (C-2), 128.0 (C-4), 128.4 (C-3), 137.9 (C-1), 172.2 (CO).

4.3.4.2. Attempted synthesis

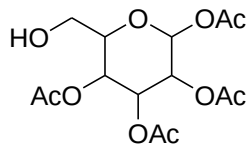
4.3.4.2.1. Synthesis of tetra-O-acetyl-D-glucuronic acid 86



p-Toluenesulfonic acid (2.4 g, 13 mmol) was dissolved in acetic anhydride (53 ml) and cooled to 0ºC. Sodium D-glucuronic acid (2.8 g, 12 mmol) was added in one portion and the mixture was left to stir for 3 hr. A white precipitate formed but it disappeared on

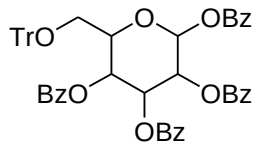
addition of sodium acetate (4.1 g, 50 mmol). The solution was extracted sequentially with ether (75 ml), dichloromethane (2 x 100 ml). The combined organic phases were washed with water (3 x 100 ml) to remove excess acetic anhydride. The organic phase was dried over magnesium sulphate, the solvents evaporated to give an oil (0.3 g, 11%). ^{1}H NMR ($CDCl_3$) δ_H: 1.97 (s, 3H, CH_3), 1.98 (s, 6H, 2 x CH_3), 2.05 (s, 3H, CH_3), 4.19 (d, 1H, *J* 8.5, CH), 5.07 (1H, *J* 7.6, CH), 5.25 (m, 2H, 2 x CH), 5.73 (d, 1H, *J* 7.2, CH), 8.54 (br, 1H, OH). ^{13}C NMR ($CDCl_3$) δ_C: 20.6 (4 x CH_3), 68.5 (CH), 70.2 (CH),71.8 (CH), 72.4 (CH), 91.3 (CH), 169.2 (CO), 169.4 (CO), 169.5 (CO), 169.8 (CO), 170.8 (CO).[81]

4.3.4.2.2. Synthesis of 1,2,3,4-tetra-O-acetyl-β-D-glucose 75



Anhydrous D-glucose (6 g, 33 mmol) and trityl chloride (9.7 g, 35 mmol) were dissolved in anhydrous pyridine (50 ml) by warming on a steam bath. Acetic anhydride (30 ml) was added to the hot solution and the mixture was left to cool to room temperature and kept at that temperature for 12 hr. The mixture was poured as a thin stream into a mixture of ice water and acetic acid with vigorous stirring. After 2 hr of stirring, the precipitate which formed was isolated by filtration and the gummy residue was immediately added to into fresh ice water. This was stirred for 10 min to the remove residual pyridine. The precipitate was filtered and washed with water and left to air-dry. This was followed by the separation of the α- and β-isomers by differential solubility in dry ether. The β-isomer dissolved in ether and after removal of the solvent it was recrystallized with hot ethanol. Impurities were still present and these were difficult to remove.

4.3.4.2.3. Synthesis of 1,2,3,4-tetra-O-benzoyl-6-O-triphenylmethyl-α and β-D-glucopyranose 77



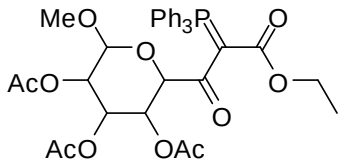
A mixture of D-glucose (5.0 g, 28 mmol), DMAP (1.7 g, 14 mmol), triethylamine (7 ml) and trityl chloride (9.2 g, 33 mmol) in DMF (20 ml) was stirred for 18 hr at room temperature. Pyridine (83 ml) was added followed by benzoyl chloride (25.8 ml, 222 mmol) in portions over a period of 30 min at -20ºC and this was left to stir for 2 hr. The reaction mixture was poured into ice-water (200 ml) and extracted with dichloromethane (3 x 150 ml). The combined organic layer was washed with 3M sulfuric acid (2 x 50 ml) and saturated aqueous sodium hydrogen carbonate solution (30 ml), dried over magnesium sulphate, filtered and the solvent evaporated. The residue was purified by flash column chromatography (toluene/ ethyl acetate, 10:1). The purified compound was an anomeric mixture which was separated by preparative TLC (toluene) to give α-isomer (25%, mp 95°C) and β-isomer (38%, mp 83°C). ^{1}H NMR and ^{13}C NMR spectroscopy were complex.

4.3.5. Synthesis of sugar-derived β,β'-dioxo ylides

General method 4: Acylation by carboxylic acid

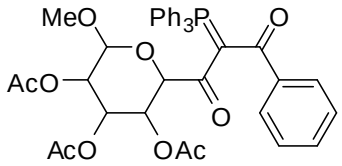
EDCI-HCl (1.1 equivalent) and DMAP were added to a stirring solution of the ylide (1 equivalent) and sugar acid (1 equivalent) in dry dichloromethane at 0ºC. The mixture was stirred, under nitrogen, for an extra 30 min at 0ºC, then allowed to warm up to room temperature overnight. The mixture was poured into brine, extracted with dichloromethane and then combined organic extracts were dried over magnesium sulphate, filtered and the solvent evaporated.

4.3.5.1. Ethyl methyl 2,3,4-tri-*O*-acetyl-7-deoxy-7-(triphenylphosphoranylidene)oct-6-ulosepyranosiduronate 107a



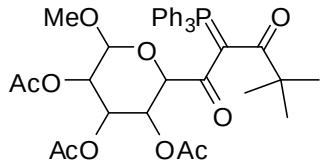
Prepared according to method 3, **95** (0.5 g, 2 mmol) in dichloromethane (20 ml), oxalyl chloride (1 ml); The acid chloride in dry dichloromethane (20 ml), (ethoxycarbonylmethylene)triphenylphosphorane **67a** (0.52 g, 2 mmol) and triethylamine (0.2 ml, 2 mmol) in toluene (20 ml). The mixture was poured into water (40 ml). The product was isolated as an oil (0.13 g, 13%).^{31}P NMR ($CDCl_3$) δ_p: +17.2, ^{1}H NMR ($CDCl_3$) δ_H: 0.75 (t, *J* 7.1, CH_3), 1.85 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.77 (m, 2H, CH_2), 4.90 (dd, 1H, *J* 3.0, *J* 3.5, CH), 4.99 (d, 1H, *J* 3.5, CH), 5.26 (t, 1H, *J* 9.6, CH), 5.52 (t, 1H, *J* 10.1, CH), 5.77 (d, 1H, *J* 10.1, CH), 7.43- 7.65 (m, 15H, CH-aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 13.7 (CH_3), 20.6 (CH_3), 20.7 (2 x CH_3) 55.9 (OMe), 58.9 (CH_2), 67.8 (d, *J* 9.5, CH), 70.7 (CH), 70.9 (2 x CH), 72.9 (d, *J* 108.3, C=P), 97.2 (CH), 125.7 (d, *J* 93.7, C-1), 128.6 (d, *J* 12.4, C-3), 131.8 (d, *J* 2.9, C-4), 133.0 (d, *J* 10.3, C-2), 167.0 (d, *J* 13.9, CO), 169.0 (CO), 170.1 (CO), 170.3 (CO), 187.6 (d, *J* 4.4, CO). IR ν_{max}/cm^{-1}: 3060(C-H, sp^2), 2979, 2930 (C-H, sp^3), 2361, 1751 (C=O), 1672,1564, 1439, 1366, 1302, 1225. ESI-MS, *m/z* $[M + H]^+$ 665 (100).

4.3.5.2. Methyl 5,6,7-tri-*O*-acetyl-2-deoxy-1-phenyl-2-(triphenylphosphoranylidene) octodialdo-8,4-pyranosid-3-ulose 107b



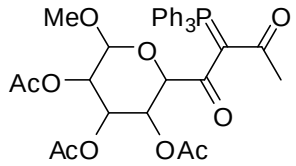
Prepared according to method 3, **95** (0.5 g, 2 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (benzoylmethylene) triphenylphosphorane **67b** (0.57 g, 2 mmol) and triethylamine (0.2 ml, 2 mmol) in dry toluene (20 ml). The mixture was poured into water (40 ml). The product was isolated as an oil (0.1 g, 10%). ^{31}P NMR ($CDCl_3$) δ_p: +18.8, ^{1}H NMR ($CDCl_3$) δ_H: 2.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 4.31 (dd, 1H, *J* 2.0, *J* 6.6, CH), 4.38, (d, 1H, *J* 2.0, CH), 5.08 (t, 1H, *J* 9.6, CH) ,5.16 (d, 1H, *J* 3.0, CH), 5.18 (d, 1H, *J* 3.5, CH), 5.28 (d, 1H, *J* 3.0, CH), 7.34- 7.75 (m, 20H, CH-aromatic). ^{13}C NMR ($CDCl_3$)δ_C: 20.9 (CH_3), 21.1 (2 x CH_3) 56.7 (CH_3), 66.4(CH), 68.5 (CH), 81.7 (d, *J* 103.2, C=P), 97.1 (CH), 101.9 (CH), 125.3 (d, *J* 92.2, C-1, Ph_3P), 127.9 (C-3, Ph), 128.8 (d, *J* 13.2, C-3), 128.9 (C-2, Ph), 130.6 (C-4, Ph), 132.2 (d, *J* 2.9, C-4), 133.6 (d, *J* 10.3, C-2), 143.0 (C-1, Ph), 151.1 (d, *J* 11.7, CO), 169.8(CO), 170.0 (CO), 184.8 (d, *J* 6.6, CO), 192.9 (d, *J* 7.3, CO). IR ν_{max}/cm^{-1}: 3058(C-H, sp^2), 2998, 2929 (C-H, sp^3), 2361, 2340, 1744 (C=O), 1670, 1536, 1439, 1369, 1223. ESI-MS, *m/z* $[M + H]^+$ 697 (4), 637 (100), 423 (19).

4.3.5.3. Methyl 2,3,4-tri-*O*-acetyl-9,9-dimethyl-7-(triphenylphosphoranylidene) decopyranoside-6,8-diulose 107c



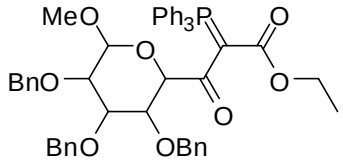
Prepared according to method 3, **95** (0.5 g, 2 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (trimethylacetylmethylene) triphenylphosphorane **37c** (0.54 g, 2 mmol) and triethylamine (0.2 g, 2 mmol) in dry toluene (20 ml). The mixture was poured into water (40 ml). The product was isolated as an oil (0.05 g, 5%). ^{31}P NMR ($CDCl_3$) δ_p: +17.1, ^{1}H NMR ($CDCl_3$) δ_H: 1.16 (s, 9H, 3 x CH_3), 1.98 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.43 (s, 1H, CH), 3.47 (s, 3H, OCH_3), 4.85 (dd, 1H, *J* 2.5, *J* 7.6, CH), 4.89 (d, 1H, *J* 2.0, CH), 5.49 (dd, 1H, *J* 2.53, *J* 7.83, CH), 5.53 (d, 1H, *J* 3.0, CH), 7.46-7.68 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 20.9 (CH_3), 20.9 (CH_3), 21.1 (CH_3), 28.2 (3 x CH_3), 45.3 (d, *J* 5.1, C), 56.6 (OCH_3), 66.9 (CH), 69.1 (2 x CH), 78.9 (d, *J* 101.7, C=P), 97.9 (CH), 103.2 (CH), 125.9 (d, *J* 92.9, C-1), 128.6 (d, *J* 12.4, C-3), 131.9 (d, *J* 2.2, C-4), 133.7 (d, *J* 9.5, C-2), 169.9 (CO), 170.1 (CO), 171.1 (CO) 181.2 (d, *J* 8.8, CO), 205.9 (d, *J* 4.4, CO). IR ν_{max}/cm^{-1}: 3058(C-H, sp^2), 2975, 2931 (C-H, sp^3), 2361, 1751 (C=O), 1673, 1564, 1439, 1366, 1302, 1225. ESI-MS, *m/z* [M + H – Na^+]$^+$ 654 (3), 617 (100), 557 (23), 443 (10), 279 (22).

4.3.5.4. Methyl 2,3,4-tri-*O*-acetyl-7,9-dideoxy-7-(triphenylphosphoranylidene) nonopyranoside-6,8-diulose 107d



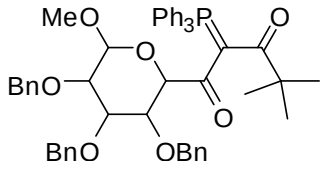
Prepared according to method 3, **95** (0.5 g, 2 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (acetylmethylene) triphenylphosphorane **67d** (0.48 g, 2 mmol) and triethylamine ((0.2 g, 2 mmol) in dry toluene (20 ml). The mixture was poured into water (40 ml). The product was isolated as an oil (0.04 g, 4%). ^{31}P NMR ($CDCl_3$) δ_p: +16.7, ^{1}H NMR ($CDCl_3$) δ_H: 1.87 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 4.89 (dd, 1H, *J* 3.54, *J* 10.10, CH), 5.02 (d, 1H, *J* 4.0, CH), 5.27 (d, H, *J* 1.0, CH), 5.28 (d, H, *J* 1.0, CH), 5.50 (m, 1H, CH), 7.45-7.63 (m, 15H, CH-aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 20.8 (3 x CH_3), 30.8 (CH_3), 56.7 (CH_3), 70.0 (d, 1H, *J* 9.5, CH), 70.7 (2 x CH), 77.3 (CH), 89.4 (d, *J* 100.3, C=P), 97.7 (CH), 125.8 (d, *J* 92.2, C-1, Ph_3P), 128.7 (d, *J* 12.4, C-3), 131.9 (d, *J* 2.9, C-4), 133.0 (d, *J* 9.5, C-2), 168.9 (CO), 170.1 (CO), 170.5 (CO), 186.8 (d, *J* 6.6,CO), 192.8 (d, *J* 8.1,CO). IR ν_{max}/cm^{-1}: 3060(C-H, sp^2), 2979, 2930 (C-H, sp^3), 2361, 1751 (C=O), 1673,1564, 1439, 1366, 1302, 1225. ESI-MS, *m/z* $[M + H]^+$ 635 (4), 575 (100), 515 (5).

4.3.5.5. Ethyl methyl 2,3,4-tri-*O*-benzyl-7-deoxy-7-(triphenylphosphoranylidene)oct-6-ulosepyranosiduronate 108a



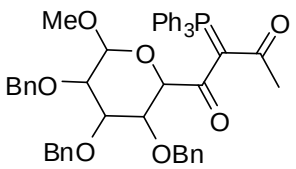
Prepared according to method 3, **98** (1.0 g, 2 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (ethoxycarbonylmethylene)triphenylphosphorane **67a** (0.7 g, 2 mmol) and triethylamine (0.3 ml, 2 mmol) in dry toluene (20 ml). The mixture was poured into water (40 ml). The product was isolated as an oil (0.03 g, 20%). ^{31}P NMR ($CDCl_3$) δ_p: +17.0; ^{1}H NMR ($CDCl_3$) δ_H: 0.63 (t, 3H, *J* 7.1, CH_3), 1.26 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.00 (s, 2H, CH_2), 3.06 (s, 1H, CH), 3.13 (s, 1H, CH) 3.64 (s, 3H, CH_3), 4.30 (s, 1H, CH), 4.33 (s, 1H, CH), 4.53 (s, 1H, CH), 4.56 (s, 1H, CH), 4.67 (s, 1H, CH), 4.70 (s, 1H, CH), 4.91 (d, 1H, *J* 12.1, CH), 5.06 (d, 1H, J 4.0, CH), 5.88 (d, 1H, *J* 9.1, CH), 7.23-7.42 (m, 30H, aromatic); ^{13}C NMR ($CDCl_3$) δ_C: 13.6 (CH_3), 56.1(CH_3), 59.0 (CH_2), 71.8 (CH), 71.9 (CH), 72.3 (3 x CH_2), 80.0 (CH), 80.6 (CH), 102.4 (CH), 125.7 (d, *J* 92.9, C-1, Ph_3P), 127.3 (C-2, Ph-CH_2), 128.1 (C-4, Ph-CH_2),128.5 (C-3, Ph-CH_2), 128.6 (d, *J* 12.4 C-3, Ph_3P), 131.9 (C-4, Ph_3P), 133.1 (d, *J* 9.5, C-2 Ph_3P), 137.8 (d, *J* 113.4, C-1, Ph-CH_2), 188.2 (CO), 203.0 (CO). C=P peaks are hidden by $CDCl_3$ peaks. ESI-MS, *m/z* $[M + H]^+$ 665 (100)

4.3.5.6. Methyl 2,3,4-tri-*O*-benzyl-9,9-dimethyl-7-(triphenylphosphoranylidene) nonopyranoside-6,8-diulose 108c



Prepared according to method 3, **98** (0.4 g, 1 mmol) in dichlromethane and oxalyl chloride (1 ml); (trimethylacetylmethylene) triphenylphosphorane **67c** (0.3 g, 1 mmol) and triethylamine (0.12 ml, 1 mmol). The product was isolated as an oil (0.27 g, 41%). ^{31}P NMR ($CDCl_3$) δ_p: +17.7; ^{1}H NMR ($CDCl_3$) δ_H: 1.22 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 3.62 (dd, *J* 3.5, *J* 3.5, CH), 3.74 (t, *J* 9.3. CH), 3.99 (t, *J* 9.3, CH), 4.41 (d, *J* 10.1, CH), 4.64-4.69 (m, 6H, 3 x CH_2), 5.00 (d, J 11.1, CH), 7.29-7.36 (m, 30H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 21.5 (3 x CH_3), 41.8 (d, *J* 5.1 ,C), 70.7 (CH), 73.4 (CH_2), 74.5 (CH_2), 75.7 (CH_2), 79.2 (CH), 79.3 (CH), 81.1 (CH), 98.8 (CH) 126.3 (d, *J* 92.9, C-1, Ph_3P), 127.3 (C-2, Ph-CH_2), 128.1 (C-4, Ph-CH_2), 128.8 (C-3, Ph-CH_2), 128.9 (d, *J* 12.4 C-3, Ph_3P), 132.5 (C-4, Ph_3P), 133.7 (d, *J* 9.5, C-2 Ph_3P), 138.4 (d, *J* 111.2, C-1, Ph-CH_2), 162.4 (CO), 162.5 (CO).C=P peaks are hidden by $CDCl_3$ peaks.

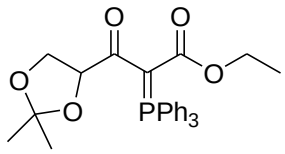
4.3.5.7. Methyl 2,3,4-tri-*O*-benzyl-7,9-dideoxy-7-(triphenylphosphoranylidene) nonopyranoside-6,8-diulose 108d



Prepared according to method 3, **98** (0.3 g, 1 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml), (acetylmethylene) triphenylphosphorane **67d** (0.2 g, 1 mmol) and triethylamine (0.09 ml, 1 mmol) in dry toluene (20 ml). The mixture was poured into water (40 ml). The

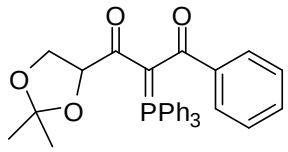
product was isolated as an oil (0.06 g, 15%). ^{31}P NMR ($CDCl_3$) δ_p: +19.8; ^{1}H NMR ($CDCl_3$) δ_H: 2.59 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 3.59 (dd, *J* 3.03, *J* 3.54, CH), 3.74 (t, *J* 9.3, CH), 4.03 (t, *J* 9.3, CH), 4.24 (d, *J* 10.1, CH), 4.64-4.86 (m, 6H, 3 x CH_2), 4.98 (d, *J* 10.6, CH), 7.30-7.38 (m, 30H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: weak spectrum.

4.3.5.8. Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxo-2-(triphenylphosphoranylidene)propanoate 109a



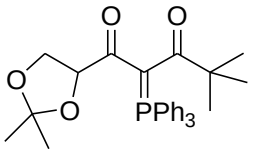
Prepared according to method 3, sugar derivative **88** (1.0 g, 5 mmol) and oxalyl chloride (1 ml); (ethoxycarbonylmethylene)triphenylphosphorane **67a** (1.7 g, 5 mmol) and triethylamine (0.7 ml, 5 mmol) to give an impure yellow solid. ^{31}P NMR ($CDCl_3$) δ_p: multiple peaks.

4.3.5.9. 1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-phenyl-2-(triphenylphosphoranylidene)butane-1,3-dione 109b



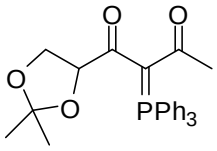
Prepared according to method 3, sugar-derived acid (1.0 g, 5 mmol) and oxalyl chloride (1 ml); (benzoylmethylene) triphenylphosphorane **67b** (1.9 g, 5mmol) and triethylamine (0.7 ml, 5 mmol) to give an impure dark solid (1.92 g). ^{31}P NMR ($CDCl_3$) δ_p: +18.1. The crude product was used in the next step without purification.

4.3.5.10. 1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4,4-dimethyl-2-(triphenylphosphoranylidene)pentane-1,3-dione 109c



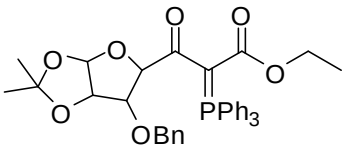
Prepared according to method 3, sugar-derived acid (0.4 g, 2.2 mmol) and oxalyl chloride (1 ml); (trimethylacetylmethylene) triphenylphosphorane **67c** (0.8 g, 2.2 mmol) and triethyl amide (0.3 ml, 2.2mmol) to give a yellow, impure, solid (0.89 g). ^{31}P NMR ($CDCl_3$) δ_p: +16.7. The crude product was used in the next step without purification.

4.3.5.11. 1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(triphenylphosphoranylidene)butane-1,3-dione 109d



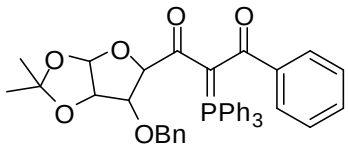
Prepared according to method 3, sugar-derived acid (1.0 g, 5.0 mmol) and oxalyl chloride (1 ml); (acetylmethylene) triphenylphosphorane **67d** (1.6 g, 5.0 mmol) and triethylamine (0.7 ml, 5.0 mmol) to give a yellow, impure, solid. ^{31}P NMR ($CDCl_3$) δ_p: +16.1.

4.3.5.12. Ethyl 3-*O*-benzyl-6-deoxy-1,2-*O*-(1-methylethylidene)-6-(triphenylphosphoranylidene)hept-5-ulosefuranuronate 113a



Prepared according to general method 4, using EDCI-HCl (0.7 g, 4 mmol), DMAP (0.2 g) in a solution of (ethoxycarbonylmethylene)triphenylphosphorane **67a** (1.2 g, 3 mmol) and sugar derivative **82** (1.0 g, 3 mmol) in dry dichloromethane (20 ml), to give an oil (1.06 g, 50%). ^{31}P NMR ($CDCl_3$) δ_p: +17.5, ^{1}H NMR ($CDCl_3$) δ_H: 0.72 (t, 3H, *J* 7.1, CH_3), 1.35 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 3.75 (m, 2H, CH_2), 4.63 (d, 1H, *J* 12.1, CH), 4.68 (d, 1H, *J* 4.0, CH), 4.73 (d, 1H, *J* 11.6, CH), 4.88 (d, 1H, *J* 4.6, CH), 5.84 (d, 1H, *J* 3.5, CH), 6.11 (d, 1H, *J* 3.5, CH), 7.28-7.65 (m, 20H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 13.8 (CH_3), 26.8 (CH_3), 27.3 (CH_3), 58.6 (CH_2), 70.4 (d, *J* 112.0, C=P), 71.9 (CH_2), 83.3 (CH), 83.6 (d, *J* 9.5, CH), 84.0 (CH), 105.0 (CH), 111.7 (C), 126.3 (d, *J* 92.9, C-1, Ph_3P), 127.5 (C-4, Ph), 127.9(C-3, Ph), 128.3(C-2, Ph), 128.4 (d, *J* 13.2, C-3, Ph_3P), 131.4 (d, *J* 2.2, C-4, Ph_3P), 133.2 (d, *J* 9.5, C-2, Ph_3P), 138.1 (C-1, Ph), 167.1 (d, *J* 14.6, CO), 188.9 (d, *J* 3.7, CO). IR ν_{max}/cm^{-1}: 3061(C-H, sp^2), 2982, 2933 (C-H, sp^3), 2361, 1724 (C=O), 1660, 1582, 1439, 1374, 1294, 1219. ESI-MS, *m/z* $[M + H]^+$ 625 (100).

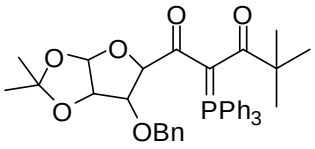
4.3.5.13. 5-O-benzyl-2-deoxy-6,7-O-(1-methylethylidene)-1-phenyl-2-(triphenylphosphoranylidene)heptodialdo-7,4-furanos-3-ulose 113b



Prepared according to general method 4, using EDCI-HCl (0.7 g, 4 mmol), DMAP (0.2 g) in a solution of (benzoylmethylene)triphenylphosphorane **67b** (1.3 g, 3 mmol) and sugar derivative **82** (1.0 g, 3 mmol) in dry dichloromethane (20 ml), to give an oil (0.05 g, 2%). ^{31}P NMR ($CDCl_3$) δ_p: +17.3, ^{1}H NMR ($CDCl_3$) δ_H: 1.22 (s, 6H, 2 x CH_3), 4.13 (d, *J* 7.6, CH), 4.46 (m, 3H, CH, CH_2), 5.18 (d, 1H, *J* 4.8, CH), 5.92 (d, 1H, *J* 3.5, CH), 7.21-7.68 (m, CH, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 26.7 (s, CH_3), 27.1 (s, CH_3), 71.9 (CH_2), 82.5 (d, J 9.5, CH), 83.1 (CH), 84.0 (CH), 84.5 (d, *J* 102.5, C=P), 104.9 (CH),

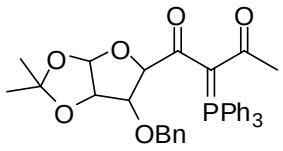
111.7 (C), 125.5 (d, J 92.9, C-1, Ph_3P), 127.6 (C-4, $PhCH_2$), 127.8 (C-3, $PhCH_2$), 128.2 (C-2, $PhCH_2$), 128.3 (C-3, PhCO), 128.5 (d, *J* 12.4, C-3, Ph_3P), 128.7 (C-4, PhCO), 130.7 (C-2, PhCO), 131.6 (d, *J* 2.9, C-4, Ph_3P), 133.5 (d, *J* 10.3, C-2, Ph_3P), 137.9 (C-1, $PhCH_2$), 143.6 (d, *J* 5.9, C-1, PhCO), 187.5 (d, *J* 3.7, CO), 192.7 (d, *J* 10.3, CO). IR ν_{max}/cm^{-1}: 3059(C-H, sp^2), 2982, 2932 (C-H, sp^3), 2361, 1751 (C=O), 1670,1563, 1439, 1372, 1302, 1223. ESI-MS, *m/z* $[M + H]^+$ 656 (100), 637 (5), 278 (2), 91 (4).

4.3.5.14. 1-[6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-4,4-dimethyl-2-(triphenylphosphoranylidene)pentane-1,3-dione 113c



Prepared according to general method 4, using EDCI-HCl (0.7 g, 4 mmol), DMAP (0.2 g) in a solution of (trimethylacetylmethylene)triphenylphosphorane **67c** (1.2 g, 3 mmol) and sugar derivative **82** (1.0 g, 3 mmol) in dry dichloromethane (20 ml), to give an oil (0.04 g, 2%). ^{31}P NMR ($CDCl_3$) δ_p: +16.7, ^1H NMR ($CDCl_3$) δ_H: 1.07 (s, 9H, 3 x CH_3), 1.25 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 4.26 (d, 1H, *J* 3.0, CH), 4.41 (d, 1H, *J* 3.5, CH), 4.50 (q, 2H, *J* 12.6, CH_2), 5.84 (d, 1H, *J* 3.5, CH), 7.29- 7.75 (m, 20H, CH-aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 26.5 (CH_3), 26.9 (CH_3), 28.0 (3 x CH_3), 46.2 (d, *J* 5.1, C), 72.5 (CH_2), 79.2 (d, *J* 98.1, C=P), 82.3 (CH), 83.9 (d, *J* 6.6, CH), 84.0 (CH), 105.4 (CH), 111.9 (C-$(CH_3)_2$), 126.3 (d, *J* 92.2, C-1, Ph_3P), 127.3 (C-4, Ph), 127.4 (C-3, Ph), 128.2 (d, *J* 12.4, C-3, Ph_3P), 128.3 (C-2, Ph), 131.6 (d, *J* 2.9, C-4, Ph_3P), 134.0 (d, *J* 9.5, C-2, Ph_3P), 138.5 (C-1, Ph), 184.9 (d, *J* 5.1, CO), 208.2 (d, *J* 6.6, CO). IR ν_{max}/cm^{-1}: 3059 (C-H, sp^2), 2978, 2931 (C-H, sp^3), 2361, 1751 (C=O), 1672, 1564, 1439, 1366, 1302, 1225. ESI-MS, *m/z* $[M + H]^+$ 637 (100), 547 (3), 279 (55), 200 (4), 91 (4).

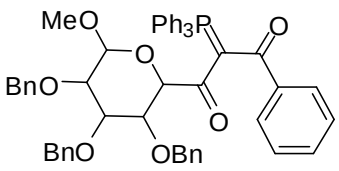
4.3.5.15. 3-*O*-benzyl-6,8-dideoxy-1,2-*O*-(1-methylethylidene)-6-(triphenylphosphoranylidene)octofuranose-5,7-diulose 113d



Prepared according to general method 4, using EDCI-HCl (0.7 g, 3.7 mmol), DMAP (0.2 g) in a solution of (acetylmethylene)triphenylphosphorane **67d** (1.1 g, 3.4 mmol) and sugar derivative **82** (1.0 g, 3.4 mmol) in dry dichloromethane (20 ml), to give an oil (0.1 g, 5%).^{31}P NMR ($CDCl_3$) δ_p: +15.6, ^{1}H NMR ($CDCl_3$) δ_H: 1.30 (s, CH_3), 1.43 (s, CH_3), 1.78 (CH_3), 4.60 (d, 1H, *J* 4.0, CH), 4.67 (q, 2H, *J* 12.1, CH_2), 4.80 (d, 1H, *J* 4.0, CH), 5.42 (d, 1H, *J* 4.0, CH), 5.99 (d, 1H, *J* 3.5, CH), 7.31-7.69 (m, 20H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 26.8(CH_3), 27.2 (CH_3), 30.1 (CH_3), 72.3 (CH_2), 83.0 (CH), 84.5(CH), 84.6(d, *J* 6.6, CH), 86.9 (d, *J* 105.4, C=P), 105.1 (CH), 111.9 (C), 126.2 (d, *J* 92.9, C-1, Ph_3P), 127.6 (C-4, Ph), 127.8 (C-3, Ph), 128.4 (d, *J* 5.1, C-2, Ph), 128.7 (d, *J* 12.4, C-3, PPh_3), 131.8 (d, *J* 2.2, C-4, Ph_3P), 133.4 (d, *J* 9.5, C-2, Ph_3P), 138.0 (C-1, Ph), 191.3 (d, *J* 7.3, CO), 192.5 (d, *J* 13.9, CO). IR ν_{max}/cm^{-1}: 3060(C-H, sp^2), 2979, 2930 (C-H, sp^3), 2361, 1751 (C=O), 1673, 1564, 1439, 1366, 1302, 1225. ESI-MS, *m/z* $[M + H]^+$ 595 (100), 537 (10), 279 (22), 91 (14).

4.3.5.16. Attempted synthesis

4.3.5.16.1. Methyl 5,6,7-tri-*O*-benzyl-2-deoxy-1-phenyl-2-(triphenylphosphoranylidene) octodialdo-8,4-pyranosid-3-ulose 108b



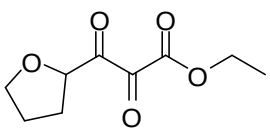
Prepared according to method 3, **98** (1.0 g, 2 mmol) in dichloromethane (20 ml) and oxalyl chloride (1 ml); the acid chloride in dry dichloromethane (20 ml) (benzoylmethylene) triphenylphosphorane **67b** (0.7 g, 2 mmol) and triethylamine (0.3 ml, 2 mmol) in dry toluene (20 ml). The mixture was poured into water (40 ml).

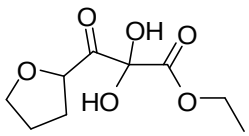
4.3.6. Oxidation of β,β'-dioxo ylides

General method 5: Oxone® (1.5 equivalent) was added in one portion to the mixture of sugar-ylide (1 equivalent), THF and water and stirred vigorously. The reaction mixture was monitored by TLC. At completion, the reaction mixture was diluted with water, followed by the extraction with ethyl acetate (3 x 15 ml). The crude product was purified by adding cold ether and purifying the product by running it through a small column.

4.3.6.1. Oxidation of β,β'-dioxo heterocyclic ylide

4.3.6.1.1. Oxidation of ethyl 3-oxo-3-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)propanoate 114a

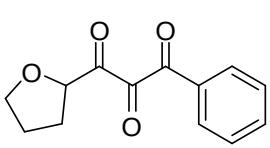
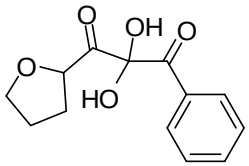




Prepared according to general method 5, using oxone (0.08 g, 0.1 mmol), ylide **104a** (0.04 g, 0.09 mmol), THF (0.9 ml) and water (0.45 ml). ^{1}H NMR ($CDCl_3$) δ_H: 1.39 (d, 3H, *J* 7.3, CH_3), 1.96 (q, 2H, *J* 7.1, CH_2), 2.13 (m, 1H, CH), 2.32 (m, 1H, CH), 3.94 (q, 1H, *J* 7.8, CH), 4.06 (q, 1H, *J* 7.8, CH), 4.34 (q, 2H, *J* 7.1, CH_2), 4.50 (q, 1H, *J* 5.6, CH). ^{13}C NMR ($CDCl_3$) δ_C: 14.0 (CH_3), 25.5 (CH_2), 30.1 (CH_2), 62.7 (CH_2), 69.7 (CH_2), 76.6

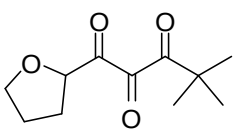
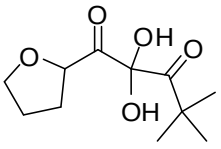
(CH), 159.0 (CO), 159.3(CO), 174.5 (CO). IR ν_{max}/cm^{-1}: 3369 (br, OH), 2987, 2929 (C-H, sp^3), 1722 (C=O), 1617, 1422, 1348, 1266.

4.3.6.1.2. Oxidation of 1-phenyl-3-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)propane-1,3- dione 114b

Prepared according to general method 5, using oxone (0.19 g, 0.3 mmol), ylide **104b** (0.1 g, 0.2 mmol), THF (2.1 ml) and water (1.05 ml). ^{1}H NMR ($CDCl_3$) δ_H ($CDCl_3$): 1.93 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 3.93 (q, 1H, *J* 7.3, CH), 4.04 (q, 1H, *J* 7.3, CH), 4.49 (dd, 1H, *J* 5.6, *J* 5.6, CH), 7.55-7.60 (m, 5H, aromatic), 9.27 (brd, 2H, 2 x OH). ^{13}C NMR ($CDCl_3$) δ_C: 25.4 (CH_2), 30.2 (CH_2), 69.6 (CH_2), 76.5 (CH), 128.6 (d, *J* 12.4, C-3), 130.1 (C-4), 132.2 (d, J 9.5, C-2), 133.3 (C-1), 170.6 (CO), 176.2 (CO). IR ν_{max}/cm^{-1}: 3490 (br, OH), 3059 (C-H, sp^2), 2987, 2922 (C-H sp^3), 1703 (C=O), 1603, 1584, 1452, 1418, 1319, 1267. ESI-MS, *m/z* $[M + H]^+$ 251(73), 217 (100), 205 (40), 157 (40), 105 (39).

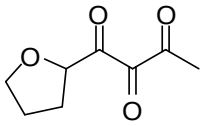
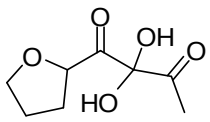
4.3.6.1.3. Oxidation of 4,4-dimethyl-1-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)pentane-1,3-dione 114c

Prepared according to general method 5, using oxone (0.12 g, 0.2 mmol), **104c** (0.06 g, 0.13 mmol), THF (1.3 ml) and water (0.65 ml). ^{1}H NMR ($CDCl_3$) δ_H: 1.19 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.91 (m, 2H, CH_2), 2.06 (m, 1H, CH), 2.26 (m, 1H,

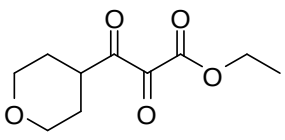
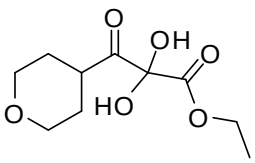
CH), 3.91 (q, 1H, *J* 7.3, CH), 4.03 (q, 1H, *J* 7.3, CH), 4.46 (q, 1H, *J* 5.6, CH), 9.23 (brd, 2H, 2 x OH). ^{13}C NMR ($CDCl_3$) δ_C: 25.3 (CH_2), 25.8 (2 x CH_3), 27.1 (CH_3), 30.2 (CH_2), 38.4 (C-(CH_3)$_3$), 68.6 (CH_2), 76.5 (CH), 103.7 (C-(OH)$_2$), 175.9 (2 x CO). IR ν_{max}/cm^{-1}: 3442 (br, OH), 2978, 2932 (C-H, sp^3), 1734 (C=O), 1634, 1482, 1461, 1422, 1366, 1267. ESI-MS, *m/z* $[M + H]^+$ 231 (28), 197 (100), $[M + H_2O]^+$ 157 (96), 71 (85).

4.3.6.1.4. Oxidation of 1-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)butane-1,3-dione 114d

Prepared according to general method 5, using oxone (0.22 g, 0.4 mmol), **104d** (0.1 g, 0.2 mmol), THF (2.4 ml) and water (1.2 ml). ^{1}H NMR ($CDCl_3$) δ_H: 1.98 (m, 4H, 2 x CH_2), 2.08 (m, 3H, CH_3), 2.47 (m, 2H, CH_2), 4.34 (t, 1H, *J* 7.1, CH). ^{13}C NMR ($CDCl_3$) δ_C: 22.3 (CH_3), 25.3 (CH_2), 30.2 (CH_2), 69.4 (CH_2) 76.6 (CH), 176.7 (CO), 177.8 (CO), 180.4 (CO). IR ν_{max}/cm^{-1}: 3352 (br, OH), 2987, 2929 (C-H, sp^3), 1722 (C=O), 1624, 1523, 1365, 1349, 1266. ESI-MS, *m/z* $[M + H - CO]^+$ 155 (6), $[M - 1 + NH_4^+]$ 134(100), 59 (35)

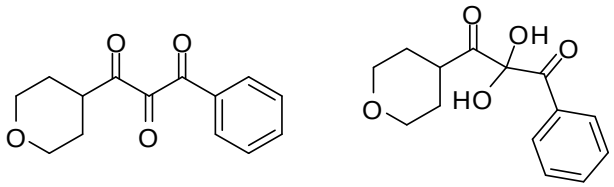
4.3.6.1.5. Oxidation of ethyl 3-oxo-3-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene) propanoate 115a

Prepared according to general method 5, using oxone (0.2 g, 0.3 mmol), ylide **105a** (0.1 g, 0.2 mmol), THF (2.2 ml) and water (1.1 ml). ^{1}H NMR ($CDCl_3$) δ_H: 1.35 (t, 3H, *J* 7.1,

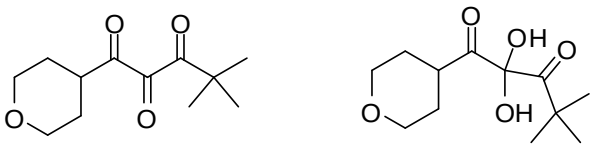
CH3), 1.82 (m, 2H, CH_2), 2.56 (m, 1H, CH), 3.45 (dt, 2H, *J* 3.0, *J* 11.1, CH_2), 3.97 (td, 2H, *J* 3.7, *J* 11.4, CH_2), 4.33 (p, 2H, *J* 7.1, CH_2), 9.79 (br, 2H, 2 x OH). ^{13}C NMR ($CDCl_3$) δ_C: 13.9 (CH_3), 28.5 (2 x CH_2), 39.7 (CH), 62.7 (CH_2), 67.0 (2 x CH_2), 159.1 (CO), 178.4 (CO). IR ν_{max}/cm^{-1}: 3449 (br, OH), 2963, 2933, 2855 (C-H, sp^3), 1709 (C=O), 1448, 1422, 1389, 1294, 1267. ESI-MS, *m/z* $[M]^+$ 214 (100), $[M + H_2O]^+$ 187 (22), 129 (16).

4.3.6.1.6. Oxidation of 1-phenyl-3-(tetrahydro-2H-pyran-4-yl)-2-(triphenylphosphoranylidene)propane-1,3-dione 115b



Prepared according to general method 5, using oxone (0.19 g, 0.3 mmol), **105b** (0.1 g, 0.2 mmol), THF (2.0 ml) and water (1.0 ml). ^{1}H NMR ($CDCl_3$) δ_H: 1.82 (m, 4H, 2 x CH_2), 2.57 (m, 1H, CH), 3.45 (dt, 2H, *J* 3.0, *J* 11.1, CH_2), 3.97 (td, 2H, *J* 3.8, *J* 11.6, CH_2), 7.57-8.10 (m, 5H, aromatic), 9.47 (br, 2H, 2 x OH). ^{13}C NMR ($CDCl_3$) δ_C: 28.5 (2 x CH_2), 39.8 (CH), 67.1 (2 x CH_2), 99.5 (C-$(OH)_2$), 128.6 (d, *J* 12.4, C-3), 132.2 (d, *J* 10.3, C-2), 132.2 (d, *J* 2.9, C-4), 132.3 (C-1), 170.5 (CO), 178.7 (CO). IR ν_{max}/cm^{-1}: 3466 (br, OH), 3055 (C-H, sp^2), 2960, 2928, 2855 (C-H, sp^3), 1705 (C=O), 1605, 1451, 1421, 1389, 1319, 1266. ESI-MS, *m/z* $[M + H]^+$ 265(3), $[M + H]^+$ 231 (100), 214 (26), 135 (13).

4.3.6.1.7. Oxidation of 4,4-dimethyl-1-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene) pentane-1,3-dione 115c



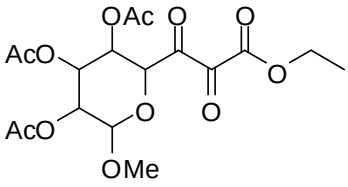
Prepared according to general method 5, using oxone (0.2 g, 0.3 mmol), **105c** (0.1 g, 0.2 mmol), THF (2.1 ml) and water (1.05 ml). ^{1}H NMR ($CDCl_3$) δ_H: 1.18 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.80 (m, 3H, CH, CH_2), 2.04 (m, 1H, CH), 2.54 (m, 1H, CH), 3.42 (dt, 2H, *J* 2.9, *J* 11.1, CH_2), 3.94 (td, 2H, *J* 3.5, *J* 11.1, CH_2), 8.89 (br, 2H, 2 x OH). ^{13}C NMR ($CDCl_3$) δ_C: 25.8 (CH_3), 27.1 (CH_3), 27.5 (CH_3), 31.8 (CH_2), 32.8 (CH_2), 38.4 (C-$(CH_3)_3$), 39.8 (CH), 63.5 (CH_2), 68.5 (CH_2), 107.8 (C-$(OH)_2$), 199.2 (CO), 206.0 (CO). IR ν_{max}/cm^{-1}: 3443 (br, OH), 2967, 2931, 2858 (C-H, sp^3), 1707 (C=O), 1448, 1422, 1389, 1353, 1266. ESI-MS, *m/z* $[M + H]^+$ 211 (100).

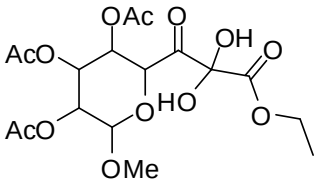
4.3.6.1.8. Oxidation of 1-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene)butane-1,3-dione 115d

Prepared according to general method 5, using oxone (0.21 g, 0.3 mmol), **105d** (0.1 g, 0.2 mmol), THF (2.3 ml) and water (1.15 ml). ^{1}H NMR ($CDCl_3$) δ_H: 1.27 (s, 3H, CH_3), 1.82 (m, 4H, 2 x CH_2), 2.56 (m, 1H, CH), 3.45 (dt, 2H, *J* 2.8, *J* 11.1, CH_2), 3.97 (td, 2H, *J*= 3.7, *J* 11.4, CH_2), 8.94 (brd, 2H, 2 x OH). ^{13}C NMR ($CDCl_3$) δ_C: 27.8 (CH_3), 28.5 (2 x CH_2), 39.8 (CH), 67.1 (2 x CH_2), 107.9 (C-$(OH)_2$), 178.5 (2 x CO). IR ν_{max}/cm^{-1}: 3472 (br, OH), 2962, 2931, 2855 (C-H, sp^3), 1708 (C=O), 1448, 1422, 1389, 1294, 1266.

4.3.6.2. Oxidation of sugar-derived phosphorus ylides

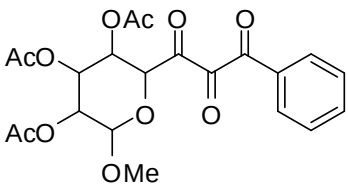
4.3.6.2.1. Oxidation of ethyl methyl 2,3,4-tri-*O*-acetyl-7-deoxy-7-(triphenylphosphoranylidene)oct-6-ulosepyranosiduronate 116a

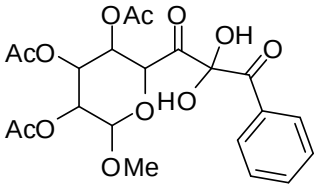




Prepared according to general method 5, using oxone (0.04 g, 0.068 mmol), ylide **107a** (0.03 g, 0.045 mmol), THF (0.5 ml) and water (0.25 ml) to give an oil (1 mg, 5%).^{1}H NMR ($CDCl_3$) δ_H: 1.32 (t, 3H, *J* 7.1, CH_3), 2.03 (d, 3H, *J* 1.5, CH_3), 2.05(d, 3H, *J* 1.5, CH_3), 2.09 (d, 3H, *J* 1.5, CH_3), 3.47 (d, 3H, *J* 5.6, CH_3), 4.33 (m, 2H, CH_2), 4.71 (d, 1H, *J* 9.6, CH), 4.93 (dd, 1H, *J* 3.5, CH), 4.97 (d, 1H, *J* 3.5, CH), 5.26 (t, 1H, *J* 9.6, CH), 5.50 (t, 1H, *J* 4.6, CH). ^{13}C NMR ($CDCl_3$) δ_C: 14.0 (CH_3), 20.7 (3 x CH_3), 55.9 (CH_3), 62.7 (CH_2), 67.7 (CH), 69.4 (CH), 69.5 (CH), 70.5 (CH), 96.9 (CH), 168.1 (CO), 169.1 (CO), 169.5 (CO), 170.0 (CO), 193.6 (CO), 198.2 (CO). IR ν_{max}/cm^{-1}: 3478 (br, OH), 2963, 2938, 2853 (C-H, sp^3), 1751 (C=O), 1427, 1372, 1216. ESI-MS, *m/z* $[M + NH_4^+]^+$ 454 (100), $[M + H - 2Ac]^+$ 352 (50), $[M - H + NH_4^+ - C_2H_5]^+$ 338 (10).

4.3.6.2.2. Oxidation of methyl 5,6,7-tri-*O*-acetyl-2-deoxy-1-phenyl-2-(triphenylphosphoranylidene) octodialdo-8,4-pyranosid-3-ulose 116b

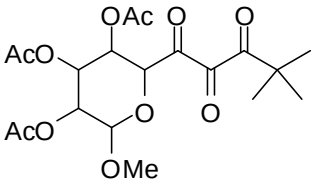


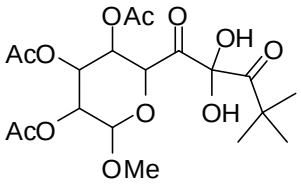


Prepared according to general method 5, using oxone (0.13 g, 0.22 mmol), ylide **107b** (0.1 g, 0.14 mmol), THF (1.4 ml) and water (0.7 ml) to give an oil (16 mg, 25%). ^{1}H NMR ($CDCl_3$) δ_H: 2.09 (s, 9H, 3 x CH_3), 3.39 (s, 3H, OCH_3), 3.46 (s,1H, OH), 3.52 (s,

1H, OH), 4.95 (dd, 1H, *J* 3.0, CH), 5.27 (d, 1H, *J* 3.0, CH), 5.48 (dd, 1H, *J* 3.0, CH), 5.74 (dd, 1H, *J* 2.5, CH), 6.19 (d, 1H, *J* 3.0, CH), 7.54-7.89 (m, 5H, aromatics). IR ν_{max}/cm^{-1}: 3479 (br, OH), 2928, 2856 (C-H, sp^3), 1700 (C=O), 1603, 1584, 1452, 1417, 1373, 1319, 1217. ESI-MS, *m/z* $[M - Ac]^+$ 407 (34), $[M – H + H_2O]^+$ 381 (96), $[M – H + NH_4^+ - Ac]^+$ 338 (22), 292 (32), 105 (55), 64 (100).

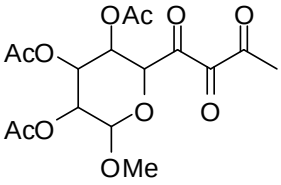
4.3.6.2.3. Oxidation of methyl 2,3,4-tri-*O*-acetyl-9,9-dimethyl-7-(triphenylphosphoranylidene)decopyranoside-6,8-diulose 116c

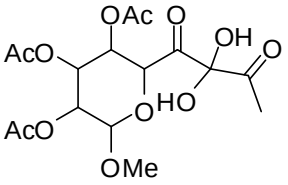




Prepared according to general method 5, using oxone (0.07 g, 0.11 mmol), ylide **107c** (0.05 g, 0.074 mmol), THF (0.7 ml) and water (0.35 ml) to give an oil (6 mg, 19%). ^1H NMR ($CDCl_3$) δ_H: 1.33 (s, 9H, 3 x CH_3), 2.12 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 5.48 (m, 1H, CH), 5.65 (dd, 1H, *J* 2.5, *J* 3.0, CH), 5.72 (dd, 1H, *J* 3.0, CH), 6.09 (d, 1H, *J* 3.0, CH), 6.18 (d, 1H, *J* 3.0, CH). ^{13}C NMR ($CDCl_3$) δ_C: 20.7 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 25.6 (3 x CH_3), 42.8 (C), 57.0 (OMe), 66.1 (CH), 68.7 (CH), 77.2(CH), 98.6 (CH), 113.6 (CH), 170.0 (CO), 170.1 (CO), 170.2 (CO). IR ν_{max}/cm^{-1}: 3468 (br, OH), 2981, 2930(C-H, sp^3), 1710 (C=O), 1454, 1439, 1397, 1384, 1297. ES-MS, *m/z* $[M + NH_4]^+$ 412 (21), $[M + H + OAc – 2Ac]^+$ 361 (100).

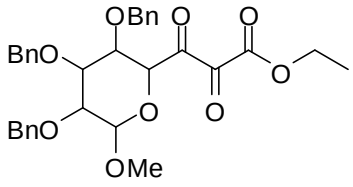
4.3.6.2.4. Oxidation of methyl 2,3,4-tri-*O*-acetyl-7,9-dideoxy-7-(triphenylphosphoranylidene) nonopyranoside-6,8-diulose 116d

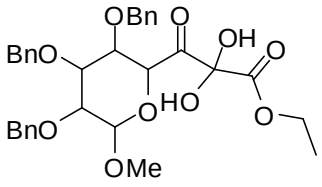




Prepared according to general method 5, using oxone (0.06 g, 0.095 mmol), ylide **107d** (0.04 g, 0.063 mmol), THF (0.6 ml) and water (0.3 ml) to give an oil (1 mg, 4%). ^{1}H NMR ($CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 4.37 (t, 1H, *J* 7.1, CH), 5.17 (s, 1H, CH), 5.19 (s, 1H, CH), 5.65 (dd, 1H, *J* 3.0, *J* 3.0, CH), 6.12 (d, 1H, *J* 3.0, CH). ^{13}C NMR ($CDCl_3$) δ_C: 20.8 (3 x CH_3), 20.9 (CH_3), 54.5 (CH_3), 56.8 (CH), 66.6 (CH), 69.0 (CH), 77.2 (CH), 98.3 (CH), 170.2 (3 x CO), 188.4 (CO), 188.9 (CO), 189.6 (CO). IR ν_{max}/cm^{-1}: 3459 (br, OH), 2932, 2853 (C-H, sp^3), 1743 (C=O), 1433, 1373, 1216.

4.3.6.2.5. Oxidation of ethyl methyl 2,3,4-tri-*O*-benzyl-7-deoxy-7-(triphenylphosphoranylidene)oct-6-ulosepyranosiduronate 117a

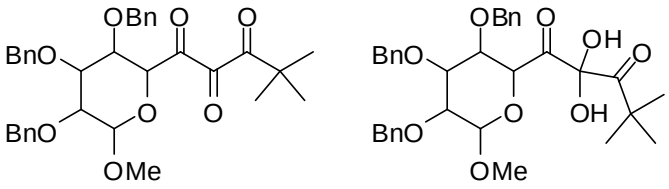




Prepared according to general method 5, using oxone (0.03 g, 0.056 mmol), ylide **108a** (0.03 g, 0.037 mmol), THF (0.4 ml) and water (0.2 ml) to give an oil (3 mg, 14%). ^{1}H NMR ($CDCl_3$) δ_H: 1.38 (t, 3H, *J* 7.3, CH_3), 3.01, (brd, 2H, CH_2), 3.15 (brd, 2H, CH_2), 3.44 (t, 3H, *J* 4.0, CH_3), 3.46-3.58 (m, 5H, 5 x CH), 4.35 (q, 2H, *J* 7.1, CH_2), 4.59 (m, 2H, CH_2), 7.55-7.61 (m, 15H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 14.0 (CH_3), 55.8 (CH_3),

62.8 (CH_2), 71.5 (CH_2), 71.9 (CH), 72.7 (CH_2), 72.8 (CH_2), 79.0 (CH), 79.7 (CH)79.9 (CH), 101.7 (CH), 128.4 (C-4), 128.6 (d, *J* 12.4, C-3), 132.2 (d, *J* 9.5, C-2), 137.0 (C-1), 159.0 (CO), 187.5 (CO), 200.1 (CO). IR ν_{max}/cm^{-1}: 3468 (br, OH), 2986, 2929, 2855 (C-H, sp^3), 1730 (C=O), 1452, 1422, 1266. ES-MS, *m/z* $[M + H]^+$ 579 (5), $[M + H]^+$ 547 (100), 528 (37), 181 (50), 91 (67).

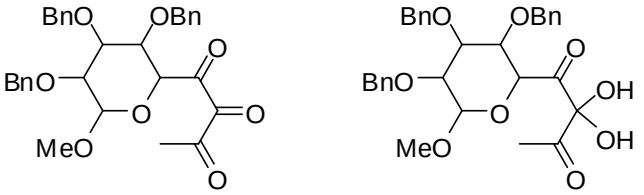
4.3.6.2.6. Oxidation of methyl 2,3,4-tri-*O*-benzyl-9,9-dimethyl-7-(triphenylphosphoranylidene)nonopyranoside-6,8-diulose 117c



Prepared according to general method 5, using oxone (0.11 g, 0.18 mmol), ylide **108c** (0.1 g, 0.12 mmol), THF (1.2 ml) and water (0.6 ml) to give an oil (6 mg, 9%).

IR ν_{max}/cm^{-1}: 3369 (br, OH), 3055, 2987, 2929 (C-H, sp^3), 1722 (C=O), 1422, 1348, 1265. ESI-MS, *m/z* $[M + H + Ac - 3Bn]^+$ 259 (26), 231 (50), 214 (100), 199 (20).

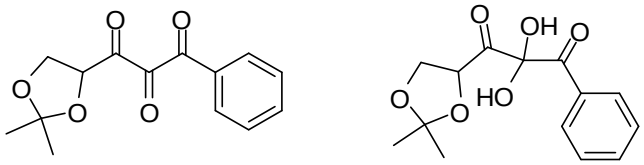
4.3.6.2.7. Oxidation of methyl 2,3,4-tri-*O*-benzyl-7,9-dideoxy-7-(triphenylphosphoranylidene) nonopyranoside-6,8-diulose 117d



Prepared according to general method 5, using oxone (0.07 g, 0.012 mmol), ylide **108d** (0.06 g, 0.077 mmol), THF (0.8 ml) and water (0.4 ml) to give an oil (3 mg, 7%).

IR ν_{max}/cm^{-1}: 3459 (br, OH), 2932, 2853 (C-H, sp^3), 1743 (C=O), 1433, 1373, 1216. ESI-MS, *m/z* $[M - 2OH - CH_3]^+$ 501 (72), $[M + H + Na^+ - 2Bn]^+$ 295 (62), 233 (46), 181 (61), 105 (95), 91 (100).

4.3.6.2.9. Oxidation of 1-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-phenyl-2-(triphenylphosphoranylidene)butane-1,3-dione 118a

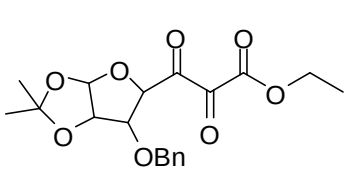
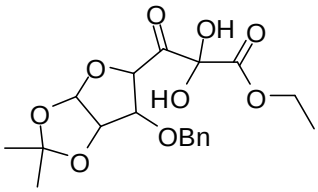


Prepared according to general method 5, using oxone (0.07 g, 5.67 mmol), ylide **109b** (1.92 g, 4 mmol), THF (38 ml) and water (19 ml) to give an oil (81 mg, 7 %). IR ν_{max}/cm^{-1}: 3231 (br, OH), 3054, 2987, 2948 (C-H, sp^3), 1738 (C=O), 1421, 1265. ESI-MS, *m/z* $[M + H]^+$ 279 (100), 105 (40).

4.3.6.2.10. Oxidation of 1-(2,2-dimethyl-1,3-dioxolan-4-yl)-4,4-dimethyl-2-(triphenylphosphoranylidene)pentane-1,3-dione 118b

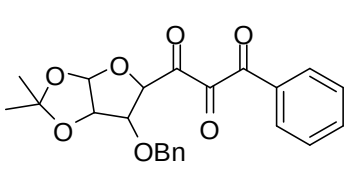
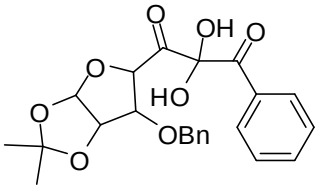
Prepared according to general method 5, using oxone (1.4 g, 2.21 mmol), ylide **109c** (0.72 g, 1.5 mmol), THF (14.8 ml) and water (7.4 ml) to give an oil (26 mg, 7%). IR ν_{max}/cm^{-1}: 3364 (br, OH), 2989, 2935 (C-H, sp^3), 1731 (C=O), 1439, 1383, 1216. ESI-MS, *m/z* $[M + H + Na^+ - OH]^+$ 267 (100), $[M + H - OH]^+$ 227 (65), 111 (44).

4.3.6.2.11. Oxidation of ethyl 3-*O*-benzyl-6-deoxy-1,2-*O*-(1-methylethylidene)-6-(triphenylphosphoranylidene)hept-5-ulosefuranuronate 119a

Prepared according to general method 5, using oxone (0.2 g, 0.32 mmol), ylide **113a** (0.1 g, 0.21 mmol), THF (2.1 ml) and water (1.0 ml) to give an oil (21 mg, 27%).[1]H NMR ($CDCl_3$) δ_H: 1.33 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 4.33 (s, 1H, CH), 4.34 (s, 2H, CH_2), 4.60 (d, 1H, *J* 3.5, CH), 4.62 (s, 2H, CH_2), 4.87 (d, 1H, *J* 3.5, CH), 6.09 (d, 1H, *J* 3.5, CH), 7.55-7.59 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 14.0 (CH_3), 26.4 (CH_3), 27.0 (CH_3), 62.7 (CH_2), 72.8 (CH_2), 79.8 (CH), 82.2 (CH), 82.5 (CH), 105.9 (CH), 112.8 (C-$(OH)_2$), 128.6 (d, *J* 12.4, C-3), 132.2 (d, *J* 10.3, C-2), 132.3 (d, *J* 2.2, C-4), 136.9 (C-1),159.0 (CO), 159.2 (CO), 169.4 (CO). IR ν_{max}/cm^{-1}: 3451 (br, OH), 3020, 2960, 2927, 2855 (C-H, sp^3), 1730 (C=O), 1604, 1585, 1454, 1377, 1262, 1216. ESI-MS, *m/z* $[M - Et]^+$ 349 (100), [M – 2O] 317, 295 (28), 277 (20).

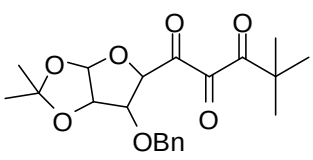
4.3.6.2.12. Oxidation of 5-*O*-benzyl-2-deoxy-6,7-*O*-(1-methylethylidene)-1-phenyl-2-(triphenylphosphoranylidene)heptodialdo-7,4-furanos-3-ulose 119b

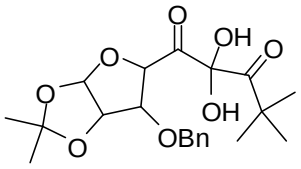



Prepared according to general method 5, using oxone (0.06 g, 0.092 mmol), ylide **113b** (0.04 g, 0.061 mmol), THF (0.6 ml) and water (0.3 ml) to give an oil (6 mg, 24%).

IR ν_{max}/cm^{-1}: 3433 (br, OH), 3021, 2961, 2936 (C-H, sp^3), 1724 (C=O), 1695, 1605, 1585, 1453, 1417, 1377, 1262, 1216. ESI-MS, *m/z* $[M]^+$ 317 (36), 312 (53), 123 (100), 102 (40).

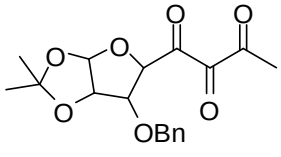
4.3.6.2.13. Oxidation of 1-[6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-4,4-dimethyl-2-(triphenylphosphoranylidene)pentane-1,3-dione 119c

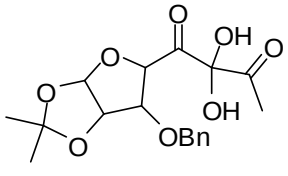




Prepared according to general method 5, using oxone (0.06 g, 0.094 mmol), ylide **113c** (0.04 g, 0.063 mmol), THF (0.6 ml) and water (0.3 ml) to give an oil (5 mg, 20%).^{1}H NMR ($CDCl_3$) δ_H: 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.50 (s, 6H, 2 x CH_3), 3.71 (t, 1H, *J* 6.1, CH), 4.37 (t, 1H, *J* 7.1, CH), 4.62 (s, 2H, CH_2), 4.87 (d, 1H, *J* 3.5, CH), 6.09 (d, 1H, *J* 3.5, CH), 7.54-7.60 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 26.4 (2 x CH_3), 27.1 (3 x CH_3), 29.7 (C-$(CH_3)_3$), 72.8 (CH_2), 79.8 (CH), 82.2 (CH), 82.6 (CH), 105.9 (CH), 112.7 (C), 128.4, (C-4), 128.3 (d, *J* 12.4, C-3), 132.2 (d, *J* 10.3, C-2), 132.4 (C-1), 169.6 (CO). IR ν_{max}/cm^{-1}: 3451 (br, OH), 3020, 2994, 2929, 2856 (C-H, sp^3), 1732 (C=O), 1604, 1522, 1455, 1262, 1216. ESI-MS, *m/z* $[M + H - 2CH_3]^+$ 361 (100), 317 (35), 91 (28).

4.3.6.2.14. Oxidation of 3-*O*-benzyl-6,8-dideoxy-1,2-*O*-(1-methylethylidene)-6-(triphenylphosphoranylidene)octofuranose-5,7-diulose 119d





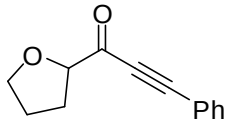
Prepared according to general method 5, using oxone (0.16 g, 0.25 mmol), ylide **113d** (0.1 g, 0.17 mmol), THF (1.7 ml) and water (0.85 ml) to give an oil (31 mg, 52%).[1]H NMR ($CDCl_3$) δ_H: 1.28 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.34-4.67 (m, 5H, 3 x CH, CH_2), 6.10 (dd, 1H, *J* 3.5, *J* 3.5, CH), 7.55-7.63 (m, 5H, aromatic). [13]C NMR ($CDCl_3$) δ_C: 26.4 (CH_3), 27.0 (2 x CH_3), 72.5 (CH_3), 79.7 (CH), 82.2 (CH), 84.0 (CH), 105.9 (CH), 112.6 (C), 128.4 (C-4), 128.6 (d, *J* 12.4, C-3), 132.2 (d, *J* 10.3, C-2), 136.9 (C-1), 170.2 (CO), 188.6 (CO), 201.2 (CO). IR ν_{max}/cm^{-1}: 3419 (br, OH), 3021, 2993, 2935, 2874 (C-H, sp^3), 1724 (C=O), 1695, 1605, 1585, 1453, 1417, 1385, 1377, 1288, 1217. ESI-MS, *m/z* $[M - O - CH^3]^+$ 317 (60), 91 (100).

4.3.7 Pyrolysis of β,β'-dioxo ylides

General method 6: The β,β'-dioxo ylides were gradually heated up to 240°C, using a Kugelrohr distillation oven illustrated in the picture bellow.

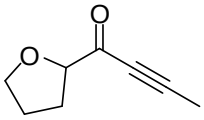
4.3.7.1. Pyrolysis of β,β'-dioxo heterocyclic ylides

4.3.7.1.1. Pyrolysis of 1-phenyl-3-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)propane-1,3- dione 120b



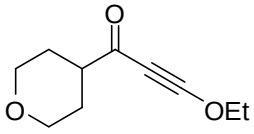
Ylide **104b** (10 mg, 0.021 mmol) was heated to give **120b** (5 mg, 50 %) as an impure oil. IR ν_{max}/cm^{-1}: 3054, 2987 (C-H, sp^3), 2306 (C≡C), 1711 (C=O), 1612, 1432, 1422.

4.3.7.1.2. Pyrolysis of 1-(tetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene) butane-1,3-dione 120d



Ylide **104d** (5 mg, 0.012 mmol) was heated to give **120d** (5 mg, 100%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 2.06 (s, 3H, CH_3), 3.71 (t, 1H, *J* 6.7, CH), 3.83 (q, 1H, *J* 7.3, CH), 3.91 (m, 1H, CH), 3.99 (m, 1H, CH), 4.69 (m, 1H, CH), 4.83 (m, 1H, CH), 6.29 (s, 1H, CH). IR ν_{max}/cm^{-1}: 3056, 2983 (C-H, sp^3), 2254 (C≡C), 1704 (C=O), 1469, 1384.

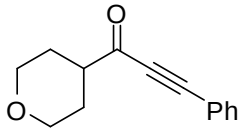
4.3.7.1.3. Pyrolysis of ethyl 3-oxo-3-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene)propanoate 121a



Ylide **105a** (31 mg, 0.067 mmol) was heated to give **121a** (2 mg, 6%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 0.61 (t, 3H, *J* 7.2, CH_3), 3.41 (dt, 2H, *J* 2.6, *J* 11.4, CH_2), 3.51 (dt,

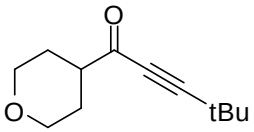
2H, *J* 2.2, *J* 11.6, CH_2), 3.68 (q, 2H, *J* 7.2, CH_2), 3.79 (m, 1H, CH), 3.94 (m, 4H, 2 x CH_2). IR ν_{max}/cm^{-1}: 3155, 2982 (C-H, sp^3), 2254 (C≡C), 1712 (C=O), 1468, 1438.

4.3.7.1.4. Pyrolysis of 1-phenyl-3-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene)propane-1,3-dione 121b



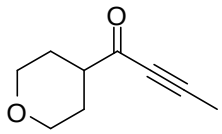
Ylide **105b** (15 mg, 0.03 mmol) was heated to give **121b** (42 mg, 31%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.75 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 2.52 (m, 1H, CH), 3.40 (dt, 2H, *J* 2.6, *J* 11.3, CH_2), 3.92 (td, 2H, *J* 3.6, *J* 11.3, CH_2), 7.51-7.54 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 28.8 (2 x CH_2), 40.0 (CH), 67.3 (2 x CH_2), 177.3 (CO). The quaternary carbons could not be seen. IR ν_{max}/cm^{-1}: 3062, 2958 (C-H, sp^3), 2256 (C≡C), 1711 (C=O), 1611, 1439.

4.3.7.1.5. Pyrolysis of 4,4-dimethyl-1-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene)pentane-1,3-dione 121c



Ylide **105c** (16 mg, 0.034 mmol) was heated to give **121c** (10 mg, 63%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.19 (s, 9H, 3 x CH_3), 1.74 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 2.48 (m, 1H, CH), 3.38 (dt, 2H, *J* 2.6, *J* 11.3, CH_2), 3.91 (td, 2H, *J* 3.6, *J* 11.3, CH_2). ^{13}C NMR ($CDCl_3$) δ_C: 8.74 (3 x CH_3), 28.9 (2 x CH_2), 40.1 (CH), 45.8 (C), 67.3 (2 x CH_2), 176.9 (CO). The quaternary carbons could not be seen. IR ν_{max}/cm^{-1}: 3062, 2980 (C-H, sp^3), 2254 (C≡C), 1710 (C=O), 1470, 1438.

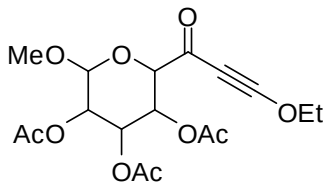
4.3.7.1.6. Pyrolysis of 1-(tetrahydro-2*H*-pyran-4-yl)-2-(triphenylphosphoranylidene) butane-1,3-dione 121d



Ylide **105d** (50 mg, 0.116 mmol) was heated to give **121d** (34 mg, 68%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.79 (m, 3H, CH_2, CH), 1.83 (s, 3H, CH_3), 2.22 (s, H, CH), 2.52 (m, 1H, CH), 3.42 (m, 2H, CH_2), 3.96 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ_C: 14.2 (CH_3), 29.0 (2 x CH_2), 38.8 (CH), 68.3 (2 x CH_2), 191.0 (CO). The quaternary carbons could not be seen. IR ν_{max}/cm^{-1}: 3062, 2980 (C-H, sp^3), 2254 (C≡C), 1710 (C=O), 1470, 1438.

4.3.7.2. Pyrolysis of sugar-derived phosphorus ylides

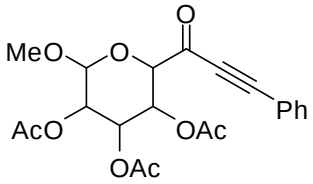
4.3.7.2.1. Pyrolysis of ethyl methyl 2,3,4-tri-*O*-acetyl-7-deoxy-7-(triphenylphosphoranylidene)oct-6-ulosepyranosiduronate 122a



Ylide **107a** (50 mg, 0.075 mmol) was heated to give **122a** (9 mg, 18%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.27 (t, 3H, *J* 7.2, CH_3), 1.99 (s, 3H, CH_3),2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.42 (s, 3H, OCH_3), 4.62 (d, 1H, *J* 10.1, CH), 4.84 (dd, 1H, *J* 3.6, CH), 4.95 (d, 1H, *J* 3.6, CH), 5.14 (t, 1H, *J* 9.8, CH), 5.40 (t, 1H, *J* 9.8, CH). ^{13}C NMR ($CDCl_3$) δ_C: 14.1 (CH_3), 20.6 (CH_3), 20.8 (2 x CH_3), 56.2 (OCH_3), 60.2 (CH), 62.5 (CH_2), 69.4 (CH), 70.5 (CH), 70.7 (CH), 78.0 (C≡C), 80.7 (C≡C), 97.2 (CH), 152.6

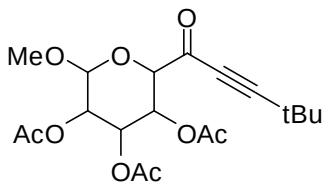
(CO), 169.4 (CO), 170.1 (CO), 170.2 (CO). IR ν_{max}/cm^{-1}: 3155, 2980 (C-H, sp^3), 2254 (C≡C), 1743 (C=O), 1438, 1384.

4.3.7.2.2. Pyrolysis of methyl 5,6,7-tri-*O*-acetyl-2-deoxy-1-phenyl-2-(triphenylphosphoranylidene)octodialdo-8,4-pyranosid-3-ulose 122b



Ylide **107b** (31 mg, 0.044 mmol) was heated to give **122b** (19 mg, 61%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 2.10 (s, 3H, CH_3), 2.11 (s, 6H, 2 x CH_3), 3.53 (s, 3H, OCH_3), 5.08 (d, 1H, *J* 2.4, CH), 5.50 (dd, 1H, *J* 3.4, CH), 5.68 (d, 1H, *J* 3.3, CH), 5.72 (dd, 1H, *J* 3.1, CH), 6.36 (d, 1H, *J* 3.1, CH), 7.66-8.09 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 21.0 (CH_3), 21.1 (CH_3), 21.1 (CH_3), 57.2 (OCH_3), 66.6 (CH), 68.6 (CH), 68.9 (CH), 85.7 (C≡C), 93.7 (C≡C), 98.5 (CH), 111.9 (CH), 119.6 (C-1), 128.9 (C-3), 129.8 (C-4), 132.1 (C-2), 170.2 (2 x CO), 170.3 (CO), 177.1 (CO). IR ν_{max}/cm^{-1}: 3155, 2982 (C-H, sp^3), 2254 (C≡C), 1744 (C=O), 1438, 1378.

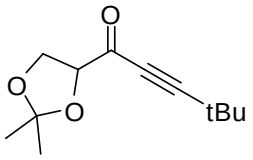
4.3.7.2.3. Pyrolysis of methyl 2,3,4-tri-*O*-acetyl-9,9-dimethyl-7-(triphenylphosphoranylidene)decopyranoside-6,8-diulose 122c



Ylide **107c** (16 mg, 0.024 mmol) was heated to give **122c** (14 mg, 88%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.28 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.09 (s, 6H, 2 x CH_3), 3.49 (s, 3H, OCH_3), 5.12 (m, 1H, CH), 5.15 (t, 2H, *J* 2.6, 2 x CH), 5.67 (dd, 1H, *J* 3.1,

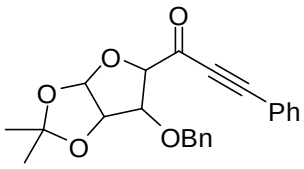
CH), 6.21 (d, 1H, *J* 3.1, CH). ^{13}C NMR ($CDCl_3$) δ_C: 20.8 (CH_3), 20.9 (CH_3), 21.1 (CH_3), 25.9 (C), 30.0 (3 x CH_3), 57.1 (OCH_3), 66.8 (CH), 69.0 (CH), 98.4 (CH), 98.5 (CH), 104.5 (C≡C), 111.4 (C≡C), 112.7 (CH), 170.2 (2 x CO), 170.3 (CO), 172.1 (CO). IR ν_{max}/cm^{-1}: 3155, 2978 (C-H, *sp*^{3}), 2254 (C≡C), 1747 (C=O), 1438, 1383.

4.3.7.2.4. Pyrolysis of 1-(2,2-dimethyl-1,3-dioxolan-4-yl)-4,4-dimethyl-2-(triphenylphosphoranylidene)pentane-1,3-dione 123c



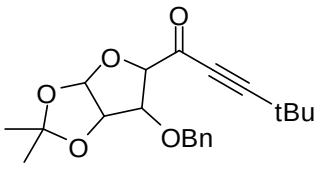
Ylide **109c** (3 mg, 0.006 mmol) was heated to give **123c** (3 mg, 100%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.19 (s, 9H, 3 x CH_3), 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.85 (m, 1H, CH), 4.01 (m, 1H, CH), 4.09 (m, 1H, CH). IR ν_{max}/cm^{-1}: 3155, 2986 (C-H, *sp*^{3}), 2254 (C≡C), 1718 (C=O), 1438, 1384.

4.3.7.2.5. Pyrolysis of 5-*O*-benzyl-2-deoxy-6,7-*O*-(1-methylethylidene)-1-phenyl-2-(triphenylphosphoranylidene)heptodialdo-7,4-furanos-3-ulose 124b



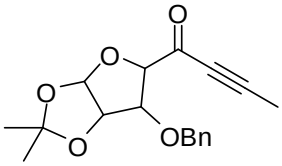
Ylide **113b** (1 mg, 0.002 mmol) was heated to give **124b** (1 mg, 100%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.31 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 4.13 (d, 2H, *J* 3.4, CH_2), 4.45 (d, 1H, *J* 3.8, CH), 4.94 (d, H, *J* 3.9, CH), 5.08 (d, 1H, *J* 2.9, CH), 5.27 (s, 1H,CH) 7.33-7.65 (m, 10H, aromatic). IR ν_{max}/cm^{-1}: 3155 (C-H, *sp*^{3}), 2254 (C≡C), 1736 (C=O), 1647, 1471, 1384.

4.3.7.2.6. Pyrolysis of 1-[6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-4,4-dimethyl-2-(triphenylphosphoranylidene)pentane-1,3-dione 124c



Ylide **113c** (10 mg, 0.016 mmol) was heated to give **124c** (4 mg, 40%) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 1.29 (s, 9H, 3 x CH_3), 1.52 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 4.43 (d, 1H, *J* 3.5, CH), 4.62 (d, 2H, *J* 4.6, CH_2), 4.76 (s, 1H, CH), 4.88 (d, 1H, *J* 3.5, CH), 6.12 (d, 1H, *J* 3.5, CH), 7.30-7.38 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 25.9 (CH_3), 26.5 (CH_3), 27.2 (C), 30.1 (3 x CH_3), 72.9 (CH_2), 82.0 (CH), 83.5 (CH), 86.4 (CH), 106.1 (CH), 112.7 (C). The quaternary carbons from C=O and C≡C could not be seen. IR ν_{max}/cm^{-1}: 3154 (C-H, sp^3), 2254 (C≡C), 1736 (C=O), 1458, 1384.

4.3.7.2.7. Pyrolysis of 3-*O*-benzyl-6,8-dideoxy-1,2-*O*-(1-methylethylidene)-6-(triphenylphosphoranylidene)octofuranose-5,7-diulose 124d



Ylide **113d** (10 mg, 0.017 mmol) was heated to give **124d** (7 mg, %) as an impure oil. ^{1}H NMR ($CDCl_3$) δ_H: 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 5.99 (d, 2H, *J* 3.6, CH_2), 6.10 (d, 2H, *J* 3.1, CH_2), 6.13 (m, 1H, CH), 6.49 (d, 1H, *J* 2.9, CH), 7.45-7.53 (m, 5H, aromatic). IR ν_{max}/cm^{-1}: 3054, 2987 (C-H, sp^3), 2306 (C≡C), 1721 (C=O), 1647, 1422, 1385.

5. Conclusions and Further work

5.1 Conclusions

The aims of this project were to synthesise, characterise and investigate the reactivity of various β,β'-dioxo sugar-derived phosphorus ylides. Four precursor stabilized phosphonium ylides, (ethoxycarbonylmethylene)triphenylphosphorane **67a**, (benzoylmethylene)triphenylphosphorane **67b**, (trimethylacetylmethylene)triphenyl phosphorane **67c** and (acetylmethylene)triphenylphosphorane **67d**, were easily synthesised using literature procedures and characterised by ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy.

The synthesis of the sugar derivatives was more challenging as expected. Initially, D-glucuronic acid and D-glucose were used. The secondary hydroxyl groups were protected as phenyl esters and acetates. However problems were encountered during the purification steps and low yields and impure products were isolated. Problems were also experienced in separating the α- and β-anomers.

An alternative synthetic strategy using D-mannitol and methyl-α-D-glucopyranoside was investigated. D-Mannitol was protected as diacetone-D-mannitol and then readily converted using standard protecting group chemistry to 2,3-isopropylideneglycerate. Methyl-α-D-glucopyranoside was used to synthesise methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoic acid and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoic acid. Difficulties were encountered during the preparation of intermediates; this includes acetyl migration during detritylation and purification steps, leading to low yields.

D-glucose was protected as diacetone-D-glucose, capturing the furanose form of glucose. Subsequent protection of the hydroxyl group at C-3 was achieved with benzyl

bromide. These intermediates were isolated in good yields. The fully protected sugar was then converted to 3-*O*-benzyl-2,3-isopropylidene-α-D-glucofuranuronic acid. Although different protecting strategies were explored, the final products were still obtained in low yields.

Prior to the preparation of the β,β'-dioxo sugar-derived ylides, model reactions were carried out in order to establish the optimum reaction conditions. Tetrahydro-2-furoic acid and tetrahydro-2*H*-pyran-4-carboxylic acid were the chosen model compounds due to their structural similarity to the sugar precursors. The heterocyclic compounds were coupled to the stabilized phosphorus ylides **67a-d** by acylation using the acyl chloride methodology. The target β,β'-dioxo ylides **104a-d** and **105a-d** were obtained, however decomposition of the products were encountered during the aqueous work-up leading to the formation of triphenylphosphine oxide and to low yields after purification.

Following the successful acylation reactions in the model reactions, the method was extended to the reaction of the sugar derivatives with the stabilized phosphorus ylides **67a-d**. This methodology was not compatible with all sugar derivatives; 3-O-benzyl-1,2-isopropylidene-α-D-glucopyranoic acid **82**, which possesses an acid-labile protecting group, required an alternative strategy. The Wasserman method, which employs a peptide coupling reagent, is known to mediate the coupling of a carboxylic compound with an ylide. The novel β,β'-dioxo sugar-derived ylides **113a-d** were obtained in low yields and were characterised by ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy and mass spectrometry.

The reactivity of the β,β'-dioxo ylides **104a-d**, **105a-d**, **107a-d**, **108a, c-d**, **109b-d** and **113a-d** was subsequently investigated. They were subjected to oxidation and pyrolysis. Both methods eliminated triphenylphosphine oxide. ^{31}P NMR spectroscopy was used to

verify the formation of triphenylphosphine oxide (+30 ppm) and the disappearance of the signal arising from the ylide (+14.3 - +19.8 ppm).

The oxidation reaction was conducted using oxone, produced a mixture of vicinal tricarbonyls and their hydrates **114-119**. They were analysed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. Analysis of the mass spectra by electro-spray ionisation did not yield molecular ions; the fragments corresponded to the expected compounds.

Prior to the pyrolysis procedure, thermal stability of four dioxo sugar ylides, one from each series excluding the model compounds, were studied in order to estimate the temperature to perform the pyrolysis studies. TGA analysis showed that the ylides are generally stable from 120-180°C. Pyrolysis experiments were conducted using a Kugelrohr distillation oven at 240°C; small quantities of 13 examples of alkynes were obtained. They were analysed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

5.2 Further work

The formation of α- and β-isomers was one of the main problems encountered in the synthesis of sugar derivatives. This was solved by using a sugar with the hydroxyl group at the anomeric carbon already protected, such as methyl-α-D-glucopyranoside. Hence protecting the secondary hydroxyl groups as esters would be more successful. Another concern was the acetyl migration during deprotection of the trityl group at C-6. This was the main cause of the low yields obtained during the preparation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside **94a**. The pH of the solution needs to be controlled so as to avoid or reduce the migration, which is difficult with this protecting group. Ideally the problem could be solved by using a sugar-derived acid, such as *p*-tolyl-β-D-glucuronide, with the hydroxyl group at the anomeric carbon protected. The

sugar derivative would be reacted with acetic anhydride to give the acetylated sugar **126**. The acylation by esters method could be investigated as a route to β,β'-dioxo ylides phosphorus ylides (Figure 3.54).

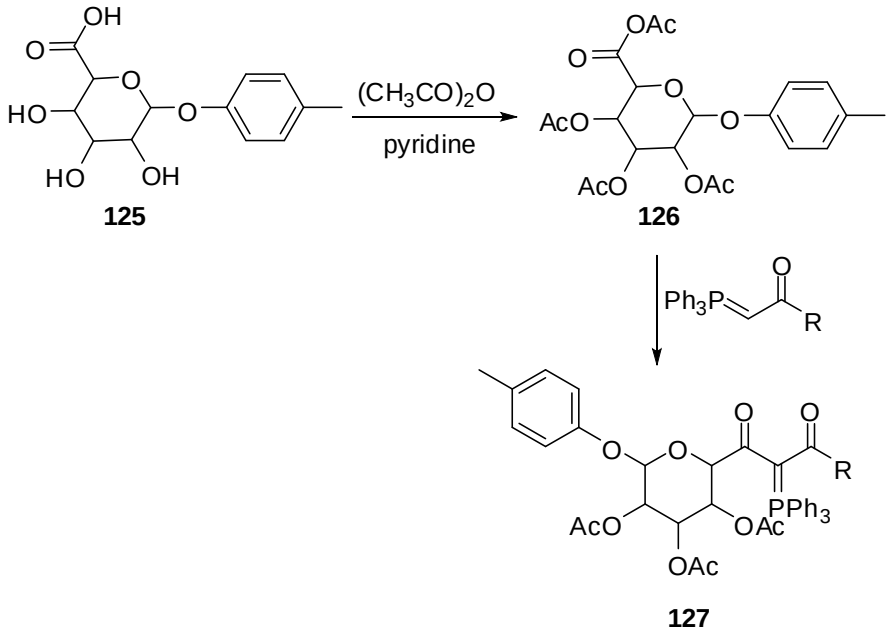


Figure 5.1: An alternative route to β,β'-dioxo ylides phosphorus ylides

Another interesting modification strategy is the formation of the diacetal **130**, a reaction that involves selective protection of *cis* hydroxyl groups.

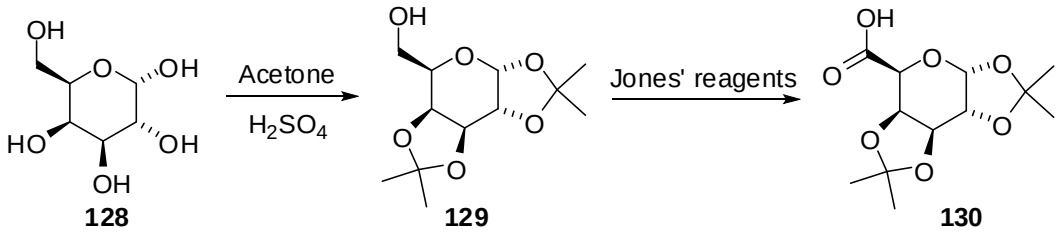


Figure 5.2: Preparation of diacetone-D-galacturonic acid

This procedure will be less time consuming, an advantage over the other procedures, and possibly produce higher yields. The conversion of D-glucose into 3-*O*-benzyl-1, 2-isopropylidene-α-D-glucopyranoic acid **82** is worth repeating and modifying the final step, oxidation, in order to increase the yield.

The novel β,β'-dioxo sugar-derived phosphorus ylides were obtained in low yields. The methods used for their preparation are good and are still the method of choice. Strategies are required to reduce or eliminate the decomposition of the ylides during workup. Purification by column chromatography was necessary in obtaining pure ylides mainly for characterisation. However this meant exposing the ylides to silica gel which caused further decomposition.

Oxidation and pyrolysis of the dioxo ylides eliminate triphenylphosphine oxide to create new functional groups. Therefore, one solution could be to omit the purification procedures which are required for the removal of triphenylphosphine oxide and the reactions could be conducted using the crude products. Storing crude compounds under inert atmosphere immediately after preparation would reduce their exposure.

While novel alkynes have been produced using a kugelrohr oven, these compounds were produced in very small quantities which made their characterisation difficult. Future work could explore flash vacuum pyrolysis (FVP) as an alternative technique.

The novel sugar-derived tricarbonyls and alkynes are very reactive compounds. These compounds could act as intermediates to new routes for the preparation of carbohydrate mimics and higher sugar skeleton. Therefore, the β,β'-dioxo sugar-derived phosphorus ylides are a route to these potentially valuable compounds.

6. References

1. L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley-Interscience, 2000.
2. J. Cadogan, *Organophosphorus reagents in organic synthesis*, New York : Academic Press, 1979.
3. A. W. Johnson, *Ylides and Imines of Phosphorus*, Wiley-Interscience, 1993.
4. A. Michaelis, Gimborn, H.V., *Berichte der Deutschen Chemischen Gesellschaft*, 1894, **27**, 272.
5. O. I. Kolodiazhnyi, *Phosphorus Ylides: Chemistry and Application in Organic Synthesis*, Wiley-VCH, 1999.
6. M. Taillefer and H. J. Cristeau, *Topics in Current Chemistry: New Aspects in Phosphorus Chemistry III*, 2003.
7. O. I. Kolodiazhnyi, *Russian Chemical Reviews*, 1997, **66**, 225.
8. E. Serrano, R. Navarro, T. Soler, J. J. Carb, A. Lleds and E. P. Urriolabeitia, *Oganic Chemistry*, 2009, **48**, 6823.
9. M. M. Said, S. S. Maigali, M. A. Abd-El-Maksoud and F. M. Soliman, *Monatshefte für Chemie*, 2008, **139**, 1299.
10. M. J. Calhorda, A. Krapp and G. Frenking, *Journal of Physical Chemistry A*, 2007, **111**, 2859.
11. M. Seno, S. Tsuchiya, H. Kise and T. Asahara, *Bulletin of the Chemical Society of Japan*, 1975, **48**, 2001.
12. O. I. Kolodiazhnyi, *Tetrahedron*, 1996, **52**, 1855.
13. J. S. Clark, *Nitrogen, Oxygen and Sulfur Ylide Chemistry (Practical Approach in Chemistry Series)*, OUP Oxford, 2002.
14. A. H. Li, L. X. Dai and V. K. Aggarwal, *Chemical Reviews*, 1997, **97**, 2341.

15. V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *Journal of the American Chemical Society*, 2002, **124**, 6244.

16. R. A. Aitken, C. E. R. Horsburgh, J. G. McCreadie and S. Seth, *Journal of the Chemical Society-Perkin Transactions 1*, 1994, **13**, 1727.

17. S. T. D. Gouch and S. Trippett, *Journal of the Chemical Society*, 1964, **109**,508.

18. P. A. Chopard, R. J. G. Searle and F. H. Devitt, *Journal of Organic Chemistry*, 1965, **30**, 1015.

19. P. J. Murphy and S. E. Lee, *Journal of the Chemical Society-Perkin Transactions 1*, 1999, **21**, 3049.

20. H. J. Bestmann and B. Arnason, *Chemische Berichte*, 1962, **95**, 1513.

21. H. J. Bestmann, R. Dostalek and B. Bauroth, *Angewandte Chemie-International Edition in English*, 1992, **31**, 1064.

22. N. Karodia, University of St Andrews, Edinburgh, 1995.

23. H. H. Wasserman, D. S. Ennis, P. L. Power, M. J. Ross and B. Gomes, *Journal of Organic Chemistry*, 1993, **58**, 4785.

24. S. J. Coats and H. H. Wasserman, *Tetrahedron Letters*, 1995, **36**, 7735.

25. H. H. Wasserman, J. H. Chen and M. D. Xia, *Helvetica Chimica Acta*, 2000, **83**, 2607.

26. K. D. Wehrstedt, P. A. Wandrey and D. Heitkamp, *Journal of Hazardous Materials*, 2005, **126**, 1.

27. H. M. Meshram, G. S. Reddy, M. Muralidhar Reddy and J. S. Yadav, *Tetrahedron Letters*, 1998, **39**, 4107.

28. J. M. J. Tronchet, A. P. Bonenfant, F. Perret, A. Gonzalez, J. B. Zumwald, E. M. Martinez and B. Baehler, *Helvetica Chimica Acta*, 1980, **63**, 1181.

29. J. M. J. Tronchet and M. J. Valero, *Helvetica Chimica Acta*, 1979, **62**, 2788.

30. S. Jarosz and M. Mach, *Journal of the Chemical Society-Perkin Transactions 1*, 1998, **23**, 3943.

31. S. Jarosz, P. Salanski and M. Mach, *Tetrahedron*, 1998, **54**, 2583.

32. A. Dondoni, M. Kleban, H. Zuurmond and A. Marra, *Tetrahedron Letters*, 1998, **39**, 7991.

33. S. Jarosz, *J. Carbohydr. Chem.*, 2001, **20**, 93.

34. M. Isobe, R. Nishizawa, S. Hosokawa and T. Nishikawa, *Chemical Communications*, 1998, **24**, 2665.

35. V. Aucagne, A. Tatibouet and P. Rollin, *Tetrahedron*, 2004, **60**, 1817.

36. M. B. Rubin, *Chemical Reviews*, 1975, **75**, 177.

37. M. B. Rubin and R. Gleiter, *Chemical Reviews*, 2000, **100**, 1121.

38. H. H. Wasserman, V. M. Rotello, D. R. Williams and W. Benbow, *Journal of Organic Chemistry*, 1989, **54**, 2785.

39. H. H. Wasserman and C. B. Vu, *Tetrahedron Letters*, 1990, **31**, 5205.

40. H. H. Wasserman, J. Fukuyama, N. Murugesan, J. Van Duzer, L. Lombardo, V. Rotello and K. McCarthy, *Journal of the American Chemical Society*, 1989, **111**, 371.

41. H. H. Wasserman, C. M. Baldino and S. J. Coats, *Journal of Organic Chemistry*, 1995, **60**, 8231.

42. H. H. Wasserman and J. Parr, *Accounts of Chemical Research*, 2004, **37**, 687.

43. V. Nair and A. Deepthi, *Tetrahedron Letters*, 2006, **47**, 2037.

44. J. Mecinovicacute, R. B. Hamed and C. J. Schofield, *Angewandte Chemie International Edition*, 2009, **48**, 2796.

45. F. Eymery, B. Iorga and P. Savignac, *Synthesis-Stuttgart*, 2000, **2**, 185.

46. R. A. Aitken, J. I., *Journal of chemical society, Perkin Transactions 1*, 1994, **10**, 1281.

47. O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser and P. Zeller, *Helvetica Chimica Acta*, 1957, **40**, 1242.

48. F. Ramirez and S. Dershowitz, *Journal of Organic chemistry*, 1957, **22**, 41.

49. M. I. Shevchuk, E. M. Volynskaya and A. V. Dombrovskii, *Zh. Obshch. Khim*, 1970, **40**, 48.

50. A. Michaelis and E. Kohler, *Berichte der Deutschen Chemischen Gesellschaft* 1899, **32**, 1566.

51. A. Nakamura and S. Otsuka, *Journal of the American Chemical Society*, 1973, **95**, 5092.

52. J. M. Brittain and R. A. Jones, *Tetrahedron*, 1979, **35**, 1139.

53. C. F. Ingham, R. A. Massywestropp, G. D. Reynolds and W. D. Thorpe, *Australian Journal of Chemistry*, 1975, **28**, 2499.

54. P. Froyden, and D. G. Morris, *Acta Chem. Scand.*, 1977, **31**, 256.

55. P. F. D. E. Levy, *The Organic Chemistry of Sugars* CRC Press 2006.

56. P. Collins and R. Ferrier, *Monosaccharides: Their Chemistry and Their Roles in Natural Products*, 1995.

57. T. W. Greene and P. G. Wutts, *Protective Groups in Organic Synthesis*, 1999.

58. R. L. Whistler and M. L. Wolfrom, *Methods in Carbohydrate Chemistry II*, Academic Press, New York, 1963.

59. J. J. Li, *Name Reactions: A Collection of Detailed Reaction Mechanisms*, 2006.

60. www.wikipedia.org/wiki/Mannitol.

61. R. C. Bernotas, M. A. Pezzone and B. Ganem, *Carbohydrate Research*, 1987, **167**, 305.

62. E. C. Horning, *Organic syntheses Collective* 1955.

63. R. N. Rej, J. N. Glushka, W. Chew and A. S. Perlin, *Carbohydrate Research*, 1989, **189**, 135.

64. P. Kovác, E. A. Sokoloski and C. P. J. Glaudemans, *Carbohydrate Research*, 1984, **128**, 101.

65. E. M. Fly, *Journal of the American Chemical Society*, 1955, **77**, 3915.

66. V. Fedi, et al., *Journal of Medicinal Chemistry*, 2007, **50**, 4793.

67. A. J. Pearson and W. J. Roush, *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*, 1999.

68. L. Perreux, A. Loupy and F. Volatron, *Tetrahedron*, 2002, **58**, 2155.

69. E. Petricci, C. Mugnaini, M. Radi, F. Corelli and M. Botta, *Journal of Organic chemistry*, 2004, **69**, 7880.

70. O. Isler, et al., *Helv. Chim. Acta*, 1957, **40**, 1242.

71. F. Ramirez and S. Dershowitz, *J. Org. Chem.*, 1957, **22**, 41.

72. M. I. Shevchuk, E.M. Volynskaya and A.V. Dombrovskii, *Zh. Obsch. Khim.*, 1970, **40**, 48.

73. A. Michaelis and E. Kohler, *Ber. Dtsch Chem. Ges.*, 1899, **32**, 1566.

74. J. M. Brittain and R. A. Jones, *Tetrahedron*, 1979, **35**, 1139.

75. C. F. Ingham, R. A. Massey-Westropp, G. D. Reynolds and W. D. Thorpe, *Aust. J. Chem.*, 1975, **28**, 2499.

76. G. J. F. Chittenden, *Carbohydr. Res.*, 1980, **84**, 350.

77. T. C. Bruice and D. Piszkiewicz, *J. Am. Chem. Soc.*, 1967, **89**, 3568.

78. J. S. Brimacombe and O. A. Ching, *Carbohydrate Research*, 1968, **8**, 82.

79. A. Rosenthal and L. B. Nguyen, *Journal of Organic Chemistry*, 1969, **34**, 1029.

80. P. M. Chincholkar, V. G. Puranik and A. R. A. S. Deshmukh, *Tetrahedron*, 2007, **63**, 9179.

81. B. P. Ross, S. E. DeCruz, T. B. Lynch, K. Davis-Goff and I. Toth, *Journal of Medicinal Chemistry*, 2004, **47**, 1251.

82. P. Sahai, M. Chawla and R. A. Vishwakarma, *Journal of The Chemical Society, Perkin Transactions 1*, 2000, **8**, 1283.