Studies toward the syntheses of carbohydrate analogs containing a phosphonate group via oxaphospholene chemistry
by Todd Aksel Madsen

A thesis submitted in partial fulfillment of the requirements for the degree of Masters of Science in Chemistry
Montana State University

Abstract:
Previous studies toward 3-deoxy-3-phosphonomethyl-D-arabinose using oxaphospholene methodology have found a problem in a crucial step of the synthesis. In an attempt to fix this problem, a new aminal protecting group was pursued. The new aminal proved to be too bulky to react with the oxaphospholene. However, in the process of making the aminal there was room for variation that should produce an aminal that is less hindered and should therefore react with the oxaphospholene.

Another issue addressed is the stereochemistry of the aldol condensation of a chiral aldehyde and the oxaphospholene. The product of this reaction is a β-hydroxy ketone phosphonate with two new stereocenters. The aldehyde is chiral and derived from 5-ethyl lactate and contains a protected alcohol. The method envisioned for the determination of the stereochemistry is protection of the hydroxyl group of the β-hydroxy ketone then deprotection of the alcohol. This should then cyclize onto the phosphonate yielding a six membered cyclic phosphonate otherwise known as a phostone. The six membered phostones are known in literature and the J coupling values for the protons around the ring are published. Thus, by comparison of the J coupling values from the phostone that we make to the literature references we will know the stereochemistry of the six membered phostone, which we could then relate back to the aldol product.

STUDIES TOWARD THE SYNTHESES OF CARBOHYDRATE ANALOGS CONTAINING A PHOSPHONATE GROUP VIA OXAPHOSPHOLENE CHEMISTRY

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APPROVAL

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Todd Aksel Madsen

This thesis has been read by each member of the thesis committee and has been found to satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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ABSTRACT

Previous studies toward 3-deoxy-3-phosphonomethyl-D-arabinose using oxaphospholene methodology have found a problem in a crucial step of the synthesis. In an attempt to fix this problem, a new aminal protecting group was pursued. The new aminal proved to be too bulky to react with the oxaphospholene. However, in the process of making the aminal there was room for variation that should produce an aminal that is less hindered and should therefore react with the oxaphospholene.

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CHAPTER 1

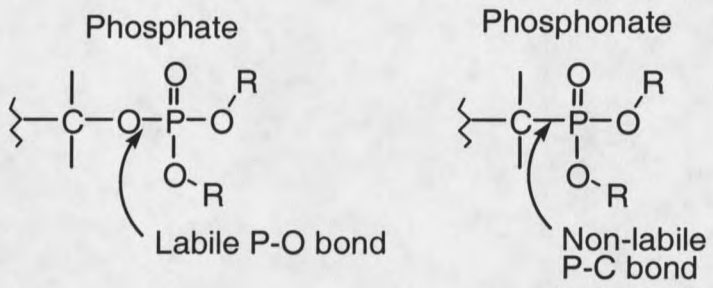
INTRODUCTION

Background

Organic phosphates play important roles in biological systems. Phosphates form the backbone of DNA and RNA. The loss of a phosphate group in the conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) liberates free energy that is used to drive reactions such as muscle contraction.[1] Phosphates play a large role in glycolysis and gluconeogenesis. Phospholipids are one of two main types of lipids that occur in biological membranes.[2] The role of phosphates makes them key targets in controlling or inhibiting metabolic functions.[2]

Phosphonates differ from phosphates by replacing the labile oxygen-phosphorus bond with a carbon-phosphorus bond (see Figure 1.1). This difference could be exploited by using phosphonate analogs of phosphates to interrupt biological pathways.[3] Phosphonate derivatives of naturally occurring compounds can be used to inhibit or perturb biosynthetic pathways, because the carbon-phosphorus bond cannot be hydrolyzed like the oxygen-phosphorus bond.[3c] Our research group is exploring the synthesis of phosphonate analog targets using pentacovalent oxaphospholene methodology.

Figure 1.1 Phosphates vs. Phosphonates

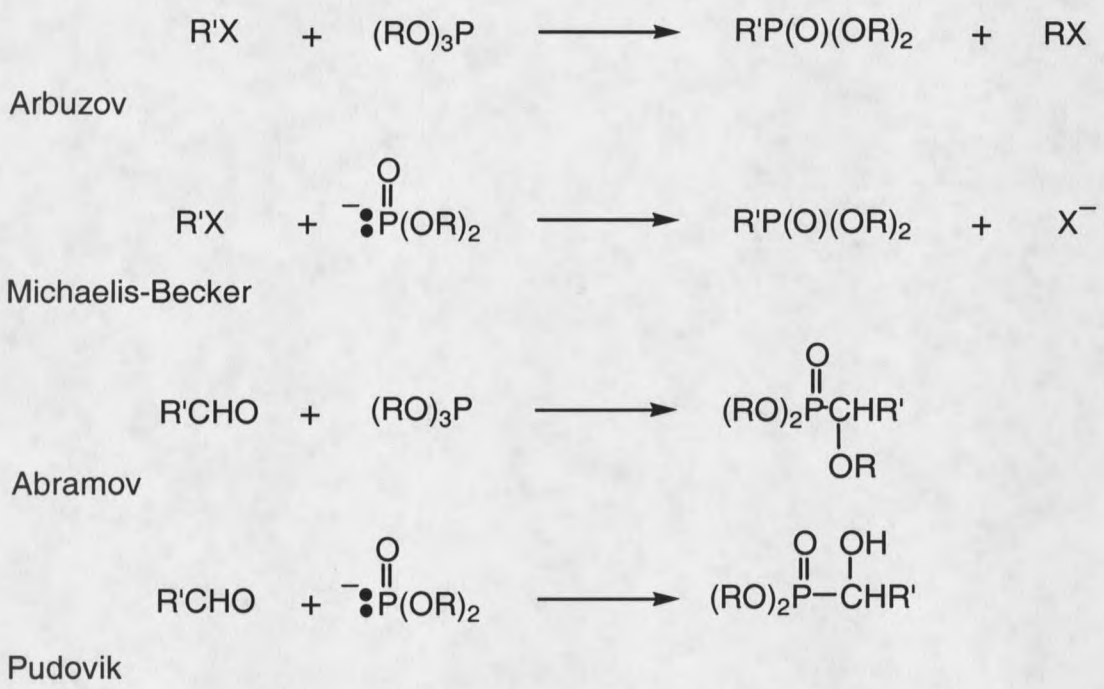


The course of study described herein is the exploration of a possible route to carbohydrate derivatives containing phosphonate moieties via the condensation of an aminal protected glyoxal derivative with a pentacovalent oxaphospholene. A study of stereocontrol using chiral aldehydes in condensation reactions with pentacovalent oxaphospholenes to affect the stereochemistry of the final products is also presented.

Classical Methods for Phosphonates

There are several classical methods available to make phosphonates. The Arbuzov or Michaelis-Arbuzov reaction is simply the reaction of a trialkyl phosphite and an alkyl halide to provide the phosphonate. A variation on this theme is the Michaelis-Becker reaction, which involves a displacement of a halide ion from a saturated carbon by a dialkyl phosphite anion. The Abramov reaction is the treatment of an aldehyde with trialkyl phosphite. The Pudovik is a variation of the Abramov using a dialkyl phosphite anion in place of the trialkyl phosphite. These reactions are shown in Scheme 1.1.[4] These classical methods only produce the carbon-phosphorus bond.

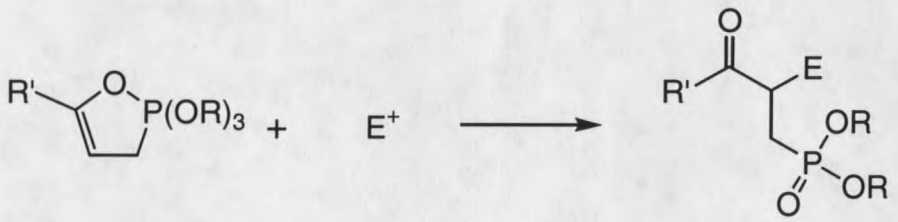
Scheme 1.1 Alternative Methods to Prepare Phosphonates



Pentacovalent Oxaphospholene Methodology

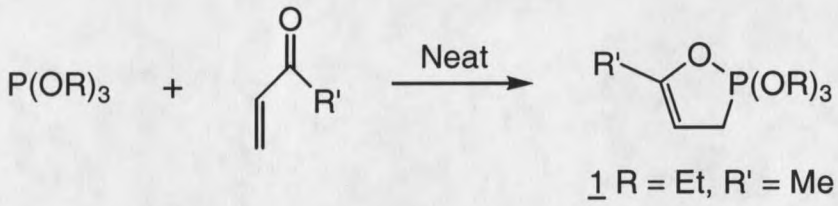
The methodology developed in our group uses a pentacovalent 1,2λ^5-oxaphospholene that is condensed with an electrophile to produce a phosphonate (Scheme 1.2).[5] A benefit of this methodology is that it can be done in one pot if desired (e.g. the oxaphospholene generated in situ, then the electrophile added) to produce a carbon-phosphorus bond and a carbon-carbon, carbon-nitrogen, carbon-oxygen, or carbon-bromine bond.[5]

Scheme 1.2 Reaction of Oxaphospholene and an Electrophile



Pentacovalent 1,2λ^5-oxaphospholene **1** (or simply oxaphospholene) is the product of the reaction of a trialkyl phosphite with an α,β-unsaturated ketone (Scheme 1.3).

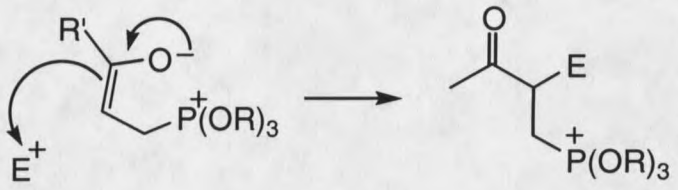
Scheme 1.3 Synthesis of a Pentacovalent Oxaphospholene



1 R = Et, R' = Me

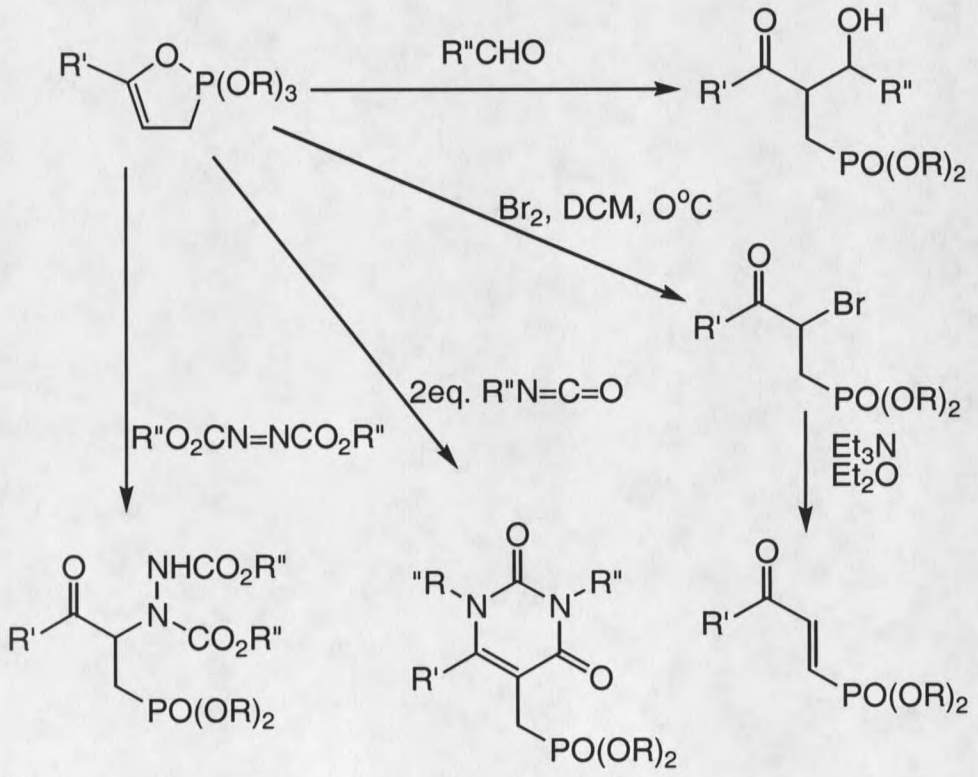
The resultant oxaphospholene is then condensed with an electrophile resulting in a phosphonate compound. The proposed mechanism is shown in Scheme 1.4. The pentacovalent oxaphospholenes can be distilled and kept stored in a freezer sealed under argon for months with little or no degradation.

Scheme 1.4 Proposed Nucleophilic Addition Mechanism



Various electrophiles have been explored in this reaction, several of which are illustrated in Scheme 1.5. The formation of bisphosphonates is also possible using this methodology by subjecting a keto vinyl β-phosphonate (produced from the reaction of the oxaphospholene and bromine followed by subsequent elimination) to a trialkyl phosphite.

Scheme 1.5 Pentacovalent Oxaphospholene Methodology



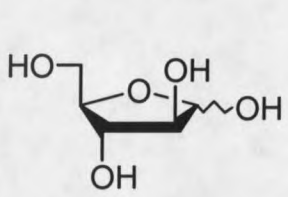
The product would then be a pentacovalent oxaphospholene containing a phosphonate.

There are many choices of electrophiles as shown in Scheme 1.5. My research, however, has focused on using aldehydes as the electrophiles. Condensations with aldehydes produce β-hydroxy ketone phosphonates containing two new chiral centers. With the proper choices of R' and R", the condensation product can be transformed into an acyclic carbohydrate. With this in mind, two goals are presented; first an easy route to a carbohydrate with a phosphonate group in place of a hydroxyl group, and secondly, stereocontrol of the newly formed chiral centers from the aldol condensation. The first goal involves choosing the appropriate vinyl ketone and aldehyde moieties that could be deprotected or modified to give the desired acyclic carbohydrate. The second goal involves the use of a chiral aldehyde to see if chirality transfers to the condensation product from the aldehyde.

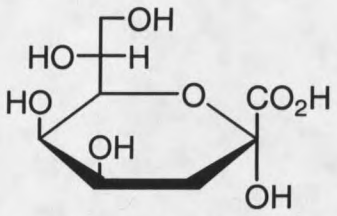
Proposed Target

Our target is the 3-deoxy-3-phosphonomethyl-D-arabinose derivative. Gram-negative bacteria use D-arabinose (Figure 1.2) to produce 3-deoxy-D-manno-2-octulosonic acid (KDO) (Figure 1.2). KDO is the key component used to make the lipopolysaccharides that constitute the outer membrane of gram-negative bacteria.

Figure 1.2



D-Arabinose



3-Deoxy-D-Manno-2-Octulosonic Acid
KDO

The KDO pathway is exclusive to gram-negative bacteria and therefore is an attractive candidate for inhibition. The biosynthesis of KDO is shown in Scheme 1.6.[6] Any inhibition of the biosynthesis of KDO would affect the formation of lipopolysaccharides, which would compromise the integrity of the outer membrane of the bacteria and allow it to be more vulnerable to outside attack from either the host's natural defenses or other antibiotics.

As shown in Scheme 1.6, KDO is formed from D-arabinose 5-phosphate. From labeling studies, it was found that the hydroxyl group at the three position of D-arabinose becomes the ring oxygen in KDO. With this in mind, one possible route to inhibit the KDO 8-phosphate synthetase enzyme is by replacing the 3- hydroxyl group with a phosphonomethyl moiety (Figure 1.3). The stronger carbon-phosphorus bond should prevent the enzyme from hydrolyzing off the phosphonate. This would prevent the formation of KDO and the subsequent formation of the lipopolysaccharide.