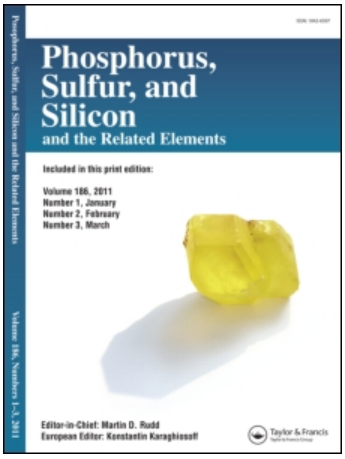

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Formation of Cyclic Acetals from Allylic Hydroxy Phosphonates via Intramolecular Oxymercuration

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FORMATION OF CYCLIC ACETALS FROM ALLYLIC HYDROXY PHOSPHONATES *VIA* INTRAMOLECULAR OXYMERCURATION

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Treatment of allylic hydroxy phosphonates in aldehyde solution with mercuric trifluoroacetate, followed by the reduction of the organomercurial intermediate, afforded the cyclic acetal derivatives. The reaction displays high diastereo- and regio-selectivity. ^{31}*P NMR studies showed the formation of an intermediate hemiacetal and rapid formation of the organomercurial upon addition of mercuric trifluoroacetate. However, the oxymercuration was reversible, and attempts to remove the excess aldehyde often led to recovery of the starting material. Fortunately, reduction of the organomercurial intermediate with sodium cyanoborohydride in the presence of the aldehyde led to more reproducible yields.*

Keywords: Diastereoselectivity; hydroxy phosphonate; oxymercuration

INTRODUCTION

Hydroxy allylic phosphonates of high enantiomeric excess are becoming increasingly more available due, in particular, to rapid advances in methods for asymmetric phosphonylation of aldehydes and enzymatic resolution.[1–3] It is well established that allylic alcohols possess the ability to efficiently control stereochemical induction in a number of alkene addition reactions.[4] Allylic hydroxy phosphonates display some of the chemistry associated with allylic alcohols.[5] However, the presence of

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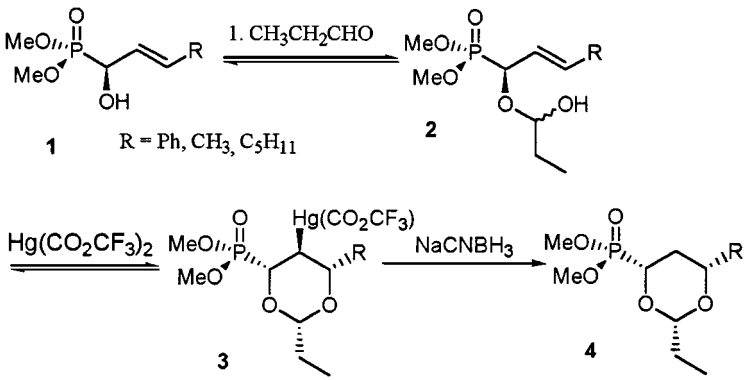
the phosphoryl group is advantageous in many ways. The steric and electronic influence of the phosphorus moiety helps to define the stereochemical and regiochemical outcome of the reactions.[5] We have recently begun to explore applications of this new technology to the asymmetric synthesis of structurally more complex and biologically interesting molecules.

In 1974, Overman showed[6] that hemiacetals derived from chloral and allylic alcohols would undergo a mercuric ion-induced ring closure to give, after reduction of the intermediate organomercurial, a cyclic acetal with good stereocontrol. More recently, Leighton showed[7] that using the aldehyde as solvent overcomes the unfavorable hemiacetal/alcohol equilibrium in the intramolecular oxymercuration of homoallylic alcohols. This finding allows the use of a wider range of aldehydes for acetal formation. Having recently observed the preference of *E*-allylic hydroxy phosphonates to undergo highly diastereoselective 6-endo cyclizations,[5b] the acetal-induced intramolecular oxymercuration attracted our attention as a possible method for the stereocontrolled introduction of oxygen substitutions into the 3-position of allylic hydroxy phosphonates. We report here the results of this study.

RESULTS AND DISCUSSION

The allylic hydroxy phosphonates **1** were dissolved in propionaldehyde and treated with mercury (II) trifluoroacetate ($Hg(O_2CCF_3)_2$ to give the organomercurial **3** (Scheme 1). The solution was evaporated and the residue was dissolved methanol and treated with $NaBH_4$. The resulting cyclic acetal **4** was isolated as a single diastereoisomer, but in extremely variable yields.



SCHEME 1

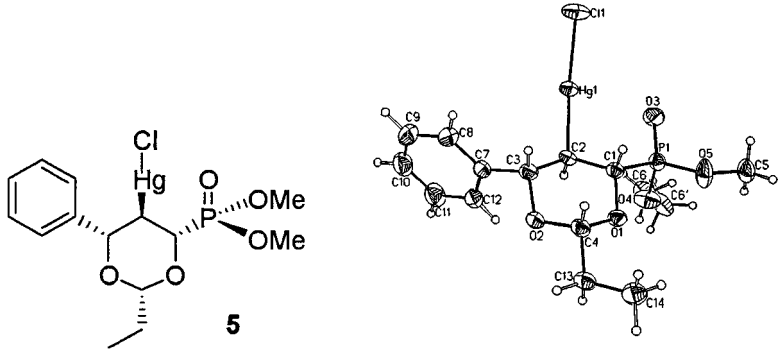
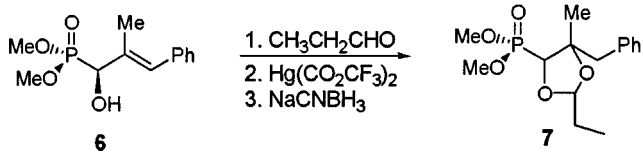


FIGURE 1 X-ray structure for chloromercurials.

A mechanistic investigation revealed that the oxymercuration step is reversible. A solution of the alcohol in propionaldehyde contained a 70:30 mixture of a free alcohol and the hemiacetal as indicated by ^{31}P NMR spectroscopy. The addition of $Hg(O_2CCF_3)_2$ induced the rapid formation of a single compound **3**. Reduction of the mercurial **3** *in the aldehyde solution* with sodium cyanoborohydride gave moderate (42–70%) but reproducible yields of the cyclic acetals. The relative stereochemistry of the acetals was assigned from the x-ray crystal structure of the chloromercurial intermediate **5** (Figure 1), prepared by treating the trifluoroacetate with saturated brine solution.

Interestingly, allylic hydroxy phosphonate **6** affords the five-membered ring acetal **7** rather than the expected six-membered ring (Scheme 2) under the same reaction conditions. In cases where the reaction failed, ^{31}P NMR data clearly showed formation of the acetal and organomercurial compounds. However, attempted reduction resulted in reformation of the starting material.



SCHEME 2

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