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Diels-Alder Reactivity of a Keto Vinylphosphonate. Empirical and Theoretical Observations. Application to the Syntheses of Phosphonate Analogues of *Myo*-Inositol.

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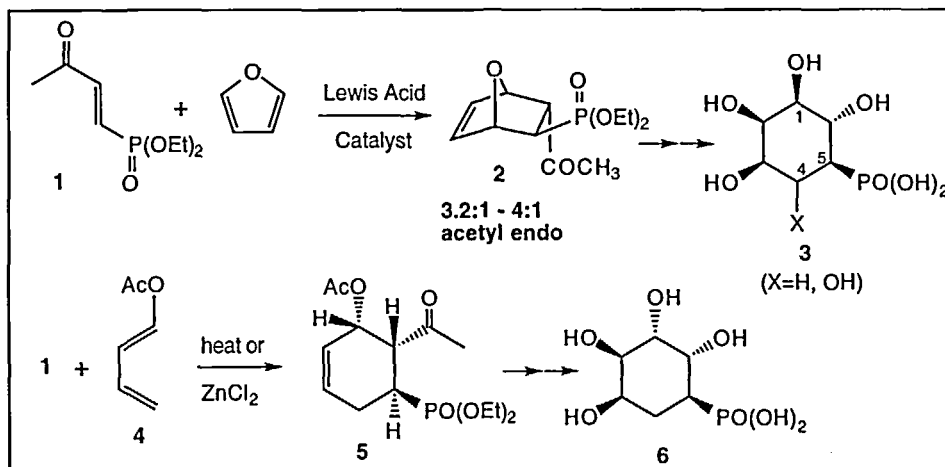
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DIELS-ALDER REACTIVITY OF A KETO VINYLPHOSPHONATE. EMPIRICAL AND THEORETICAL OBSERVATIONS. APPLICATION TO THE SYNTHESSES OF PHOSPHONATE ANALOGUES OF *MYO*-INOSITOL.

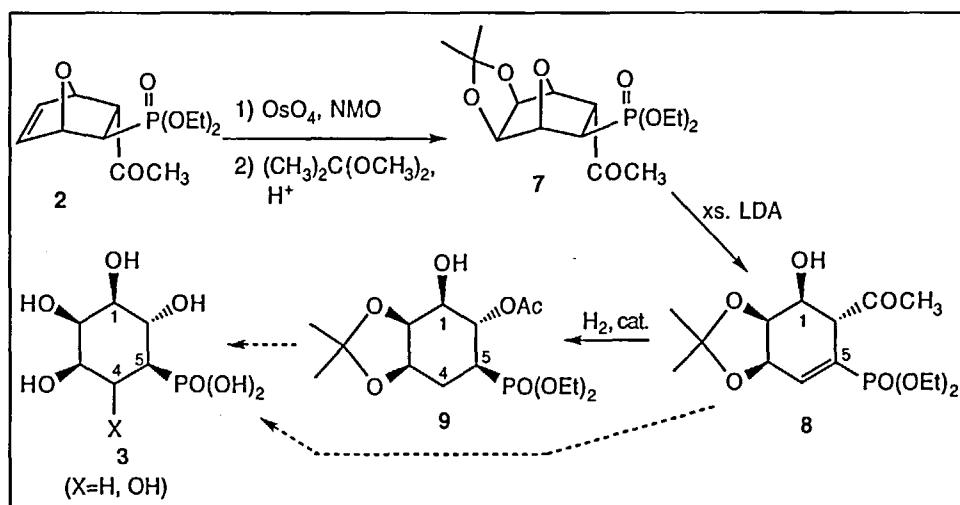
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 59171

Abstract The Diels-Alder reactivity of the keto vinylphosphonate **1** with furan, cyclopentadiene and E-1-acetoxy-1,3-butadiene was investigated with and without Lewis acid assistance. The acetyl group directed in each case. LUMO molecular orbital coefficients were obtained via *ab initio* (3-21G*) calculations, and support the experimental data. The Diels-Alder products from the reactions with furan and 1-acetoxybutadiene are being carried on to phosphonate analogs of inositols.

We are currently investigating the Diels-Alder reactivity of the keto vinylphosphonate **1** with various dienes, the ultimate targets being phosphonate analogues of *myo*-inositol phosphates. *Myo*-inositol phosphates are key players in cellular signal transduction, and are second messengers in a large array of cellular processes.² Two routes to the phosphonate inositol analogues are being pursued: (a) via a Lewis acid catalyzed Diels-Alder reaction of **1** with furan, and (b) via a Diels-Alder reaction of **1** with (E)-1-acetoxy-1,3-butadiene (**4**).

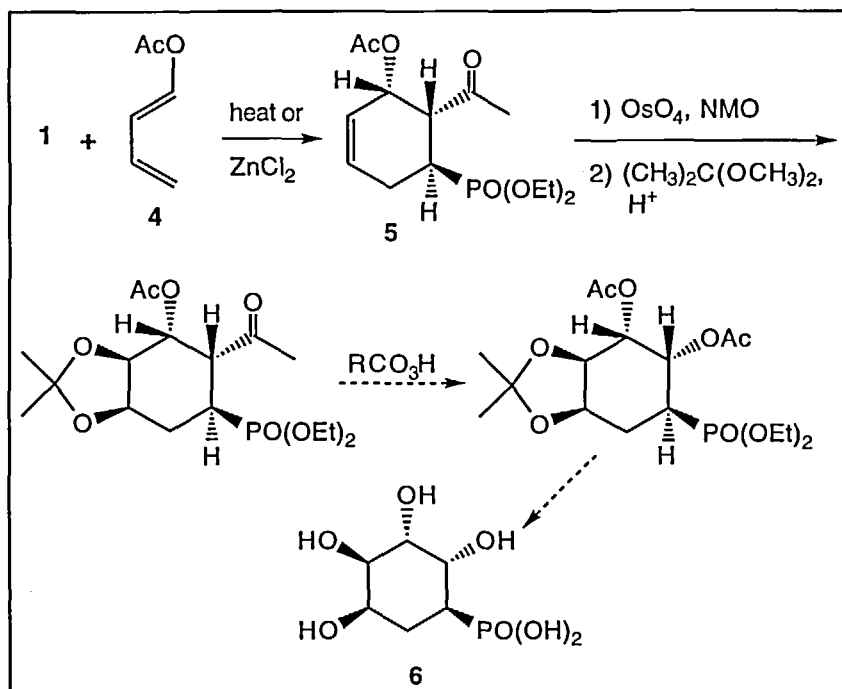


The acetyl endo furan adduct, **2**, was carried on in the synthesis of the inositol phosphonate analog **3**. Osmylation of the alkene, followed by protection of the diol, proceeded in good yields. Attempts at inducing a Baeyer-Villiger reaction on the acetyl group at this point gave only starting material. We also tried to open the bridge using acetyl bromide, dry HBr, or FeCl₃/Ac₂O. None of these conditions produced any products, and only starting material was recovered. However, we found that upon

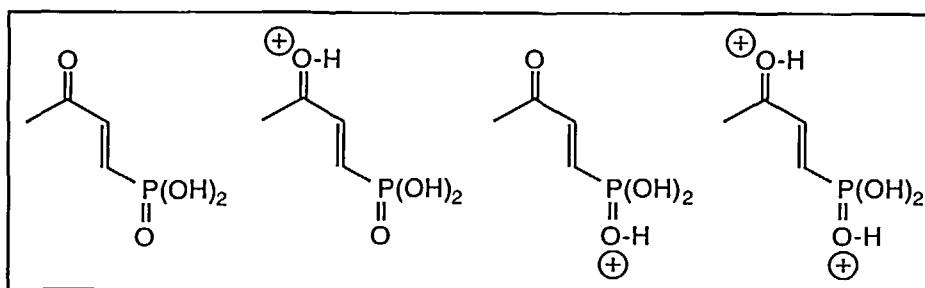


treatment with 2.2 eq. of LDA, we could deprotonate α to the phosphonate and effect a ring opening of the bridge to form the vinylphosphonate, **8**, in 80% yield, but only 30% conversion. Attempts to push the reaction produced aromatized by-products. Hydrogenation of **8** produced the expected isomer in quantitative yield. We are currently at this stage of the synthesis, and plan to pursue other methods for opening the oxygen bridge.

In contrast to the non-polarized dienes above, Diels–Alder reaction of **1** with E-1-acetoxy-1,3-butadiene, **4**, produced only one regio- and stereo-isomer, **5**, under thermal or Lewis acid (ZnCl_2) assisted conditions. Its structure was determined to be as shown via 2-D COSY, HETCOR and J-Resolved experiments. This regio- and stereo-isomer (acetyl directing endo) is in contrast to that reported by Darling using the same diene, but where the phosphonate group was replaced with a diphenyl phosphine oxide.⁵ They reported isolation of only one product where the phosphine oxide had directed in the exo mode. Our Diels–Alder adduct, **5**, is being carried on to (\pm)-1-epi-4-deoxy-5-phosphono-*myo*-inositol **6** (also called (\pm)-3-deoxy-4-phosphono-*dl*-inositol) as shown. Osmylation and protection of the diol have proceeded in good yields. We are currently at this stage of the synthesis.



To further investigate the effects Lewis acids have on the Diels-Alder reactivity of keto vinylphosphonates analogous to **1**, we have also performed theoretical (*ab initio* RHF/3-21G*) calculations using a model Lewis acid (H^+) and the phosphonic acid analogue of **1** (see figure below). The resulting LUMO levels of these model dienophiles exhibited a lowering of the relative energies upon going from non-protonated, to mono-protonated (either carbonyl or phosphoryl oxygens) to di-protonated at both the carbonyl and phosphoryl oxygens, as expected. The molecular orbital coefficients varied as expected with the complexation, and supported the empirical data.



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5. S.D. Darling and S.J. Brandes, *J. Org. Chem.*, **31**, 3236 (1982). However, it was reported in the Ph.D. thesis of one of Darling's students that the stereochemistry and regiochemistry of the Diels-Alder product of their keto vinylphosphine oxide (diphenyl) was identical to our adduct **5**. (S.C. Park, Univ. of Akron, OH, 1992).