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Structure Determination of the Diels-Alder Product of a Ketovinylphosphonate with *E*-1-Acetoxy-1,3-Butadiene.

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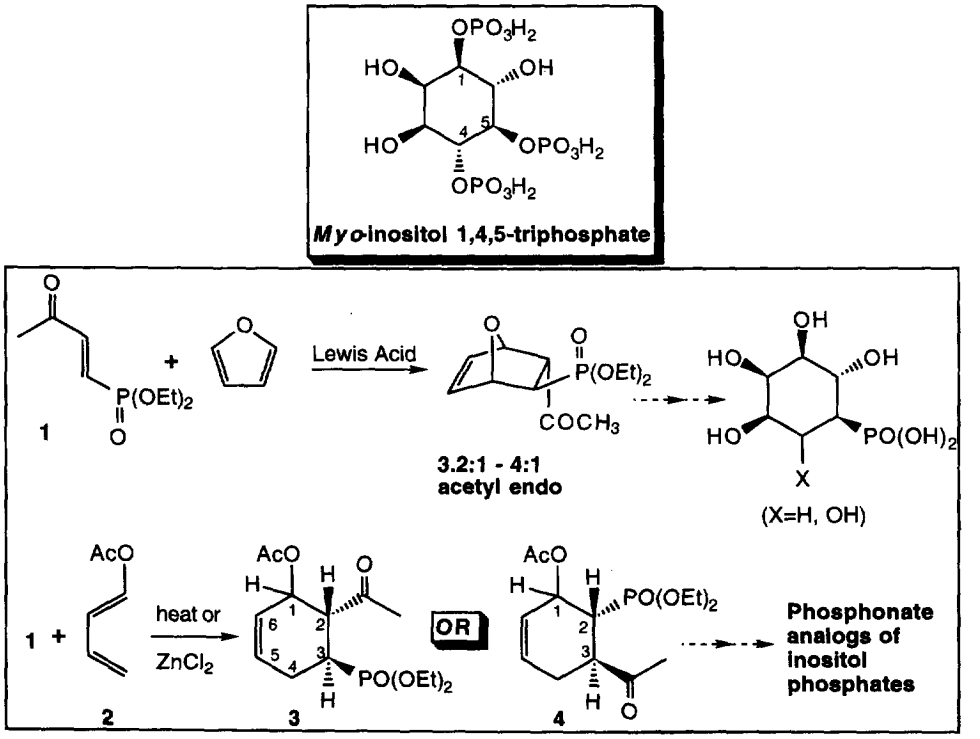
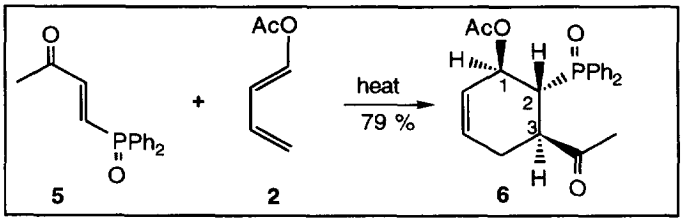
Summary: The Diels-Alder reaction between diethyl ketovinylphosphonate **1** and *E*-1-acetoxy-1,3-butadiene was performed with and without Lewis acid assistance to yield only *one* regio- and stereoisomer. Various 2-D NMR experiments confirmed that the *acetyl group* directed endo.

We are currently investigating the Diels-Alder reactivity of the ketovinylphosphonate **1**[3] with various dienes[4], the ultimate targets being phosphonate analogues of *myo*-inositol phosphates. *Myo*-inositol phosphates are key players in cellular signal transduction, and are second mesengers in a large array of cellular processes.[4] Two routes to the phosphonate inositol analogues are being pursued: (a) via a Lewis acid assisted Diels-Alder reaction of **1** with furan[5], and (b) via the Diels-Alder reaction of **1** with *E*-1-acetoxy-1,3-butadiene (**2**).



A report in the literature indicated that the Diels-Alder reaction between our diene of interest, *E*-1-acetoxy-1,3-butadiene, and the diphenyl ketovinyl*phosphine oxide*, **5**, produced the "unexpected" isomer **6**, with the phosphine oxide α to the acetate group.[6] The Diels-Alder reaction of our ketovinyl*phosphonate*, **1**, with *E*-1-acetoxy-1,3-butadiene under Darling's thermal conditions (neat, sealed vial, 100°C, 48 hrs) produced two compounds in a 5:1 ratio and 85% yield. The minor product was shown to be a phosphonate-containing cyclic diene (*vide infra*). Under Lewis acid assisted conditions (8 eq. $ZnCl_2$, Et_2O, rt), the Diels-Alder reaction between **1** and **2** produced only *one* regio- and stereoisomer that was identical to the major product of the thermal Diels-Alder reaction.



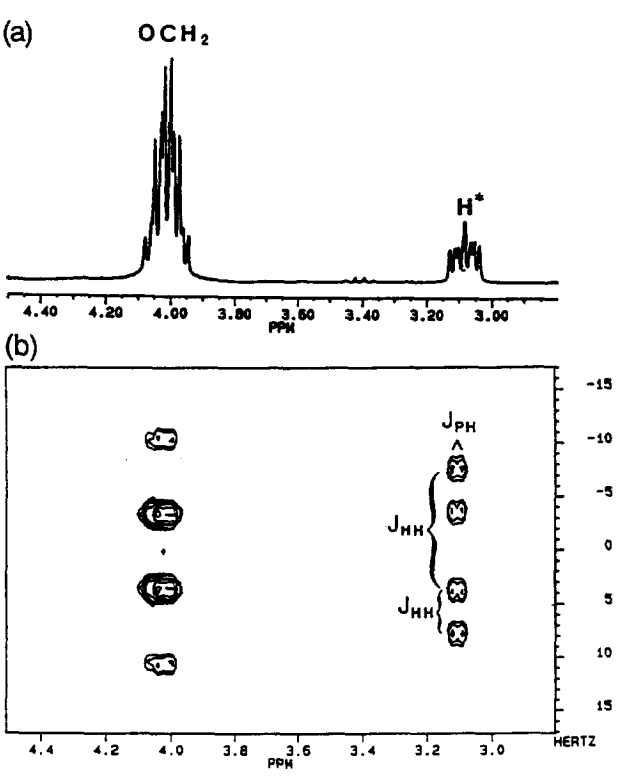
The two possible Diels-Alder regioisomers, **3** and **4**, were not distinguishable by standard 1-D NMR experiments. Overlapping multiplets and heteronuclear coupling to the phosphorus precluded resolution of the regiochemical and stereochemical questions via only homonuclear spin decoupling experiments. Chemical shifts were therefore confirmed via a 2D-COSY spectrum. By standard chemical shift analysis, the allylic methine that was α to the acetate (H1) was expected to be between 5 and 6 ppm. The COSY spectrum indicated that the multiplet at 5.55 ppm was coupled to the vinyl proton at 5.77 ppm and to the multiplet due to one proton at 3.12 ppm. The multiplet at 3.12 was also coupled to the multiplet at approx. 2.6-2.8 ppm (integrates to one proton). The one proton multiplet at 5.98 ppm was coupled to the two proton multiplet between 2.3-2.6 ppm. Therefore, this assigns the multiplet at 5.55 ppm to H1, the multiplet at 3.12 ppm to H2, the multiplet at 2.6-2.8 ppm to H3, the multiplet at 5.77 ppm to the vinyl proton H6, and the multiplet at 5.98 ppm to the vinyl proton H5. But, due to the long-range phosphorus couplings and the expected chemical shifts for protons H2 and H3, we could not definitively assign H2 as α to the acetyl or α to the phosphonate (i.e., compounds **3** or **4**).

The regiochemistry was confirmed via a HETCOR (heteronuclear chemical shift correlation) experiment.[7] We know that the carbon at 28 ppm was attached to the phosphorus due to the very large J_{PC} of 144 Hz. From the HETCOR spectrum, the carbon at 28 ppm correlated to the proton between 2.6-2.8 ppm, NOT to the proton at 3.12 ppm. Thus, the major Diels-Alder product was **3**, with the *acetyl* at C2, indicating that the phosphonate group did NOT direct the Diels-Alder reaction in this case.

The structure of the initial Diels-Alder product, **3**, contains three stereocenters, yielding four possibilities of the relative stereochemistry between the three methine protons (H1,H2 - H2,H3): trans-trans, trans-cis, cis-trans, or cis-cis. Since the acetyl and phosphonate will be trans to each other due to the trans olefin in the starting ketovinylphosphonate, the relative stereochemistry in **3** can be only trans-trans or cis-trans for H1,H2 - H2,H3. Since in a six-membered ring, the vicinal coupling constants between protons on adjacent carbons are generally large (6-15 Hz) if the two protons are trans diaxial and small (< 5 Hz) if the protons are trans diequatorial or axial/equatorial (cis), this knowledge should make it relatively easy to distinguish stereochemistry via the coupling constants available from a standard 1D spectrum. However, in this case, assignments of coupling

constants between H1, H2 and H3 were complicated by severe spectral overlap in the upfield region of the 250 MHz proton spectrum, and by the heteronuclear P-H coupling.

A J-Resolved 2D experiment[8] can resolve heteronuclear coupling in cases where this interaction cannot be decoupled due to hardware limitations. This 2D experiment treats heteronuclear coupling (here J_{PH}) as a chemical shift difference along the f1-dimension (x-axis), and homonuclear (proton-proton) coupling as a chemical shift difference along the f2-dimension (y-axis). The J-Resolved spectrum of the Diels-Alder product **3** yielded $^3J_{PH}$ = 7 Hz for the coupling between H2 and the phosphorus (**Figure 1**). The H-H coupling constants read from the y-axis were 4 Hz and 11 Hz. Irradiating H1 (α to the acetate) in a selective homonuclear decoupling yielded a doublet of doublets (dd) for H2 at 3.1 ppm with J = 7 Hz and 11 Hz. Since J_{PH} = 7 Hz, then $J_{H1\text{-}H2}$ is 4 Hz (equatorial/axial cis orientation), and $J_{H2\text{-}H3}$ is 11 Hz (trans-diaxial orientation). The relative stereochemistry between carbons C1 and C2, and C2 and C3 is therefore cis-trans: cis acetate and acetyl (as expected based on the endo rule for the Diels-Alder reaction), and trans acetyl and phosphonate (as seen in the starting material **1**). If the stereochemistry at C1 had been inverted, the protons H1 and H2 would have been trans, and would have exhibited a larger coupling constant than 4 Hz (since H2 is axial). As a check on these assignments, the alkene was hydrogenated to induce a better chair conformation in the product. The coupling constants obtained from this compound via the selective homonuclear decoupling experiments were very similar to those obtained for compound **3**.[9]



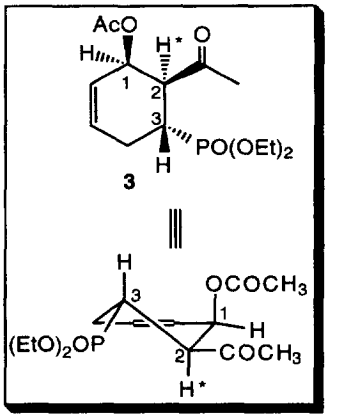
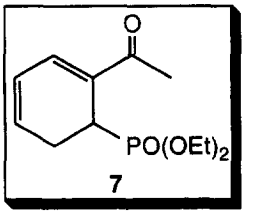


Figure 1. Expansion of (a) the 250 MHz spectrum and (b) the 2D J-Resolved spectrum of **3**.

The minor product from the thermal reaction was shown by proton and carbon NMR to be **7**, the product from elimination of the acetate group.[10] Confirmation was acquired by thermalizing **3** under the original reaction conditions (neat, 100°C) to produce the diene **7**. Thus, the ketovinylphosphonate, **1**, readily reacts with a polarized, acyclic diene under thermal or Lewis acid assisted conditions to produce in excellent yields *only one regio- and stereoisomer* due to the acetyl group directing endo. Application of this Diels-Alder product to the syntheses of phosphonate analogs of inositol phosphates is currently underway, and will be reported in due course.



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6. Darling, S.D. and Brandes S.J. *J. Org. Chem.* **1982**, *31*, 3236. 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 diphenyl ketovinylphosphine oxide was identical to our adduct **3** (S.C. Park, Univ. of Akron, OH, 1992).
7. In this experiment, the ^{13}C spectrum is plotted along the f1-dimension (x-axis) and the ^{1}H spectrum along the f2-dimension (y-axis). The carbon shift of a peak in the HETCOR spectrum is read on the x-axis, and the shift corresponding to the proton attached to that carbon is read on the y-axis.
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9. All NMR data were acquired on a Bruker AM-250 (250 MHz), and are reported in ppm downfield from TMS. **3: ^{1}H NMR :** 5.98 (m, 1H, H5), 5.77 (m, 1H, H6), 5.55 (dd, 1H, J = 4.0, 3.4 Hz, H1), 4.05 (qd, 4H, J = 7.0 Hz, $J_{P\text{-}H}$ = 4.5 Hz, OCH_2), 3.12 (ddd, 1H, $J_{P\text{-}H}$ = 6.5 Hz, $J_{H\text{-}H}$ = 11.4, 4.0 Hz, H2), 2.75-2.57 (m, 1H, H3), 2.56- 2.26 (m, 2H, H's on C4), 2.24 (s, 3H, acetyl CH_3), 1.98 (s 3H, OCH_3), 1.20 (t, 3H, J = 7.1, CH_2CH_3), 1.19 (t, 3H, J = 7.1, CH_2CH_3). **^{13}C:** 205.7, 170.1, 131.1 (d, $J_{P\text{-}C}$ = 12.7 Hz), 123.1, 63.8 (d, $J_{P\text{-}C}$ = 12.0 Hz), 61.8 (d, $J_{P\text{-}C}$ = 7.0 Hz), 61.6 (d, $J_{P\text{-}C}$ = 7.0 Hz), 50.0 (d, $J_{P\text{-}C}$ = 3.3 Hz), 30.43, 28.1 (d, $J_{P\text{-}C}$ = 144.0 Hz), 24.7 (d, $J_{P\text{-}C}$ = 3.7 Hz), 20.8, 16.14 (d, $J_{P\text{-}C}$ = 5.9 Hz), 16.09 (d, $J_{P\text{-}C}$ = 5.8 Hz).
10. **7: ^{1}H NMR:** 6.96 (dd, $J_{P\text{-}H}$ = 5.6 Hz, $J_{H\text{-}H}$ = 5.6 Hz), 6.11 (m, 2H), 4.00 (m, 4H), 3.56 (dd, $J_{P\text{-}H}$ = 25.6 Hz, $J_{H\text{-}H}$ = 10.5 Hz), 2.86 (dddm (app. tdm) 1H, $J_{P\text{-}H}$ = 19.1 Hz, $J_{H\text{-}H}$ = 19.1, 5.7 Hz), 2.54 (dddm, 1H, $J_{P\text{-}H}$ = 53.0 Hz, $J_{H\text{-}H}$ = 19.1, 10.7 Hz), 2.32 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.0 Hz). **^{13}C:** 196.4 (d, $J_{P\text{-}C}$ = 3.3 Hz), 134.7 (d, $J_{P\text{-}C}$ = 10.1 Hz), 132.95 (d, $J_{P\text{-}C}$ = 5.7 Hz), 132.2 (d, $J_{P\text{-}C}$ = 9.4 Hz), 123.7 (d, $J_{P\text{-}C}$ = 4.7 Hz), 62.0 (d, $J_{P\text{-}C}$ = 5.2 Hz), 61.9 (d, $J_{P\text{-}C}$ = 6.6 Hz), 28.0 (d, $J_{P\text{-}C}$ = 134.8 Hz), 25.1, 23.85 (d, $J_{P\text{-}C}$ = 5.3 Hz), 16.34 (d, $J_{P\text{-}C}$ = 2.3 Hz), 16.25 (d, $J_{P\text{-}C}$ = 2.6 Hz).

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