124.5 (q, $^1J_{CF}$ = 280 Hz, CF_3), 127.3 (s, C arom), 128.2 (s, CH arom), 130.2 (s, CH arom), 156.0 (s, C arom); ^{19}F NMR ($CDCl_3/CFCl_3$) δ -71.7 (d, $^3J_{HF}$ = 7 Hz); IR ($CHCl_3$) 3550 cm^{-1} (ν_{OH}). Anal. Calcd for $C_{10}H_{10}O_2ClF_3$: C, 47.17; H, 3.96. Found: C, 47.48; H, 3.80.

General Procedure for Cyclization of Chlorohydrins 5aI or 5bI. To chlorohydrin **5aI** or **5bI** (0.94 mmol) in anhydrous Et_2O (10 mL) were added powered KOH (8 equiv) and a catalytic amount of 18-crown-6. After being stirred at room temperature for 30 min, the mixture was filtered over silica gel 70-230 mesh (h = 3 cm, ϕ = 7 cm). The silica gel was rinsed with Et_2O (100 mL). The organic phases were combined, and the solvent was removed to give the crude epoxide **1a** or **1b** which was used for the next step without purification.

General Procedure for Opening of Epoxides 1a or 1b. To the crude epoxide **1a** or **1b** (0.94 mmol) in a mixture of $MeOH/H_2O$ (9/2, 10 mL) was added sodium azide (5 equiv) in one fraction. The mixture was stirred under reflux for 10 h. After concentration of the solution (half) Et_2O (100 mL) and water (20 mL) were added. The organic phase was separated and the aqueous phase extracted with Et_2O (2 × 20 mL). The combined ether layers were dried over $MgSO_4$, and the solvent was removed to give the crude compound **6aI** or **6bI**.

6aI: uncolored oil; 75% yield after purification by flash chromatography (h = 20 cm, ϕ = 3 cm, Et_2O/hexane 20/80, R_f = 0.27); ^{1}H NMR ($CDCl_3$) only one isomer was observed, δ 2.40 (s, CH_3), 3.01 (d, 1 H, OH), 4.10 (m, 1 H, CHO), 5.14 (d 1 H), 7.28 (m, 3 H arom), 7.48 (m, 1 H arom); ^{13} NMR ($CDCl_3$) δ 19.7 (s, CH_3), 60.9 (s, CHN_3), 73.0 (q, $^2J_{CF}$ = 30 Hz, CHO), 124.6 (q, $^1J_{CF}$ = 283 Hz, CF_3), 127.4 (s, CH arom), 128.0 (s, CH arom), 129.6 (s, CH arom), 131.7 (s, CH arom), 134.2 (s, C arom), 135.9 (s, C arom); ^{19}F NMR ($CDCl_3/CFCl_3$) δ -77.56 (d, $^3J_{FH}$ = 7 Hz); IR (neat) 3440 (ν_{OH}), 2180 cm^{-1} (νN_3). Anal. Calcd for $C_{10}H_{10}ON_3F_3$: C, 48.98; H, 4.11; N, 17.14. Found: C, 49.10; H, 4.32; N, 16.17.

6bI: uncolored oil; 95% yield after purification by flash chromatography (h = 20 cm, ϕ = 3 cm, Et_2O/hexane 30/70, R_f = 0.30); ^{1}H NMR ($CDCl_3$) only one isomer was observed, δ 2.88 (d, 1 H), 3.89 (s, CH_3), 4.21 (1 H), 5.35 (d, 1 H), 6.95 (d, 1 H arom, ^3J = 7.5 Hz), 7.04 (t,1 H arom, ^{3}J = 7.5 Hz), 7.36 (dd, 1 H arom, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.44 (td, 1 H arom, ^3J = 7.5 Hz, ^4J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.4 (s, CH_3O), 58.6 (s, CHN_3), 71.2 (q, $^2J_{CF}$ = 30 Hz, CHO), 110.6 (s, CH arom), 120.9 (s, CH arom), 123.6 (s, C arom), 124.1 (q, $^1J_{CF}$ = 283 Hz, CF_3), 128.1 (s, CH arom), 130.1 (s, CH arom), 156.1 (s, C arom); IR (neat) 3440 (ν_{OH}), 2120 cm^{-1} (νN_3). Anal. Calcd for $C_{10}H_{10}O_2N_3F_3$: C, 45.98; H, 3.86; N, 16.09. Found: C, 46.19; H, 3.65; N, 15.60.

Supplementary Material Available: Tables of anisotropic thermal parameters (S1), hydrogen atomic positional parameters (S2), and bond distances (S3) and angles (S4) for **5bI** (6 pages). Ordering information is given on any current masthead page.

Phosphonate Analogues of Chorismic Acid: Synthesis and Evaluation as Mechanism-Based Inactivators of Chorismate Mutase

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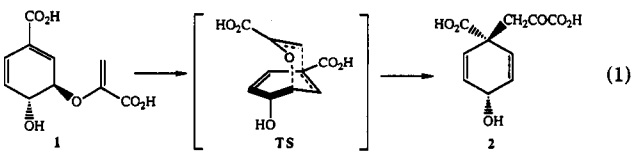
The mechanism of chorismate mutase, the enzyme which catalyzes the Claisen arrangement of chorismic to prephenic acid, remains a fascinating area for bioorganic research. This paper describes the enantioselective synthesis of phosphonochorismic acids **3** and **4**, two potential mechanism-based mutase inactivators, utilizing new transition-metal-catalyzed insertion reactions of tetraalkyl diazophosphonates. Models establish that such systems undergo smooth Claisen rearrangement and that the product acylphosphonates are good acylating agents for amines and alcohols. By contrast, thermolysis of phosphonochorismates **3** and **4** in the presence of enzyme led to *p*-hydroxybenzoic acid, with no trace of [3,3] rearrangement to the corresponding prephenates or phenylpyruvates. The half-life for elimination of **3** was 8.3 h (75° C, 2:1 CD_3OD/D_2O) while for **4** the half-life was 4.3 h. When tested over a wide range of concentrations against the *E. coli* chorismate mutases (so-called T- and P-proteins), neither **3** nor **4** interacted with the enzyme, either as a competitive inhibitor or as a substrate, perhaps reflecting the stringent demands of the rearrangment transition state. Earlier studies strongly suggest that the enol pyruvate carboxyl group is markedly tilted against the carbocyclic ring during [3,3] sigmatropy, and similar flattening of the tetrahedral phosphonate could create unfavorable steric as well as π-π interactions.

Introduction and Background

The biosynthesis of aromatic compounds in bacteria, fungi, and higher plants takes place either from acetate, by the polyketide pathway, or from glucose, by the shikimate pathway. The latter pathway commences with the condensation of erythrose-4-phosphate and phosphoenol pyruvate and proceeds via a sequence of unusually functionalized alicyclic carboxylic acids to the key branch-point intermediate, chorismic acid **1**.[1] Separate pathways from this pivotal substance lead to the aromatic amino acids (via prephenate and anthranilate), the isoprenoid quinones (via *p*-hydroxybenzoate), and folate coenzymes (via *p*-aminobenzoate).

The first committed step in the biosynthesis of phenylalanine and tyrosine involves the [3,3] sigmatropic (Claisen) rearrangement of **1** to prephenic acid **2**, a reaction which is catalyzed by the enzyme chorismate mutase (eq 1). While the nonenzymic rearrangement is unusually fast



(1)

in aqueous solution ($t_{1/2}$ for **1** = 16 h, 30 °C), chorismate mutase accelerates the process (2 × 10^6)-fold (37 °C, pH 7.5).[2] Both the enzymic[3] and nonenzymic[4,5] reactions

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proceed via a chairlike transition state. Because it is a rare example of an enzyme-catalyzed pericyclic reaction,[6] the chorismate-to-prephenate rearrangment has prompted numerous investigations on the mechanism of both the in vitro[7] and in vivo[8] processes.

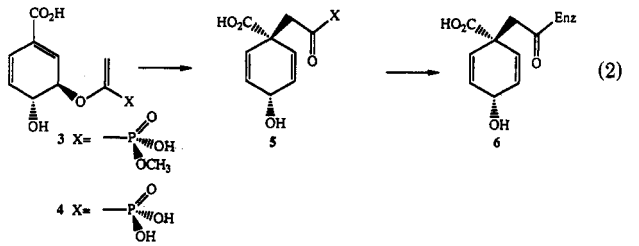
The role of the enzyme is the subject of considerable speculation. Early MO calculations[9] and other observations[10] suggest that binding of 1 in its pseudodiaxial, chairlike conformation might be stabilized by ionic interactions involving the substrate's carboxylate groups as well as hydrogen bonding of its C4-hydroxyl function. However, recent work indicates that the resulting stabilization would be insufficient to account for the observed rate acceleration.[8a,11] Alternatively, hydrophobic and/or π-electron (i.e., ion-dipole) interactions have been proposed to stabilize the enzyme-bound diene system of 1.[12] These hypotheses also seem unlikely in view of a detailed study establishing that only the two carboxylates on the allyl vinyl ether framework of 1 are required for mutase-catalyzed Claisen rearrangement.[13] When the enzyme reaction in *S. cerevisiae*[14] or *B. subtilis*[15] is monitored by NMR spectroscopy, no unbound intermediates are found to accumulate.

Protein inactivation experiments with iodoacetamide and 5,5′-dithiobis(2-nitrobenzoate) have implicated a single cysteine residue in the mutase activity of both *E. coli* and *A. aerogenes* chorismate mutase-prephenate dehydrogenase,[16] suggesting that a thiol group may play a key role in the enzymatic mechanism. Consistent with this observation and with indications that many facile Claisen rearrangements involve dipolar transition states,[7] Guilford et al. have proposed a mechanism involving rate-limiting attack by an enzymic nucleophile at C5 of 1 and heterolytic rearrangement of the enolpyruvyl anion in S_N2' fashion to afford 2.[11]

Chorismate mutase has been cloned and overexpressed from both bacterial[17] and yeast[18] sources, yet relatively little sequence similarity is evident among the different enzymes.[17a,19] Antibodies raised to a putative transition-state analogue also catalyze the rearrangement,[20] and rate enhancements of up to 10^4 have been noted. While much effort has gone into studying isotope effects[8a,11] and devising competitive inhibitors of the mutases,[21] no irreversible inactivators are known which might covalently modify any important catalytic residues on the enzyme.

Rationale

We reasoned that by designing chorismate analogues intended to function as substrates and, upon Claisen rearrangement, to intercept any active site nucleophiles, a traditional mechanism-based inactivation strategy[22] might be employed to investigate the enzymatic mechanism. Replacement of the sidechain carboxyl group in 1 with phosphonate functionality as in 3 and 4 (eq 2) was an



(2)

attractive possibility for several reasons. Because they are isosteric with carboxyl groups and exhibit similar charge and H bonding characteristics, phosphonic acid analogues of pharmacologically active carboxylic acids frequently demonstrate comparable or elevated biological activity.[23] In fact, adamantane-1-phosphonic acid[24] and other, related phosphonates[21] have been documented in recent years as good competitive inhibitors of chorismate mutase-prephenate dehydrogenase. The target structures, phosphonochorismates 3 and 4, should undergo mutase-catalyzed [3,3] rearrangement to unmask an electrophilic acyl phosphonate group in 5 capable of covalently modifying any nearby nucleophiles in the active site.

Simple dialkyl acylphosphonates have previously been prepared from acid chlorides[25] and were known to acylate amines[26] and alcohols[27] under mild conditions. At the outset of this work, however, no general methods for the synthesis of α-alkoxy-substituted alkenylphosphonates had been reported,[28] and little was known about the propensity of such compounds to participate in [3,3] sigmatropic rearrangements. This paper describes new transition-metal-catalyzed insertion reactions of tetraalkyl diazodiphosphonates culminating in a short and versatile synthesis of α-alkoxy-substituted alkenylphophonates. Model

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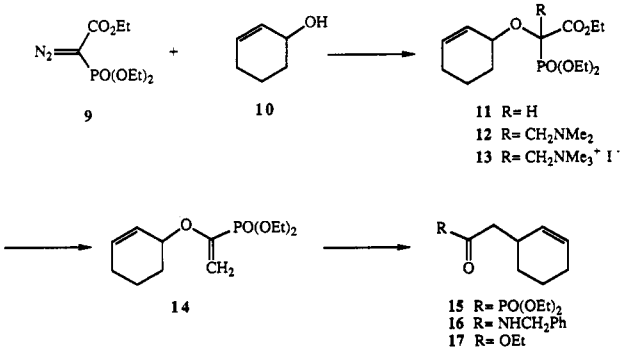
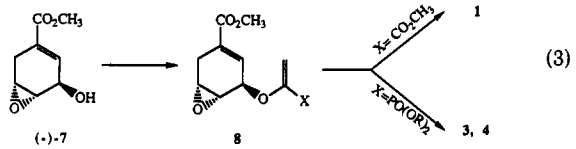
Scheme I



studies with a simple allyl (1-phosphonovinyl) ether prepared in this fashion established that such systems underwent smooth Claisen rearrangement and that the product acylphosphonates reacted readily with amines and alcohols. The enantioselective synthesis of phosphonochorismates **3** and **4** was successfully achieved, and these substances were tested as substrates or inhibitors against several chorismate mutases. Bioassays also revealed some major unexpected differences in the behavior of these enzymes towards adamantane-1-phosphonic acid, a well-known competitive inhibitor of chorismate mutase.

Results and Discussion

One approach to **3** and **4**, outlined in eq 3, parallels a published enantioselective route to (−)-**1** from epoxyol (−)-**7**.[29] The two-stage synthesis involves (i) attachment

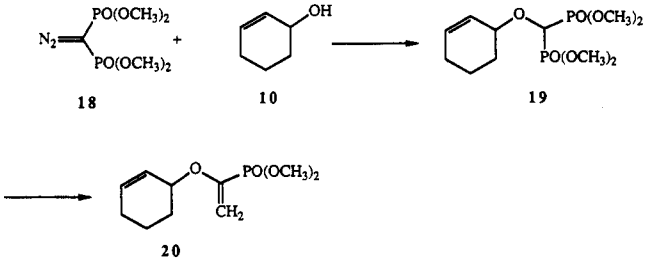


(3)

of the requisite sidechain to the OH group of **7** using the rhodium(II)-catalyzed[30] insertion of trimethyl diazophosphonoacetate followed by a Horner–Emmons methylation and (ii) nucleophilic opening of the epoxide **8** (X = CO_2CH_3) with PhSeNa, followed by oxidative elimination to generate chorismate's 1,3-cyclohexadiene system. Recently, we reported an efficient and expedient synthesis of (−)-**7** from naturally occurring (−)-shikimic acid, thus completing a simple total synthesis of **1**.[31] With an ample supply of (−)-**7** in hand for the preparation of **3** and **4**, attention was directed to methods for introducing the key enol phosphonate sidechain in **8** [X = $PO(OR)_2$] and to explore [3,3] sigmatropic rearrangements of the resulting allyl vinyl ethers.

Scheme I depicts our first approach to the synthesis of model 1-phosphonovinyl ethers. In a reaction independently developed by us as well as by Pawlak and Berchtold,[29] rhodium acetate catalyzed insertion of triethyl phosphonoacetate **9** with 2-cyclohexenol **10** afforded the expected alkoxyphosphono ester **11** in 65% yield. While MIT group utilized this mixed functionality to create enol pyruvates, our laboratory employed the expendable carboxyl group in a Mannich-type construction of the desired

Scheme II



unsaturated phosphonate **14**. Thus, **11** was condensed with Eschenmoser's salt (CH_2=$NMe_2^+I^-$) to afford amine **12** as a mixture of diastereomers (46%). Methylation (CH_3I–THF) followed by decarboxylative elimination of salt **13** (NaOH, rt, 20 h) afforded **14** (32%).

The Claisen rearrangement of **14** was monitored in a sealed NMR tube (toluene-d_8, 115 °C, 38 h) and took place as expected to furnish unsaturated acylphosphonate **15** in good yield. This material was identified spectroscopically and fully characterized as its stable 2,4-DNP derivative.[36] The structure of **15** was further confirmed by its ready reaction with benzylamine or ethanol to afford amide **16** (56%) and ester **17** (64%), respectively. The latter product was identical with an authentic sample prepared from **10** by a standard Claisen rearrangement using triethyl orthoacetate.[37]

The modest yields encountered in the Mannich approach to **14** led us to consider other, more efficient constructions of the phosphonochorismate sidechain. It was of interest to determine whether diazoalkanes like tetramethyl diphosphonodiazomethane **18** (Scheme II), stabilized only by phosphonyl groups, might undergo transition-metal-promoted insertions into the OH bond of **10** without competing cyclopropanation[32] or epoxide deoxygenation.[33] Compound **18** has been prepared by potassium *tert*-butoxide induced diazo transfer from tosyl azide to tetramethyl methylenediphosphonate in published yields of 15–20%;[34] however, by working with freshly prepared base, we have improved yields of **18** to 50–55%.

The $Rh_2(OAc)_4$-catalyzed insertion of **18** with **10** under standard conditions (benzene, reflux) proved to be exceedingly slow. Besides the desired product **19**, significant amounts of both starting materials could be recovered after 14 h at reflux. No cyclopropane or other phosphonate-containing byproducts were detected, and no catalyst poisoning or decomposition was observed. Similar results were obtained using the more soluble rhodium octanoate as catalyst. These findings contrasted with the much more rapid insertion reactions of most ketone or ester-stabilized diazoalkanes, where competing dimerizations of the intermediate rhodium carbenoids also occur at an appreciable rate.[32] However, when the rhodium catalyst was omitted in control experiments with **18**, only starting materials were recovered and no product whatsoever was detected. Apparently, diphosphonodiazomethane **18** was only slowly converted to the corresponding rhodium carbenoid species, which then inserted into **10** much more rapidly than it dimerized. Optimal conditions were developed using toluene as solvent (36 h, reflux) to afford **19** in 48% yield (72% corrected for recovered **10**) after flash column chromatography.

The requisite enol double bond was introduced using the Horner–Emmons reaction. Following a published proce-

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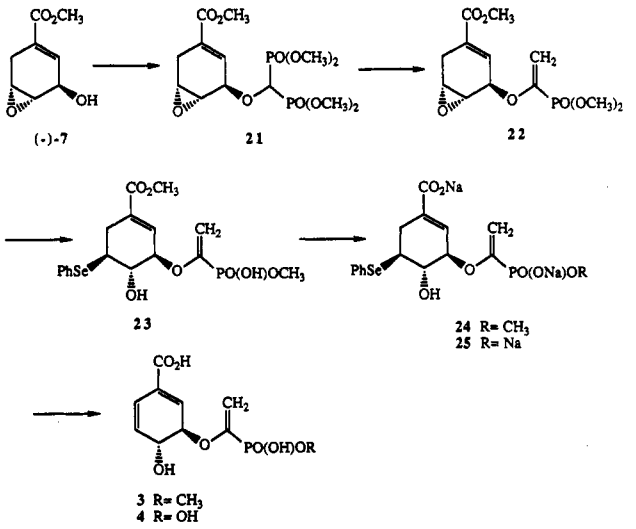
Scheme III



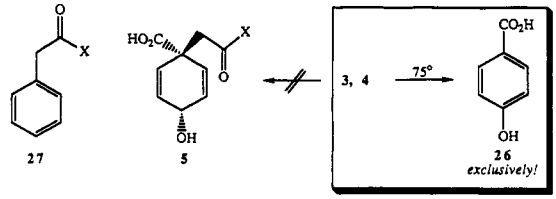
dure for phosphono esters,[29,35] diphosphonate **19** was converted to its lithium salt using lithium diisopropylamide (LDA, THF, 0 °C) and an excess of gaseous formaldehyde passed through the solution to afford **20** in 78% yield after chromatographic purification.

With improved synthetic methodology for the phosphonochorismate sidechain, and bolstered by promising results from the rearrangement of a model system, work on the target structures **3** and **4** commenced (Scheme III). Like the earlier insertion into cyclohexenol, reaction of tetramethyl methylenediphosphonate **18** (1.2 equiv) with epoxyol (-)-**7** catalyzed by rhodium octanoate was exceedingly slow (benzene, reflux, 4 d) but did not afford the desired ether **21** in 40% yield (73% based on recovered **7**). The epoxide group survived these conditions, which is noteworthy since stabilized rhodium carbenoids have been found to deoxygenate epoxides;[33] indeed, an earlier report of the Rh(II)-catalyzed reaction of (-)-**7** with triethyl diazophosphinoacetate described this side reaction.[29] Horner–Emmons olefination of **21** using $LiN(TMS)_2/CH_2{=}O$/THF furnished monophosphonate **22** in 78% yield. As hoped, conditions for nucleophilic opening of the epoxide ring in **22** with PhSeNa (3 equiv, CH_3OH, rt) also cleanly formed the phosphono monoester **23** in 90% yield. Saponification of the carboxylic ester (NaOH, H_2O, 5 °C) set the stage for a mild oxidative elimination of the phenylselenide group (1.1 equiv of H_2O_2, 3,5-dimethoxyaniline, rt, 80–90% overall), thus affording pure **3** after chromatography.

In order to obtain **4**, complete hydrolysis of the phosphonodiester group was performed in two stages. Thus, disalt **24** reacted with bromotrimethylsilane (6 equiv, 5 °C, pyridine/CH_2Cl_2) whereupon workup with aqueous base afforded trisalt **25** in 90% yield. Oxidation of **25** and in situ selenoxide elimination proceeded smoothly as before to produce **4** (75% after chromatography).

Spectroscopic data for **3** and **4** were very similar to parent structure **1**, and both new phosphonates exhibited the characteristic chorismate diene UV absorbance at λ = 274 nm. Before undertaking enzymatic studies, the effect of the phosphonate group on [3,3] sigmatropic rearrangement was investigated. Compounds **3** and **4** were heated at 75 °C in 2:1 CD_3OD/D_2O and monitored by NMR to determine the half-life of each phosphonochorismate. These conditions paralleled those of an earlier, comprehensive study of chorismate analogues in which rate constants for both rearrangement and elimination were measured.[7]

In the absence of enzyme, both **3** and **4** underwent only elimination to *p*-hydroxybenzoic acid **26**, with no trace of [3,3] rearrangement to the corresponding prephenates **5** or phenylpyruvates **27** (eq 4). The half-life for elimination



(4)

of **3** and **26** was determined by NMR monitoring to be 8.3 h (75 °C, 2:1 CD_3OD/D_2O) while for **4** to **26** the half-life was 4.3 h. By comparison, both chorismate **1** and dimethylchorismate underwent rearrangement twice as fast as elimination, with half-lives of 21 and 28 min, respectively, under the same conditions.[7] Thus, the charge carried by the sidechain acid in each series has little impact on overall reactivity or product distribution within that series. However, replacing the sidechain carboxylic acid with a phosphonic acid group in chorismate reduced the overall thermal reactivity of the system and suppressed the desired rearrangement. Since MNDO calculations indicated that allyl (1-phosphonovinyl) ether should rearrange more exothermically ($\Delta H°$ = -22 kcal/mol) than allyl (1-carboxyvinyl) ether ($\Delta H°$ = -16 kcal/mol), the absence of phosphonoprephenates **5** in the thermal chemistry of **1** and **2** must be due to a kinetic effect.[38]

A considerable body of evidence now suggests that both the elimination and rearrangement of chorismic acid and its congeners proceed by reactions whose transition states involve some degree of dissociation of the C–O bond linking the sidechain to the ring.[7] Both processes are accelerated by polar media. Moreover, substituents on the allyl vinyl ether framework can also stabilize the ionic fragments of C–O heterolysis by σ-inductive or π-delocalization effects. Although the transition states for rearrangement and elimination are likely similar, kinetic isotope effects suggest that the two processes involve distinct, unconnected pericyclic reactions.[7]

Part of the phosphonate group's rate-retarding effect on nonenzymic Claisen rearrangement may be due to its shape and size. Unlike the carboxylate group, the phosphonate carbon is sp^3-hybridized. Moreover phosphonic acids, unlike carboxylic acids, exert primarily inductive effects on attached substituents. In the chorismate series, the weaker electron-withdrawing capacity of the phosphonate could diminish the significance of the dissociative pathway, thus retarding Claisen rearrangement. Moreover, with its larger van der Waals radius and markedly different geometry, tetrahedral phosphonate anion might be less likely to assume the preferred chair conformation for steric reasons.

A detailed investigation of the chorismate mutase-catalyzed rearrangement of **3** and **4** was next undertaken. Historically, the bifunctional enzyme chorismate mutase-/prephenate dehydrogenase from either *E. coli* or *Klebsiella pneumoniae* has been used most extensively to evaluate inhibitors of the mutase reaction. When tested at concentrations ranging from 30–400 μM against the *E. coli* enzyme (so-called T-protein; substrate K_m = 91 μM), neither of the phosphonochorismates **3** and **4** showed activity as competitive inhibitors or substrates. In fact, both analogues could be recovered intact after prolonged incubation with the enzyme.

(38) We thank our colleague Professor Barry K. Carpenter for performing these calculations.

Our results are particularly surprising in view of the pronounced inhibition of the T-protein observed with adamantane-1-phosphonic acid (Ad-1-P; I_{50}/K_m = 0.0054).[24] Given that the sidechain phosphonate group in 3 and 4 clearly affects binding unfavorably, it would appear that the polar group in hydrophobic Ad-1-P is likely positioned where the cyclohexenyl carboxyl group of chorismate binds and that this interaction effectively inhibits the T-protein.

Compounds 3, 4, and Ad-1-P were also evaluated as inhibitors of chorismate mutase/prephenate dehydratase from *E. coli*. This enzyme, termed the P-protein, has recently been subcloned and overproduced,[17c] so that large quantities of homogeneous material are now available. Moreover, its distinct mutase domain has been expressed as a small monofunctional enzyme which retains the same specific activity as the P-protein mutase, but without any prephenate dehydratase activity.[17b] Phosphonochorismates 3 and 4 were inert as inhibitors or as substrates of the intact P-protein at concentrations ranging from 25 to 1000 μM. Further studies with monoester 3 showed it was inert toward the genetically engineered monofunctional mutase. We were also surprised to observe that Ad-1-P had no effect on either of these mutases. To our knowledge, this represents the first report of major differences in mutase behavior towards this widely used inhibitor.

The surprising failure of phosphonochorismates 3 and 4 to interact mutases is reminiscent of work by Ife et al., who observed that the sidechain monomethyl ester of 1 was neither a substrate for chorismate mutase nor an inhibitor of enzymatic processing of 1.[39] Since a phosphonate mono or dianion cannot be substituted for chorismate's enol pyruvate carboxylate group, the size and shape of the sidechain functionality (as well as its charge) is apparently also important for binding. The bulky phosphonate groups in 3 and 4 may simply not fit in a sterically constrained active site.

The fact that 3 and 4 are not processed by the enzyme may also reflect stringent demands of the rearrangement transition state. Several bicyclic chorismate analogues have been synthesized as mutase inhibitors,[21,40] the most potent of which strongly suggest that the enol pyruvate carboxyl group is markedly tilted or compressed against the carbocyclic ring during [3,3] sigmatropy. Similar flattening of the tetrahedral phosphonate could create unfavorable steric as well as π-π interactions.

In summary, two new phosphonate analogues of chorismic acid have been prepared in enantiomerically pure form to probe the mechanism of chorismate mutase. Their failure to undergo mutase-catalyzed Claisen rearrangement may be due to the phosphonate's reduced electron-withdrawing ability or to the larger size and tetrahedral geometry of this substituent. However, such notions must be considered speculative, since all mechanistic studies on chorismate mutase to date have been singularly unsuccessful in illuminating the detailed chemical events at the active site of the enzyme. Future work will focus on the protein itself to obtain a clearer understanding of this remarkable biochemical transformation.

Experimental Section

General. Chemical ionization spectra were obtained using isobutane as reagent gas; electron impact spectra were run at 70 eV ionizing voltage. Fast atom bombardment spectra were obtained in glycerol matrix.

Chorismate mutase assays were performed as described by Gething et al.[41] Chorismic acid was isolated from *Klebsiella pneumoniae* strain 62-1 using the procedure of Gibson.[42]

Synthesis of Alkoxy Phosphono Ester 11. A solution of cyclohexenol 10 (150 μL, 1.51 mmol) and a catalytic amount of rhodium acetate in benzene (19 mL) was heated to reflux. Then, a solution of the diazo phosphonoacetate 9 (344 mg, 1.38 mmol) in benzene (1 mL) was added over 70 min. After 19 h of reflux, the green solution was concentrated in vacuo and the resulting residue flash chromatographed over SiO_2 (10:1 ether:hexane) to afford insertion product 11 (287 mg, 65%) as a mixture of diastereomers: R_f 0.20; ^{1}H NMR ($CDCl_3$) 5.82–5.95 (m, 1 H), 5.7–5.8 (m, 1 H), 4.43, 4.44 (2d, 1 H, diastereomers), 4.10–4.30 (m, 6 H), 4.02 (br s, 1 H), 1.45–2.10 (m, 6 H), 1.24–1.34 (m, 9 H),; IR ($CHCl_3$) 3000, 2940, 1755, 1438, 1255, 1105, 1050, 1025 cm^{-1}; CIMS m/z 241 (M + 1 - C_6H_8, 100).

Synthesis of Amino Phosphono Ester 12. To a solution of phosphonoacetate 11 (46 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added CH=NMe_2^+ I^- (88 mg, 3.77 mmol). Triethylamine (70 μL) was added to the resulting suspension, and the reaction mixture turned homogenous after stirring at rt for 28 h. Direct chromatography of the reaction mixture (1:1 $CHCl_3$/ether) afforded Mannich product 12 (25 mg, 46%) as a colorless oil, which crystallized at 4 °C (mixture of diastereomers): R_f 0.27 (1:1 $CHCl_3$/ether); ^{1}H NMR ($CDCl_3$) 5.97–6.17 (m, 1 H), 5.70–5.82 (m, 1 H), 4.49 (br s, 1 H), 4.05–4.35 (m, 6 H), 2.99–3.15 (m, 1 H), 2.71 (m, 1 H), 2.29 (s, 6 H), 1.45–2.10 (m, 6 H), 1.26–1.35 (m, 9 H); IR ($CHCl_3$) 2995, 2940, 1750, 1250, 1050, 1040, 1020, 970 cm^{-1}; CIMS m/z 378 (M + 1, 100), 298 (M + 1 - C_6H_8, 94).

Synthesis of Unsaturated Phosphonate 14. To a solution of phosphono acetate 12 (50 mg, 0.13 mmol) in anhydrous THF (600 μL) was added CH_3I (10 μL, 0.16 mmol) and the resulting solution stirred at rt for 5 days. The reaction mixture was concentrated in vacuo, vacuum dried for 28 h, then resuspended in anhydrous THF (1 mL). Base (130 μL of 1 N NaOH) was added, and after stirring 20 h at rt, the bulk of THF was removed at the rotary. The aqueous residue was diluted (1 mL H_2O) and extracted 5 × 3 mL with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and chromatographed (1:1 EtOAc/hexane) to afford the desired phosphonate 14 (11 mg, 32%) as a pale yellow oil: R_f 0.22 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$) 5.88–5.97 (m, 1 H), 5.74–5.82 (m, 1 H), 5.23 (dd, 1 H, J = 13.6, 2.9 Hz), 4.87 (dd, 1 H, J = 39, 2.9 Hz), 4.57 (br s, 1 H), 4.04–4.22 (m, 4 H), 1.50–2.10 (m, 6 H), 1.28–1.36 (m, 6 H); IR ($CHCl_3$) 3005, 2950, 1610, 1260, 1050, 1030, 908, cm^{-1}; CIMS m/z 261 (M + 1, 15), 181 (100).

Rearrangement of 14 to Acyl Phosphonate 15. A solution of 14 (11.5 mg, 0.04 mmol) in C_6D_6 (600 μL) was sealed in an NMR tube and heated at 115–120 °C for 90 h. The rearrangement product 15 was characterized without workup: R_f 0.25 (1:1 EtOAc/hexane, partial decomposition); ^{1}H NMR δ 5.58–5.74 (2 m, 2 H, alkene), 4.00–4.12 (m, 4 H), 2.80–3.00 (m, 3 H), 1.15–1.90 (m, 6 H), 1.07–1.12 (m, 6 H); IR ($CHCl_3$) 2990, 2940, 1700, 1260, 1020, 975 cm^{-1}; CIMS m/z 261 (M + 1, 100).

The remaining sample of 15 was transferred to a flask, concentrated in vacuo, and treated with a standard solution of 2,4-DNP (400 μL, 0.06 mmol).[25d] Within several minutes a yellow precipitate appeared. The suspension was concentrated in vacuo and triturated several times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated to a yellow oil. Flash chromatography afforded the Z hydrazone of 15 as a yellow solid (5.7 mg, 29%; eluant = 2.1 hexane/EtOAc): mp 85–85 °C; R_f 0.52 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 13.50 (s, 1 H, NH), 9.12 (dd, 1 H, J = 2.7 Hz), 8.32 (dd, 1 H, J = 10, 2.7 Hz), 7.98 (d, 1 H, J = 9.5 Hz), 5.70–5.80 (m, 1 H), 5.55–5.65 (m, 1 H), 4.15–4.30 (m, 4 H), 2.70 (br s, 1 H), 2.48–2.53 (m, 2 H), 1.23–2.01 (m, 12 H); IR ($CHCl_3$) 3170, 3010, 2930, 1620, 1600, 1520, 1505, 1335, 1315, 1140, 1035, 1015 cm^{-1}; CIMS m/z 441 (M + 1, 100).

Continued elution (eluant = 1:1 hexane/EtOAc) afforded the E hydrazone (8.6 mg, 44%): R_f 0.14 (1:1 hexane/EtOAc); ^{1}H NMR

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(42) Gibson, F. *Biochem. Prepn.* **1968**, *12*, 94–97.

($CDCl_3$) 11.50 (s, 1 H, NH), 9.12 (d, 1 H, J = 2.4 Hz), 8.37 (dd, 1 H, J = 9.5, 2.5 Hz), 8.03 (d, 1 H, J = 9.5 Hz), 5.73–5.80 (m, 1 H), 5.51–5.55 (m, 1 H), 4.18–4.28 (m, 4 H), 2.60–2.71 (m, 3 H), 1.30–2.15 (m, 12 H); IR ($CHCl_3$) 3320, 3010, 2935, 1620, 1600, 1520, 1505, 1425, 1340, 1310, 1250, 1110, 1045, 1020 cm^{-1}; CIMS m/z 441 (M + 1, 100).

Reaction of 15 with Benzylamine: Synthesis of Amide 16. A fresh sample of **14** (12.5 mg; 0.05 mmol) was thermally rearranged (toluene-d_8, 115–120 °C, 38 h) then cooled to rt, and benzylamine (10 μL; 9.15 10^{-5} mol) was added. The solution was then kept at rt for 23 h and directly chromatographed (1:1 hexane/Et_2O) to afford amide **16** (6.2 mg, 56%) as a white solid: mp 106–108 °C; R_f 0.35 (1:1 hexane/EtOAc); ^1H NMR ($CDCl_3$) 7.23–7.31 (m, 5 H), 5.60–5.80 (m, 2 H), 5.50–5.57 (m, 1 H), 4.38–4.43 (m, 2 H), 2.64 (br s, 1 H), 2.07–2.25 (m, 2 H), 1.20–2.00 (m, 6 H); IR ($CHCl_3$) 3450, 3010, 2935, 1665, 1515 cm^{-1}; CIMS m/z 230 (M + 1, 100).

Rearrangement of 14 in Ethanol: Synthesis of Ester 17. An ethanol solution of **14** (10.6 mg, 0.04 mmol in 600 μL) was sealed in an NMR tube and heated (110 °c, 5 d) until starting material had disappeared. After cooling and concentration, the residue was chromatographed (30:1 hexane/ether) to afford ethyl ester **15** (4.4 mg, 64%) as a colorless oil, identical in every respect with an authentic sample.[37]

Synthesis of Tetramethyl Diphosphonodiazomethane (18). A solution of tetramethyl methylenediphosphonate (500 mg, 2.15 mmol, Alfa) in benzene (1.5 mL) was added to a stirring slurry of freshly prepared potassium *tert*-butoxide (482 mg, 4.3 mmol) in benzene (1.5 mL) under argon in a flame-dried flask. After heating at reflux for 15 min, the homogeneous solution was cooled to 5 °C and neat tosyl azide (530 mg, 2.69 mmol) was added dropwise. The reaction was warmed to rt and stirred for 4 h then concentrated in vacuo. The resulting residue was taken up in CH_2Cl_2 (10 mL) and washed with H_2O (2 × 5 mL). The aqueous layers were reextracted with CH_2Cl_2 (1 × 5 mL); the combined organic layers were dried and evaporated to yield a yellow oil (565 mg, crude) which was chromatographed over SiO_2 (5:5:1 CH_2Cl_2/ether/CH_3OH) to afford **18** as a low-melting solid (284 mg, 51%): R_f 0.31 (5:5:1 CH_2Cl_2/ether/CH_3OH); ^1H NMR ($CDCl_3$) 3.80–3.84 (m, 12 H); IR ($CHCl_3$) 3020, 2970, 2140 s, 1270, 1035, 845 cm^{-1}; CIMS m/z 259 (M + 1, 100).

Synthesis of Alkoxydiphosphonate 19. A solution of diazodiphophonate **18** (15 mg) and cyclohexenol **10** (6 μL) in toluene (1 mL) containing a catalytic quantity of rhodium acetate (1 mg) was heated to reflux for 18 h, then an additional 200 μL of **10** was added. After heating another 24 h, the green reaction mixture was cooled and filtered through Celite. The filtrate was concentrated in vacuo and the resulting green oil chromatographed (SiO_2, 1:1 $CHCl_3$/ether, then 5:5:1 $CHCl_3$/ether/CH_3OH) to afford pure **19** (16 mg, 48%) as a pale oil: TLC R_f 0.27 (5:5:1 $CHCl_3$/ether/CH_3OH); ^1H NMR ($CDCl_3$) δ 5.85–5.92 (m, 1 H, alkene), 5.75–5.83 (m, 1 H, alkene), 4.18 (br s, 1 H), 4.16 (t, 1 H, J = 17.5 Hz), 3.80–3.87 (m, 12 H), 1.45–2.10 (m, 6 H); IR ($CHCl_3$) 3010, 2960, 1255, 1045 cm^{-1}; CIMS (isobutane) m/z 329 (M + 1, 13), 249 (100).

Synthesis of Unsaturated Phosphonate 20. A solution of alkyloxydiphosphonate **19** (8 mg, 0.024 mmol) in anhydrous THF (900 μL) at 0 °C was treated with LDA (110 μL of a 0.2 M solution) and the reaction stirred for 30 min, during which time it slowly turned yellow. Formaldehyde gas, generated by heating paraformaldehyde (10 equiv) in adjacent flask, was transferred into the anion by cannula, and the resulting white suspension stirred for 1 h at rt. After addition of NH_4Cl (2 mL), the white suspension was filtered and the residue washed with CH_2Cl_2 (5 mL). The filtrate was extracted with CH_2Cl_2 (4 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography of the oily residue (2:1 EtOAc/hexane) furnished **20** as a colorless oil (4.5 mg, 78%): R_f 0.17 (1:1 EtOAc/hexane); ^1H NMR ($CDCl_3$) 5.90–6.00 (m, 1 H), 5.74–5.83 (m, 1 H), 5.24 (dd, 1 H, J = 13.5, 2.8 Hz), 4.91 (dd, 1 H, J = 39, 2.8 Hz), 4.59 (br s, 1 H), 3.76 (d, 6 H, J = 11 Hz), 1.50–2.10 (m, 6 H); IR ($CHCl_3$) 3015, 2960, 1610, 1270, 1235, 1035 cm^{-1}; CIMS m/z 153 (M + 1 − C_6H_8, 100).

Synthesis of Alkoxyphosphonate 21. A solution of epoxyol **7** (80.0 mg, 0.470 mmol),[31] tetramethyl diphosphonodiazomethane (**18**; 121.3 mg, 0.470 mmol), and rhodium octanoate (67.0 mg, 0.05 mmol) in benzene (2.5 mL) was heated to reflux under argon with stirring for 4 d. The benzene was removed in vacuo and the residue chromatographed (5:5:1 CH_2Cl_2/ether/CH_3OH) to afford recovered **7** (38 mg, 48%) along with the desired diphosphonate **21** as a light yellow oil (75 mg, 40%): R_f 0.26 (5:5:1 CH_2Cl_2/ether/CH_3OH); $[\alpha]_D$ −22.5° (c = 3.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) 6.80 (m, 1 H), 4.60 (m, 1 H), 4.23 (t, 1 H, J = 17.5 Hz), 3.75–3.88 (m, 12 H), 3.72 (s, 3 H), 3.41 (br s, 2 H), 2.90 (dm, 1 H, J = 20.1 Hz), 2.61 (dm, 1 H, J = 20.1 Hz); ^{13}C NMR ($CDCl_3$) 166.6, 130.6, 128.4, 74.7 (t, J = 5.0 Hz), 72.7, 70.6, 52.1, 50.5, 50.4, 24.5; IR (film) 3000, 1720, 1440, 1215, 1050 cm^{-1}; CIMS m/z 401 (M + 1, 28), 79 (100).

Synthesis of Unsaturated Phosphonate 22. Lithium hexamethyldisilazide (0.97 M, 185 μL, 0.179 mmol) in dry THF was added to a solution of bisphosphonate **21** (65 mg, 0.162 mmol) in THF (1.2 mL) at −20 °C under argon in a flame-dried flask. The resulting mixture was stirred for 10 min, and then gaseous formaldehyde generated as before from anhydrous paraformaldehyde (65 mg, 1.62 mmol) was bubbled through the reaction. The mixture was warmed to rt, and stirring was continued for 10 min. Saturated NH_4Cl (1.5 mL) and H_2O (1.5 mL) were added, the bulk of THF was removed in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (5 × 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the crude product was flash chromatographed (10:10:1 CH_2Cl/ether/CH_3OH) to afford **22** as a clear oil (38 mg, 78%): R_f 0.45; $[\alpha]_D$ −80.3° (c = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$) 6.76 (m, 1 H), 5.35 (dd, 1 H, J = 13.4, 3.6 Hz), 5.13 (dd, 1 H, J = 38.2, 3.6 Hz), 4.98 (br s, 1 H), 3.77 (d, 3 H, J = 4.1 Hz), 3.74 (d, 3 H, J = 4.1 Hz), 3.73 (s, 3 H), 3.43 (br t, 1 H, J = 3.3 Hz), 3.32 (m 1 H), 2.92 (dm, 1 H, J = 20.0 hz), 2.69 (dq, 1 H, J = 20, 2.5 Hz); ^{13}C NMR ($CDCl_3$) 166.4, 151.7 (d, J = 225.3 Hz), 129.3, 129.0, 101.3 (d, J = 24.5 Hz), 69.0 (d, J = 9.7 Hz), 53.3 (d, J = 4.9 Hz), 52.1, 50.6 24.3; IR (film) 2950, 1715, 1610, 1420, 1265, 1225, 1015 cm^{-1}; CIMS m/z 305 (M + 1, 10), 153 (100).

Synthesis of Seleno Ester 23. A solution of sodium phenylselenide (1.17 M, 2.0 mL, 0.33 mmol) in anhydrous CH_3OH was added to a stirred solution of epoxide **22** (33 mg, 0.110) in anhydrous CH_3OH (0.4 mL) under argon. The clear mixture slowly turned yellow and was stirred at rt for 16 h. The reaction was diluted with H_2O (2 mL) and CH_2Cl_2 (2 mL) and the pH of the aqueous layer was adjusted to 7 by dropwise addition of saturated NH_4Cl. The bulk of solvent was removed in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (6 × 5 mL) to remove selenium impurities. The aqueous layer was lyophilized to a white residue which was triturated with acetone (10 × 1 mL). The combined acetone fractions were evaporated to afford pure seleno alcohol **23** (46.7 mg, 95%) as a white paste: R_f 0.63 (10:2:1 CH_3CN/H_2O/HOAc); $[\alpha]_D$ −14.8° (c = 1.2, H_2O); ^1H NMR (D_2O) 7.52 (m, 2H), 7.23 (m, 3 H), 6.60 (br s, 1 H), 4.88 (dd, 1 H, J = 12.2, 3.3 Hz), 4.47 (dd, 1 H, J = 34.3, 3.3 Hz), 4.61 (br s, 1 H), 3.68 (dd, 1 H, J = 11.4, 7.5 Hz), 3.53 (s, 3 H), 3.39 (d, 3 H, J = 11.4 Hz), 3.34 (m, 1 H), 2.63 (dd, 1 H, J = 18.3, 5.4 Hz), 2.26 (dm, 1 H, J = 18.3 Hz); ^{13}C NMR (D_2O, acetone internal standard) 170.8, 157.5 (d, J = 212.1 Hz), 138.6, 136.7, 134.1, 132.0, 131.2, 128.6, 100.0 (d, J = 21.8 Hz), 80.2 (d, J = 8.2 Hz), 74, 55, 54.9 (d, J = 4.7 Hz), 44.3, 34.7; IR (KBr) 1720, 1610, 1440, 1240, 1065, 1000 cm^{-1}; FABMS m/z 447 (M − 1, 100).

Hydrolysis of 23 to 24. Aqueous sodium hydroxide (1.0 M, 0.103 mL, 0.103 mmol) was added to a stirred solution of ester **23** (21 mg, 0.047 mmol) in H_2O (0.3 mL) at 5 °C. After 5 h, lyophilization afforded the disodium salt of **24** (22.4 mg, 100%) as a solid: R_f 0.43 (10:2:1 CH_3CN/H_2O/HOAc); [a]$_D$ −9.6° (c = 0.55, H_2O); ^1H NMR (D_2O) 7.58 (m, 2 H), 7.25 (m, 3 H), 6.25 (br s, 1 H), 4.88 (dd, 1 H, J = 12.2, 3.1 Hz), 4.77 (dd, 1 H, J = 34.3, 3.1 Hz), 4.60 (br s, 1 H), 3.70 (dd, 1 H, J = 11.4, 7.5 Hz), 3.45 (m, 1 H), 3.42 (d, 3 H, J = 11.0 Hz), 2.65 (dd, 1 H, J = 18.0, 5.3 Hz), 2.35 (ddt, 1 H, J = 18.0, 10.8, 2.9 Hz); ^{13}C NMR (D_2O, $CDCl_3$ external standard) 164.7, 145.5 (d, J = 210.2 Hz), 128.0, 126.2, 119.7, 118.8, 118.2, 116.7, 87.5 (d, J = 21.9 Hz), 68.7 (d, J = 9.5 Hz), 62.4, 42.5 (d, J = 5.5 Hz), 33.1, 24.1; IR (KBr) 3400, 2940, 1600, 1400, 1240, 1075 cm^{-1}; FABMS m/z 433 (M − 23,100).

Synthesis of Phosphonochorismate 3. A solution of 30% H_2O_2 (2.0 μL, 0.018 mmol) was added to selenide **24** (7.6 mg, 0.016 mmol) in anhydrous CH_3OH (0.16 mL) at 5 °C under argon. The mixture was stirred for 1 h, then 3,5-dimethoxyaniline (7.4 mg,

0.048 mmol) was added and the reaction warmed to rt with continued stirring for 36 h. Water (2 mL) was added, and the aqueous layer was washed with CH_2Cl_2 (5 × 1 mL), then lyophilized to a yellow residue. The crude product was chromatographed (10:2:1 CH_3CN/H_2O/HOAc) to afford diene **3** (4.1 mg 80%) as an oil: R_f 0.48; $[\alpha]_D$ -194° (c = 0.18, H_2O); ^1H NMR (D_2O) 6.44 (br s, 1 H), 6.20 (dt, 1 H, J = 10.0, 2.0 Hz), 5.83 (dd, 1 H, J = 10.0, 2.7 Hz), 4.90-4.76 (m, 3 H), 4.59 (dt, 1 H, J = 11.4, 2.6 Hz), 3.43 (d, 3 H, J = 11.0 Hz); ^{13}C NMR (D_2O, acetone external standard) 173.1, 154.0 (d, J = 211.8 Hz), 133.8, 129.3, 128.4, 123.5, 96.8 (d, J = 22.2 Hz), 78.7 (d, J = 9.8 Hz), 69.4, 51.7 (d, J = 5.3 Hz); IR (KBr) 3400, 1425, 1240, 1085, 1050 cm^{-1}; FABMS m/z 297 (monosodium salt, M - 1, 5).

Deesterification of 24 to 25. A precooled solution of TMSBr (69 μL, 0.52 mmol) and pyridine (85 μL, 1.04 mmol) in CH_2Cl_2 (0.3 mL) was added to a stirred suspension of monomethyl phosphonate **24** (24.9 mg, 0.052 mmol) in CH_2Cl_2 (0.22 mL) at 5 °C under argon in a flame-dried flask. The mixture was stirred for 3 h, then poured into basic H_2O (5.0 mL, to pH 10 with NaOH). Solvents were removed in vacuo, and the aqueous residue was lyophilized. The resulting solid was triturated with anhydrous CH_3OH (4 × 1 mL), and the combined CH_3OH layers were evaporated then triturated again with absolute ethanol (4 × 1 mL). The insoluble portion from trituration was dissolved in H_2O and lyophilized to afford the desired phosphonate **25** as its sodium salt (pale yellow solid, 22.8 mg, 90%): R_f 0.45 (10:2:1, CH_3CN/H_2O/HOAc); $[\alpha]_D$ -7.7° (c = 1.14, H_2O); ^1H NMR (D_2O) 7.57-7.59 (m, 2 H), 7.23-7.29 (m, 3 H), 6.28 (br s, 1 H), 4.58 (d, 1 H, J = 33.3 Hz), 4.57 (br s, 1 H), 4.40 (d, 1 H, J = 29.7 Hz), 3.68 (dd, 1 H, J = 11.7, 7.8 Hz), 3.43 (dt, 1 H, J = 11.7, 5.8 Hz), 2.63 (dd, 1 H, J = 17.7, 5.8 Hz), 2.34 (ddm, 1 H, J = 17.7, 11.2 Hz); ^{13}C NMR (D_2O, acetone as external standard) 174.4, 162.8 (d, J = 141.7 Hz), 136.9, 135.6, 129.1, 128.7, 126.3, 91.8 (d, J = 20.5 Hz), 78.0 (d, J = 5.5 Hz), 72.2, 42.5; IR (KBr) 3400, 1585, 1400, 1340, 1225, 1100, 990 cm^{-1}; FABMS m/z 441 (M - 1, 100).

Synthesis of Phosphonochorismate 4. A solution of 30% H_2O_2 (5.5 μL, 0.047 mmol) was added to triacid **25** (20 mg, 0.043 mmol) in anhydrous CH_3OH (0.4 mL) at 5 °C under argon. The mixture was stirred for 1 h, then 3,5-dimethoxyaniline (20 mg, 0.129 mmol) was added; the reaction mixture warmed to rt and stirred an additional 36 h. Water (1 mL) was added; the aqueous layer was washed with CH_2Cl_2 (5 × 2 mL) then lyophilized. The residue was chromatographed (10:2:1 CH_3CN/H_2O/HOAc) to afford **4** as a pale yellow solid (mono-Na salt, 9.2 mg, 75%); R_f 0.26 (10:2:1 CH_3CN/H_2O/HOAc), $[\alpha]_D$ -147° (c = 0.34, H_2O); ^1H NMR (D_2O) 6.81 (br s, 1 H), 6.24 (br d, 1 H, J = 10.1 Hz), 5.91 (dd, 1 H, J = 10.0, 2.6 Hz), 4.94 (br d, 1 H, J = 11.6 Hz), 4.88 (dd, 1 H, J = 12.2, 3.2 Hz), 4.70 (dm, 1 H, J, = 11.6 Hz), 4.60 (dd, 1 H, J = 31.3, 3.2 Hz); ^{13}C NMR (D_2O, acetone as external standard) 179.1, 163.1 (d, J = 209.8 Hz), 139.6, 135.6, 135.2, 129.6, 100.3 (d, J = 21.7 Hz), 84.9 (d, J = 9.5 Hz), 75.9; IR (KBr) 3400, 1420, 1085, 980 cm^{-1}; FABMS m/z 265 (monosodium salt, M - 18, 15).

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Supplementary Material Available: NMR spectra (^1H and/or ^{13}C) for compounds **11**, **12**, **14-20**, **21-25**, **3**, and **4** (16 pages). Ordering information is given on any current masthead page.

The Reaction of Benzoyl-Substituted Heterocyclic Ketene Aminals with Aryl Azides

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The reaction between heterocyclic ketene aminals, 2-(benzoylmethylene)imidazolidines **3**, -hexahydropyrimidines **4**, and phenyl azides **5** was investigated. Both the reaction rate and products were strongly dependent on the substituents on **3** or **4** and **5**. The reaction rate decreased with the decrease of the electron-withdrawing ability of the Y on the aryl azide **5** with the order NO_2 > Cl > H > CH_3O, as well as with the decrease of the electron-donating ability of the X on the **3** or **4** following the order CH_3O > CH_3 > H > Cl. Substituents X and Y affected the course of the reaction. Thus, **3** or **4** reacted with *p*-nitrophenyl azide **5a** to give exclusively highly substituted 1,2,3-triazole derivatives **6aa-da** and **7aa-da**. The reaction between **3** or **4** and other aryl azides **5b-d** afforded respectively fused triazoles **8a-d** or **9a-d** (6-31%) in addition to triazoles **6ab-bd** or **7ab-bd** (8-76%). It is concluded that **3** and **4** behave mostly as nucleophiles rather than 1,3-dipolarophiles in reaction with aryl azides **5**. Only in the case of unfavorable electronic factors may **3** and **4** act as 1,3-dipolarophiles toward **5**.

Introduction

Since the reports by Stork et al.,[1] a great development of enamine chemistry in many aspects has been achieved. As important intermediates, enamines have shown their potential in synthetic organic chemistry.[2] Heterocyclic ketene aminals or cyclic 1,1-enediamines belong to the family of enamines. Although earlier reports of such compounds may date back to 1950s,[3] there are only a few research results on them in the literature, especially compared with many papers concerned with enamines. Much attention has been given to them from the 1970s when Shell Oil Company patented a series of cyclic enediamines with nitro groups possessing biological activities that could be used as herbicides and pesticides.[4]

The general structure of cyclic 1,1-enediamines can be described by Figure 1. Due to the effects of the conjugation of the two strongly electron donating amino groups

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