Reactions of 1,2-Oxaphospholenes. 7.[1,2] Anomalous Low Reactivity of a Tertiary Allylic Bromide. The Crystal and Molecular Structure of (*E*)-4,5-Dibromo-3,5-di-*tert*-butyl-2-phenyl-1,2-oxaphosphol-3-ene 2-Oxide

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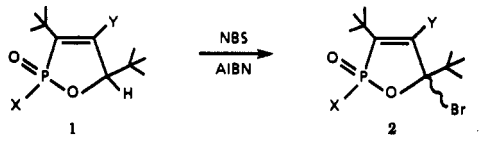
Reaction of 2,2,6,6-tetramethyl-4-heptyn-3-ol (**5**) with dichlorophenylphosphine leads to (2,2,6,6-tetramethyl-3,4-heptadien-3-yl)phenylphosphinic acid (**7**), which undergoes Ag^+-catalyzed cyclization to 3,5-di-*tert*-butyl-2-phenyl-1,2-oxaphosphol-3-ene 2-oxide (**1e**, 75–55% *Z*, 25–45% *E*). Electrophilic bromination of **7** affords **1f**, the 4-bromo derivative of **1e**, as a 75% *Z*, 25% *E* diastereomer mixture from which pure (*Z*)-**1f** can be isolated. Free radical allylic bromination of **1e** and **1f** leads to the corresponding 5-bromo derivatives **2e** and **2f**, each as a single diastereomer. X-ray analysis proved that **2f** has the *E* configuration, which is therefore also assigned to **2e**. All other diastereomeric configurations were assigned on the basis of ^1H NMR. Allylic bromide (*E*)-**2e** is at least 1700 times more reactive than (*E*)-**2f** toward methanolysis, though both yield the corresponding 5-methoxy derivatives ((*Z*-**4e** and (*Z*)-**4f**) with *inversion* of configuration. The retardation of (*E*)-**2f** relative to (*E*)-**2e** is ascribed to steric interference between the C_4 bromine and the C_5 *tert*-butyl group in the methanolysis intermediate (**3f**), an effect which is supported by a low-temperature ^1H NMR study of (*E*)-**2f**. Reaction of (*E*)-**2f** with $AgBF_4$ or AgOTFA in THF gives the 5-fluoro and 5-trifluoroacetoxy derivatives, respectively, further indication of the instability of **3f**. ^{31}P NMR indicates that the phosphoryl oxygen in (*E*)-**2f** can be reductively cleaved by DIBALH, but the resulting product is quickly reoxidized to (*E*/*Z*)-**2f** by air. Reaction of (*E*)-**2f** with $NaBH_4$ leads to reductive cleavage of the C_4 bromine, as well as the C_5 bromine, leading to the formation of **1e**, **1f**, and **4e**. Extended Huckel calculations are in agreement with the stereochemical preferences observed in this work, as well as the solvolysis rate-retarding effect of the phosphoryl oxygen. In view of the dramatic solvolysis rate reduction caused by the 4-bromo group in (*E*)-**2f** and related compounds, the normal solvolytic reactivity of **2c**, the 2-hydroxy analogue of **2f**, is ascribed to a mechanism involving reversible ring opening.

Introduction

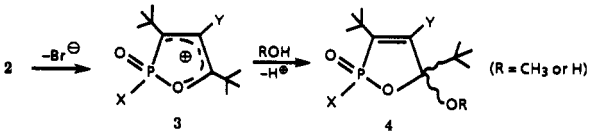
We recently reported[1] that the C_5 (allylic) hydrogen (H) in 1,2-oxaphosphol-3-ene phosphonates of generic structure **1** can be efficiently replaced by bromine under free radical conditions to give the corresponding heterocyclic allylic bromides **2**. Because the C_5 bromine in **2** was "tertiary,"



1 2

(a) X = OH, Y = H
(b) X = OCH_3, Y = H
(c) X = OH, Y = Br
(d) X = OCH_3, Y = Br
(e) X = Ph, Y = H
(f) X = Ph, Y = Br

allylic, and further activated by the neighboring endocyclic oxygen, it was no surprise that compounds **2a**, **b**, and **c** were very labile and underwent virtually instantaneous solvolysis to give cyclic (hemi)ketals **4**, presumably via delocalized oxycarbocation **3**. Phosphonic acid (hemi)-



3 4

ketals **4a** and **4c** (pK_a ca. 2) were themselves reasonably reactive toward exchange of the alkoxy (or hydroxyl) group, though the corresponding ester **4b** (R = CH_3) was solvolytically inert except in the presence of a strong acid (e.g., HBr).

The surprise came when the behavior of bromo ester **2d** was examined. It was found to be *less* reactive toward solvolysis than **2a–c** by a factor of over 1000. Of the four bromides, it was the only one that survived chromatographic purification. We speculated[1] that one reason for the low reactivity of **2d** might involve steric crowding in carbocation intermediate **3d**, where both *tert*-butyl groups and the large C_4 bromine are all forced to occupy the same plane. Yet, this same effect should have been operative in **2c** which, instead, possessed the expected high reactivity.

We now report the synthesis and chemical behavior of two new members of this class of compounds, and the X-ray crystal structure of one of them, which together demonstrate that the "anomalous" reactivity of **2d** may represent a general phenomenon.

Results and Discussion

I. Synthesis of 2e and 2f. The assignment of stereoisomeric configurations to the diastereomers of **1**, **2**, and **4** (when the phosphorus substituent X is not OH, vide infra) is made possible by the consistently higher field ^1H resonance of C_5 substituents trans to the phosphoryl oxygen, relative to the same group cis to the phosphoryl oxgyen.[1,3] To augment this effect, as well as reduce the reactivity of phosphorus substituent X, we undertook the preparation of several 2-phenyl phosphinates with the generic structures below. The remote phenyl group was expected to enhance the shielding of groups cis to it, relative to the same group trans to it. Note that the stereoisomer label (*E*/*Z*) in these structures depends on the relative Cahn–Ingold–Prelog (CIP) priority of group A relative to the *tert*-butyl carbon.

(1) Paper 6 in the series: Rardon, D.; Macomber, R. S. *J. Org. Chem.* **1990**, *55*, 1493.

(2) Taken in part from the Ph.D. Dissertation of D.E.R., University of Cincinnati, 1991. This work was presented in part at the 201st National Meeting of the American Chemical Society, Atlanta, April 19, 1991, Abstract No. 343.

(3) Macomber, R. S.; Krudy, G. A.; Seff, K.; Rendon-Diazmiron, L. E. *J. Org. Chem.* **1983**, *48*, 1425.

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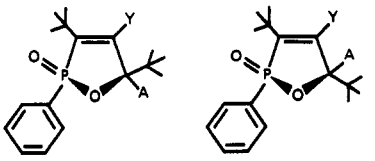
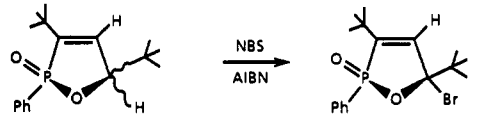


configuration { Priority of A < carbon: Z / E
Priority of A > carbon: E / Z

Heterocyclic phosphinates **1e** and **1f** were prepared from propargyl alcohol **5**[4] by the sequence of reactions shown in Scheme I.[1,3,5,6] It should be noted that by virtue of the chiral allene linkage and the asymmetric phosphorus, **6** is capable of existing in two diasteromeric forms. However, because rapid proton transfer renders both oxygens in **7** equivalent, the latter exists as a single diastereomer. An analogous situation exists in oxaphospholenes **1** and **2** when X = OH.[1,7,8]

Compounds **1b** and **1d** were previously found[3] to form as mixtures of diastereomers slightly favoring the configuration with the C_5 *tert*-butyl cis to the phosphoryl oxygen. So it comes as no surprise that both **1e** and **1f** are also formed as diastereomer mixtures. The silver ion-catalyzed cyclization of **7** in THF affords a 55/45 mixture[9] of **1e** with a catalytic rate constant of 1.0×10^{-5} M^{-1} s^{-1} (70 °C), half as fast as the analogue of **7** where the phenyl group is replaced by a second OH.[6] We assign the major isomer of **1e** the *Z* configuration (C_5 *tert*-butyl cis to P=O) because it exhibits the *more* shielded C_5 hydrogen (δ 4.69 vs 4.86) and the *less* shielded C_5 *tert*-butyl group (δ 1.05 vs 1.03), consistent with the proximity of the phenyl group as well as spectroscopic data for analogous compounds.[1,3] Similarly, electrophilic bromination of **7** gives **1f** as a 75/25 mixture, again favoring the *Z* isomer on the basis of the *more* shielded C_5 hydrogen (δ 4.69 vs 4.88) and the *less* shielded C_5 *tert*-butyl group (δ 1.21 vs 1.14). It is logical to ascribe the somewhat greater diastereoselectivity in the formation of **1e**[9] and **1f** than of **1b** and **1d** to the fact that a phenyl group has greater steric requirements than a methoxy group,[10] forcing the C_5 *tert*-butyl group to remain trans to it.

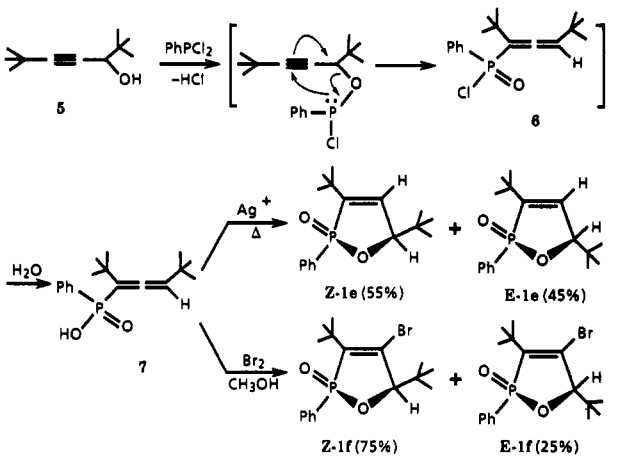
Free-radical bromination of (*E*/*Z*)-**1b** and -**1d** was reported[1] to give allylic bromides **2b** and **2d** as diastereomer mixtures favoring retention of configuration. However, the fact that the diastereomer ratio was greater for both bromides than in their respective precursors[1] suggested that product stereochemistry was determined during capture of the intermediate radical, not by the configuration of the starting material. Bromination of (*Z*/*E*)-**1e** under the same conditions gives **2e** (100% crude yield)



1e (55% Z) → NBS, AIBN → **E-2e** (<5% Z)

with at least 95% diastereomeric purity; ^1H NMR signals for the other isomer, if present, are too weak to assign with confidence. As with bromides **2a-c**, **2e** is very reactive toward solvolysis (vide infra), so it could not be rigorously purified. And since only one isomer was apparent by NMR, it was not at first possible to assign stereochemistry from the data at hand. But for reasons described below, we are confident that the predominant (or sole) isomer of **2e** formed in this reaction bears the *E* (retained relative) configuration.

Scheme I



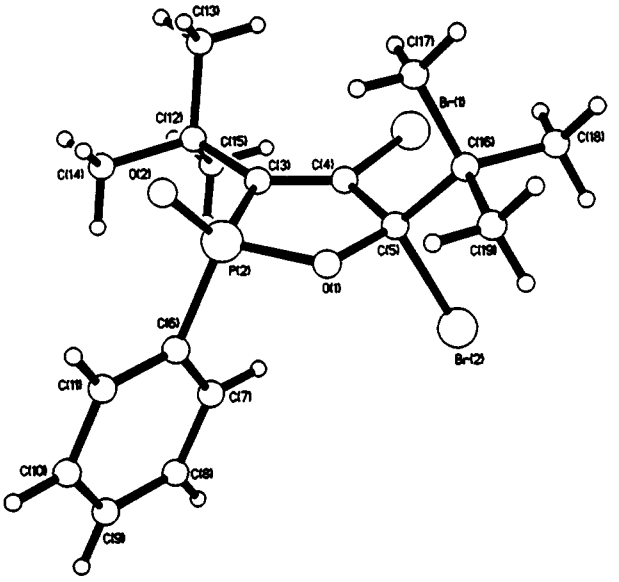
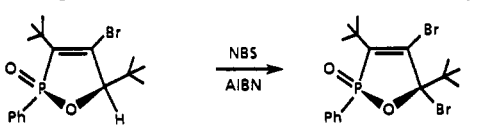


Figure 1. PLUTO drawing from X-ray diffraction analysis of crystalline (*E*)-**2f**.

When (*Z*)-**1f** is subjected to the same allylic bromination conditions, it not only gives a crude product showing only one diastereomer, but this product is sufficiently stable (vide infra) that it can be recrystallized to give pure **2f** in 95% yield. The quality of these crystals permitted an X-ray diffraction structure study, which shows unequivocally that **2f** possesses the *E* stereochemistry (Figure 1).

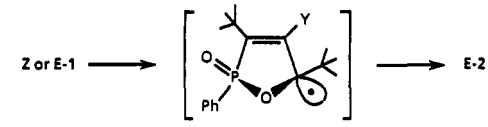


Z-1f → NBS, AIBN → **E-2f** (<1% Z)

By analogy we see no reason to doubt that **2e** is also the *E* isomer. This means that in both cases the bromine is delivered to radical intermediates **8e** and **f** from the presumably *more* hindered face (cis to the phenyl).

The stability of **2f** shows that this stereochemical preference cannot be the result of equilibration after the

(4) Borden, W. T.; Corey, E. J. *Tetrahedron Lett.* **1969**, 313.
(5) Macomber, R. S. *J. Am. Chem. Soc.* **1977**, *99*, 3072.
(6) Mualla, M.; Macomber, R. S. *Synth. Commun.* **1989**, *19*, 1997.
(7) Elder, R. C.; Florian, L. R.; Kennedy, E. R.; Macomber, R. S. *J. Org. Chem.* **1973**, *38*, 4177.
(8) Macomber, R. S.; Kennedy, E. R. *J. Org. Chem.* **1976**, *41*, 3191.
(9) When deuteriomethanol is used as solvent the ratio is substantially greater, approximately 3/1 *Z*/*E*.
(10) The *A* values (kcal/mol) are as follows: Ph, 2.9; OCH_3, 0.75, Br, 0.55. March, J. *Advanced Organic Chemistry*, 3rd Ed.; Wiley-Interscience: New York, 1985; p 126.



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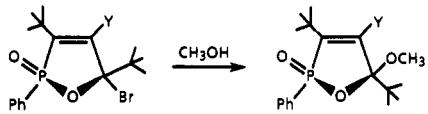
bromine has been delivered. Therefore, we suggest that **8e** and **8f** may in fact be locked in a conformation where C_5 remains essentially sp^3-hybridized, with the C_5 *tert*-butyl group trans to Ph. Nonetheless, the fact that allylic bromination takes place so cleanly indicates there is significant interaction of the unpaired C_5 electron with the neighboring π-bond.

II. Solvolytic Reactions of (*E*)-2e and (*E*)-2f. Two astounding observations come from comparison of the solvolytic reactivity of (*E*)-**2e** and **f**. When a sample of (*E*)-**2e** is dissolved in methanol and immediately evaporated (all at room temperature), it is quantitatively converted to a 10/1 diastereomeric mixture of **4e** (R = CH_3). This time, however, the predominant isomer has the *more* shielded C_5 *tert*-butyl group (δ 1.02 vs 1.08) and the *less* shielded methoxy group (δ 3.37 vs 3.33), leading to an assignment of *Z* configuration. If these configurational

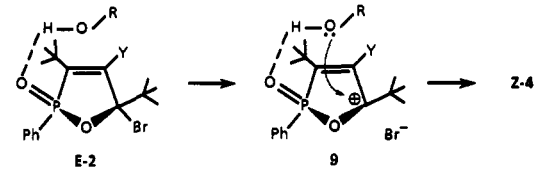


E-2 Z-4

assignments are correct, this result requires that nucleophilic substitution of a highly activated bromide occurs with essentially exclusive *inversion of configuration to give what must be the less stable diastereomer*! The same result had been previously observed with the methanolysis of (*E*/*Z*)-**2b**.[1]

By contrast, (*E*)-**2f** could be recovered unchanged after dissolution in methanol. Only at 50 °C does it begin to undergo methanolysis, and even then the half-life is ca. 5 h. This shows that (*E*)-**2e** (like **2a–c**) is >1700 times more reactive[11] than (*E*)-**2f** (and **2d**[1]). However, although it is far less reactive, (*E*)-**2f** again affords **4f** (R = CH_3) as a 9:1 diastereomer mixture favoring the *Z* (inverted) configuration, with the *more* shielded C_5 *tert*-butyl group (δ 1.09 vs 1.20) and *less* shielded methoxy group (δ 3.38 vs 3.31). The methanolysis of (*E*)-**2f** can be promoted at 25 °C by stoichiometric reaction with silver(I) salts (e.g., perchlorate, tetrafluoroborate, trifluoroacetate) in methanol, precipitating AgBr in quantitative yield. Nonetheless, the **4f** thereby produced exhibits the same 9/1 *E*/*Z* stereochemistry as in the direct methanolysis. To ensure that this ratio does not result from epimerization of **4f** after methanolysis, the mixture could be heated to 50 °C for 7 d with an excess of HBr in CD_3OD. Neither epimerization *nor methoxy exchange* are observed.

Given the stereochemical preference in **1e**, **1d**, **2e**, and **2f** for the C_5 *tert*-butyl to remain trans to the phenyl, and the fact that a methoxy group is sterically smaller than *tert*-butyl,[10] it is hard to imagine why (*Z*)-**4e** or **f** should be more stable than (*E*)-**4e** or **f**. Therefore, a simple S_N1 solvolysis mechanism involving **3** would be expected to produce **4e** or **f** with a preference for the (retained) *E* isomer. Instead, the observed preference for formation of the inverted diastereomer must indicate kinetic control. This result is fully consistent with our previous suggestion[1] that the observed inversion may result from a hydrogen bonding interaction between the attacking solvent and the phosphoryl oxygen, as in **9**.



E-2 9

Interestingly, Jencks and Banait have recently reported[12] that nucleophilic substitution reactions of α-D-glucopyranosyl fluoride are kinetically first order in nucleophile and occur with inversion of configuration, classic traits of an S_N2 mechanism. This result suggests that the often-invoked glucosyl oxocarbenium intermediate, if formed at all, is extremely unstable and rapidly captured by nucleophiles.

The greatly diminished reactivity of (*E*)-**2f** vs (*E*)-**2e** must reflect a direct effect of the C_4 bromine on the stability of the solvolysis transition state. As mentioned in the Introduction, we previously ascribed[1] the low reactivity of **2d** to a steric interaction between the C_5 *tert*-butyl group and the C_4 bromine when they attempt to occupy the ring plane simultaneously, as in carbocation **3** (or radical **8**, if planer). We now find further evidence for this type of interaction in a variable-temperature 250-MHz ^1H NMR study of (*E*)-**2f**. While the C_5 *tert*-butyl singlet (δ 1.293)[13] remains sharp from 25 °C to −43 °C, the C_3 *tert*-butyl singlet (δ 1.360) changes dramatically from a sharp singlet at 25 °C to a broadened shoulder of the δ 1.29 singlet at −43 °C. By contrast, *both tert*-butyl singlets in (*Z*)-**4a** (R = CH_3) remain sharp at −43 °C. Thus, the C_3 *tert*-butyl group (already in plane of the C_4 bromine) exhibits hindered rotation at −43 °C, while the C_5 *tert*-butyl (geminal to the C_5 bromine and out the ring plane) does not. This result suggests that the C_5 *tert*-butyl group would encounter similar hindrance if it were brought into the ring plane during rehybridization of C_5 to form **3f** or **8f**.[21]

III. Attempts To Generate Oxycarbocation 3f and Its Stabilized Derivatives. The instability of intermediate **3f** implied by the above solvolysis results was subjected to further testing. When (*E*)-**2f** was treated with silver tetrafluoroborate *in THF* with hopes of generating the tetrafluoroborate salt of **3f**, the reaction leads to quantitative precipitation of AgBr. But instead of a salt, the 5-fluoro derivative **10**, a stable high melting solid, is formed! Apparently, carbocation **3f** is so reactive that it abstracts fluoride ion from BF_4^-, rather than forming a salt with it. The BF_3 liberated in this process does not seem to have any further effect. Reaction of (*E*)-**2f** with silver trifluoroacetate in THF gives the 5-trifluoroacetoxy derivative **11**, an unstable solid which slowly decomposes to **10**. Interestingly, in **10** and **11** both *tert*-butyl groups have identical ^1H NMR chemical shifts, even at 400 MHz.[13] (This accidental equivalence is *not* seen in their ^{13}C NMR spectra.) Therefore, it is not yet possible to determine whether these two products are formed as one or two diastereomers or the stereochemistry of these substitutions.

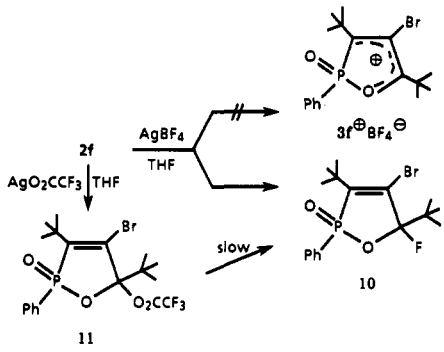
It was also suggested earlier[1] that if the phosphorus atom in **3** were to contribute an empty d orbital, the resulting four-electron cyclic π-system might exhibit antiaromatic

(11) Estimating a methanolysis half-life for **2e** of <1 m and a rate factor of $2^{2.5}$ for the temperature change 25 to 50 °C.

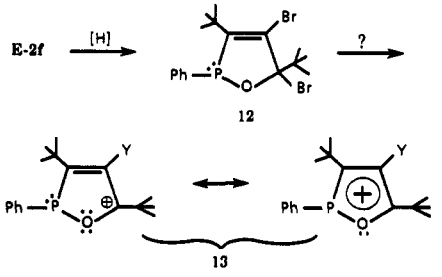
(12) Banait, N. S.; Jancks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951, 7958.

(13) In ^1H NMR spectra, the C_3 *tert*-butyl group is virtually always found downfield of the C_5 *tert*-butyl group,[1,3,5,7,14] this being due to the sp^2 hybridization at C_3 and the proximity of the phosphoryl. The only known exceptions are **10** and **11** where the signals are coincident.

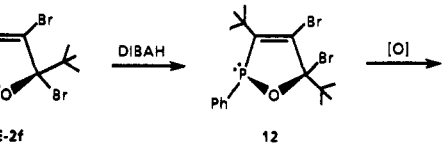
(14) Krudy, G. A.; Macomber, R. S. *J. Org. Chem.* **1978**, *43*, 4656. Tacheva, J. I.; Angelov, C. M. *Phosphorus, S.* **1990**, *47*, 243. Macomber, R. S.; Constantinides, I.; Garrett, G. *J. Org. Chem.* **1985**, *50*, 4711.



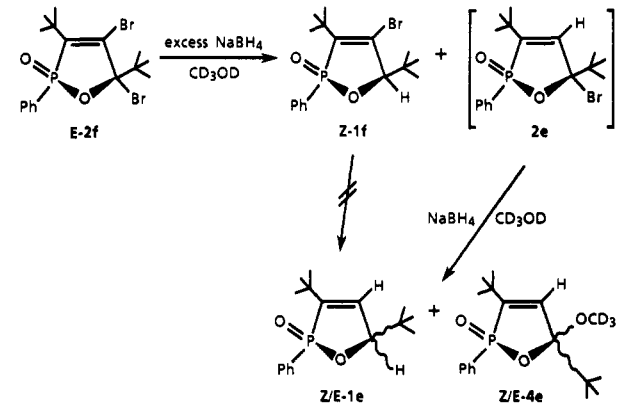
properties. On the other hand, if the phosphoryl oxygen were reductively eliminated, the resulting six π electron ion **13** might exhibit some level of aromatic stabilization. We tested this idea in a preliminary way by attempting to reduce **2f** at phosphorus and examining the reactivity of the expected phosphinite bromide **12**.



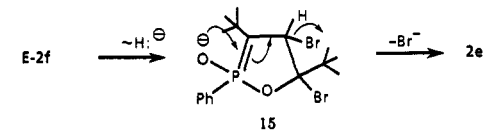
We previously found[15] that the phosphoryl group in **14**, an analogue of **1e**, could be reduced by either BH_3 or $HSiCl_3$, though the resulting trivalent phosphorus heterocycle was extremely reactive toward reoxidation and had to be stabilized by coordination of the phosphorus lone pair to a suitable Lewis acid (e.g., BH_3 or $W(CO)_5$). Unfortunately, (*E*)-**2f** proved to be completely inert toward both of these reducing reagents, perhaps because its C_3 *tert*-butyl group sterically inhibits their approach. However, DIBALH *does* react with (*E*)-**2f** to give a reaction mixture with the powerfully unpleasant odor characteristic of trivalent phosphorus compounds. In the ^{31}P NMR spectrum of the reaction mixture, the orginal signal for (*E*)-**2f** (δ 48.4) is replaced by one at δ 138.2, consistent[16] with reduction of the phosphoryl group to form **12**. Unfortunately, this product undergoes rapid reoxidation to **2f** in the presence of even a trace of air, judging from both ^{31}P (δ 48.5) and ^1H NMR spectra. A less intense ^{31}P singal at δ 52.7 and ^1H singlets at δ 1.26 and 1.32 also suggest that **2f** may be reformed as a mixture of stereoisomers still favoring the *E* isomer.



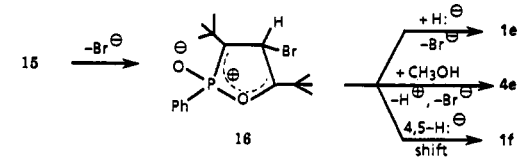
In a related experiment, (*E*)-**2f** was allowed to react with an excess of sodium borohydride (in deuteriomethanol) at room temperature, conditions previously shown to be inert toward both the P=O and C=C bonds of oxaphospholene **14**.[15] While hydrogen evolves, dibromide **2f** is rapidly consumed to give a complex product mixture comprising two major (ca. 30% each) and at least four minor components (ca. 13%, 13%, 7%, and 7% by ^1H NMR of the *tert*-butyl region). Although not all of these products have yet been fully characterized, it is clear from ^1H NMR and GC–MS that **4f** is *not* among them. The two least abundant components (7% each) are starting material (*E*)-**2f** and (*Z*)-**1f**, the C_5 bromine having been replaced by hydrogen. One of the major and one of the 13% products exhibit spectral data consistent with **4e** (R = CD_3) where again the C_4 bromine has been replaced by hydrogen. The other major product is **1e**. Compounds **1e** and **4e** presumably arise via reduction and methanolysis of **2e**, respectively, indicating that reduction of the C_4 bromine of **2f** (to give **2e**) is competitive with reduction of the C_5 bromine (to give **1f**). Furthermore, in a separate experiment under the same conditions, (*Z*/*E*)-**1f** was demonstrated to be essentially inert toward $NaBH_4$.



Reduction of the C_4 bromine of (*E*)-**2f** at first suggests a nucleophilic addition/elimination mechanism facilitated by the electron-withdrawing phosphoryl group. Yet, the



same type of mechanism should be available to **1f** which, in fact, was inert to the conditions. We are led to speculate that perhaps the formation of **15** is facilitated by simultaneous loss of the C_5 bromine to give zwitterion **16**, which can serve as a precursor of all the identified products.



IV. Extended Huckel Calculations for Ionization at C_5 in 2 and 12. Several of the mechanistic observations described in the above sections are consistent with the results of extended Huckel molecular orbital calculations[17] on several model structures,[18] as shown in Scheme II.

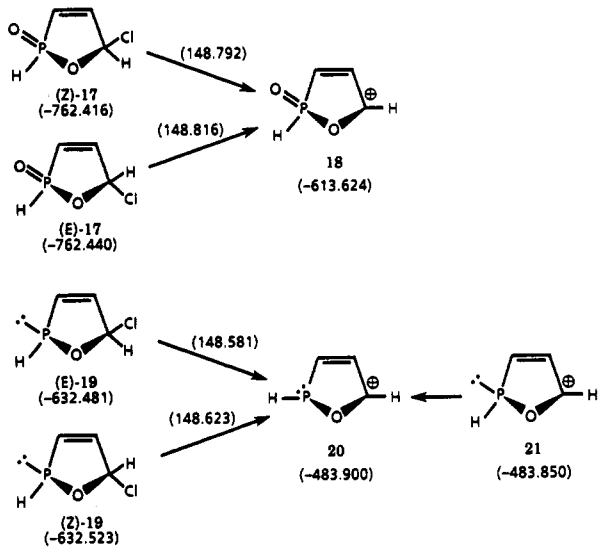
(15) Mualla, M.; Macomber, R. S. *Phosphorus Sulfur Relat. Elem.* **1990**, *47*, 15.

(16) $(CH_3)_2POC_2H_5$ shows a ^{31}P NMR signal at δ 112.6, while $(CH_3)_2P(O)OC_2H_5$ appears at δ 53.3: Quin, L. D.; Tang, J.-S.; Keglevich, G. *Heteroatom. Chem.* **1991**, *2*, 283. We thank Professor Quin for calling our attention to this reference.

(17) Calculations were performed with program QCMP011 (available from the Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University), authored by J. Howell, A. Rossi, D. Wallace, K. Haraki, and R. Hoffmann and converted by J. E. Bartmess and D. Thomas.

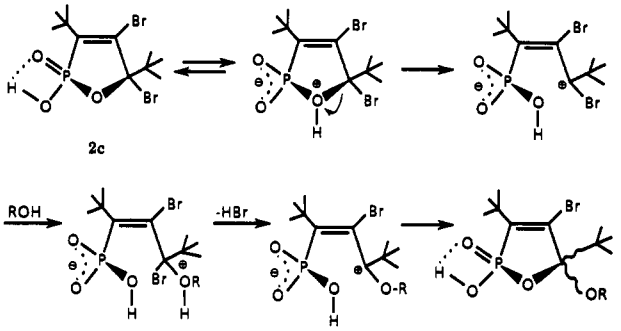
(18) The atomic coordinates for these structures were derived from the crystallographic parameters for ring atoms in **2f** with both *tert*-butyl groups and the phenyl replaced by hydrogens and the bromine replaced by chlorine.

Scheme II[a]

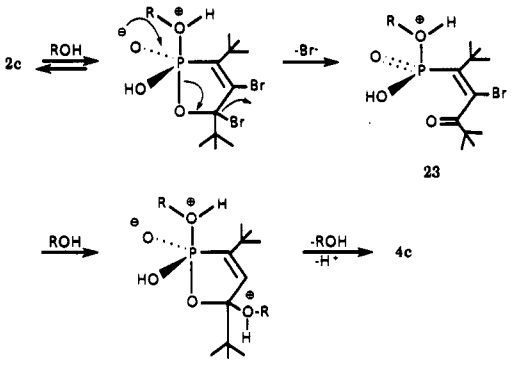


[a] All energies in eV.

Scheme III



Scheme IV



First, it is found that halogen has an electronic preference of 0.75 ± 0.2 kcal/mol for being trans to the phosphoryl oxygen (in **17**) or phosphorus lone pair (in **19**). This is the same stereochemical preference observed for **2b, d, e,** and **f**. Second, the hydrogen substituent on phosphorus in carbocation **20** prefers by 1.1 kcal/mol to be *in* the ring plane, allowing the phosphorus lone pair to occupy an orbital which better overlaps the rest of the cyclic π system. Indicative of this, calculated charge density on the phosphorus of ion **20** is +0.26, while it is only +0.12 in ion **21**. Most important, the formation of ion **20** from **19** is predicted to be significantly less endothermic electronically (ca. 4.6 kcal/mol) than formation of **18** from **17**. Thus, the phosphoryl group does appear to *de*stabilize formation of **3**, and there should be less of this destabilization in structures such as **13**.

Conclusions

The results of these experiments and calculations suggest that formation of solvolysis intermediate **3** from **2** can be assisted by conjugation with the neighboring π system and oxygen lone pair only if C_5 becomes sp^2-hybridized. Although readily accomplished in **2a, b,** and **e**, the motion of the C_5 *tert*-butyl group into the ring plane is prevented in **2d** and **f** by the C_4 bromine. The preferential inversion of configuration at C_5 during solvolysis of **2d, e,** and **f** indicates an S_N2-like substitution mechanism,[12] even though C_5 is neopentyl, allylic, and oxygen substituted. This mechanism may also involve hydrogen bonding between the nucleophile and the phosphoryl oxygen (cf. **9**).

The above mechanistic model provides a self-consistent account of the relative reactivity of **2a,b,d,e,f**. But compound **2c** presents an anomaly: although (like **2d** and **2f**) it possesses a bromine at C_4, it exhibits the same high solvolytic reactivity as **2a, b,** and **e**. Thus, **2c** must have access to a mechanism for solvolysis at C5 which is *not* inhibited by the C_4 bromine as are the S_N2 or S_N1 (via **3**) mechanisms. This alternate mechanism may involve reversible opening of the oxaphospholene ring, which avoids requiring both *tert*-butyl groups and the C_4 bromine to occupy the same plane. Further, this alternate mechanism must require the phosphorus substituent X (in **2**) to be OH because the reaction fails when X = OR or Ph. Two reasonable mechanisms can be advanced. The first one involves *intra*molecular proton transfer to the ring oxygen, followed by rate-limiting cleavage, substitution, and reclosure (Scheme III). Notice that **22**, which resembles the intermediate involved in electrophilic cyclization of allenic phosphonates (e.g., **7** → **1**),[3,5,7,8] does *not* require allylic stabilization of the carbocation charge[5] and therefore does not require the C_5 *tert*-butyl group to occupy the same plane as the C_4 bromine. It is important to emphasize that this mechanism would require *intra*molecular POH proton transfer, since heating **4f** with excess HBr in CD_3OD results in *neither* epimerization nor exchange of the RO group (above, Section II). We have previously invoked such intramolecular POH proton transfer in certain related reactions.[1]

Alternatively, the ring opening might involve reversible cleavage of the endocyclic P–O bond as seen in certain nucleophilic substitutions at oxaphospholene phosphorus.[19] Thus, perhaps when X = OH, the phosphorus is more accessible to nucleophilic attack than when X = OR or Ph, leading to pentavalent coordination of the phosphorus and subsequent reversible endocyclic cleavage (Scheme IV). In support of this mechanism, ketones similar to **23** have been isolated under certain conditions, and they do tend to recyclize under acidic conditions.[1] Finally, if either of these alternate mechanisms are operative for **2c**, the same one(s) may be involved in the solvolysis of **1a** as well.

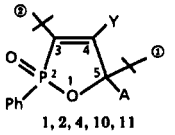
Experimental Section

General. The instruments and analytical procedures used in this study have been previously described.[1] Spectroscopic data are summarized in Tables I–IV.

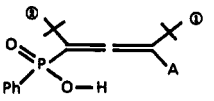
Synthesis of (2,2,6,6-Tetramethyl-3,4-heptadien-3-yl)-phenylphosphinic Acid (7). With a steady flow of dry nitrogen (for HCl removal) passing through a stirred solution of 3.02 g (18.0 mmol) of **5**[4] in 40 mL of dry CH_2Cl_2, a solution of 4.35 g (24.3 mmol) of dichlorophenylphosphine in 30 mL of CH_2Cl_2 was added dropwise over 90 min. After addition, nitrogen sweep was con-

(19) Macomber, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 4386.

Table I. 250-MHz ^{1}H NMR Spectroscopic Data for Compounds in This Study[a]



1, 2, 4, 10, 11

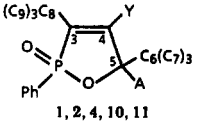


7

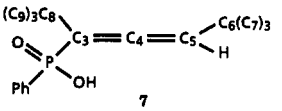
compd	A	Y	δ tBu_1	δ tBu_2	δ A	δ Y	δ Ph
7	H	H	0.78	1.18	5.02 (12)		7.34 (m), 7.72 (12.2, 7.6)
(*Z*)-1e	H	H	1.05	1.11	4.69 (8.4)	6.72 (39.4)	7.5 (m), 7.72 (12.7, 8)
(*E*)-1e	H	H	1.03	1.13	4.86 (2.8)	6.74 (38.0)	7.5 (m), 7.88 (13.3, 5.5)
(*Z*)-1f	H	Br	1.21	1.26	4.69 (13)		7.5 (m), 7.72 (13, 6)
(*E*)-1f	H	Br	1.14	1.31	4.88 (3)		7.5 (m), 7.88 (13, 6)
(*E*)-2e	Br	H	1.13	1.24		6.96 (39.1)	7.5 (m), 8.02 (13.5, 7.4)
(*E*)-2f	Br	Br	1.29	1.36			7.5 (m), 7.96 (14, 7)
(*Z*)-4e	OCH_3	H	1.02	1.21	3.37	6.64 (40.2)	7.5–7.6 (m), 7.85 (14, 7)
(*E*)-4e	OCH_3	H	1.08	1.11	3.33	*b*	*b*
(*Z*)-4f	OCH_3	Br	1.09	1.38	3.38		7.6 (m), 7.85 (14, 7)
(*E*)-4f	OCH_3	Br	1.20	1.32	3.31		7.6 (m), 7.85 (14, 7)
10	F	Br	1.26	1.26			7.52 (m), 7.62 (m), 7.83 (13, 6)
11	CF_3CO_2	Br	1.32	1.32			7.54 (m), 7.62 (m), 8.09 (13, 6)

[a] $CDCl_3$ solution, internal TMS reference unless otherwise noted. Values in parentheses are doublet coupling constants in Hz. Stereoisomers were analyzed as mixtures, with assignments based on relative intensities. [b] Signal too weak to be assigned.

Table II. 250-MHz ^{1}H NMR Spectroscopic Data for Compounds in This Study[a]



1, 2, 4, 10, 11



7

compd	δ C_3	δ C_4	δ C_5	δ C_6	δ C_7	δ C_8	δ C_9	δ A	δ Ph
7	134.2 (140)	206.10	105.7 (15)	32.0	29.6	34.9 (6)	30.5		132.4 (91), 131.5, 131.3, 127.7 (13)
(*Z*/*E*)-1e	146.8 (85)	139.7 (19)	91.3	35.6	25.9	30.6 (13)	29.7		132.3 (56) 132.3, 130.5 128.5 (13)
		139.1 (19)	90.6	35.2	25.6	30.5 (7)			132.2 (56) 128.3 (13)
(*Z*/*E*)-1f	141.0 (95)	132.2 (10)	93.4	37.0	27.0	33.8 (11)	28.6 (5)		133.2 (73), 133.2, 131.2, 128.6 (15)
(*E*)-2e[b]	145.3 (99)	141.9 (19)	110.8	42.7	26.0	33.2 (11)	30.2		132.8 (57), 132.8, 132.5, 128.6 (15)
(*E*)-2f[b]	142.1 (92)	132.4 (13)	110.7	44.6	27.0	34.1 (10)	28.3 (5)		137.9, 132.8 (79), 130.9, 128.7 (16)
(*Z*)-4e[b]	150.2 (98)	140.6 (16)	116.1	39.4 (5)	25.6	33.9 (10)	30.9 (5)	51.9	132.7 (48), 132.2, 130.1, 128.5 (13)
(*Z*)-4f[b]	145.0 (96)	131.5 (13)	116.0	40.9	26.6	34.7 (8)	28.4 (5)	51.4	137.4 (35), 133.29, 130.5, 128.8 (16)
10	145.4 (85)	132.6 (13)	119.9 (242)[c]	39.9 (27)[d]	25.7	34.0 (11)	28.1 (5)		132.7 (70), 131.5, 131.0, 128.8 (13)
11[e]	145.7 (85)	132.9	114.5	41.9	25.8	34.3	28.2 (5)	154.5 (50)[d] 114.8 (290)[c]	133.0 (62), 131.8, 130.9, 128.8 (16)

[a] See footnote a, Table I. When two values are given, it represents the signals of each diastereomer. [b] Signals for minor (*Z*) isomer too weak to assign. [c] $^1J_{CF}$. [d] $^2J_{CF}$. [e] 75-MHz ^{13}C spectrum.

Table III. Mass Spectroscopic Data for Compounds in This Study[a]

compd	*m*/*e* (rel ab)
7	292.1579 (100, calcd 292.1592), 277 (33), 236 (58), 221 (30), 109 (15), 95 (11), 67 (10), 57 (31)
(*Z*/*E*)-1e	292.1602 (38, calcd 292.1594), 237 (14), 236 (92), 221 (100), 77 (10), 57 (20)
(*Z*/*E*)-1f	371.0852/373 (5/5, M + H, calcd 371.0777), 355/357 (2/2), 314/316 (100/100), 299/301 (72/72), 125 (44), 105 (25), 77 (65), 57 (42)
(*E*/*Z*)-2e	313.0083/316 (7.7 M − C_4H_8, calc. 314.0072), 229/301 (3/3), 291.1521 (100, M − Br, calcd 291.1515), 261 (149 (64), 77 (18)
(*E*)-2f	449/450.9776/452.9758 (3/12/6, M + H, calcd 450.9861, 450.9841), 392/396 (4/8/4), 369/371 (51/50, M − Br), 314/316 (50/50), 299/301 (38/38), 77 (63), 41 (100)
(*Z*/*E*)-4e	322.1692 (19, calcd 322.1699), 307 (12), 291 (8), 279 (9), 265 (100), 251 (36), 155 (31), 141 (16), 109 (28), 77 (12)
(*Z*/*E*)-4f	385.0590 (calcd for M − CH_3 385.0568)/387 (1/1), 369/371 (7/8), 343/345 (100/100), 205 (3), 155 (7), 139 (7), 77 (13)
10	388.0630/390.0542 (calcd 388.0604/390.0584, 4/4), 373/375 (2/2), 369/371 (0.2/0.3), 332/334 (56/55), 317/319 (18/18), 125 (95), 77 (100), 57 (35)
11	482.0508/484.0480 (calcd 482.0470/484.0450, 0.5/0.5), 426/428 (25/26), 329.331 (100/100), 141 (18), 77 (12)

[a] Diastereomer mixtures were analyzed by GC/MS, and only the data for the major isomer are given. In all cases the minor isomer exhibited a virtually identical mass spectrum.

Table IV. IR Spectroscopic Data for Compounds in This Study

compd	$\bar{\nu}$, cm^{-1}
7	2963, 2902, 2862, 1940, 1439, 1363, 1230, 1175, 1129, 985, 942
(*Z*/*E*)-1e	3078, 3057, 2963, 2865, 1770, 1608, 1592, 1475, 1439, 1395, 1306, 1277, 1260, 1245, 1185, 1120, 1071, 1011, 970, 938, 902, 861, 837
(*E*)-2e	3063, 2969, 2873, 1610, 1592, 1477, 1465, 1440, 1398, 1368, 1283, 1227, 1124, 1076, 996
(*E*)-2f	2970, 1566, 1440, 1369, 1253, 1215, 1123, 1046, 1010, 863
(*Z*)-4e	3064, 2967, 2909, 2874, 1610, 1592, 1564, 1464, 1439, 1396, 1366, 1287
(*Z*)-4f	3063, 2971, 1572, 1479, 1463, 1439, 1396, 1365, 1245, 1121, 1062, 1042, 1021, 950, 898, 858
10	2970, 1577, 1440, 1231, 1147, 1125, 1066, 1043, 549
11	2970, 1803, 1578, 1440, 1247, 1228, 1178, 1147, 1053, 974, 872

tinued for 2 h, and then the reaction mixture was stirred under a nitrogen atmosphere for 46 h at 35 °C. Rotary evaporation left 7.29 g of crude **6** as a yellow oil which was then added simultaneously with a solution of 1.4 g (17 mmol) of $NaHCO_3$ in water to 40 mL of rapidly stirred water. After the resulting suspension was heated to 45 °C for 45 min and then cooled, a white solid was isolated by filtration, dissolved in acetone to remove inorganic salts, evaporated, and finally recrystallized from 60/40 ethanol/water to give 4.4 g (85%) of **7** as colorless crystals, mp 93–95 °C. Anal. Calcd for $C_{17}H_{25}O_2P\cdot^1/_2H_2O$: C, 67.67; H, 8.81. Found: C, 67.76; H, 8.70.

Synthesis of 3,5-Di-*tert*-butyl-2-phenyl-1,2-oxaphosphol-3-ene 2-Oxide (1e). A solution of 520 mg (1.78 mmol) of **7** and 1.68 g (8.12 mmol) of $AgClO_4$ in 23.5 mL of dry THF was heated to 70.0 °C for 236 h. (The reaction was monitored by ^1H NMR, using a solution of comparable concentrations in THF-d_8.) Precipitation of 54 mg of black silver was noted. The mixture was centrifuged and the supernatant filtered and rotary evaporated, leaving 2.43 g of a dark yellow oil. This was dissolved in 35 mL of ether, washed once with water and once with brine (considerable AgCl precipitate), dried over $MgSO_4$, and rotary evaporated to give 415 mg (80%) of **1e** as a nearly colorless oil which solidified upon standing, and did not remelt below 95 °C. ^1H NMR (Table I) indicated a 55% *Z*, 45% *E* mixture.

Synthesis of 4-Bromo-3,5-di-*tert*-butyl-2-phenyl-1,2-oxaphosphol-3-ene 2-Oxide (1f). To a suspension of 1.21 g (4.22 mmol) of **7** in 30 mL of dry CH_3OH at 25 °C under argon was added dropwise a solution of 769 mg (4.81 mmol) of Br_2 in 25 mL of CH_3OH over 15 m. The resulting yellow suspension was stirred for 72 h and then rotary evaporated to leave 1.88 g of a dark oil. Recrystallization from hepane afforded 908 mg (58%) of **1f** as a crystalline 3/1 *Z*/*E* mixture. Further recrystallization from heptane gave the pure *Z* isomer, mp 125–126 °C, in 15% overall yield. Anal. Calcd for $C_{17}H_{24}BrO_2P$: C, 55.00; H, 6.52. Found: C, 55.29; H, 6.55.

Synthesis of (*E*)-5-Bromo-3,5-di-*tert*-butyl-2-phenyl-1,2-oxaphosphol-3-ene 2-Oxide (2e). The following reaction was carried out in oven-dried glassware under a blanket of argon. A mixture of 146 mg (0.500 mmol) of (*Z*)-**1e**, 112 mg (0.629 mmol) of recrystallized NBS, and 8.3 mg of AIBN in 4.0 mL of dry CCl_4 was heated to 75 °C for 5.75 h. The color of Br_2 appeared within 10 min and slowly disappeared as the reaction proceeded. The mixture was cooled and then filtered to remove undissolved succinimide (a small amount remains dissolved) and rotary evaporated to give 166 mg (100%) of **2e** as a pale yellow solid, mp 98–116 °C. Because of the solvolytic instability of this compound, no further purification was attempted.[1] Spectroscopic data (Tables I–IV) indicated one predominant (95%) isomer, assigned the *E* configuration.

Synthesis of (*E*)-4,5-Dibromo-3,5-di-*tert*-butyl-2-phenyl-1,2-oxaphosphol-3-ene 2-Oxide (2f). A suspension of **1f** (337 mg, 0.91 mmol), freshly recrystallized NBS (240 mg, 1.33 mmol), and AIBN (10 mg, 0.06 mmol) in 30 mL of dry CCl_4 was degassed with argon and then heated to 76 °C for 3 h. After cooling and filtration, the solution was rotary evaporated leaving 415 mg of a colorless semisolid. Recrystallization from heptane afforded 388 mg (95%) of **2f** as large colorless prisms, mp 120.5–122.5 °C: ^{31}P NMR δ 48.4. Anal. Calcd for $C_{17}H_{23}Br_2O_2P$: C, 45.36; H, 5.15. Found: C, 45.46; H, 5.11. The details of the X-ray crystal structure determination for (*E*)-**2f** are given in the supplementary material.

Methanolysis of 2e. A 117-mg sample of **2e** was dissolved in 4.0 mL of anhyd methanol over 3 m at 25 °C. Immediate rotary evaporation at 25 °C and 0.20 mm provided crude **4e** as a yellow oil (116 mg). Spectroscopic data (Tables I–IV) indicated a 10/1 *Z*/*E* mixture.

Methanolysis of 2f. To a solution of 38 mg (83 μmol) of **2f** in 2 mL of dry CH_3OH was added 17 mg (84 μmol) of silver perchlorate in 0.5 mL of CH_3OH. After being swirled for 2 min the mixture was filtered to give 16 mg (102%) of AgBr. Rotary evaporation of the filtrate afforded 34 mg (100%) of 4-bromo-3,5-di-*tert*-butyl-5-methoxy-2-phenyl-1,2-oxophosphol-3-ene-2-oxide (**4f**) as a colorless oil. ^1H NMR indicated a 9/1 *Z*/*E* mixture (Table I). The same stereochemical result was observed when either silver tetrafluoroborate or silver trifluoroacetate were used or if the methanolysis was carried out in the absence of silver salts at 50 °C. In the last case, the half-life was 5 h, and the rate of methanolysis and stereochemical outcome were independent of added HBr.

Reaction of 2f with Silver Tetrafluoroborate in THF. To a suspension of 135 mg (300 μmol) of **2f** in 5 mL of dry THF at 25 °C was added a solution of 58 mg (300 μmol) of $AgBF_4$ in 2 mL of dry THF, followed by stirring at 25 °C for 5 min. Filtration gave 57 mg (100%) of AgBr. Rotary evaporation of the filtrate left 146 mg of crude 4-bromo-3,5-di-*tert*-butyl-5-fluoro-2-phenyl-1,2-oxaphosphol-3-ene 2-oxide (**10**) as an oil. This material slowly crystallized from $CDCl_3$ to give colorless solid, mp 284–284.5 °C, whose mass spectrum was identical to that of the oil: ^{31}P NMR δ 47.48. Anal. Calcd for $C_{17}H_{23}BrFO_2P$: C, 52.46; H, 596. Found: C, 52.39; H, 5.89.

Reaction of 2f with Silver Trifluoroacetate in THF. To a suspension of 96 mg (210 μmol) of **2f** in 8 mL of dry THF at 25 °C was added a solution of 47 mg (210 μmol) of AgO_2CCF_3 in 4 mL of dry THF, and the resulting mixture was stirred for 10 m. Filtration afforded 38 mg (96%) of AgBr. Rotary evaporation of the filtrate left 90 mg (89%) of 4-bromo-3,5-di-*tert*-butyl-5-(trifluoroacetoxy)-2-phenyl-1,2-oxaphosphol-3-ene 2-oxide (**11**) as a white solid, mp 220–221 °C. This material was somewhat unstable. After several weeks at 0 °C its mp was depressed and broad. Trituration from aqueous MeOH gave a solid identical to **10**.

Reduction of 2f with DIBALH. The 101-MHz ^{31}P spectrum of a solution of 20 mg (45 μmol) of **2f** in 0.5 mL of $CDCl_3$ exhibited one sharp signal at δ 48.4 (downfield of external 85% H_3PO_4). DIBALH (60 μL of a 1.0 M solution in cyclohexane, 60 μmol) was added. The signal at δ 48.4 disappeared, being replaced by one signal at δ 138.2 for **12**. Over time the latter signal decayed and was replaced by two roughly equally intense signals at δ 48.5 and 52.7.

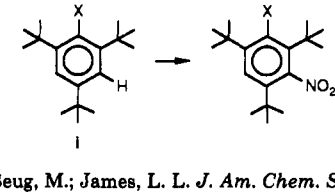
Reaction of 2f with $NaBH_4$. A solution of 13.7 mg (0.030 mmol) of **2f** in 0.40 mL of CD_3OD was added to 7.3 mg (193 mmol) of $NaBH_4$ in an NMR tube. For approximately 5 min there was a continuous evolution of hydrogen gas during the exothermic reaction. When the reaction subsided, the mixture was analyzed by ^1H NMR and GC/MS and found to comprise at least five components. ^1H NMR (the *tert*-butyl region, δ 0.9–1.4, and the C_4 vinyl region, δ 6.5–7.0) indicated at least six components. GC/MS analysis also indicated six components, A–F (in the order of elution). Components C, D, E, and F exhibited mass spectra essentially identical with those of **1e**, (*E*)- and (*Z*)-**4e** (with *m*/*e* adjusted for CD_3 vs CH_3), and **1f**, respectively. Components A and B exhibited very similar mass spectra, suggesting that they are stereoisomers of each other, as well as structural isomers **4e**: *m*/*e* 325, 270, 269, 255, 176 (base), 158, 135, 77. ^1H NMR signals at δ 0.98 and 1.28 were also dissimilar to other compounds encountered in this study.[20]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the Americal Chemical Society, for partial support of this research. The able technical assistance of Mr. Ioannis Constantinides is also gratefully acknowledged.

Registry No. (*E*)-**1e**, 141091-43-2; (*Z*)-**1e**, 141091-42-1; (*E*)-**1f**, 141091-45-4; (*Z*)-**1f**, 141091-44-3; (*E*)-**2e**, 141091-46-5; (*E*)-**2f**, 141091-47-6; (*E*)-**4e**, 141091-49-8; (*Z*)-**4e**, 141091-48-7; (*E*)-**4f**,

(20) Interestingly, **1a** exhibits a base peak at *m*/*e* 176 and ^1H NMR signals at δ 0.97 and 1.31,[1,7] suggesting some similarity in structure to A and B.

(21) **Note Added in Proof.** A closely related steric effect has been noted during electrophilic aromatic nitrations of the molecules depicted as **i**. The larger the group X is, the slower the deprotonation (second) step becomes.



i

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141091-51-2; (Z)-4f, 141091-50-1; 5, 93303-13-0; 7, 141091-41-0; 10, 141091-52-3; 11, 141091-53-4; 12, 141091-54-5; (E)-17, 141091-56-7; (Z)-17, 141091-55-6; 18, 141091-57-8; (E)-19, 141091-58-9; (Z)-19, 141091-59-0; 20, 141091-60-3; $PhPCl_2$, 644-97-3.

Supplementary Material Available: X-ray data for (E)-2f (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereoselective Synthesis of Verruculogen TR-2 Featuring the Mild Formation of a Dihydro-β-carboline as an Intermediate

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Reaction of indolyldiketopiperazine **5** with 2,3,4,5,6,6-hexachlorocyclohexadien-1-one (**25**) in dichloromethane/methanol provided the methoxyindolenine **29**, which in the presence of TFA rearranged to the dehydrodiketopiperazine **6**. This compound was elaborated to verruculogen TR-2 (**2**) employing osmium tetroxide oxidation.

Increased research on mycotoxins has led to the discovery of fungal metabolites that induce neurological manifestations in vertebrate animals that include sustained or intermittent tremors.[1-13] Fungi capable of producing tremorgic metabolites can be found on a variety of important agricultural commodities. The fungal tremorgens can be classified into six groups based on their chemical relationship.[9] The compounds of one of these groups—the fumitremorgin–verruculogen group—are biochemically derived from tryptophan, proline, and one or more mevalonic acid moieties.[6,13] Seven members of this group are at the moment isolated and identified, including in most cases their stereochemistry; two members are given in Chart I. In efforts to determine the mode of action of fungal tremorgens, it has become apparent that they provide useful tools in the study of central nervous system functions. In general, they interfere in mechanisms responsible for the release of CNS neurotransmitters.[14-19] Although particular molecular features responsible for the tremorgenic activity in the fumitremorgin–verruculogen group have not been completely identified, there are indications that the conformation and configuration of the dioxopiperazine moiety affects tremorgenic activity.[17]

We became interested in the fumitremorgins as attractive synthetic targets not only because of their biological activity but also because of their structure.

Recently, we reported[20,21] the total synthesis of fumitremorgin C (**1**) and three of its epimers. Our approach was based on the reaction sequence **3** → **4** → **5** → **1** (Scheme I).

The target of this study is the more functionalized verruculogen TR-2 (**2**),[3,6,8,9,11] a mycotoxin initially isolated from *Aspergillus fumigatus*. Recently, it was suggested[22] that the biogenetic relationship between tryptophan on one hand and α-substituted and α,β-dehydrotryptophan derivatives on the other hand might proceed via *N*-hydroxytryptophan derivatives. Moreover, it was demonstrated[22] that *N*-hydroxytryptophan derivatives deserve attention as synthons in the preparation of natural products having α-functionalized and α,β-dehydrotryptophan as structural elements.

On the basis of these considerations we wondered whether the *N*-hydroxytryptophan derivative **4** could be

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