observed 1-phenylethanol produced.

Styrene Oxide Reduction. (1) With AlD_3 Generated from $LiAlD_4$ and $AlCl_3$ (3:1). Into a 25-mL, round-bottomed flask fitted with a septum cap and stir bar was placed sublimed $AlCl_3$ (131 mg, 0.98 mmol) under N_2. To this at 0 °C was added 2.0 mL of ether, and the mixture was stirred until homogeneous. Then, 7.17 mL of 0.41 M $LiAlD_4$ solution (2.94 mmol) was slowly added with stirring. After 30 min at 0 °C a solution of (*R*)-(+)-styrene oxide (1.75 mmol) in 1.0 mL ether was added slowly. After being stirred for 30 min at 0 °C, the reaction mixture was hydrolyzed by the addition of 0.5 mL of H_2O and 2.0 mL of 10% HCl. The ether layer was separated, the aqueous layer was extracted (2 × 10 mL ether), and the combined ether layers were dried ($MgSO_4$). A precisely weighed amount of 1-octanol (internal standard) was added, and the products were analyzed by VPC. A pure sample of **7** was obtained by preparative VPC and analyzed by NMR spectroscopy. When the NMR in the presence of 1 equiv of $Eu(dcm)_3$ was taken, the sample was found to be 97.7 ± 1.5% enantiomerically pure. A sample of (*R*)-**7** prepared by a different route[16] was added to this NMR sample; this gave rise to a new, further downfield, benzylic resonance. Thus, the absolute configuration of **7** obtained in the epoxide reduction is *S*. The results are summarized in Table I.

(2) With AlD_3 Generated from $LiAlD_4$ and $AlCl_3$ (3:1) with Added Dioxane. The procedure above was repeated. Before addition of the epoxide to the reagent, 480 μL of dry dioxane was added. A heavy white precipitate appeared. To the solution was then added a solution of **5** in ether. The products were treated and analyzed as above.

(3) With AlD_3 Generated from $LiAlD_4$ and 100% H_2SO_4. Into a dry, 25-mL, round-bottomed flask fitted with a septum stopper, magnetic stirring bar, and N_2 inlet was placed 8.54 mL of 0.41 M $LiAlD_4$ solution. To this at 0 °C was slowly added 93.2 μL of 100% H_2SO_4. This produced a dense white precipitate. After 40 min at 0 °C, a solution of **5** (1.75 mmol) in 2 mL of anhydrous ether was added. After 30 min at 0 °C no noticeable change occurred, and the reaction was worked up and analyzed as above. The results are summarized in Table I.

(4) With $AlCl_2H$ Generated from $LiAlH_4$ and $AlCl_3$ (1:4) in Ether. Into a 25-mL, round-bottomed flask equipped with a rubber septum, stirring bar, and N_2 inlet was placed 485 mg (3.64 mmol) of $AlCl_3$ and 2.0 mL of anhydrous ether at 0 °C. After all dissolved, 0.70 mL of a 1.29 M $LiAlH_4$ solution (titrated as above) was added slowly. A clear solution resulted even after stirring 40 min at 0 °C. To this was added a solution of **5** (1.75 mmol) in 2.0 mL of anhydrous ether. A white precipitate formed with the addition. After 30 min at 0 °C, 0.5 mL of water followed by 2.0 mL of 10% HCl were added. The layers were separated, the aqueous layer was extracted (ether 2 × 10 mL), and the ether layers were combined and dried over $MgSO_4$. Analysis showed 67% of **10** and 12% of a higher boiling component, and the rest was polymer from styrene oxide. Integration of an NMR spectrum of VPC-purified **10** showed the ratio of benzylic protons to carbinol protons to be 1.0:1.0. In the presence of $Eu(dcm)_3$ the sample was found to be 24 ± 2% ee *S* at the benzylic center.

A second purified sample of **10** (23 mg, 0.185 mmol) was converted into its camphanate ester with (−)-camphanic acid chloride (44 mg, 0.2 mmol) in dry pyridine (300 μL).[24] Examination of the NMR spectrum of the camphanate ester (50 mg) in the presence of $Eu(dpm)_3$ showed two sets of doublets centered at 6.15 and 5.85 ppm.[25] Integration of this region revealed the sample to be a 50:50 (±2%) mixture of diastereomers [(1*R*,2*S*)-**10** and (1*S*,2*S*)-**10**].

Acknowledgment. We are indebted to the NIH (Grant No. GM 19554) for financial support of these studies.

Registry No. 5, 78638-63-8; **6**, 78638-64-9; **7**, 63423-65-4; (1*R*,2*S*)-**10**, 78684-41-0; (1*S*,2*S*)-**10**, 78684-42-1; (1*R*,2*R*)-**10**, 78684-43-2; (1*S*,2*R*)-**10**, 78684-44-3; AlO_3, 10294-03-8; $AlCl_2H$, 13497-97-7.

Reactions of Oxaphospholenes. 1. Solvolysis and Ring Opening

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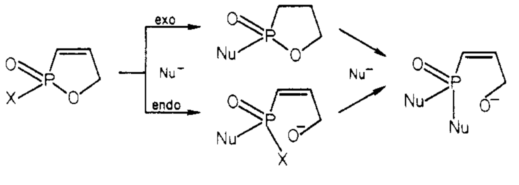
The hydrolysis of 2-methoxy-2-oxo-5,5-dimethyl-1,2-oxaphosphol-3-ene (**3**) in neutral or acidic media gives the corresponding 2-hydroxy derivative (**5**). The reaction is subject to acid catalysis and is also autocatalytic. Potassium hydroxide promoted hydrolysis occurs instantaneously at 25 °C to give the potassium salt of **5** (**13**), while the much slower reaction of **3** with sodium methoxide in methanol provides the sodium salt of **5**. All of these reactions involve alkyl–oxygen cleavage, not attack at phosphorus. When **13** is heated in the presence of excess hydroxide, attack at phosphorus does occur to give the product of endocyclic cleavage, dipotassium (3-hydroxy-3-methyl-1-(*Z*)-butenyl)phosphonate. Similarly, the reaction of 2-chloro-5,5-dimethyl-2-oxo-1,2-oxaphosphol-3-ene with methyllithium gives ring-opened (3-hydroxy-3-methyl-1-(*Z*)-butenyl)dimethylphosphine oxide.

Studies of the hydrolysis of phosphate esters and related compounds have been central in shaping our understanding of nucleophilic substitution at phosphorus.[1] The concept of pseudorotation was refined through this area of research, but the importance of understanding these reactions goes beyond their interest to the physical organic chemist. Indeed, crucially important biochemical processes such as phosphorylation involve just such reactions. For these reasons the area remains an active one today.[2]

Scheme I



Several years ago we discovered[3] a general synthetic entry into a novel family of phosphorus heterocycles,

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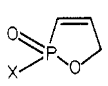
[1] Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.

[2] See, for example: Gorenstein, D. G.; Rowell, R. *J. Am. Chem. Soc.* **1980**, *102*, 6165 and references therein.

[3] Macomber, R. S. *J. Org. Chem.* **1971**, *36*, 2713. For a leading reference to subsequent work, see: Macomber, R. S.; Krudy, G. A. *Ibid.* **1978**, *43*, 4656.

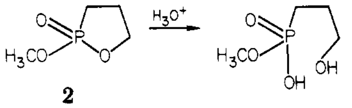
1,2-oxaphosphol-3-ene 2-oxides (1). While our work



1

continues on the preparation of various derivatives of 1, we have also engaged in a detailed study of reactions which involve the phosphorus functional group X: $Cl \rightarrow OH$,[4] $Cl \rightarrow OR$,[4] $OH \rightarrow OCH_3$,[5] $OH \rightarrow Cl$,[6] $Cl \rightarrow NR_2$,[6] etc. As part of this work we have examined the acid- and base-promoted reactions of the esters of 1 (X = OR) and related compounds. This preliminary report is prompted by a belief that our observations serve to unite and correct a variety of isolated reactions mentioned in the recent literature.

The key question in our work is related to the fate of the oxaphospholene ring during nucleophilic substitution: would the reaction involve exocyclic cleavage (retaining the ring), endocyclic cleavage (opening the ring), or both (Scheme I)? A classic observation in this area is that oxaphospholane 2 undergoes very rapid (compared to acyclic models) acid-catalyzed hydrolysis with exclusive endocyclic cleavage.[7] Recently it was reported[8] that, while (degenerate) methanolysis of ester 3 occurred slowly and without ring opening, acetate-"buffered" hydrolysis of 3 occurred to give the cyclic acid 5, but NMR data (not clearly specified) led the authors to suggest an acyclic intermediate, "probably 4". This report was in direct contradiction to our observations in the area and related work described in the literature. Several groups' results attest to the high stability of the oxaphospholene ring system. In the reactions we have described so far[3-6,9-11] ring opening has never occurred. Machida reported that phosphonate 6 spontaneously cyclized to 7, which in turn hydrolyzed readily (24 h, 25 °C) to 8.[12] Acid-catalyzed hydrolysis of 9 is accompanied by dehydration, but the ring is retained.[13] However, replacement of the methoxy in 9 by ethyl gave ring opening.[13]



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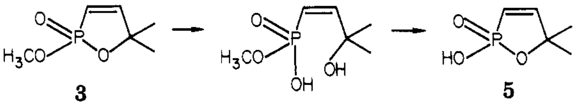
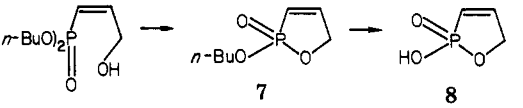
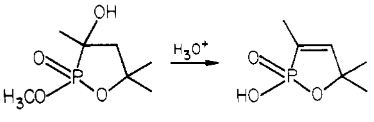


3 4 5



6 7 8



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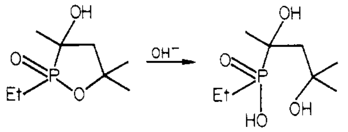
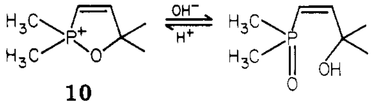
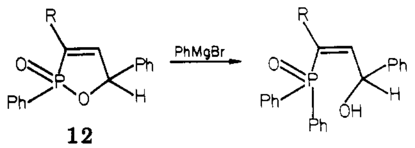
Spectroscopic evidence has been described[14] to suggest that phosphonium salt 10 can be opened to 11 under basic conditions and recylized in acid (though 11 was not isolated, nor was its structure firmly established; vide infra).





10 11

But again, when the phosphorus methyls were replaced by hydroxy or alkoxy groups, no ring-opened products were detected.[14] Finally, it has been shown that attack by the highly nucleophilic phenyl Grignard on 12 leads to ring opening.[15] In order to understand the factors which favor endo vs. exocyclic cleavage of cyclic phosphonates, we have studied the solvolysis of methyl ester 3, which has served as a prototype in several of our previous studies.[3,6,11]

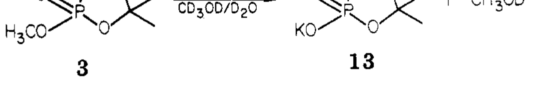


12

Results and Discussion

When 3 was dissolved in 1:1 v/v[16] methanol-d_4/deuterium oxide, hydrolysis occurred slowly at 25 °C, with less than 10% conversion to 5 after 18 h by ^{1}H NMR. Complete hydrolysis required 5.5 h at 68 °C. The spectral parameters of all relevant compounds are listed in Table I. Kinetics measurements established that the reaction is subject to Brønsted acid catalysis, and it is also autocatalytic because 5 itself is a sufficiently strong acid (pK_a ≈ 2.5). At no point was any other compound or intermediate detected by ^{1}H NMR.

We were surprised to find, however, that 3 was hydrolyzed within 30 s at 25 °C when the aqueous methanol contained potassium hydroxide. Thus, when 0.27 mmol of 3 was dissolved in 0.50 mL of 1.8 M KOH in 1:1 v/v methanol-d_4/D_2O, ^{1}H NMR indicated complete conversion to 13 within the time required to scan the spectrum. The consumption of hydroxide was confirmed by titration of the remaining KOH with standard HCl to a bromophenol blue endpoint.



3 13

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(4) Macomber, R. S., Kennedy, E. R. *J. Org. Chem.* **1976** *41*, 3191.

(5) Macomber, R. S. *Synth. Commun.* **1977**, *7*, 405.

(6) Macomber, R. S.; Krudy, G. A., unpublished results. For one example of the $OH \rightarrow Cl$ conversion see the Experimental Section of this paper.

(7) Westheimer, F. H., et al. *J. Am. Chem. Soc.* **1969**, *91*, 6066.

(8) van Aken, D.; Castelijns, A. M. C. F.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 322.

(9) Elder, R. C.; Florian, L. R.; Kennedy, E. R.; Macomber, R. S. *J. Org. Chem.* **1973**, *38*, 4177.

(10) Macomber, R. S. *J. Am. Chem. Soc.* **1977**, *99*, 3072.

(11) Macomber, R. S. *J. Org. Chem.* **1978**, *43*, 1832.

(12) Machida, Y.; Sarto, I. *J. Org. Chem.* **1979**, *44*, 865.

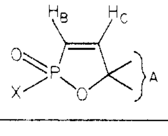
(13) Rizpolozhenskii, N. I.; Mukhametov, F. S.; Samitov, Y. Y. *Izv. Akad. Nauk SSSR, Ser. Khimi.* **1970**, 910.

(14) Petrov, A. A., et al. *Dokl. Akad. Nauk SSSR* **1978**, *241*, 1095.

(15) Campbell, I. G. M., Raza, S. M. *J. Chem. Soc. C* **1971**, 1836.

(16) Volume ratio before mixing.

Table I. ^{1}H NMR Spectral Data for 3, 5, 11, 13, 14, and 16[a]



compd	X	solvent	chemical shift A	chemical shift B	chemical shift C	chemical shift OCH_3
3	OCH_3	CCl_4	1.43, 1.48	5.96 (31, 8)	7.00 (47.5, 8)	3.68 (11.5)
3	OCH_3	$CDCl_3$	1.48, 1.52	6.03 (31.5, 8)	7.03 (47, 8)	3.79 (11.5)
3	OCH_3	D_2O/CD_3OD[b]	1.59	6.21 (34, 8.5)	7.38 (49, 8.5)	3.72 (13)
5	OH	D_2O/CD_3OD[b]	1.45	6.10 (33, 8)	7.20 (47, 8)	c
13	O^-K^+	D_2O/CD_3OD[b]	1.39	6.03 (31, 8)	6.75 (43, 8)	c
16	O^-Na^+	CD_3OD	1.40	6.02 (30, 8)	6.60 (44, 8)	
14[d]		D_2O/CD_3OD[b]	1.33	6.03 (38, 14.5)	5.53 (br s)	
14[e]		D_2O	1.33	6.01 (41, 14.5)	5.68 (9, 14.5)	
11[d,f]		D_2O	1.37	6.74 (41, 14)	5.72 (25, 14)	

[a] In δ downfield from Me_4Si or DSS; J_{PH} and J_{HH}, respectively, are given in hertz in parentheses. [b] 1/1 vv before mixing. [c] CH_3OH at δ 3.35. [d] 60 MHz. [e] 100 MHz; assignments from LAOCOON III simulation. See footnote 17. [f] PCH_3 at δ 1.67 (J = 13 Hz).

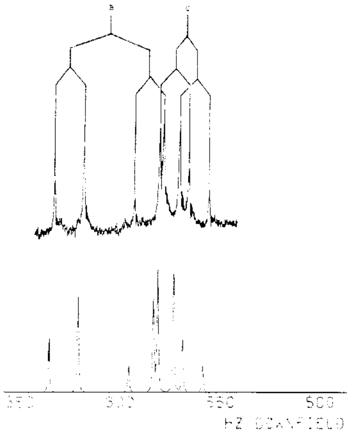
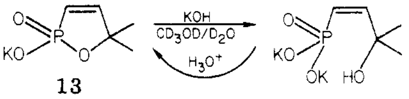


Figure 1. Top: the 100-MHz ^{1}H NMR spectrum of the vinyl protons in 14. Bottom: the LAOCOON III simulated spectrum, obtained by using parameters in Table I.

Perhaps most surprising was that continued heating of **13** in the presence of excess hydroxide led cleanly to a new compound, **14**. Although this reaction did *not* occur in the absence of hydroxide, titration did *not* indicate consumption of hydroxide during the formation of **14**. At 70.0 °C this reaction was first order in **13** and first order in hydroxide, with $k = 9.2 \times 10^{-3}$ m^{-1} M^{-1}. Neutralization of the solution with trifluoroacetic acid instantaneously converted **14** back to **13** or **5**, depending on the amount of acid added. This suggested that the conversion of **13** to **14** required 1 molar equiv of hydroxide, which was readily released upon neutralization or titration.

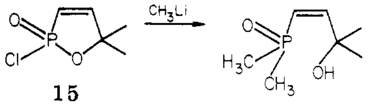


13 14

The 60-MHz ^{1}H NMR spectrum of **14** was somewhat misleading.[17] Examination of the isolated product at 100 MHz, however, gave a more revealing set of parameter (Figure 1 and Table 1). Further, the ^{31}P NMR of **14** showed a doublet of doublets (J = 39 and 10 Hz) centered at δ 10.3.[18,19] The resonance for **5** occurs at δ 41.9[4,18] On the basis of these data, we assign the open salt structure to **14**.

Several attempts were made to convert **14** into a neutral derivative, including reaction with methyl iodide, methyl sulfate, diazomethane,[5] and dicyclohexyl amine,[11] but none was successful.

In support of this structural assignment, we have found that treatment of acid chloride **15** with excess methyllithium provides ring-opened phosphine oxide **11**.[20] The

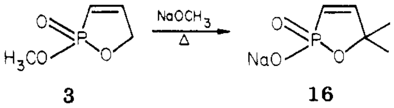


15 11

proton NMR of 11 (see Table I and Experimental Section) is highly similar to that of 14, especially the H–H coupling constants and the methyl chemical shift. This represents the first isolation of 11, though its existence was previously postulated.[14]

To compare with the ring-opening by hydroxide, we have examined the reaction of **3** with anhydrous methanol and methoxide. When a solution of **3** in freshly opened neutral methanol-d_4 was heated to 73 °C for 36 h, no change whatsoever was observed, in direct contradiction to van Aken's report.[8] However, addition of formic acid to the solution (15% v/v) caused hydrolysis *and* exchange to occur ($t_{1/2} \approx 42$ h at 73 °) give **5** and **3** (with a deuteriomethoxy group).

If, instead of formic acid, sodium methoxide was added stepwise to a solution of **3** in methanol, the ester was



3 16

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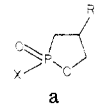
[17] The δ 5.53 broad singlet (Table I) resolved into a doublet of doublets at 60 MHz when the isolated solid is redissolved in D_2O. Whether the broad singlet is a result of a solvent effect or some type of dynamic process when **14** is originally formed is not yet clear.

[18] ^{31}P chemical shifts are positive downfield of external H_3PO_4.

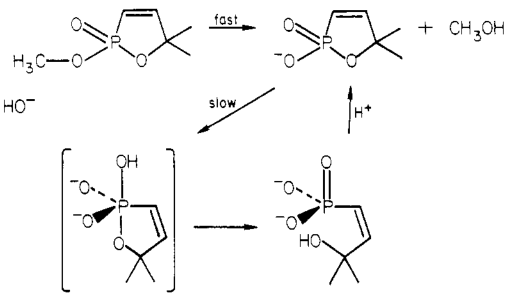
[19] While the ^{31}P chemical shifts of oxaphospholene oxides occur in the range δ 40–45,[4] allenic and vinyl phosphonyl derivatives come nearer to δ 15.[4,9]

[20] Three questions about this reaction are receiving further attention: (1) does ring opening precede or follow displacement of chloride, (2) will other organometallic reagents prefer a Michael-type addition to give, e.g., and (3) will attack by an alkyllithium on **3** proceed with *alkyl* oxygen cleavage?



a

Scheme II



cleanly converted (72 °C, 4 h) to salt **16**, complete conversion requiring 1 molar equiv of methoxide. These observations *require* that, at least in the case of methoxide and presumably in the case of much more reactive hydroxide, the loss of the methoxy group in **3** occurs by alkyl–oxygen cleavage rather than by phosphonyl–oxygen cleavage. Thus, the simple hydrolysis reactions do not involve a pentacoordinate phosphorus intermediate, nor do they result in endocyclic cleavage.

Finally, we have reexamined van Aken's hydrolysis experiment.[8] We found that when equimolar amounts of **3** and sodium acetate were dissolved in D_2O, no significant reaction took place until the solution was warmed. Then, with a half-life of ca. 10 h at 72 °C, **3** was cleanly converted to **16** *not* **5**, because the pK_a of acetic acid exceeds that of **5**). At *no time* were any significant resonances observed except those of **3**, **16**, acetate, methanol, and HOD. Comparison with an authentic sample established that methyl acetate was *not* formed. Here again, the reaction must proceed by attack of H_2O and OH^- on the *methyl carbon*, with no evidence for attack at phosphorus nor any evidence of a ring-opened intermediate.

We can summarize as follows. Oxaphospholene ester **3** undergoes slow solvolysis in neutral media with exclusive exocyclic cleavage. The reaction is catalyzed by acids and bases and is virtually instantaneous with hydroxide at 25 °C. These reactions appear to involve exclusive alkyl–oxygen cleavage (see Scheme II). Endocyclic cleavage *can* be made to occur under basic conditions, but only with potent nucleophiles, highly basic media, or higher temperatures will attack at phosphorus occur. Ring-opened products which possess two or more oxygen functionalities on phosphorus will cyclize immediately and *irreversibly* under acid conditions and more slowly under neutral conditions. Phosphine oxides such as **11**, on the other hand, exist in the open form in neutral and basic media, cyclizing *reversibly* in acid (vide supra). Our results also explain the relatively slow hydrolysis if **15** (X = Cl) and its derivatives[3,9] where nucleophilic substitution requires attack at phosphorus.

Experimental Section

General procedures and instrumentation were as previously described.[3-6] Ester **3** was prepared by the reaction of acid **5**[4] with diazomethane as previously described.[5] Kinetics determinations were made on the NMR scale by integrating the gem-dimethyl resonance of the starting material and product and reducing the data to standard form with a least-squares fit. The elemental analyses were graciously performed by Dr. Art Sill and Dr. Ruth Homan of Merrill National Laboratory.

Preparation of Dipotassium (3-Hydroxy-3-methyl-1-(*Z*)-butenyl)phosphonate (14). A 156-mg (1.05 mmol) sample of **5**[21] was dissolved in 3.4 mL of 0.86 M KOH (2.9 mmol) in 50% aqueous methanol,[11] and the solution was heated to 80.5 °C for 72 h. At this point ^1H NMR indicated complete conversion to **14**. Evaporation of solvent at 0.1 mm left 310 mg of a mixture of **14** and KOH (theoretical 301 mg). ^1H NMR spectral data for **14** are given in the text: ^{13}C {H} NMR (D_2O) δ 32.3 (s), 73.6 (d, J_{PC} = 7.7 Hz), 129.0 (d, J_{PC} = 162 Hz), 149.0 (s).

2-Chloro-5,5-dimethyl-2-oxo-1,2-oxaphosphol-3-ene (15). A suspension of 380 mg (2.6 mmol) 5,5-dimethyl-2-hydroxy-2-oxo-1,2-oxaphosphol-3-ene (**5**)[4] in 2.8 g (24 mmol) of distilled thionyl chloride and refluxed (with exclusion of moisture) for 20 h. The acid dissolved slowly during the period. After the mixture cooled to room temperature, excess thionyl chloride was stripped, leaving an oil which crystallized on standing. Sublimation [38 °C (0.05 mmHg)] gave 350 mg (81%) of colorless crystals: mp 83–85.5 °C. (lit.[8] mp 133–136 °C, lit.[22] mp 71–2 °C); ^1H NMR ($CDCl_3$) δ[23] 1.62 (s, 6 H), 6.28 (dd, J_{PH} = 38.5 Hz, J_{HH} = 8 Hz, 1 H), 7.08 (dd, J_{PH} = 55.5 Hz, J_{HH} = 8 Hz, 1 H); IR ($CHCl_3$) 3010 (m), 2990 (m), 1460 (m), 1370 (m), 1320 (vs), 1270 (vs), 1225 (m), 1165 (s), 1065 (w), 955 (vs), 940 (vs), 855 (s), 840 (vs), 620 (s), 585 cm^{-1}(vs); mass spectrum (70 eV), *m/e* 168 ($M^{+}\cdot$), 166 ($M^{+}\cdot$), 151 (base).

Anal. Calcd. for $C_5H_8ClO_2P$: C, 36.06; H, 4.84. Found: C, 36.20; H, 4.79.

(3-Hydroxy-3-methyl-1-(*Z*)-butenyl)dimethylphosphine Oxide (11). Methyllithium (5 mL, 1.4 M, 7 mmol) in diethyl ether was added, via syringe, to a stirred solution of 416 mg (2.5 mmol) of 2-chloro-5,5-dimethyl-1,2-oxaphosphol-3-ene 2-oxide (**15**) in 40 mL of anhydrous ether at -78 °C under nitrogen. After being stirred for 0.5 h, the mixture was warmed to room temperature and washed with H_2O (4 × 10 mL). The aqueous layers were combined and extracted with chloroform (5 × 10 mL). The combined organic layers were dried over magnesium sulfate. Evaporation of solvent left 260 mg of crude product, mp 68–70 °C. Sublimation [32 °C (0.1 mmHg)] gave 210 mg (52%) colorless solid: mp 72–74 °C; ^1H NMR (D_2O) δ 1.37 (s, 6 H), 1.67 (d, J_{PH} = 13 Hz, 6 H), 5.72 (dd, J_{PH} = 25, Hz, J_{HH} = 14 Hz, 1 H), 6.74 (d d, J_{PH} = 41 Hz, J_{HH} = 14 Hz, 1 H); ^{13}C {H} NMR ($CDCl_3$) δ 18.35 (d, J_{PC} = 74.1 Hz, dq[24]), , 30.15 (s, q[24]), 71.29 (d, J_{PC} = 0.4 Hz, d[24]), 119.44 (d, J_{PC} = 93.6 Hz, dd[24]), 160.46 (s, d[24]); IR (CCl_4) 3265 (br), 2980 (s), 2940 (sh), 1640 (m), 1470 (w), 1360 (m), 1305 (s), 1290 (s), 1260 (s), 1160 (vs), 970 (m), 940 (vs), 870 (vs), 715 (vs); mass spectrum (70 eV), *m/e* 147 (base)[25]

Anal. Calcd for $C_7H_{15}O_2P$: C, 51.84; H, 9.32. Found: C, 51.63; H, 9.50.

Registry No. 3, 59474-17-8; **5**, 59474-16-7; **11**, 68120-80-9; **13**, 78592-64-0; **14**, 78592-65-1; **15**, 75779-67-8; **16**, 78592-66-2.

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[21] Or an equivalent amount of **3**.

[22] Mikhailova, T. S., et al. *Zh. Obshch. Khim.* **1980**, *50*, 1690. Perhaps van Aken's sample was contaminated with **5** (mp 156–157.5 °C[4]) or some other acidic impurity.

[23] Determined by LAOCOON III simulation.

[24] Obtained from off-resonance proton-decoupled ^{13}C NMR.

[25] No molecular ion could be detected. This is not uncommon for tertiary alcohols.