Reactions of 1,2-Oxaphospholene 2-Oxides. 6.[1] Free-Radical and Nucleophilic Substitution at C_5: Anomalous Proton-Transfer Behavior of Cyclic Ketals

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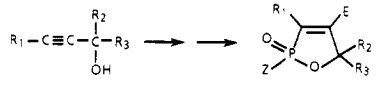
The free-radical bromination of 3,5-di-*tert*-butyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**1b**) with *N*-bromosuccinimide (NBS) gave the corresponding 5-bromo-3,5-di-*tert*-butyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**3**) in good yield. Bromide **3** was extremely labile and could not be purified rigorously, but it readily underwent methanolysis to give 3,5-di-*tert*-butyl-2-hydroxy-5-methoxy-1,2-oxaphosphol-3-ene 2-oxide (**7**) or hydrolysis to 3,5-di-*tert*-butyl-2,5-dihydroxy-1,2-oxaphosphol-3-ene 2-oxide (**8**), both crystalline compounds. Compounds **7** and **8**, though somewhat less reactive than **3**, were readily interconverted. Treatment of **8** with diazomethane led to dimethyl (*Z*)-2,2,6,6-tetramethyl-3-oxohept-4-en-5-ylphosphonate (**10**), indicating that **8** is in equilibrium with its open phosphonic acid isomer. Ketal **7** underwent methoxy exchange at 35.5 °C with a first-order rate constant of 0.075 m^{-1}, and the rate was only slightly increased by a large excess of trifluoroacetic acid. The conjugate base of **7** did not undergo exchange. By contrast, 3,5-di-*tert*-butyl-2,5-dimethoxy-1,2-oxaphosphol-3-ene 2-oxide (**11**), the methyl ester of **7**, was totally inert toward methoxy exchange except in the presence of excess HBr at high temperature for extended periods. The contrasting solvolytic behavior of **7** and **11** under acidic conditions has been interpreted as evidence for an *intramolecular* proton transfer from an oxygen on phosphorus to the nucleofuge. Ketal-ester **11** underwent slow ring opening in base, which was immediately reversed upon neutralization. The methyl ester (**1c**) of **1b**, the 4-bromo derivative (**1d**) of **1b**, and its methyl ester (**1e**) all undergo similar reactions with NBS. However, 4,5-dibromide **20** was anomalously unreactive toward nucleophilic substitution.

Introduction

A wide variety of 1,2-oxaphosphol-3-ene 2-oxides (**1**) can be prepared from propargyl alcohols, via allenic phosphonates and related compounds.[2] We have previously

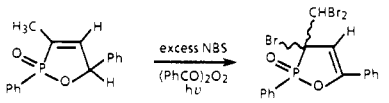


1 a: $R_1 = CH_3$; $E = R_2 = H$; $R_3 = Z = Ph$
b: $R_1 = R_2 = C(CH_3)_3$; $R_3 = E = H$; $Z = OH$
c: $R_1 = R_2 = C(CH_3)_3$; $R_3 = E = H$; $Z = OCH_3$
d: $R_1 = R_2 = C(CH_3)_3$; $E = Br$, $R_3 = H$, $Z = OH$
e: $R_1 = R_2 = C(CH_3)_3$; $E = Br$, $R_3 = H$, $Z = OCH_3$

studied both mechanistic and synthetic aspects of these reactions, as well as investigating the chemical behavior of this highly functionalized heterocyclic ring system. Particular attention has been directed toward nucleophilic substitution and reduction at phosphorus,[1,3] and the reactivity of the carbon–carbon double bond toward addition, oxidation, and reduction reactions.[1,4] To complete our chemical voyage around this ring system, we began investigating the reactivity of an allylic hydrogen at C_5 (**1**, R_2 or R_3 = H) as an entry to further functionalization at that position.

During our previous work in this area, we had found that the cyclic structure of **1** was highly stable under neutral, acidic, or electrophilic conditions. However, strongly basic or nucleophilic media often led to ring opening subsequent to nucleophilic attack at phosphorus.[1-4] It was not too surprising, therefore, that initial attempts to carry out the LDA-promoted electrophilic substitution of the C_5 hydrogen in phosphinate **1a** proved to be unsuccessful.[5]

Attention was next directed to the less hostile procedure of free-radical bromination of **1a** with *N*-bromosuccinimide (NBS).[6] Preliminary experiments[5] indicated that a 3-fold excess of NBS was required to consume all starting material. The product isolated from this reaction in 73% yield was tentatively identified by its spectral data as allylically rearranged tribromide **2**.[5] This result suggested that allylic hydrogens in the R_1 methyl group were at least comparably reactive to the allylic hydrogen at C_5, and that a phenyl group at C_5 helped induce migration of the double bond to the conjugated position.



1a **2**

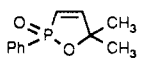
We have now examined substrates for the NBS reaction that avoid both allylic hydrogens in R_1 and conjugating substituents at C_5. These reactions lead to the desired bromination at C_5 and thereby provide substrates with which to study nucleophilic substitution at that carbon.

Results and Discussion

Oxaphospholene **1b**, synthesized previously,[7] was selected as an improved substrate. Not only does this structure avoid the pitfalls presented by **1a**, but the two *tert*-butyl groups were expected to inhibit possible condensation polymerization involving the OH group on one molecule of the expected bromide and the C_5 bromine on another. As with all derivatives of **1** where Z = OH, **1b** exists as a single diastereomer because the OH hydrogen is rapidly exchanged between the two oxygens on phosphorus, rendering them equivalent.[7]

(1) Paper 5 in the series: Mualla, M.; Macomber, R. S. *Phosphorus Sulfur* **1990**, *47*, 15.
(2) As a leading reference, see: Macomber, R. S.; Krudy, G. A.; Seff, K.; Diaz-Miron, L. E. R. *J. Org. Chem.* **1983**, *48*, 1425.
(3) As a leading reference, see: Macomber, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 4386.
(4) Macomber, R. S.; Constantinides, I.; Garrett, G. *J. Org. Chem.* **1985**, *50*, 4711.
(5) Mualla, M., Ph.D. Dissertation, University of Cincinnati, 1988.

(6) Under *polar* conditions, *N*-bromoacetamide reacts with **i** via *electrophilic* addition to the double bond, followed by ring opening.[4]

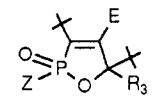


i

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

0022-3263/90/1955-1493$02.50/0

Table I. ^{1}H NMR Spectral Data for Compounds Described in the Text[a]



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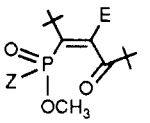
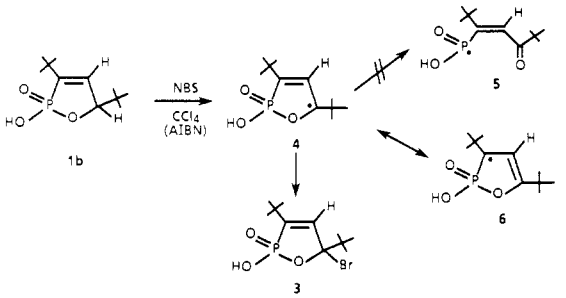


10, 12, 22

compound	$\delta_{t\text{-}Bu_1}$	$\delta_{t\text{-}Bu_2}$	δ_{R_3}	δ_E	δ_Z
1b (E = R_3 = H, Z = OH)[b]	0.97	1.31	4.48 (4.7, 1.7)	6.57 (46, 1.7)	13.00
3 (E = H, R_3 = Br, Z = OH)	1.14	1.30	–	6.76 (48)	11.26
7 (E = H, R_3 = OCH_3, Z = OH)	1.00	1.32	3.21	6.29 (48)	11.58
8 (E = H, R_3 = Z = OH)	1.03	1.28	7.2	6.50 (48)	7.2
10[c] (E = H, Z = OCH_3)	1.19	1.26	–	6.77 (47)	3.70 (11)
11 (E = H, R_3 = Z = OCH_3)	*E** 0.97	1.28	3.23	6.30 (48)	3.86 (11)
	*Z** 1.00	1.28	3.18	6.30 (48)	3.87 (11)
12[d] (E = H, Z = O^-)	1.20	1.28	–	6.56 (40)	3.47 (11)
13[d] (E = H, R_3 = OH, Z = OCH_3)	1.03	1.27	–	6.71 (48)	3.74 (12)
1c[e] (E = R_3 = H, Z = OCH_3)	*Z* 0.91	1.21	4.39 (5, 1.5)	6.56 (45, 1.5)	3.78 (12)
	E 0.95	1.21	4.30 (4.5, 1.5)	6.56 (45, 1.5)	3.65 (12)
15 (E = H, R_3 = Br, Z = OCH_3)	*E** 1.11	1.24	–	6.78 (49)	3.87 (12)
	*Z** 1.14	1.27	–	6.78 (49)	3.85 (12)
1d (E = Br, R_3 = H, Z = OH)[f]	1.11	1.43	4.46 (8.75)	–	12.31
16 (E = R_3 = Br, Z = OH)	1.15	1.26	–	–	10.79
17 (E = Br, R_3 = Z = OH)	1.15	1.42	–	–	*g*
18 (E = Br, R_3 = OCH_3, Z = OH)	1.08	1.39	3.18	–	*g*
1e (E = Br, R_3 = H, Z = OCH_3)[e]	*Z* 1.09	1.41	4.47 (8.6)	–	3.87 (11.5)
	E 1.14	1.41	4.40 (8.9)	–	3.72 (12.1)
20 (E = R_3 = Br, Z = OCH_3)	*E** 1.25	1.43	–	–	3.91 (13.3)
	*Z** 1.29	1.44	–	–	3.81 (13.0)
21 (E = Br, R_3 = OH, Z = OCH_3)	*E** 1.13	1.39	–	–	3.80 (11.5)
	*Z** 1.17	1.39	–	–	3.70 (12.2)
22 (E = Br, Z = OCH_3)[h]	1.37	1.46	–	–	3.69 (11), 3.71 (11)[i]

*Tentative stereochemical assignment; see text. [a] $CDCl_3$ solution (TMS reference) unless otherwise noted. Values in parentheses are coupling constants (Hz). [b] Reference 7. [c] IR 1690 cm^{-1}. [d] Basic CD_3OD. [e] Reference 2. [f] Reference 15. [g] O–H resonance too broad to be located. [h] IR 1696 cm^{-1}. [i] See text.

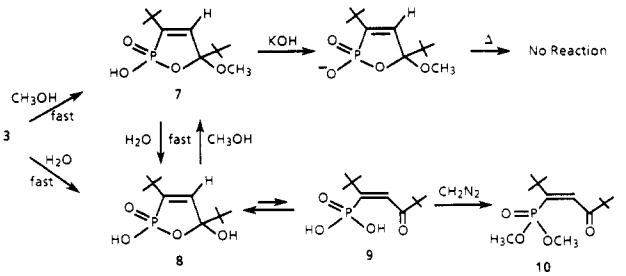
Reaction of **1b** with NBS in carbon tetrachloride led to an unstable product whose spectral data (Tables I–III) and reactivity (vide infra) were fully consistent with unrearranged bromide **3**. Especially significant were the disappearance of the ^{1}H NMR signal for the C_5 hydrogen (as well as its coupling to the C_4 vinyl hydrogen),[8] preservation of the 47-Hz $^3J_{PH}$ for the C_4 hydrogen, and the downfield shift of 17.6 ppm in the ^{13}C signal of C_5, compared to the spectral data for **1b** (Table II).



The formation of **3** from **1b** indicates two important facts. First, ring opening of allylic radical **4** to **5** is not occurring (though products related to this general structure will be described below), even though a strong carbonyl group would have resulted. Second, resonance structure **6** does not impact on the product-determining step, in contrast to the behavior of **1a**.

Because its bromine is tertiary, allylic, and further activated by the endocyclic oxygen, **3** exhibited high reactivity toward adventitious moisture or hydroxylic solvents. For this reason, **3** proved to be extremely labile and impossible to purify rigorously. Nonetheless, **3** could be readily converted to other derivatives which, in addition to being more stable and fully characterizable, also led the way toward an investigation of the mechanism of nucleophilic substitution at C_5 of **1**.

For example, simply dissolving **3** in methanol led within 3 min (the time required to generate its ^{1}H NMR spectrum) to cyclic "ketal" **7** (Tables I–III), which could be isolated as a crystalline solid. Similarly, hydrolysis of **3** in aqueous acetone gave the corresponding "hemiketal" **8**, also a crystalline solid. It is clear from a comparison of the NMR data for **8** with those of **7** (Tables I and II) that **8** also adopts the cyclic oxaphospholene structure, rather than the isomeric acyclic ketophosphonic acid structure **9**. Interestingly, esterification of **8** with diazomethane[9] led to dimethyl phosphonate **10**, the NMR spectra of which were very different from those of **3**, **7**, and **8**. This result demonstrates that although **8** is the preferred structure (at least in solution), there is nonetheless a rapidly attained equilibrium between **8** and **9**.

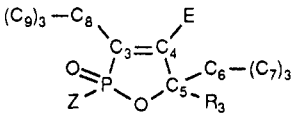


Not surprisingly, **7** and **8** were readily interconvertable. Thus, recrystallization of **7** from aqueous acetone gave **8**, and recrystallization of **8** from methanol gave **7**. In an

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

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

Table II. ^{13}C NMR Spectral Data for Compounds Described in the Text[a]



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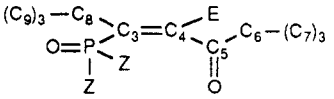

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compound	δ_{C_3}	δ_{C_4}	δ_{C_5}	δ_{C_6}	δ_{C_7}	δ_{C_8}	δ_{C_9}	δ_Z	$\delta\delta_{R_3}$	δ_{CDCl_3}
1b (E = R_3 = H, Z = OH)	142.50 (152.6)	138.56 (25.5)	86.76 (10.0)	35.28 (1.8)	25.29	32.87 (12.7)	30.03 (4.7)	–	–	77.08
3 (E = H, R_3 = Br, Z = OH)	140.60 (151.5)	141.63 (21.4)	104.32 (13.5)	42.08 (4.1)	25.65	32.80 (8.3)	29.82 (5.4)	–	–	77.08
7 (E = H, R_3 = OCH_3, Z = OH)	147.86 (147.4)	137.85 (11.7)	111.47 (11.7)	39.17 (3.8)	24.88	33.36 (13.7)	30.04 (5.1)	–	51.02	77.04
8 (E = H, R_3 = Z = OH)[b]	144.22 (146.2)	140.34 (19.3)	108.77 (12.6)	39.01 (4.8)	24.94	33.03 (11.2)	29.95 (3.9)	–	–	78.07
10 (E = H, Z = OCH_3)	142.57 (167.1)	140.58 (10.5)	211.21 (6.9)	43.96	27.01	36.41 (11.5)	30.08 (4.0)	52.13 (5.6)	–	77.08
11 (E = H, R_3 = Z = OCH_3)	*Z*[c,d] 147.8 (138)	138.45 (18.8)	111.43 (10)	39.35 (3.9)	24.91	33.25 (13.1)	30.07 (4.7)	52.92 (6.6)	51.18	77.21
	E[c,d] 147.9 (153)	138.56 (19.6)	111.08 (10.5)	39.14 (4.0)	23.94	33.27 (10.4)	29.99 (4.8)	51.15 (6.8)	50.92	
1c (E = R_3 = H, Z = OCH_3)	*E*[d,e] 141.32 (146.7)	139.15 (28.4)	86.34 (11.2)	34.91	24.86	32.38 (12.2)	29.41	52.45	–	77.00
	Z[d,e] 141.93 (151.2)	138.78 (27.0)	86.19 (11.2)	34.91	24.94	32.38 (12.2)	29.63	52.15	–	
15 (E = H, R_3 = Br, Z = OCH_3)	*Z*[c,d] 140.84 (145.4)	142.50 (21.5)	105.07 (9.0)	42.61 (4.4)	25.92	33.07 (11.6)	30.35 (4.9)	53.68 (7.1)	–	77.70
	E[c,d] 140.66 (150.0)	142.23 (21.8)	104.73 (11.7)	42.35 (3.5)	25.95	33.07 (11.6)	30.24 (8.6)	53.26 (6.9)	–	
1d (E = Br, Z = OH, R_3 = H)	137.57 (151.4)	133.79 (53.6)	89.61 (5.3)	36.79	26.79	33.78 (7.5)	28.31 (5.2)	–	–	77.00
16 (E = R_3 = Br, Z = OH)	141.60	138.72 (45.2)	92.20	44.16	26.79	34.01 (11.2)	28.06 (5.2)	–	–	77.00
17 (E = Br, R_3 = Z = OH)	140.61 (143.5)	137.80 (41.8)	109.48 (7.3)	40.95 (3.5)	26.57	34.31 (8.4)	28.54 (5.1)	–	–	–
18 (E = Br, Z = OH, R_3 = OCH_3)	142.80 (145.8)	134.74 (39.8)	112.06 (4.5)	40.65	26.08	34.23 (7.8)	28.10 (5.2)	–	50.80	77.04
1e (E = Br, Z = OCH_3, R_3 = H)	*Z*[e,f]	129.84 (131.4)	89.58 (5.0)	36.80 (5.0)	26.80	33.8 (7.0)	28.39 (5.4)	53.26 (4.0)	–	77.05
	E[e,f]	129.84 (131.4)	89.58 (5.0)	36.80 (5.0)	26.87	33.8 (7.0)	28.48 (5.3)	53.26 (4.0)	–	
20 (E = Br, Z = OCH_3, R_3 = Br)	*E*[e] 137.93 (143.3)	129.94 (119.9)	92.32	44.52	26.88	33.91 (11.1)	28.19 (4.3)	53.39 (35.3)	–	77.04
	Z[e] 137.93 (143.3)	129.94 (119.9)	92.32	44.52	26.88	33.9 (11.1)	28.19 (4.3)	53.39 (35.3)	–	
21 (E = Br, Z = OCH_3, R_3 = OH)	*E*[e] 143.25 (200)	138.58 (66.3)	109.39 (5.0)	41.01	26.58	34.24 (7.8)	28.48 (5.1)	53.50 (4.0)	–	–
	Z[e] 143.25 (200)	138.58 (66.3)	109.39 (5.0)	41.30	26.58	34.24 (7.8)	28.48 (5.1)	53.75 (4.0)	–	

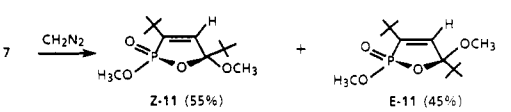
[a] See Table I for legend. [b] $CDCl_3/CD_3COCD_3$ (3/1 v/v). [c] Tentative stereochemical assignment; see text. [d] Signal assignments to major and minor isomer made on the basis of signal intensity. [e] Resolution sufficient only to resolve $J > 5$ Hz.

effort to determine the rates of these nucleophilic substitution processes, **7** was dissolved in CD_3OD. Exchange of the methoxy group was readily followed at 35.5 °C by ^1H NMR and found to be first-order with a rate constant of $(7.6 \pm 0.4) \times 10^{-2}$ min^{-1} (corresponding to a half-life of 9 min). Judging from the result of its methanolysis, **3** must be *at least* ca. 20 times as reactive as **7**.

Surprisingly, the rate of methoxy exchange of **7** was quite *in*sensitive to an excess of the relatively strong trifluoroacetic acid (TFA), whose pK_a is 0.3.[10] Thus, addition of a 6-fold excess of TFA was accompanied by only a slight increase in rate constant (0.105 ± 0.005 min^{-1}). Still, the presence of acidic hydrogens is essential to this exchange process. When ketal **7** (pK_a ca. 2.5[9]) was converted to its conjugate base by a 15-fold excess of KOH, it was found to be *completely* stable in CD_3OD (76 °C, 15 h) and in CD_3OD/D_2O (3/1 v/v, 76 °C, 20 h).

A lower limit to the rate of conversion of **7** to **8** was determined by adding D_2O (33 vol %) to a CD_3OD solution of **7** (with deuteriated methoxy group). Within 3 min, **7** had been converted into a 2:1 mixture of **7** and **8**, which was thereafter stable.

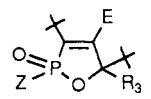
By contrast to the esterification of **8**, treatment of **7** with diazomethane led to ketal–ester **11** as a 55/45 mixture of the *Z* and *E* diastereomers. The stereochemical result of diazomethane esterification of **1b** and two of its derivatives has been established by a combination of X-ray crystallography and ^1H NMR.[2,11] Because of the small but consistent and reproducible preference for esterification trans (*E*) to the *tert*-butyl group (55 ± 3 to 45 ± 3 in all three cases), we can tentatively assign the *Z* stereochemistry to the major isomer of **11**.



(10) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 1219.

(11) The major isomer with the C_5 *tert*-butyl group trans to the methoxy group consistently had the lower field *tert*-butyl resonance and the higher field methoxy resonance.

Table III. Partial Mass Spectral Data for Selected Compounds in This Study[a]



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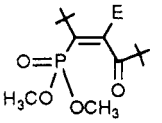
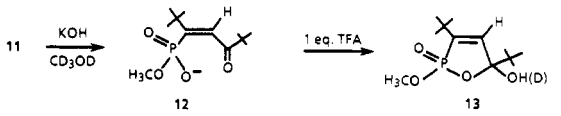


10, 22

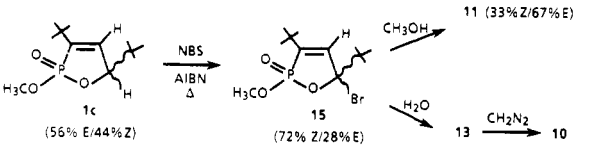
compound	MW	m/z (relative abundance, comment)
3 (E = H, R_3 = Br, Z = OH)	310/312	
7[b]	262	231 (3, M - OCH_3), 206 (12, M - C_4H_8), 205 (100, M - tBu), 191 (24), 109 (29), 81 (23), 57 (25)
8[b]	248	231.1119 [37, $C_{11}H_{20}PO_3$ (231.1151), M - OH], 215 (40), 149 (30), 133 (100)
10	276	277.1535 [87, $C_{13}H_{26}O_4P$ (277.1570), M + H], 261 (6), 233 (6), 220 (25), 219 (100, M - tBu), 191 (30), 109 (28)
11	276	276.1498 [21, $C_{13}H_{25}O_4P$ (276.1491), $M^{\cdot+}$], 244 (10, M - CH_3OH), 219 (100, M - tBu)
15	324/326	325.0591/327.0530 [0.3/0.3, $C_{12}H_{23}O_3PBr$ (325.0568/327.0548), M + H], 309/311 (0.7, M - CH_3), 245 (82, M - Br), 230 (53), 215 (74), 189 (31), 149 (100)
17	326/328	309/311 (1.7/1.7, M - OH), 283/285 (30/33), 270/272 (81/82, M - Sb), 191 (15), 161 (30), 127 (56), 57 (60), 41 (100)
1d (E = Br, Z = OH, R_3 = H)	310/312	311/313 (4.5/4.9, M + H), 254/256 (100/92.1, MH - tBu), 239/241 (65/65), 95 (12.6), 57 (45.4)
16 (E = R_3 = Br, Z = OH)[c]	388/390/392	310/317 (3.4/3.5, MH - Br), 309/311 (4.5/7.2, M - Br), 270/272 (30/28), 254/256 (100/99), 239/241 (82/70), 79/81 (28/25), 57 (85)
17 (E = Br, R_3 = Z = OH)	326/328	293/295 (2.4/2.1, MH - 20 H), 270/272 (100/92, MH - tBu), 255/257 (14,11), 191 (23), 161 (38), 127 (64), 57 (39)
18 (E = Br, R_3 = OCH_3, Z = OH)	340/342	341/343 (0.5/0.5, M + H), 309/311 (3.0/3.7, M - OCH_3), 293/285 (96/96, M - tBu), 269/271 (48/48), 254/256 (26/26), 239/241 (21/21), 161 (16), 99 (24), 57 (45)
1e (E = Br, R_3 = H, Z = OCH_3)	324/326	309/311 (1.7/1.3, M - CH_3), 268/270 (100/95, MH - tBu), 253/255 (71/88), 189 (12), 95 (24), 85 (61.5), 57 (67)
20 (E = Re = Br, Z = OCH_3)	402/404/406	346/348/350 (5.7/10.7/5.3, MH - tBu), 331/333/335 (6.5/12/5.5), 323/325 (57/52, M - Br), 267/269 (39/35), 187 (86), 148 (57), 91 (60), 57 (57)
21 (E = Br, Z = OCH_3, R_3 = OH)	340/342	323/325 (0.7/0.8, M - OH), 284/286 (19/20, MH - tBu), 167 (36), 149 (100), 57 (38)
22 (E = Br)	354/356	355/357 (10/10, M + H), 299/297 (100/93, M - 57), 191 (14), 135 (14), 109 (19), 93 (16)

[a] All spectra involved electron impact ionization. All peaks with related abundance ≥20% base, plus certain selected fragments are listed. [b] No molecular ion detected. [c] Some higher MW peaks omitted.

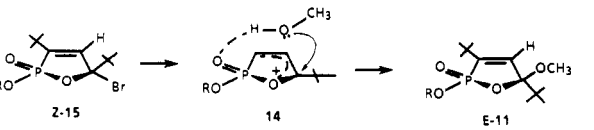
In stark contrast to the high solvolytic reactivity of **3**, and the somewhat lower reactivity of **7** and **8** in neutral or acidic media, ester **11** was *extremely* inert toward either methanolysis or hydrolysis under comparable conditions. Thus, **11** was completely stable (no methoxy exchange at either site, no hydrolysis, no ring opening) in CD_3OD, or in the presence of a 7.5-fold excess of TFA in either CD_3OD (15 h at 76 °C) or CD_3OD/D_2O (4/1 v/v, 23 h at 76 °C). However, **11** *did* react under *basic* conditions! Treatment with an 11-fold excess of KOH in CD_3OD for 23 h at 25 °C led to the formation of methanol and a compound identified as **12**, based on the similarity of its ^1H NMR spectrum with that of **10**. Careful neutralization with TFA caused an immediate change in the spectrum to give a compound identified as **13**, the methyl ester of **8**, as a single diastereomer (vide infra).



Because bromide **3** was so labile, it was of interest to determine if the corresponding ester, which lacks the acidic POH hydrogen, would be less reactive and more easily characterized. To this end, we prepared **1c**, the known[2] methyl ester of **1b**, as a 56% *E*/44% *Z* diastereomer mixture.[12] Treatment of **1c** with NBS led to a product (**15**) whose spectral data (Tables I–III) were very similar to those of **3**, except for the inclusion of a new methoxy *doublet*, and the fact that **15** was formed as a 72/28 diastereomer mixture. The major isomer could be tentatively assigned the *Z* label (methoxy cis to bromine) on the basis of ^1H chemical shifts.[11,12] Because the diastereomer ratio for **15** differed markedly from the ratio for starting material **1c**, we conclude that there is a three-to-one stereoselectivity for the bromine atom (from Br_2) to be delivered to intermediate **4** (with OCH_3 replacing OH) *cis* to the methoxy group.



Unfortunately, **15** proved to be only slightly less labile than **3**, showing that the acidic hydrogen in **3** has little effect on the high reactivity of the C_5 bromine. Thus, dissolution of **15** in methanol led immediately to a 2:1 *E*:*Z* mixture of **11**, which slowly epimerized to a 1:1 mixture. If our tentative stereochemical assignments for **11** and **15** are correct, this result requires methanolysis of **15** to occur with a preference for inversion of configuration at C_5. Such a preference suggests that the phosphoryl oxygen in intermediate **14** (R = CH_3) directs the incoming methanol (via hydrogen bonding) to attack the backside of the C–Br bond.



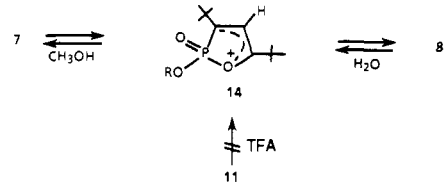
The fact that **11** formed from methanolysis of **15** *did* undergo slow epimerization (and presumably methoxy exchange) in methanol seemed to conflict with the earlier observation that **11** (prepared from **7**) was stable in methanol, even in the presence of TFA. However, the methanolysis of **15** releases 1 molar equiv of HBr, a much stronger acid than TFA. To confirm the ability of HBr to catalyze this reaction, a sample of **11** (prepared from **7**) in CD_3OD containing a 4.5-fold excess of HBr was found to undergo methoxy exchange with a half life of ca. 24 h at 76 °C.

Hydrolysis of **15** gave a compound whose ^1H spectrum was identical with that of **13**, again as a single stereoisomer. Although **13** could not be isolated in pure form, its spectral data leave no doubt as to its cyclic structure. Furthermore, as was found with **8**, hemiketal **13** reacted with diazo-

(12) Note that *Z*-**1c** has the same *relative* configuration as *E*-**11** because the C_5 hydrogen has been traded for a higher priority methoxy group.

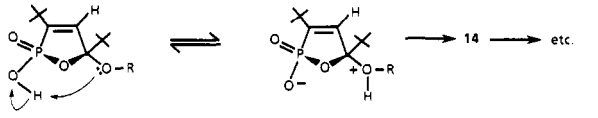
methane to give acyclic keto diester **10**.

We are left to account for the contrasting behavior of **7**, which is reactive under acidic conditions but stable in base, compared with **11** which shows the reverse pattern of reactivity. At first glance, it seems reasonable that the solvolysis of **3** to **7** or **8**, as well as the interconversion of **7** and **8**, should involve the formation of resonance-stabilized carbocation **14** (R = H). However, if phosphorus



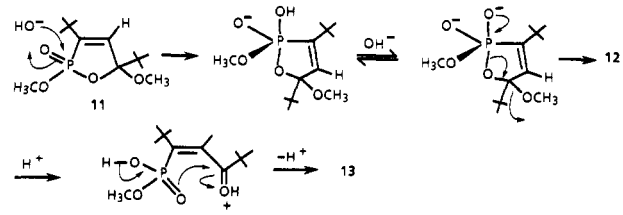
were to supply an empty d orbital to the cyclic array in **14**, the four π-electron cation would be antiaromatic. This, and the fact that bromide **15** seems to exhibit a preference for stereochemical inversion during methanolysis, suggests that perhaps **14** resists becoming planar at C_5.

By analogy with the conventional mechanism of ketal hydrolysis and transketalizations, we should expect that protonation of the leaving group (when it is a methoxy or hydroxy group, but not bromine) by a specific acid catalyst must precede formation of **14**. This would explain why the conjugate base of **7**, as well as ester **11**, do not undergo exchange, since there is no acid present to protonate the nucleofuge. But it seems inconsistent with the fact that TFA does not catalyze the exchange in **7** or **11**, while HBr does. One way to rationalize this fact is to suppose that protonation of the nucleofuge must occur by an *intramolecular* transfer of a POH hydrogen. Such a transfer would not be possible in the conjugate base of **7**, or in ester **11**, but *would* be possible in phosphonic acid **7**, and in **11** provided the P=O (in *E*-**11**) or POH (in *Z*-**11**) oxygens were first protonated. If this were true, TFA would not be expected to significantly catalyze the exchange in **7** or **11** because TFA is not a strong enough acid to protonate the phosphoryl oxygen.[13] The fact that **11** *does* epimerize in the presence of HBr is consistent with this proposal, since HBr (whose pK_a is -9[14]) *would* be strong enough to protonate the phosphoryl oxygen, followed by transfer of this proton to the nucleofuge.

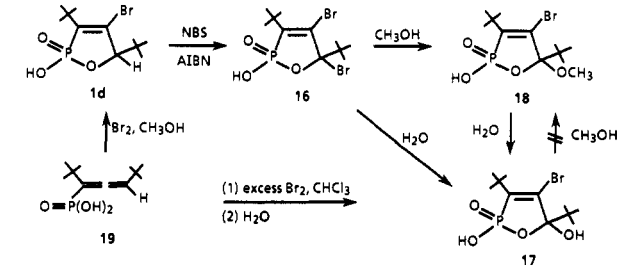


The ring opening of **11** by hydroxide is reminiscent of the behavior of other derivatives of **1**.[3] The mechanism undoubtedly involves nucleophilic attack at *phosphorus*, followed by ring opening and (presumably concerted) expulsion of the leaving group on C_5. But as soon as intermediate **12** is neutralized, it reverts to the more stable cyclic structure **13**. The conjugate base of **7** is resistant to such attack because the negatively charged exocyclic oxygen greatly reduces the electrophilicity of the phosphorus atom.

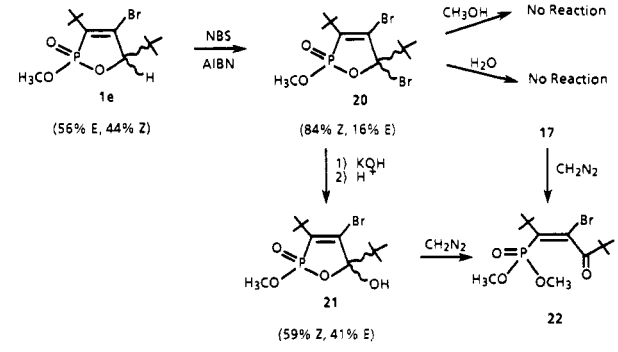
In order to gain further evidence for the generality of these NBS brominations, the reaction was extended to **1d**, the 4-bromo derivative **1b**,[15] as well as its methyl ester **1e**.[2] The reaction of **1d** with NBS gave labile bromide **16**, which



was characterized by ^1H and ^{13}C NMR analyses, and by its solvolysis products: hydrolysis to give hemiketal **17** and methanolysis to give ketal **18**. Interestingly, compound **17** proved to be identical to a previously unidentified product isolated in modest yield during the electrophilic cyclization of allenic phosphonic acid **19** to **1d**[15] with excess bromine in chloroform. By contrast to the facile interconversion of **7** and **8**, we found that although **18** could be readily hydrolyzed to **17**, the reverse reaction (methanolysis of **17**) did not occur even in boiling methanol.



Methyl ester **1e** (56% *E*/44% *Z*)[2] also underwent clean NBS bromination to give 5-bromo derivative **20** as an 84% *E*/16% *Z* diastereomer mixture. Thus, as was also true for the bromination of ester **1c**, the bromination of **1e** exhibits 5:1 stereoselectivity for substitution *Z* to the methoxy group. But the surprise came when attempting to solvolyze **20**. Unlike C_5 bromides **3**, **15**, and **16**, compound **20** proved to be completely inert toward water or methanol, even when heated. In fact, **20** was sufficiently stable to be purified by column chromatography. Only when **20** was treated with excess potassium hydroxide did the bromine undergo nucleophilic substitution to give hemiketal **21** (59% *Z*/41% *E*), undoubtedly by a ring-opening mechanism similar to that observed for **11** with base. Treatment of either **21** or **17** with excess diazomethane gave the same ketophosphonate (**22**), the bromo analogue of **10**.



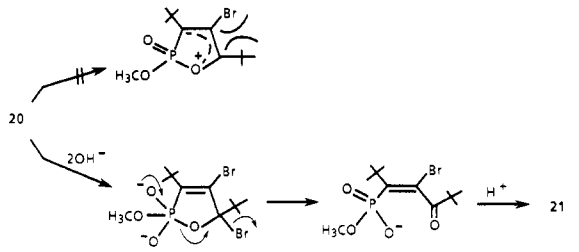
The reason that **20** is far less reactive than **15** is not clear. Part of the explanation may involve the ability of the C_4 bromine to sterically inhibit rehybridization at C_5, since that would bring the C_5 *tert*-butyl group into a cis relationship with the C_4 bromine. This factor might also explain the lessened reactivity of **17** compared to **8**. In

(13) The pK_a of protonated phosphoric acid is -7.43, while that of protonated trimethyl phosphate is -2.4: Stary, F. E., Ph.D. Dissertation, University of Cincinnati, 1969.

(14) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 220.

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

support of this supposition, the two methoxy groups in **22** are slightly nonequivalent in its ^1H spectrum (Table I), indicating that the molecule prefers a conformation where the carbonyl group (and the attached *tert*-butyl) are *not* in the same plane as the carbon–carbon double bond. However, it would seem this same effect of the C_4 bromine should also operate in **16**, yet **16** is essentially as reactive as **3**. Whatever the exact cause, the anomalously low reactivity of **20** seems to parallel that of **11** toward nucleophilic substitution at C_5. In both cases, the only available mechanism seems to be one involving nucleophilic attack at the phosphorus atom, subsequent ring opening, and ring closure upon neutralization.



To summarize, in 1,2-oxaphosphol-3-ene 2-oxides which lack other reactive hydrogens and conjugating groups, the C_5 allylic hydrogen undergoes facile substitution by bromine under free-radical conditions. The resulting tertiary allylic bromides are (with the exception of **20**) highly labile and readily solvolyzed to the corresponding oxaphospholene ketals or hemiketals. When Z (the phosphorus substituent) is OH, both ketal and hemiketal are readily interconverted in acidic or "neutral" media, but their conjugate bases do not undergo exchange. By contrast, ester **11** undergoes nucleophilic exchange only slowly in the presence of strong acid; in strongly basic solution, however, ring opening occurs, but the acyclic product recyclizes immediately upon neutralization.

Experimental Section

General. The following instruments were used in this work: IR spectra, Perkin-Elmer Models 700 and 599; ^1H NMR spectra, IBM NR-80 and Nicolet NT-300; ^{13}C NMR spectra, Nicolet NT-300 and Bruker AC 250; mass spectra, Hewlett-Packard HP-59995C GC/MS (for low resolution) and Kratos MS-80/D555 (for high resolution). Melting points were determined using an oil bath and are uncorrected. Elemental analyses were performed by Desert Analytics (samples were dried under vacuum before combustion). All spectral data are summarized in Tables I–III.

Reaction of 1b with NBS. Using oven-dried glassware, a suspension of 215.0 mg (0.927 mmol) of **1b**,[7] 176.7 mg (0.993 mmol) of recrystallized and vacuum-dried NBS, and 13.4 mg of azobisisobutyrylnitrile (AIBN) in 10.0 mL of molecular sieve dried carbon tetrachloride was degassed with dry nitrogen and then heated to 76 °C for 12.3 h. (The color of bromine developed after 4 min, rapidly disappeared, then reappeared, much like an oscillating reaction.) The resulting golden solution containing floating crystals of succinimide was filtered and rotary evaporated to 0.02 mm, leaving 313 mg (theoretical 288 mg) of crude 5-bromo-3,5-di-*tert*-butyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**3**) as a tacky semisolid. This product was contaminated with small amounts of **8** (see below), succinimide (δ 2.70), and another substance (δ 1.70) believed to be 2-bromo-2-cyanopropane (from the AIBN). Attempts to further purify **3** by recrystallization (from chloroform) or column chromatography gave impure product contaminated with increased amounts of **8**.

Reaction of 3 with Methanol. A 130-mg sample of crude **3** was dissolved in 3 mL of anhydrous methanol. The resulting solution was warmed to 50 °C and then rotary evaporated, leaving 129 mg of crude solid product. This material was redissolved in 0.60 mL of warm methanol, the solution was cooled, and 0.10 mL of water was added to barely cloud the solution. Slow evaporation of the methanol gave 46.6 mg (46% based on **1b**) of 5-methoxy-3,5-di-*tert*-butyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**7**) as fine colorless needles, mp 168–171 °C.[16] A second crop (13 mg, mp 165–168 °C) was collected and found to contain 6% **8** (by ^1H NMR). Recrystallization as above gave pure **7**.

Anal. Calcd for $C_{12}H_{23}O_4P$: C, 54.95; H, 8.84. Found: C, 55.01; H, 9.04.

When **3** was dissolved in CD_3OD and the ^1H NMR spectrum recorded with 3 min, **3** had been converted cleanly to **7** (with deuteriated methoxy group).

Hydrolysis of 3. A 173.6-mg sample of crude **3** was dissolved in 0.40 mL of hot acetone, to which was then added 0.25 mL of water. Cooling and slow evaporation left 90 mg of 3,5-di-*tert*-butyl-2,5-dihydroxy-1,2-oxaphosphol-3-ene 2-oxide (**8**). This material was recrystallized from acetone–acetonitrile (1/1 v/v) to give 90 mg (71% based on **1b**) of **8** as fine needles, mp 183.5–186.5 °C. Although this material was homogeneous by ^1H NMR, a second recrystallization gave mp 188–189 °C.[16]

Anal. Calcd for $C_{11}H_{21}O_4P$: C, 53.22; H, 8.53. Found: C, 53.46; H, 8.74.

Conversion of 7 to 8. A 5-mg sample of **7** was dissolved in 0.2 mL of acetone–water (4/1 v/v) and warmed to 90 °C for 2 min. Cooling and slow evaporation of the acetone gave 5 mg of **8**, mp 186–188 °C. The ^1H NMR spectrum of this material was superimposable on samples of **8** isolated directly from **3**. No remaining **7** was detected.

Conversion of 8 to 7. A 5-mg sample of **8** was dissolved in 0.2 mL of methanol and warmed to 90 °C for 2 min. After cooling, 1 drop of water was added. Slow evaporation of the methanol yielded 4 mg of **7** (mp 169–177 °C[16]) whose ^1H NMR spectrum was superimposable on that of samples of **7** prepared directly from **3**. No unconverted **8** was detected in the NMR spectrum of the material.

Methoxy Exchange in 7. A. In Otherwise Neutral Solution. A 13.5-mg sample of **7** was dissolved in 0.50 mL of CD_3OD, and its ^1H NMR spectrum was monitored as a function of time at a probe temperature of 35.5 °C. The methoxy signal at δ 3.21 decreased with time, while a signal for CH_3OD (δ 3.36) increased proportionately. The integrals of these two methoxy signals conformed to a first-order rate law, giving a linear fit with k = 0.076 ± 0.004 m^{-1}. All other signals in the spectrum were unchanged.

B. In the Presence of Added TFA. The above reaction was repeated with 16.1 mg (0.061 mmol) of **7** and 42.3 mg (0.37 mmol) of TFA in 0.50 mL of CD_3OD. Again, first-order methoxy group exchange was observed, this time with a slightly increased rate (k = 0.105 ± 0.005 m^{-1}).

C. In Basic Solution. A 13.5-mg (0.052-mmol) sample of **7** was dissolved in a solution of 41.3 mg (0.74 mmol) of KOH in 0.50 mL of CD_3OD. All carbon-bound proton resonances for the conjugate base of **7**, including the methoxy group, were shifted by less than 0.01 ppm compared to those of **7** in CD_3OD. Furthermore, these signals were unchanged after 15 h at 76 °C. To this solution was added 0.12 mL of D_2O. Again, there was no change in the spectrum of the solution after 20 h at 76 °C.

D. In the Presence of HBr. A 17-mg sample (0.06 mmol) of **11** was dissolved in 0.40 mL of CD_3OD, and 46 mg of 48% HBr (0.27 mmol) was added. The exchange of the C_5 methoxy group was followed by ^1H NMR. Exchange was 45% complete after 20 h at 76 °C.

Reaction of 8 with Diazomethane.[9] An 18.2-mg sample of **8** was suspended in 0.5 mL of $CDCl_3$ and treated dropwise with ethereal diazomethane until the pale yellow color persisted. Rotary evaporation, followed by evacuation to 0.1 mm at ambient temperature, left 20.8 mg (103%) of dimethyl (*Z*)-2,2,6,6-tetramethyl-3-oxo-hept-4-en-5-ylphosphonate (**10**) as an oil which could

(16) It is interesting that the first crop of **7** recrystallizes from *aqueous* methanol uncontaminated with **8**, even though the mother liquor contains **8** in proportion to the amount of water (see text). This demonstrates that **7** is less soluble in this medium, though **7** is more soluble than **8** in chloroform. The broad melting point of **7** was troubling, yet NMR and combustion analysis indicated high purity, with no detectable contamination by **8**. Subsequent recrystallization from a variety of solvents only broadened the melting point further, though the ^1H NMR spectrum remained unchanged. It is possible that varying amounts of hydrating water recrystallize with **7** and **8**.

be distilled (short path) at 0.015 mm and ca. 80 °C.

Reaction of 7 with Diazomethane.[9] An 11-mg sample of **7** was dissolved in 0.5 mL of $CDCl_3$ and treated dropwise with ethereal diazomethane until the yellow color persisted. Rotary evaporation and evacuation as above left 12 mg (100%) of 3,5-di-*tert*-butyl-2,5-dimethoxy-1,2-oxaphosphol-3-ene 2-oxide (**11**) as a colorless oil. ^1H NMR (Table I) indicated a 55/45 *Z*/*E* diastereomer mixture.

Methanolysis of 11. A. In Acidic Solution. A 10.4-mg (0.040-mmol) sample of **11** was dissolved in 0.40 mL of CD_3OD. TFA (34 mg, 0.30 mmol) was added, and the solution was heated to 76 °C for 15 h without change in its ^1H NMR spectrum. To the solution was added 0.10 mL of D_2O, and heating (76 °C) was resumed for 23 h. Again, no change was detected in the ^1H NMR spectrum of the solution.

B. In Basic Solution. An 11-mg (0.043-mmol) sample of **11** was dissolved in a solution of 26 mg (0.46 mmol) of KOH in 0.40 mL of CD_3OD. Over a period of 23 h at ambient temperature the signals for **11** were gradually and cleanly replaced by those attributed to ketophosphonate **12** (Table I). Neutralization of this solution with 50 mg (0.44 mmol) of TFA caused an immediate recyclization to **13** (Table I).

Reaction of 1c with NBS. Using oven-dried glassware, a suspension of 330 mg (1.30 mmol) of **1c**,[2] 260 mg (1.45 mmol) of recrystallized NBS, and 20 mg of AIBN in 3.0 mL of dry CCl_4 was degassed with dry nitrogen and then heated to 75 °C for 4.8 h. The resulting pale yellow solution, containing suspended succinimide, was cooled, filtered, and rotary evaporated, leaving 491 mg (theoretical 422 mg) of crude 5-bromo-3,5-di-*tert*-butyl-2-methoxy-1,2-oxaphosphol-3-ene 2-oxide (**15**) as a semisolid contaminated with a small amount of succinimide, 2-bromo-2-cyanopropane, and **13**. ^1H NMR (Table I) indicated a 72/28 *Z*/*E* diastereomer mixture. As with **3**, **15** proved to be impossible to purify rigorously.

Methanolysis of 15. A 220-mg sample of crude **15** was dissolved in 2 mL of anhydrous methanol and immediately rotary evaporated to give 204 mg (theoretical 189 mg) of a clear, colorless oil. The ^1H NMR spectrum was identical with that of **11** prepared by the diazomethane esterification of **7**, except that the diastereomer ratio was 67/33 *E*/*Z*. When a 51-mg sample of crude **15** was dissolved in CD_3OD, it was converted to the same mixture of **11** (with deuteriated C_5 methoxy group) within the time (3 min) required to obtain its ^1H NMR spectrum. After 4 h at 50 °C, the diastereomer ratio stabilized at 1:1.

Hydrolysis of 15. A 10-mg sample of crude **15** was dissolved in 0.50 mL of CD_3CN and 0.10 mL of D_2O. The ^1H NMR spectrum of the resulting solution was superimposable on that of **13**, except that (because of the different solvent) each line was shifted upfield by 0.04 ± 0.01 ppm.

Reaction of 1d with NBS. Following the procedure for bromination of **1b**, a mixture of 207.6 mg (0.667 mmol) of **1d**,[15] 121.5 mg (0.683 mmol) of NBS, and 22.5 mg of AIBN in 15 mL of CCl_4 was heated to 76 °C for 3 h. Careful filtration under nitrogen and then rotary evaporation left 322.8 mg (theoretical 260 mg) of crude 4,5-dibromo-3,5-di-*tert*-butyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**16**) as a labile white semisolid.

Hydrolysis of 16. The crude bromide from the above preparation was dissolved in 5 mL of acetone, and then 1 mL of water was added with swirling. Rotary evaporation of the pale yellow solution left a white solid which was recrystallized from acetone–acetonitrile (1/1 v/v) to give 127.4 mg (58% based on **1d**) of 4-bromo-3,5-di-*tert*-butyl-2,5-dihydroxy-1,2-oxaphosphol-3-ene 2-oxide (**17**), mp 227-230 °C. Combustion analysis indicated 0.5 mol of hydrating water.[16]

Anal. Calcd for $C_{11}H_{20}O_4PBr{\cdot}0.5H_2O$: C, 39.30; H, 6.25. Found: C, 39.29; H, 6.55.

Methanolysis of 16. Another sample of **16** was prepared from 96.9 mg (0.311 mmol) of **1d**, 60.0 mg (0.333 mmol) of NBS, and 15.7 mg of AIBN. The crude product was dissolved in 5 mL of methanol and heated to 55 °C for 20 min. After rotary evaporation, the crude oil was dissolved in $CHCl_3$, washed with water, and dried over $MgSO_4$. Exhaustive rotary evaporation (0.05 mm for 1 h) left 84.8 mg (79.8% based on **1d**) of 4-bromo-5-methoxy-3,5-di-*tert*-butyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**18**) as a dark oil, which could not be crystallized.

Reaction of 1e with NBS. Following the procedure for bromination of **1b**, a mixture of 183.8 mg (0.565 mmol) of **1e**,[2] 110.4 mg (0.613 mmol) of NBS, and 14.3 mg of AIBN in 10 mL of CCl_4 was heated to 76 °C for 2.5 h. Careful filtration under nitrogen and then rotary evaporation and column chromatography through silica gel (eluting with 20/1 $CHCl_3$/EtOAc) left 229.1 mg (96% based on **1e**) of crude 4,5-dibromo-3,5-di-*tert*-butyl-2-methoxy-1,2-oxaphosphol-3-ene 2-oxide (**20**) as a yellow oil comprised of an 84% *Z* and 16% *E* diastereomer mixture. This product was totally inert toward water or methanol, even when heated.

Reaction of 20 with KOH. A 110.3-mg (0.273-mmol) sample of **20** was dissolved in 3 mL of acetone, followed by 2 mL of water. The solution was heated to evaporate the acetone, and 2 mL of methanol was added to clarify the solution. KOH (5 mg) was added, and the mixture was warmed to dissolve the base. After cooling the solution, 2 drops of TFA was added. Pale yellow crystals were collected and recrystallized from 1/1 CH_3CN/acetone, yielding 24.3 mg (25.9%) of 4-bromo-3,5-di-*tert*-butyl-5-hydroxy-2-methoxy-1,2-oxaphosphol-3-ene 2-oxide (**21**) as colorless crystals, mp 168–171 °C. NMR (Tables I and II) indicated a 59% *Z*, 41% *E* diastereomer mixture. Further recrystallization afforded the pure *E* isomer, mp 175–176 °C.

Anal. Calcd for $C_{12}H_{22}O_4PBr$: C, 42.23; H, 6.45. Found: C, 41.74; H, 6.55.

Reaction of 21 with Diazomethane. To a 20-mg sample of **21** in 0.5 mL of methanol was added ethereal diazomethane until the color persisted. Rotary evaporation left diester **22** in quantitative yield as a pale yellow oil.

Reaction of 17 with Diazomethane. A 21-mg sample of **17** was dissolved in 1 mL of methanol and treated with ethereal diazomethane as above. Rotary evaporation left an oil identical with the product from esterification of **21**.