Cycloaddition Reactions of Phosphate Dienes

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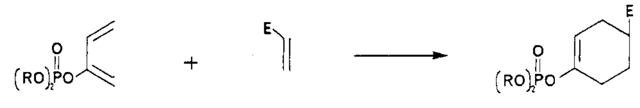
A series of phosphate dienes has been prepared and tested in 4 + 2 cycloaddition reactions with representative dienophiles such as maleic anhydride and cyclohexenone. The most reactive diene in this series, bis(2,6-dimethoxyphenyl) 1-methylene-2-propenyl phosphate (14), displays a reactivity and regioselectivity comparable to the analogous (trimethylsilyl)oxy diene in its reactions with these dienophiles. However, phosphate dienes may offer distinct advantages in a synthetic sequence, especially when coupled with the methodology recently developed for preparing β-keto phosphonates from cyclic vinyl phosphates.

We recently introduced a new and general route to cyclic β-keto phosphonates, which is based upon a 1,3-phosphorus migration in a vinyl phosphate anion.[2,3] The vinyl phosphates required for this reaction are generally available through enolate chemistry.[3] However, as our studies in this area have matured, new methods of vinyl phosphate formation have become of interest, with a premium placed upon syntheses which might allow regiospecific formation of the vinyl phosphate. For synthesis of vinyl phosphates within six-membered rings, the Diels–Alder reaction of phosphate dienes would appear to be an obvious approach (Scheme I).

Scheme I



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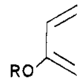
The literature contains occasional reports of phosphate dienes (e.g., 1)[4] as the diene component in a Diels–Alder reaction and isolated examples of vinyl phosphates serving as dienophiles,[5] but phosphate dienes are little used in comparison to other heterosubstituted butadienes.[6] Indeed, there is a rationale to support the view that the Diels–Alder reactions of phosphate dienes would be characterized by low reactivity and poor regioselectivity. For standard cycloadditions, that is those with electron-deficient dienophiles, diene components of high electron density would be preferred. Both enol ethers such as 2 and siloxy dienes such as 3 will partake in the Diels–Alder reaction,[6] but the siloxy dienes often are preferred because of their superior regioselectivity and the greater synthetic versatility of the products.[6,7] In comparison to the R_3Si group, the $(RO)_2P(O)$ group can be viewed as electron withdrawing and therefore deactivating. The available experimental evidence appears to support this rationale, for the cycloaddition of methyl vinyl ketone with diethyl 1-methylene-2-propenyl phosphate affords a 2:1 mixture of regioisomeric cycloadducts.[4a] Nevertheless, because of the promise inherent in a cycloaddition approach to cyclic vinyl phosphates, we resolved to explore further the cycloadditions of phosphate dienes.



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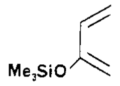
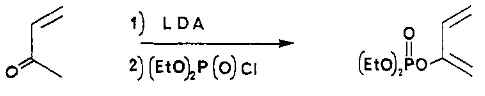


3

The diene phosphate 5 was readily prepared[4a] by treatment of methyl vinyl ketone (4) with LDA and diethyl phosphorochloridate, but the cycloadditions attempted with this diene were discouraging. While diene 5 does undergo cycloaddition with maleic anhydride (6) in good yield (Table I), complete reaction with this very reactive dienophile required 20 h at room temperature. Furthermore, with less reactive dienophiles such as cyclohexenone, attempted reaction gave only unreacted starting materials, even at reflux in toluene in the presence of $AlCl_3$.[8]



4 5

Modifications at phosphorus which temper an electron-withdrawing effect might be expected to enhance diene reactivity. Accordingly, the thiophosphate diene 8 was prepared from methyl vinyl ketone and the commercially available di-*n*-propyl thiophosphorochloridate. This diene appeared to be somewhat more reactive, for complete reaction with maleic anhydride was obtained within 12 h at room temperature. However, the less reactive dienophile cyclohexenone failed to react with this diene, even upon extended reflux in xylene or in sealed tube reactions at 200 °C.

Because these results suggested that it was possible to enhance diene reactivity through modification of the phosphorus substituents, a series of dienes was prepared with the objective of obtaining a phosphate diene at least as reactive as the siloxy diene 3. Reaction of methyl vinyl ketone enolate with the commercially available diphenyl phosphorochloridate gave the phosphate diene 10. Bis(2,6-dimethylphenyl) phosphorochloridate and bis(2,6-dimethoxyphenyl) phosphorochloridate were prepared from $P(O)Cl_3$ and the respective phenols. Reactions of

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[1] Fellow of the Alfred P. Sloan Foundation, 1985–1989.

[2] Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, 4265.

[3] Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185.

[4] (a) For a previous study of diethyl 1-methylene-2-propenyl phosphate, see: Kienzle, F.; Rosen, P. *Helv. Chim. Acta* **1979**, *62*, 442. (b) For cycloadditions of diethyl 1-methylene-2-butenyl phosphate, cf.: Liu, H. J.; Ngooi, T. K. *Can J. Chem.* **1984**, *62*, 2676. Liu, H. J.; Feng, W. M. *Synth. Commun.* **1986**, *16*, 1485.

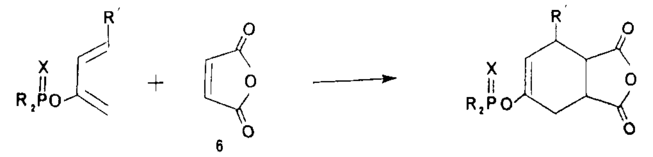
[5] Lichtenthaler, F. U. *Chem. Rev.* **1961**, *61*, 607.

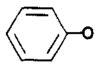
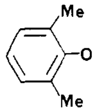
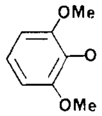
[6] Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.-P. *Natural Products Synthesis Through Pericyclic Reactions*; ACS Monograph 180; American Chemical Society: Washington, DC, 1983; Chapter 5.

[7] Jung, M. E.; McCombs, C. A. *Tetrahedron Lett.* **1976**, 2935.

[8] Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056. Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642 and references cited therein.

Table I. Cycloadditions of Phosphate Dienes with Maleic Anhydride

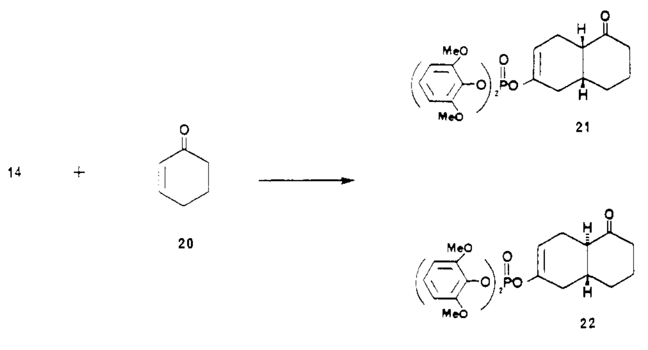


diene	R	X	R'	product	time	% yield
5	EtO	O	H	7	20 h	89
8	n-PrO	S	H	9	12 h	90
10		O	H	11	16 h	90
12		O	H	13	10 h	92
14		O	H	15	1 h	95
16	Me_2N	O	H	17	5 h	89
18	EtO	O	OMe	19	10 min	89

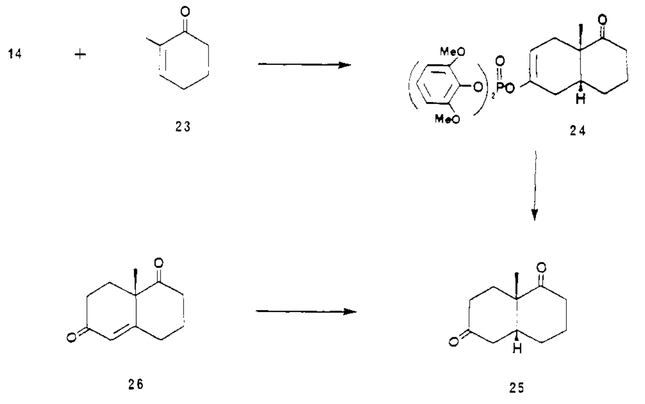
these phosphorochloridates with methyl vinyl ketone enolate gave the diene phosphates 12 and 14. However, the bis(2,6-dimethoxyphenyl) phosphorochloridate reacted slowly with this enolate, and gave the desired product in modest yield. Phosphate diene 14 was prepared more readily by reaction of the methyl vinyl ketone enolate with $P(O)Cl_3$ followed by treatment of the resulting dichloride with 2,6-dimethoxyphenoxide. The diene phosphorodiamidate 16 was prepared from commercially available tetramethylphosphorodiamidic chloride.

To gauge the effect of these modifications upon diene reactivity, cycloadditions were attempted with maleic anhydride under standard conditions. The results of this set of experiments (Table I) suggested that diene 14 was the most reactive of these six dienes. Therefore, cycloadditions of diene 14 and relatively weak dienophiles, such as cyclohexenone and 2-methylcyclohexenone, were explored in some detail.

When diene 14 and cyclohexenone (20) were heated at reflux in toluene, only traces of a cycloaddition product could be detected. However, addition of $AlCl_3$[8] to the reaction mixture resulted in a substantial increase of the cycloadduct. Thus, in the presence of this Lewis acid catalyst, diene 14 underwent cycloaddition with cyclohexenone to afford octalone 22 in approximately 40% isolated yield, following purification by column chromatography. Based on the literature precedent for octalone isomerization,[9] occasional observation of an isomeric cycloadduct, and our results with 2-methylcyclohexenone (vide infra), it was assumed that the initial cycloadduct 21 undergoes isomerization to the more stable *trans*-octalone under the reaction conditions.



With 2-methylcyclohexenone (23), cycloaddition with diene 14 gave a single product, again in approximately 40% isolated yield after column chromatography. In this case, the regiochemistry of the cycloadduct 24 was established by hydrolysis of this vinyl phosphate to the parent dione 25, and comparison with an authentic sample prepared by reduction of Wieland–Miescher ketone (26).[10]



Intuitively, it may appear that the phosphate group of a phosphate diene is more strongly electron withdrawing than the silyloxy group of a silyloxy diene, and thus phosphate dienes would be less reactive in cycloadditions of normal electron demand. However, such effects must be transmitted through the σ bond system with the intervening oxygen attenuating their impact, and changes in the phosphate esters also can affect the electronic characteristics of the molecule. In fact, the results of a number of competition experiments suggest that the phosphate diene 14 is at least comparable in reactivity to the analogous siloxy diene 3.[7] When an equimolar mixture of dienes 14 and 3 is treated with 1 equiv of maleic anhydride, the enol phosphate 15 is observed as a major product. When an equimolar mixture of dienes 14 and 3

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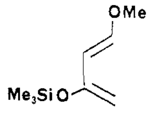
(9) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802.

(10) Bauduin, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225. Swaminathan, S.; Newman, M. S. *Tetrahedron* **1958**, *2*, 88.

is treated with 1 equiv of cyclohexenone (in toluene at reflux in the presence of $AlCl_3$), only the enol phosphate cycloadducts **21** and **22** are observed, although it is probable that the siloxy diene decomposes under these conditions.[11]

The role of the Lewis acid catalyst in phosphate diene cycloadditions is not yet completely clear. In other Lewis acid catalyzed cycloadditions, it is assumed that the Lewis acid complexes with the dienophile to enhance its reactivity. However, upon addition of phosphate diene **14** to a solution of 2-methylcyclohexenone and $AlCl_3$ in toluene, the ^{27}Al resonance shifts from 95.2 to 90.4 ppm. The same shift (90.4 ppm) is observed upon addition of $AlCl_3$ to a solution of diene **14** in toluene. These observations suggest that there is a strong association between the phosphoryl oxygen and the Lewis acid.[12]

Undoubtedly, the frequent use[13] of the methoxy siloxy diene **27** has been a major factor in establishing general perceptions of siloxy diene reactivity, but the impact of the methoxy substituent greatly outweighs the effect of silicon on the reactivity of this diene. Danishefsky's many elegant applications of diene **27**[13] and related compounds[14] prompted us to prepare the analogous phosphate diene **18** (Table I). As might be expected, substitution of a methoxy group directly on the diene framework dramatically enhances the reactivity of this phosphate diene. Complete reaction of diene **28** with maleic anhydride is found within 10 min at room temperature, despite the use of the diethyl phosphate ester.



27

In conclusion, it is clear that cycloaddition reactions of phosphate dienes can be used to prepare cyclic vinyl phosphates, although with relatively poor dienophiles such as cyclohexenone a Lewis acid catalyst may be desirable. These initial studies of substituent effects upon phosphate diene reactivity have resulted in phosphate dienes with reactivity and regioselectivity comparable to siloxy dienes, and further modifications of the substituents on phosphorus might be expected to yield even more reactive dienes. While additional studies of this reaction and the mechanism of catalysis would be in order, it is already clear that phosphate dienes may offer distinct advantages in a synthetic sequence, especially when coupled with the rearrangement of cyclic vinyl phosphates to β-keto phosphonates which we have developed.[2,3]

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Flash column chromatography was done on Merck grade 60 silica gel (230–400 mesh), while radial chromatography was done with a Chromatotron apparatus using Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. NMR spectra (^1H, ^{13}C, and ^{31}P) were recorded on either a JEOL FX-90Q or a Brucker WM-360 spectrometer, using deuteriochloroform as the solvent. The ^1H and ^{13}C chemical shifts are reported in parts per million downfield from $(CH_3)_4Si$, while the ^{31}P chemical shifts are reported in parts per million relative to H_3PO_4 (external standard). The ^{27}Al NMR spectra were recorded on a Bruker WM-360 spectrometer, using toluene as solvent. Shifts are reported in ppm downfield from $Al(NO_3)_3$ (external standard). Low-resolution electron impact (EI) mass spectra were recorded with a Hewlett-Packard 5985B instrument operating at 70 eV; only selected ions are reported here. High-resolution mass spectra were recorded on a Kratos MS-50 instrument at the Midwest Center for Mass Spectrometry or on a VG Instruments ZAB-HF spectrometer at the University of Iowa Mass Spectrometry Facility. Microanalyses were conducted by Desert Analytics, Tucson, AZ.

Diethyl *cis*-1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-5-isobenzofuranyl Phosphate (7) (General Procedure for Cycloadditions with Maleic Anhydride). To diene **5** (412 mg, 2 mmol)[4a,12] was added maleic anhydride (98 mg, 1 mmol), and the resulting mixture was stirred at ambient temperature. After 20 h, analysis by GC indicated that the reaction was complete. Purification of the reaction mixture by column chromatography (silica gel, 72% hexane, 28% EtOAc) gave the Diels–Alder adduct **7**[4a] (270 mg, 89%): ^1H NMR δ 5.64–5.61 (m, 1), 4.19–4.10 (m, 4), 3.58–3.52 (m, 1), 3.41–3.35 (m, 1), 2.74–2.44 (m, 4), 1.37–1.33 (m, 6); ^{31}P NMR −6.9; EIMS, m/z (relative intensity) 304 (M^+, 2), 232 (11), 231 (40), 203 (50), 175 (100), 127 (8), 109 (9), 99 (25), 81 (19), 77 (15); HRMS, calcd for $C_{12}H_{17}O_7P$ 304.0712, found 304.0702.

Di-*n*-propyl 1-Methylene-2-propenyl Thiophosphate (8). The anion of methyl vinyl ketone (1.67 mL, 20 mmol) was generated by treatment of the ketone with LDA (2 equiv, in 30 mL THF) at −78 °C. A mixture of di-*n*-propyl thiophosphorochloridate (4.8 mL, 24 mmol) and anhydrous triethylamine (5.6 mL, 40 mmol) was added to the enolate at −40 °C, and the resulting solution was allowed to warm to room temperature and then heated at reflux overnight. The reaction was quenched by addition of CH_3COOH (1 M in ether), and the resulting mixture was filtered through a Florisil pad. After concentration in vacuo, the residue was purified by flash column chromatography (silica gel, 95% hexane, 5% EtOAc) to give compound **8** (2.25 g, 45%): ^1H NMR δ 6.18 (ddd, 1, J_{HP} = 1.2 Hz, J = 16.6, 10.8 Hz), 5.56 (d, 1, J = 16.6 Hz), 5.20 (d, 1, J = 10.8 Hz), 5.05 (s, 1), 4.80 (s, 1), 4.12–3.97 (m, 4), 1.77–1.65 (m, 4), 0.99–0.86 (m, 6); ^{31}P NMR +62.5; EIMS; m/z (relative intensity) 250 (17), 208 (12), 167 (29), 166 (100), 133 (19), 115 (37), 114 (18), 102 (13), 97 (10), 85 (15); HRMS, calcd for $C_{10}H_{19}O_3PS$ 250.0794, found 250.0817.

Di-*n*-propyl *cis*-1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-5-isobenzofuranyl Thiophosphate (9). When the diene **8** (128 mg, 0.5 mmol) and maleic anhydride (25 mg, 0.25 mmol) were allowed to react according to the general procedure, complete reaction was obtained after 12 h. Purification of the crude product by column chromatography (silica gel, 86% hexane, 14% EtOAc) yielded adduct **9** (78 mg, 90%): ^1H NMR δ 5.64–5.57 (br s, 1), 4.10–4.00 (m, 4), 3.60–3.50 (m, 1), 3.43–3.34 (m, 1), 2.76–2.63 (m, 3), 2.56–2.41 (m, 1), 1.78–1.65 (m, 4), 1.04–0.93 (m, 6); ^{31}P NMR +62.5; ^{13}C NMR 173.3, 173.0, 146.5 (d, J_{CP} = 8.9 Hz), 109.5 (d, J_{CP} = 5.2 Hz), 70.4 (d, J_{CP} = 7.1 Hz), 40.0, 38.6, 26.7 (d, J_{CP} = 4.7 Hz), 23.3 (d, J_{CP} = 7.5 Hz), 23.0, 10.0; EIMS, m/z (relative intensity) 348 (M^+, 2), 265 (7), 237 (12), 192 (12), 191 (100), 173 (7), 139 (11), 123 (10), 114 (14), 95 (12); HRMS, calcd for $C_{14}H_{21}O_6PS$ 348.0797, found 348.0805.

Diphenyl 1-Methylene-2-propenyl Phosphate (10). To a solution of LDA (1.1 equiv, in 100 mL of THF) at −78 °C was added methyl vinyl ketone (1.25 mL, 15 mmol), and the resulting solution was stirred for 30 min. When the solution reached −50 °C, diphenyl phosphorochloridate (3.32 mL, 16 mmol) was added. After 2.25 h the reaction was quenched by addition of saturated NH_4Cl, and the aqueous layer was extracted with ether. After evaporation of the solvent in vacuo, the remaining oil (6.045 g) was purified by column chromatography (silica gel, 57% hexane, 43% EtOAc) to afford diene **10** (3.42 g, 75%): ^1H NMR δ 7.34–7.21 (m, 10), 6.16 (ddd, 1, J = 17.0, 10.9 Hz, J_{HP} = 2.9 Hz), 5.43 (d, 1, J = 17.0 Hz), 5.19–5.17 (m, 1), 5.15 (d, 1, J = 10.9 Hz), 4.84–4.82 (m, 1); ^{31}P NMR −17.9; ^{13}C NMR 150.3 (d, J_{CP} = 7.9 Hz), 130.4

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[11] Belanger, J.; Landry, N. L.; Pare, J. R.; Jankowski, K. *J. Org. Chem.* **1982**, *47*, 3649. In a control experiment where cyclohexenone, siloxy diene **3**, and $AlCl_3$ were heated in toluene, no cycloadduct was observed.

[12] Calogeropoulou, T. PhD Thesis, University of Iowa, 1987.

[13] Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

[14] Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060. Danishefsky, S.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862. Danishefsky, S. J.; Selnick, H. G.; DeNinno, M. P.; Zelle, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1572.

(d, J_{CP} = 7.2 Hz), 129.60, 129.55 (d, J_{CP} = 7.4 Hz), 125.4, 119.9 (d, J_{CP} = 5.3 Hz), 116.5, 102.0 (d, J_{CP} = 4.0 Hz); EIMS, *m/z* (relative intensity) 302 (M^+, 28), 251 (18), 170 (19), 146 (17), 128 (100), 118 (20), 94 (88), 77 (48), 65 (34), 55 (58); HRMS, calcd for $C_{16}H_{15}O_4P$ 302.0709, found 302.0697.

Diphenyl *cis*-1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-5-isobenzofuranyl Phosphate (11). Compound **10** (604 mg, 2.0 mmol) was treated with maleic anhydride (98 mg, 1.0 mmol) according to the general procedure. The reaction was complete after 16 h, and pure compound **11** was obtained (360 mg, 90%) after column chromatography (silica gel, 75% hexane, 25% EtOAc): ^{1}H NMR δ 7.34–7.10 (m, 10), 5.58 (br s, 1), 3.12–3.03 (m, 2), 2.8–2.4 (m, 4); ^{31}P NMR –17.9; ^{13}C NMR 178.1, 177.7, 150.32 (d, J_{CP} = 7.4 Hz), 150.30 (d, J_{CP} = 7.2 Hz), 145.6 (d, J_{CP} = 9.1 Hz), 129.8, 125.5, 120.0 (d, J_{CP} = 4.7 Hz), 110.0 (d, J_{CP} = 4.9 Hz), 39.8, 38.6, 27.7, 24.0; EIMS, *m/z* (relative intensity) 400 (M^+, 16), 328 (28), 327 (100), 251 (9), 152 (10), 94 (22), 78 (10), 77 (40), 65 (16), 51 (10); HRMS, calcd for $C_{20}H_{17}O_7P$ 400.0712, found 400.0712.

Bis(2,6-dimethylphenyl) 1-Methylene-2-propenyl Phosphate (12). After treatment of methyl vinyl ketone (1.25 mL, 15 mmol) with LDA (1.1 equiv, in 40 mL of THF) at –78 °C to obtain the enolate, a solution of bis(2,6-dimethylphenyl) phosphorochloridate (5.35 g, 16.5 mmol, in 40 mL of THF) was added, and the reaction mixture was allowed to warm to room temperature over 2.5 h. Addition of saturated NH_4Cl, followed by extraction with ether and concentration in vacuo, gave the crude product. Purification by column chromatography (silica gel, 75% hexane, 25% EtOAc) afforded pure compound **12** (2.57 g, 48%): ^{1}H NMR δ 7.02–6.96 (m, 10), 6.13 (ddd, 1, J_{HP} = 3.0 Hz, J = 17.0, 10.8 Hz), 5.39 (d, 1, J = 17.1 Hz), 5.11 (d, 1, J = 10.9 Hz), 5.08–5.06 (m, 1), 4.74–4.73 (m, 1), 2.345 (s, 6), 2.343 (s, 6); ^{31}P NMR –17.3; ^{13}C NMR 151.4 (d, J_{CP} = 7.8 Hz), 148.2 (d, J_{CP} = 7.2 Hz), 130.9 (d, J_{CP} = 6.8 Hz), 130.3 (d, J_{CP} = 3.9 Hz), 125.4, 120.0, 116.3, 102.0 (d, J_{CP} = 2.8 Hz), 17.0; EIMS, *m/z* (relative intensity) 358 (M^+, 8), 237 (6), 201 (26), 192 (14), 157 (64), 156 (100), 141 (41), 121 (33), 103 (33), 91 (41), 77 (46), 53 (23). HRMS, calcd for $C_{19}H_{20}O_4P$ ($M^+ - CH_3$) 343.1100, found 343.1122.

Bis(2,6-dimethoxyphenyl) Phosphorochloridate. 2,6-Dimethoxyphenol (13.77 g, 0.089 mol) was added to anhydrous benzene (50 mL), and the resulting solution was heated to reflux. To the hot reaction mixture was added phosphorus oxychloride (4.15 mL, 0.45 mol) followed by dropwise addition of pyridine (10 mL). A white precipitate was formed upon the dropwise addition of pyridine. The resulting mixture was heated at reflux for 3 days, until complete reaction was indicated by GC and ^{31}P NMR analyses. Filtration, followed by concentration of the filtrate in vacuo, afforded a viscous oil, which upon addition of diethyl ether became a white solid (14.50 g, 77%): ^{1}H NMR δ 7.09 (t, 2, J = 7.7 Hz), 6.57 (d, 4, J = 8.4 Hz), 3.8 (s, 12); ^{31}P NMR –1.9.

Bis(2,6-dimethoxyphenyl) 1-Methylene-2-propenyl Phosphate (14). (Procedure I). To the enolate of methyl vinyl ketone, formed by addition of methyl vinyl ketone (0.62 mL, 7.5 mmol) to LDA (1.1 equiv, in 40 mL of THF) at –78 °C, was added a solution of bis(2,6-dimethoxyphenyl) phosphorochloridate (3.89 g, 10 mmol, in 10 mL of THF) at –50 °C. The resulting solution was stirred 4 h and then was quenched by addition of saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. After the combined organic extracts were dried over $MgSO_4$, evaporation of the solvent in vacuo and purification of the resulting oil by column chromatography (silica gel, hexane 50%, EtOAc 50%) yielded diene **14** (778 mg, 25%): mp 68–69 °C; ^{1}H NMR δ 7.011 (t, 1, J = 8.4 Hz), 7.008 (t, 1, J = 8.3 Hz), 6.53 (d, 2, J = 8.4 Hz), 6.18 (ddd, 1, J_{HP} = 3.8 Hz, J = 17.0, 10.8 Hz), 5.62 (d, 1, J = 16.9 Hz), 5.45 (br s, 1), 5.15 (d, 1, J = 10.7 Hz), 4.76 (br s, 1), 3.72 (s, 12); ^{31}P NMR –16.7; ^{13}C NMR 152.2 (d, J_{CP} = 4.2 Hz), 151.4 (d, J_{CP} = 8.6 Hz), 131.1 (d, J_{CP} = 8.7 Hz), 129.8 (d, J_{CP} = 8.4 Hz), 124.9, 115.6, 105.0, 100.6 (d, J_{CP} = 2.7 Hz), 56.0; EIMS, *m/z* (relative intensity) 391 (M^+ – OMe, 0.1), 353 (1), 269 (1), 217 (16), 206 (20), 202 (19), 187 (6), 152 (11), 151 (100), 110 (19), 95 (33), 83 (25). Anal. Calcd for $C_{20}H_{23}O_8P$: C, 56.87; H, 5.49. Found: C, 56.89; H, 5.57.

Bis(2,6-dimethoxyphenyl) 1-Methylene-2-propenyl Phosphate (14) (Procedure II). Methyl vinyl ketone (1.54 mL, 0.020 mol) was added to an LDA solution (1.0 equiv, in 25 mL of THF) at –78 °C, and the resulting reaction mixture was stirred for 0.5 h. After dropwise addition of this anion (using a jacketed addition funnel) to a solution of phosphorus oxychloride (1.99 mL, 0.021 mol) in THF (5 mL) at –40 °C, the resulting mixture was stirred for an additional hour at the same temperature. A slurry of 2,6-dimethoxyphenoxide [prepared from 2,6-dimethoxyphenol (7.38 g, 0.048 mol) and NaH (1.44 g, 80% dispersion, 0.040 mmol)] in THF (50 mL) was added. The reaction mixture was stirred for 24 h at ambient temperature. After filtration, to remove a white precipitate, the filtrate was concentrated in vacuo to afford a viscous oil. Purification by column chromatography (silica gel, hexane 80%, EtOAc 20%) afforded diene **14** (3.95 g, 48%), identical with material prepared earlier.

Bis(2,6-dimethylphenyl) *cis*-1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-5-isobenzofuranyl Phosphate (13). Compound **12** (268 mg, 0.75 mmol) and maleic anhydride (38 mg, 0.38 mmol) were allowed to react according to the general procedure. GC analysis revealed the complete reaction after 10 h. Purification of the crude product by column chromatography (silica gel, 86% $CHCl_3$, 14% EtOAc) gave pure compound **16** (159 mg, 92%): ^{1}H NMR δ 6.98–6.97 (m, 6), 5.38 (br s, 1), 3.09–2.89 (m, 2), 2.73–2.27 (m, 4), 2.30 (s, 12); ^{31}P NMR –17.2; ^{13}C NMR 178.0, 177.6, 148.0 (d, J_{CP} = 8.9 Hz), 145.8 (d, J_{CP} = 10.2 Hz), 130.3, 129.1, 125.4, 109.5, 39.8, 38.7, 27.7 (d, J_{CP} = 5.0 Hz), 23.9, 17.0; EIMS, *m/z* (relative intensity) 456 (M^+, 23), 383 (88), 277 (23), 201 (52), 193 (36), 181 (46), 121 (40), 105 (70), 91 (83), 77 (100); HRMS, calcd for $C_{24}H_{25}O_7P$ 456.1339, found 456.1362.

Bis(2,6-dimethoxyphenyl) *cis*-1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-5-isobenzofuranyl Phosphate (15). To a suspension of diene **14** (211 mg, 0.5 mmol) in 1 mL anhydrous toluene was added maleic anhydride (24 mg, 0.25 mmol) at room temperature. The reaction mixture became clear upon the addition of maleic anhydride. The resulting solution was stirred at ambient temperature for 1 h. Evaporation of the solvent in vacuo, followed by column chromatography (silica gel, 50% hexane, 50% EtOAc) on the residue, afforded cycloadduct **15** (124 mg, 95%): ^{1}H NMR δ 7.00 (t, 2, J = 8.4 Hz), 6.52 (d, 4, J = 8.4 Hz), 5.66 (br s, 1), 3.71 (s, 12), 3.07–3.05 (m, 2), 2.86–2.82 (m, 1), 2.66–2.34 (m, 2), 2.43–2.39 (m, 1); ^{31}P NMR –16.9; ^{13}C NMR 178.0, 177.9, 152.2 (d, J_{CP} = 3.9 Hz), 146.0 (d, J_{CP} = 10.1 Hz), 125.2, 108.9 (d, J_{CP} = 5.8 Hz), 105.2, 56.2, 40.0, 38.8, 27.5 (d, J_{CP} = 7.9 Hz), 24.2; EIMS, *m/z* (relative intensity) 520 (M^+, 14), 447 (14), 353 (66), 304 (100), 279 (52), 276 (23), 217 (83), 202 (52), 154 (43), 153 (43), 110 (45), 107 (44), 79 (32); HRMS, calcd for $C_{24}H_{25}O_{11}P$ 520.1135, found 520.1116.

1-Methylene-2-propenyl Tetramethylphosphorodiamidate (16). The mixture resulting from addition of methyl vinyl ketone (1.24 mL, 15 mmol) to LDA (1.1 equiv, in 40 mL of THF at –78 °C) was stirred for 35 min prior to the addition of tetramethylphosphorodiamide chloride (10.86 mL, 75 mmol) in TMEDA (10 mL) at –50 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature and then heated at reflux overnight. The reaction was quenched by addition of water and then extracted with EtOAc (3 × 25 mL). After concentration of the combined organic extracts in vacuo, the crude oil was purified by column chromatography (silica gel, 89% $CHCl_3$, 11% EtOAc) to afford diene **16** (2.73 g, 89%): ^{1}H NMR δ 6.01 (ddd, 1, J_{HP} = 2.5 Hz, J = 17.0, 10.7 Hz), 5.37 (d, 1, J = 17.1 Hz), 4.99 (dd, 1, J_{HP} = 0.6 Hz, J = 10.7 Hz), 4.88 (d, 1, J = 1.5 Hz), 4.88 (br s, 1), 4.50 (br s, 1), 2.55 (d, 12, J = 9.5 Hz); ^{31}P NMR +15.2; ^{13}C NMR 151.0 (d, J_{CP} = 6.1 Hz), 132.2 (d, J_{CP} = 7.1 Hz), 114.6, 100.0 (d, J_{CP} = 6.0 Hz), 36.4 (d, J_{CP} = 4.1 Hz), 36.3 (d, J_{CP} = 3.6 Hz); EIMS, *m/z* (relative intensity) 204 (M^+, 14), 151 (6), 153 (100), 108 (20), 97 (18), 92 (24), 76 (10), 53 (47), 44 (98), 42 (56); HRMS, calcd for $C_8H_{17}N_2O_2P$ 204.1029, found 204.1018.

***cis*-1,3,3a,4,7,7a-Hexahydro-1,3-dioxo-5-isobenzofuranyl Tetramethylphosphorodiamidate (17).** Maleic anhydride (49 mg, 0.5 mmol) was added to diene **16** (204 mg, 1 mmol), according to the general procedure. After 5 h at ambient temperature, the reaction was judged to be complete by GC analysis. Purification of the reaction mixture by column chromatography (silica gel, starting with 86% $CHCl_3$ and 14% EtOAc, and increasing polarity) afforded vinyl phosphate **17** (134 mg, 89%): ^{1}H NMR δ 5.37 (br s, 1), 3.07–3.05 (m, 2), 2.63 (d, 12, J_{HP} = 9.9 Hz), 2.62–2.40 (m, 4); ^{31}P NMR 15.6; ^{13}C NMR 176.5, 176.3, 147.4 (d, J_{CP} = 8.0 Hz), 109.4 (d, J_{CP} = 5.0 Hz), 41.3, 40.2, 36.9 (d, J_{CP} = 4.2 Hz), 36.8

(d, J_{CP} = 4.1 Hz), 29.7 (d, J_{CP} = 3.7 Hz), 25.7; EIMS, *m/z* (relative intensity) 302 (M^+, 1), 286 (6), 229 (10), 199 (11), 153 (17), 135 (55), 92 (21), 72 (23), 45 (50), 44 (100); HRMS, calcd for $C_{12}H_{19}N_2O_5P$ 302.1033, found 302.1008.

Bis(2,6-dimethoxyphenyl) *trans*-1,4,4a,5,6,7,8,8a-Octahydro-5-oxo-2-naphthalenyl Phosphate (22). To $AlCl_3$ (66.7 mg, 0.5 mmol) was added a solution of cyclohexenone (**20**, 0.048 mL, 0.5 mmol) in anhydrous toluene (1 mL) at 22 °C. After the resulting mixture was stirred for 40 min, a solution of the diene **14** (422 mg, 1.0 mmol) in anhydrous toluene (1.5 mL) was added, and the resulting suspension was heated at 110 °C overnight. Following addition of cold water, the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried over $MgSO_4$. After concentration in vacuo, final purification of the residue by column chromatography (silica gel, 80% $CHCl_3$, 20% EtOAc) afforded compound **22** (104 mg, 40%): ^1H NMR δ 7.030 (t, 1, J = 8.4 Hz), 7.029 (t, 1, J = 8.4 Hz), 6.56 (d, 4, J = 8.4 Hz), 5.72 (m, 1), 3.75 (s, 12), 2.55–0.86 (m, 12); ^{31}P NMR −16.4; ^{13}C NMR 211.2, 152.3 (d, J_{CP} = 3.8 Hz), 146.0 (d, J_{CP} = 9.9 Hz), 124.9, 109.4 (d, J_{CP} = 5.8 Hz), 105.3, 56.3, 49.6, 41.9, 40.3, 35.0 (d, J_{CP} = 3.9 Hz), 32.4, 26.0, 23.2; EIMS, *m/z* (relative intensity) 518 (M^+, 5), 353 (21), 302 (45), 274 (30), 217 (35), 202 (32), 154 (100), 138 (32), 107 (36), 95 (25); HRMS, calcd for $C_{26}H_{31}O_9P$ 518.1706, found 518.1701.

Preparation of Octalone 24. To $AlCl_3$ (78.7 mg, 0.59 mmol) at room temperature was added a solution of 2-methyl-2-cyclohexenone[15] (**21**, 64.9 mg, 0.59 mmol) in 1 mL of anhydrous toluene. The resulting solution was stirred for 40 min at room temperature, and then a solution of diene **14** (299 mg, 0.71 mmol) in 1.5 mL of anhydrous toluene was added. After being heated at reflux overnight, the reaction mixture was allowed to cool to room temperature, and cold water was added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. After the combined organic extracts were dried over $MgSO_4$, the solvents were removed. Purification of the remaining oil by flash column chromatography (silica gel, 80% $CHCl_3$, 20% EtOAc) afforded pure compound **24** (122.4 mg, 39%): ^1H NMR δ 7.030 (t, 1, J = 8.4 Hz), 7.028 (t, 1, J = 8.3 Hz), 6.56 (d, 2, J = 8.4 Hz), 6.55 (d, 2, J = 8.4 Hz), 5.66–5.65 (m, 1), 3.75 (s, 12), 2.66–1.64 (m, 10), 1.17 (s, 3), 0.9 (m, 1); ^{31}P NMR −16.2; ^{13}C NMR 214.6, 152.4 (d, J_{CP} = 3.2 Hz), 145.6 (d, J_{CP} = 10.1 Hz), 124.9, 106.5 (d, J_{CP} = 5.8 Hz), 105.3, 56.3, 42.2, 37.2, 30.7, 30.5 (d, J_{CP} = 4.2 Hz), 27.9, 25.1, 20.1; EIMS, *m/z* (relative intensity) 532 (M^+, 24), 461 (12), 371 (23), 354 (18), 353 (99), 316 (50), 283 (28), 217 (64), 202 (62), 154 (100), 125 (30), 107 (48), 91 (65), 77 (22); HRMS, calcd for $C_{27}H_{33}O_9P$ 532.1863, found 532.1863.

Hydrolysis of Octalone 24. To a solution of HCl (0.1 N, 3 mL) and EtOH (2 mL) was added the product from the Diels–Alder reaction between diene **14** and 2-methylcyclohex-2-en-1-one. The resulting solution was heated at 85 °C for 48 h, when the reaction was judged to have reached completion. After evaporation of the solvent, the remaining oil was extracted with CH_2Cl_2, and the organic extracts were dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was purified by column chromatography (silica gel, 75% hexane, 25% EtOAc) to afford a diketone. This diketone was identical (by GC, GC–MS, TLC, and FTIR) with an authentic sample of diketone **25**, prepared by hydrogenation of ketone **26** over Pd/C.[10,12]

Diethyl 3-Methoxy-1-methylene-2-propenyl Phosphate (18). To an LDA solution (1.1 equiv, in 20 mL of THF) was added dropwise *trans*-4-methoxy-3-buten-2-one (1 mL, 10 mmol) at −78 °C. After 50 min, diethyl phosphorochloridate (1.6 mL, 11 mmol) was added at −60 °C. The resulting solution was stirred for 4 h, and the reaction was quenched by the addition of aqueous ether. Filtration through a Florisil pad, followed by evaporation of the solvent in vacuo and subsequent column chromatography (silica gel, 67% hexane, 33% EtOAc), gave the methoxy diene **18** (1.58 g, 67%): ^1H NMR δ 6.91 (d, 1, J = 12.4 Hz), 5.35 (dd, 1, J = 12.4 Hz, J_{HP} = 2.4 Hz), 4.79 (dd, 1, J = 1.9 Hz, J_{HP} = 1.9 Hz), 4.50 (dd, 1, J = 2.2 Hz, J_{HP} = 2.2 Hz), 4.26–4.09 (m, 4), 3.62 (s, 3), 1.38 (dt, 6, J = 7.1 Hz, J_{HP} = 1.0 Hz); ^{31}P NMR −6.6; EIMS, *m/z* (relative intensity) 236 (M^+, 6), 177 (5), 149 (8), 127 (9), 110 (10), 99 (26), 85 (22), 82 (100), 81 (41), 53 (12); HRMS, calcd for $C_9H_{17}O_5P$ 236.0814, found 236.0779.

Diethyl *cis*-7-Methoxy-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-5-isobenzofuranyl Phosphate (19). Diene **18** (202 mg, 0.86 mmol) was treated with maleic anhydride (42 mg, 0.43 mmol) according to the general procedure. After 10 min at room temperature complete reaction was observed by GC analysis. The reaction mixture was purified by column chromatography (silica gel, 33% hexane, 67% EtOAc) to yield compound **19** (130 mg, 89%): ^1H NMR δ 5.95–5.92 (m, 1), 4.36 (dd, 1, J = 4.1, 6.4 Hz), 4.28–4.08 (m, 4), 3.49 (ddd, 1, J = 10.1, 10.1, 4.6 Hz), 3.25 (s, 3), 3.22 (dd, 1, J = 10.1, 4.1 Hz), 2.99–2.90 (m, 1), 2.60 (dd, 1, J = 14.0, 10.0 Hz), 1.40–1.33 (m, 6); ^{31}P NMR −15.6; ^{13}C NMR 172.8, 170.0, 151.3 (d, J_{CP} = 7.3 Hz), 107.4 (d, J_{CP} = 4.3 Hz), 71.2, 64.8 (d, J_{CP} = 5.8 Hz), 63.8 (d, J_{CP} = 5.8 Hz), 56.2, 45.6, 37.1, 24.2 (d, J_{CP} = 5.9 Hz), 16.1 (d, J_{CP} = 5.8 Hz), 16.0 (d, J_{CP} = 6.9 Hz); EIMS, *m/z* (relative intensity) 303 ($M^+ - OCH_3$, 3), 261 (3), 247 (2), 236 (10), 230 (18), 201 (15), 177 (10), 175 (42), 155 (13), 127 (16), 110 (51), 109 (28), 108 (20), 104 (24), 99 (25), 94 (25), 82 (100), 81 (61), 77 (50), 66 (27); HRMS, calcd for $C_{12}H_{16}O_7P$ ($M^+ - OCH_3$) 303.0634, found 303.0623.

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