Synthesis of Conjugated Dienol Phosphates

Grzegorz Blotny, Ralph M. Pollack*

Laboratory for Chemical Dynamics, Department of Chemisty, University of Maryland Baltimore County, Baltimore, MD 21228, USA

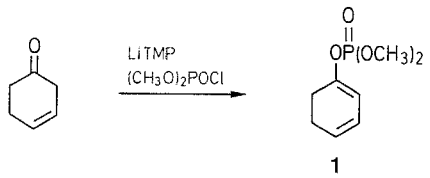
Conjugated dienol phosphates substituted at either the 1 or 2 position can be prepared from α,β- or β,γ-unsaturated ketones by treatment with lithium tetramethylpiperidine and a dialkyl or diaryl chlorophosphate. Simple enol phosphates can also be synthesized by this method.

Because of their biological activity,[1-4] and their usefulness as intermediates in organic synthesis,[5-9] enol phosphates have been the object of a number of studies in the last 25 years.[1,5-22] These compounds are generally synthesized through the Perkow reaction of the corresponding trialkyl or triarylphosphites with an appropriate α-halocarbonyl compound.[1,5,6,14,17-19,21,22]. Enol phosphates can also be prepared by treatment of a ketone with strong base, followed by quenching of the enolate with a dialkyl or diaryl chlorophosphate.[7,11-13,15,16,20,22]

In contrast to the numerous studies on simple enol phosphates, there appear to be no descriptions of the synthesis of conjugated dienol phosphates in the literature. Our interest in these compounds is as precursors to conjugated dienols. We have recently initiated a study of the rates and mechanisms of ketonization of conjugated dienols in aqueous solution.[23] In this report. we present a general method for obtaining the dienol phosphate precursors of these dienols.

The reaction scheme involves generation of the dienolate anion from an appropriate α,β- or β,γ-unsaturated ketone, followed by phosphorylation with a dialkyl or diaryl chlorophosphate. Several bases, including sodium hydride, sodium methoxide, potassium *tert*-butoxide, *n*-butyllithium, and lithium diisopropyl amide, were examined. With each of these, a mixture of products was obtained after treatment of the anions of several ketones with either a dialkyl or diaryl chlorophosphate. The most satisfactory results were obtained with dienolates generated using lithium 2,2,6,6-tetramethylpiperidide (LiTMP). In an analogous reaction, LiTMP has been shown[24] to be an effective base for deprotonation of ketones in their reaction with ethyl chloroformate to yield enol carbonates. The large steric requirement of this base precludes nucleophilic attack on the chlorophosphate.

The dienol phosphate esters **1–4** were synthesized by this procedure, as well as the simple enol phosphate esters **5a–c** (Table 1). The liquid dienol phosphates are unstable at room temperature and must be stored below 0 °C; the solid products showed no evidence of decomposition after several months at room temperature.



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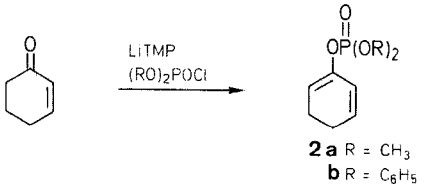
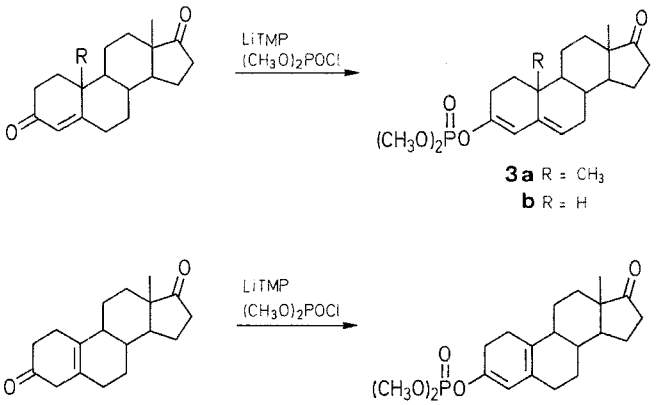
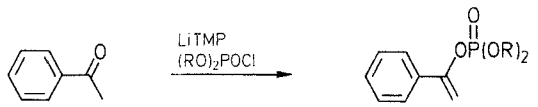


2a R = CH_3
b R = C_6H_5



3a R = CH_3
b R = H

4



5a R = CH_3
b R = C_2H_5
c R = C_6H_5

LiTMP = lithium 2,2,6,6-tetramethylpiperidide

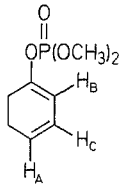
Table 1. Dialkyl and Diaryl Dienol Phosphates Prepared

Product	Yield (%)	mp (°C)	R_f Value	Molecular Formula[a] or Lit. Data
1	63[b]	oil	0.26[h]	$C_8H_{13}O_4P$ (204.1)
2a	55[c]	oil	0.23[h]	$C_8H_{13}O_4P$ (204.1)
2b	64[c]	oil	0.66[j]	$C_{18}H_{17}O_4P$ (328.2)
3a	42[d]	112–116	0.33[k]	$C_{21}H_{31}O_5P$ (394.4)
3b	51[e]	127–130	0.20[h]	$C_{20}H_{29}O_5P$ (380.4)
4	53[f]	105–108	0.14[h]	$C_{20}H_{29}O_5P$ (380.4)
5a	68[g]	oil	0.53[h]	oil[28]
5b	63[g]	oil	0.33[h]	oil[14,15]
5c	80[g]	oil	0.47[i]	oil[19]

[a] All new compounds gave acceptable elemental analyses for C, H, P (±0.4), except **1**, which showed a deviation in C of +0.5 and in P of −0.6. Cleavage of the methyl groups of **1** generated the phosphate salt which gave an acceptable elemental analyses for C, H, and P.
[b] From 3-cyclohexenone.
[c] From 2-cyclohexenone.
[d] From 4-androstene-3,17-dione.
[e] From 4-estrene-3,17-dione.
[f] From 5(10)-estrene-3,17-dione.
[g] From acetophenone.
[h] Solvent system S-1.
[i] Solvent system S-2.
[j] Solvent system S-3.
[k] Solvent system S-4.

Structures were established by ^{1}H-NMR, IR, UV and mass spectrometry (Table 2). The assignment of structures to **1**, **2a**, and **2b** was made on the basis of decoupled ^{1}H-NMR spectra at 400 MHz. Compound **1** shows multiplets corresponding to three protons in the vinyl region at $\delta = 5.60$, 5.70, and 5.82. Upon irradiation of the allyl protons at $\delta = 2.3$ to 2.4, the spectrum simplifies to a doublet at $\delta = 5.60$ ($J = 9.6$ Hz) a doublet of

doublets at $\delta = 5.70$ ($J = 5.6$, 2 Hz) and a doublet of doublets at $\delta = 5.82$ ($J = 9.6$, 5.6 Hz). These peaks were assigned to H_A, H_B, and H_C, respectively. Both H_B and H_A show up as doublets coupled to H_C; in addition, H_B shows some coupling to the



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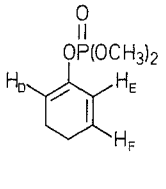

2a

phosphorus ($J = 2$ Hz). The decoupled spectrum of compound **2a**, on the other hand, shows vinyl protons at $\delta = 5.46$ (s), 5.83 (d, $J = 10$ Hz) and 5.93 (d, $J = 10$ Hz). The peak at $\delta = 5.46$ was assigned to H_D and the peaks at $\delta = 5.83$ and 5.93 were assigned to H_E and H_F, although it is unclear which is which. The clear difference in splitting patterns of **1** and **2a** is consistent with the proposed structures. The structure of **2b** was determined similarly.

Both α,β-unsaturated and β,γ-unsaturated ketones can be used as starting materials, but it is difficult to predict the predominant direction of enolization and the isomer distribution of the products. The major product from 2-cyclohexenone with both dimethyl chlorophosphate and diphenyl chlorophosphate is the cross-conjugated 2-substituted dialkylphosphate (**2a** and **2b**, respectively). In contrast, reaction of 4-androstene-3,17-dione and 4-estrene-3,17-dione with dimethyl chlorophosphate yields the linearly conjugated 3,5-dienyl phosphates **3a** and **3b**. The two β,γ-unsaturated ketones give analogous results. 3-Cyclohexenone yields predominantly the 1,3-cyclohexadienyl phosphate (**1**) and 5(10)estrene-3,17-dione produces the 3,5(10)-dienyl phosphate **4**.

The stereoselectivity of this reaction suggests that enolization by LiTMP is under kinetic control. Analogous results were obtained by Rubbotom and Gruber[25] in their examination of the formation of trimethylsilyl ethers from 3-methyl-2-cyclohexenone and 3-methyl-3-cyclohexenone with trimethylsilyl chloride and lithium diisopropylamide.

We also applied this method to the synthesis of simple enol phosphates from acetophenone with satisfactory results. It should be noted that, although treatment of acetophenone by this procedure produces enol phosphates, it is possible to convert the steroidal α,β- or β,γ-unsaturated-3,17-diones to dienol phosphates without protection of the 17-keto group.

Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1420 ratio recording infrared spectrometer. ^{1}H-NMR spectra were taken at 80 MHz on a IBM NR/80 Spectrometer or at 400 MHz on a Varian XL-400 Spectrometer. Mass spectra were run at the Mass Spectral Facility of the University of Maryland at Baltimore. Elemental analyses were obtained through Galbraith Laboratories, Inc., Knoxville, TN.

TLC was carried out on aluminum sheets coated with Silica Gel Merck 60, using the following solvent systems: S-1, hexane/EtOAc (1:1); S-2, hexane/EtOAc (3:1); S-3, $CHCl_3$/MeOH (100:1); or S-4, hexane/acetone (2:1). For flash chromatography, Silica Gel 60 (Merck) was used with an appropriate solvent system determined from TLC. All chemicals were anhydrous. THF and hexamethylphosphoramide (HMPA) were distilled from $LiAlH_4$ and CaH_2, respectively. 2,2,6,6-Trimethylpiperidine was dried over KOH, then distilled and stored under nitrogen. Liquid ketones were distilled under reduced pressure from P_2O_5, and solids were dried under vacuum for 20 h. 3-Cyclohexenone was synthesized according to the procedure of Whalen[26] and dimethylchlorophosphate

Table 2. Spectral Properties of Dialkyl and Diaryl Dienol Phosphates

Compound	UV (CH_3OH) λ_{max} (nm) (ε)	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ (J, Hz)	MS (70 eV) m/z (%)
1	260.5 (4300)	1660, 1595, 1270, 1180, 1050, 980	2.36 (m, 2H, CH_2); 3.80 (d, 6H, $J = 11.4$, CH_3O); 5.64 (m, 1H, CH); 5.72 (m, 2H, CH)[a]	204 (M^+, 16); 203 (49); 127 (43); 110 (21); 109 (22); 96 (100); 95 (26); 78 (21)
2a	258 (2400)	1655, 1600, 1275, 1155, 1050	2.21 (m, 4H, CH_2); 3.81 (d, 6H, $J = 11.0$; CH_3O); 5.45 (m, 1H, CH); 5.85 (m, 2H, CH)[b]	204 (M^+, 33); 203 (100); 171 (3); 127 (74); 109 (45); 95 (20); 78 (98)
2b	261 (4000)	1650, 1595, 1290, 1185, 1160, 1020, 1005	2.21 (m, 4H, CH_2); 5.53 (m, 1H, CH); 5.84 (m, 2H, CH); 7.15–7.36 (m, 10H, C_6H_5)[c]	328 (M^+, 15); 327 (22); 276 (8); 251 (13); 215 (10); 170 (14); 152 (12); 141 (7); 94 (56); 78 (40); 77 (100)
3a	235 (20800)	1733, 1660, 1630, 1270, 1185, 1050, 1010	0.91 (s, 3H, CH_3); 0.99 (s, 3H, CH_3); 3.79 (d, 6H, $J = 11.2$, CH_3O); 5.46 (m, 1H, CH); 5.86 (m, 1H, CH)	394 (M^+, 24); 270 (5); 173 (6); 140 (19); 127 (41); 119 (66); 110 (100); 95 (50); 91 (43); 79 (68)
3b	236 (20500)	1730, 1660, 1642, 1275, 1178, 1055, 1040	0.90 (s, 3H, CH_3); 3.82 (d, 6H, $J = 11.6$, CH_3O); 5.49 (m, 1H, CH); 5.90 (m, 1H, CH)	380 (M^+, 100); 254 (19); 229 (12); 196 (7); 183 (6); 149 (43); 127 (61); 105 (44); 91 (25); 79 (15)
4	269.5 (6800)	1732, 1670, 1615, 1275, 1180, 1045	0.89 (s, 3H, CH_3); 3.82 (d, 6H, $J = 11.7$, CH_3O); 5.49 (m, 1H, CH)	380 (M^+, 32); 254 (8); 229 (5); 215 (6); 197 (7); 142 (10); 127 (100); 115 (10); 96 (10); 91 (13)
5a	–	1635, 1260, 1185, 1040	3.84 (d, 6H, $J = 11.3$, CH_3O); 5.26 (m, 2H, CH_2); 7.30–7.53 (m, 5H_{arom})	228 (M^+, 35); 213 (11); 127 (10); 116 (23); 109 (13); 105 (14); 103 (17); 102 (100); 91 (5); 77 (9)
5b	–	1635, 1265, 1160, 1040	1.34 (dt, 6H, $J = 7.5$, 1, CH_3); 4.20 (m, 4H, CH_2); 5.24 (dq, 2H, $J_1 \approx J_2 \approx 7.5$, 2H, CH_2); 7.29–7.65 (m, 5H_{arom})	256 (M^+, 8); 130 (80); 127 (28); 105 (62); 103 (34); 102 (100); 91 (5); 77 (9)
5c	–	1635, 1290, 1185, 1160, 1020, 960	5.33 (m, 2H, CH_2); 7.25–7.33 (m, 15H_{arom})	352 (M^+, 4); 276 (10); 261 (7); 249 (7); 178 (45); 105 (100); 94 (48); 77 (41)

[a] Decoupled spectrum (400 MHz irradiation at $\delta = 2.3$–2.4) shows 5.60 (d, 1H, $J = 9.6$ Hz); 5.70 (dd, 1H, $J = 5.6$, 2 Hz); 5.82 (dd, 1H, $J = 9.6$, 5.6 Hz).

[b] Decoupled spectrum (400 MHz, irradiation at $\delta = 2.2$) shows 5.46 (s, 1H); 5.83 (d, 1H, $J = 10$ Hz); 5.93 (d, 1H, $J = 10$ Hz).

[c] Decoupled spectrum (400 MHz, irradiation at $\delta = 2.2$) shows 5.54 (s, 1H); 5.79 (dd, 1H, $J = 10$, 1 Hz); 5.92 (d, 1H, $J = 10$ Hz).

was prepared by the procedure of Fiszer and Michalski.[27] Other reagents were available commercially (Aldrich, Sigma, Steraloids) and were purified by crystallization or distillation.

Dienol Phosphates 1–5; General Procedure:
To a solution of 2,2.6,6-tetramethylpiperidine (1.69 g, 12 mmol) in THF (10 mL) contained in a three-neck flask fitted with a stirring bar, condenser with a drying tube, nitrogen gas inlet and a pressure equalizing addition funnel is slowly added dropwise a 1.6 M hexane solution of BuLi (7.5 mL, 12 mmol) under nitrogen atmosphere. After standing for 10 min, the solution of LiTMP is cooled in a dry ice-acetone bath to $-70\,^{\circ}C$ and the appropriate ketone (12 mmol) in THF (10 mL) is added dropwise through the addition funnel. The mixture is stirred at $\sim -70\,^{\circ}C$ for 15 min, the bath is removed and the solution of enolate ion is allowed to warm to room temperature. HMPA (20 mL) is added[24] and then the appropriate chlorophosphate (12 mmol) is added in one portion. After 5 min, the mixture is poured into aqueous 10% citric acid/sodium citrate buffer (50 mL, pH 4). EtOAc (50 mL) is added, the organic phase is separated and the water phase is extracted with EtOAc (2×25 mL). The combined organic extract is washed with sat. $NaHCO_3$ solution, water, and dried ($MgSO_4$). Filtration and removal of the solvent under reduced pressure gives the crude product, which is purified by flash chromatography on silica gel (eluent: see Table 1). Solids are recrystallized from EtOAc/hexane solutions. Yields and physical data for the products are presented in Tables 1 and 2.

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(1) Lichtenthaler, F. *Chem. Rev.* **1961**, *61*, 607.
(2) Schuler, M. *Chimia* **1967**, *21*, 342.
(3) Stubbe, J.A., Kenyon, G. *Biochemistry* **1971**, *10*, 2669.
(4) Morales, J.G., Whetstone, R.R., Stoutamire, D.W., Hass, K.D. *J. Med. Chem.* **1972**, *15*, 1225.
(5) Perkow, W., Ullerich, K., Meyer, F. *Naturwissenschaften* **1952**, *39*, 353.
(6) Cramer, F., Wittmann, R. *Chem. Ber.* **1961**, *94*, 328.
(7) Ireland, R.E., Pfister, G. *Tetrahedron Lett.* **1969**, 2145.
(8) Takai, K., Oshima, K., Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531.
(9) Kamata, S., Maga, N., Matsui, T., Nagata, W. *Synthesis* **1986**, 588.
(10) Sato, M., Takai, K., Oshima, K., Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1609.
(11) Heathcock, C.H., Del Mar, E.G., Graham, S.L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.
(12) House, H.O., Czuba, L.J., Gall, M., Olmstead, H.D. *J. Org. Chem.* **1969**, *34*, 2324.
(13) Batt, D.G., Takamura, N., Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 1907.
(14) Borowitz, I.J., Anschel, H., Firstenberg, S. *J. Org. Chem.* **1967**, *32*, 1723.
(15) Borowitz, I.J., Firstenberg, S., Casper, E.W.R., Crouch, R.K. *J. Org. Chem.* **1971**, *36*, 3282.
(16) Borowitz, I.J., Yee, K.C., Crouch, R.K. *J. Org. Chem.* **1973**, *38*, 1713.
(17) Frampton, R.D., Tidwell, T.T., Young, V.A. *J. Am. Chem. Soc.* **1972**, *94*, 1271.
(18) Novak, M., Roy, K.R. *J. Org. Chem.* **1984**, *49*, 4584.
(19) Gaydou, E. *Bull. Soc. Chim. Fr.* **1973**, 2275.
(20) Gaydou, E., Freze, R., Buono, G. *Bull. Soc. Chim. Fr.* **1973**, 2279.
(21) Gaydou, E., Buono, G., Freze, R. *Bull. Soc. Chim. Fr.* **1973**, 2284.
(22) Thiem, J., Rasch, D., Paulsen, H. *Chem. Ber.* **1976**, *109*, 3588.
(23) Pollack, R.M., Mack, J.P., Blotny, G. *J. Am. Chem. Soc.* **1987**, *109*, 3138.
(24) Olofson, R.A., Cuomo, J., Bauman, B.A. *J. Org. Chem.* **1978**, *43*, 2073.
(25) Rubottom, G.M., Gruber, J.M. *J. Org. Chem.* **1977**, *42*, 1051.
(26) Whalen, D.L., Weimaster, J.F., Ross, A.M., Radhe, R. *J. Am. Chem. Soc.* **1976**, *98*, 7319.
(27) Fiszer, B., Michalski, J. *Rocz. Chem.* **1952**, *26*, 688.
(28) Satterthwait, A.C., Westheimer, F.H. *J. Am. Chem. Soc.* **1980**, *102*, 4464.