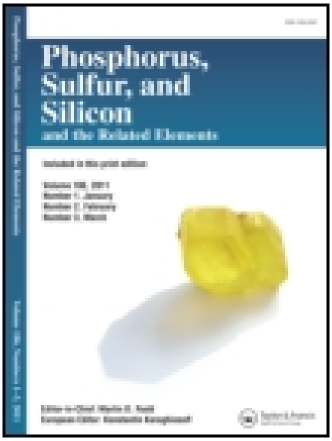

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A STEREOSELECTIVE SYNTHESIS OF UNSATURATED PHOSPHONATES BY WITTIG-HORNER REACTIONS OF BISPHOSPHONYLMETHANE WITH 5-ARYL-(3-METHYL)-2E,4E-PENTADIENALS

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A STEREOSELECTIVE SYNTHESIS OF UNSATURATED PHOSPHONATES BY WITTIG-HORNER REACTIONS OF BISPHOSPHONYLMETHANE WITH 5-ARYL-(3-METHYL)-2E,4E-PENTADIENALS

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(Revised March 03, 2000)

A new type of unsaturated phosphonates **5** were synthesized by the Wittig-Horner reactions of bisphosphonylmethane **4** with 5-aryl-2(E),4(E)-pentadienal and 5-aryl-3-methyl-2(E), 4(E)-pentadienal. The structures of all new compounds prepared were characterized by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, IR spectra, MS and elemental analyses, one of them was determined by X-ray diffraction analysis.

Keywords: Unsaturated phosphonates; plant growth regulator; Wittig-Horner reaction

INTRODUCTION

There is a growing interest in the synthesis of vinylphosphonates which can be further transformed to various products[1–3]. We have reported the synthesis of a number of unsaturated phosphonates by the Wittig-Horner reactions of bisphosphonylmethane with α,β- unsaturated aldehydes[4], which show some extent of plant growth regulation activities. Herein we designed and synthesized unsaturated phosphonates **5**. On one hand, we wish to study the structure-activity relationship of these unsaturated phosphonates; On the other hand, we attempt to use this type of unsaturated

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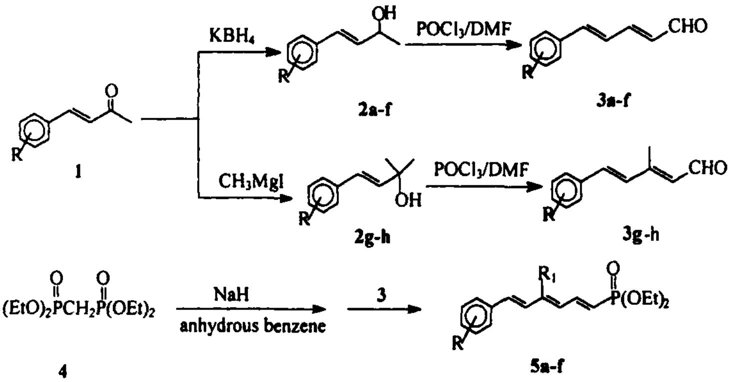
phosphonates as phosphorous reagent for the synthesis of various unsaturated compounds. The synthetic routes are shown in Schemes **1**.



a. $R=H, R_1=H$; b. $R= 4\text{-}OCH_3, R_1=H$; c. $R= 2\text{-}Cl, R_1=H$; d. $R= 4\text{-}CH_3, R_1=H$;
e. $R= 4\text{-}Cl, R_1=H$; f. $R= 3,4\text{-}OCH_2O$; $R_1=H$; g. $R= 4\text{-}Cl, R_1=CH_3$; h. $R=4\text{-}CH_3, R_1=CH_3$

SCHEME 1

RESULTS AND DISCUSSION

1. Preparation of unsaturated phosphonates 5

We try to synthesize compounds **5** by Wittig-Horner reactions of PO reagent **4** with unsaturated aldehydes **3** under typical two-phase reaction conditions (dichloromethane/50% aqueous sodium hydroxide), but the reaction did not take place. However, when a strong base (NaH) and an anhydrous solvent (benzene) was used, the reaction took place smoothly and the products **5** were obtained in high yields. Furthermore, the reaction shows good E-selectivity. The synthetic route is listed in **Scheme 1**. The experimental data of the title compound are listed in Table I.

2. The structure of the products

The molecular sructures of all new compounds obtained were confirmed by IR spectra, MS, and elemental analyses.

TABLE I Physical Data of Compounds 5

R	*R₁*	*State (m.p °C)*	*Yield (%)*	*Elemental Analysis/Found (Cacld.)*	
				C (%)	*C (%)*
H	H	Yellow Liq.	88	65.88 (65.75)	7.14 (7.19)
p-OCH_3	H	Yellow Liq.	85	63.30 (63.35)	7.02 (7.14)
o-Cl	H	Red-brown liq.	78.5	59.01 (58.80)	6.41 (6.13)
p-CH_3	H	Colorless crystal(76–77)	84	66.60 (66.67)	7.49 (7.52)
p-Cl	H	Red-brown liq.	94	58.95 (58.80)	5.92 (6.13)
3,4-OCH_2O-	H	Light yellow crystal (68–70)	96	60.69 (60.71)	6.25 (6.23)
p-Cl	CH_3	Yellow liq.	83	59.98 (59.91)	6.55 (6.46)
p-CH_3	CH_3	Yellow liq.	86	67.43 (67.50)	7.96 (7.81)

TABLE II ^{1}H NMR or ^{31}P NMR Data of Compound **5**

δ ^1H NMR or ^{31}P NMR ($CDCl_3$, TMS, ppm)
28~1.35 (t, 6H, 2×CH_3), 4.04~4.11 (dq, 4H, 2×OCH_2), 5.59~5.77 (dd, 1H, $J^2_{P\text{-}H}$=18.8 Hz, $J^3_{H\text{-}H}$=16.7Hz, CH-P), 6.30~6.43 (dd, 1H, 58~6.78 (m, 3H, 3×CH=), 7.08~7.39 (m, 6H, C_6H_5+ CH=)
24~1.31 (t, 6H, 2×CH_3), 3.74 (s, 3H, OCH_3), 3.99~4.06 (dq, 4H, 2×OCH_2), 5.51~5.69 (dd, 1H, $J^3_{H\text{-}H}$=16.7Hz, $J^2_{P\text{-}H}$=18.2Hz, CH=), 21~6.33 (t, 1H, CH=), 6.50~6.82 (m, 5H, 4×CH= +1H of Ph), 7.01~7.32 (m, 3H, 3H of Ph). ^{31}P NMR: 19.83
28~1.34 (t, 6H, 2×CH_3), 4.00~4.11 (dq, 4H, 2×OCH_2), 5.62~5.80 (dd, 1H, $J^3_{H\text{-}H}$=16.7Hz, $J^2_{P\text{-}H}$=18.8Hz, CH=), 6.33~6.45 (dd, 1H, C 61~6.85 (m, 2H, 2×CH=), 7.06~7.31 (m, 5H, 3H of Ph+2 CH=), 7.53~7.57 (q, 1H, 1H of Ph)
27~1.34 (t, 6H, 2×CH_3), 2.31 (s, 3H, CH_3), 4.02~4.10 (dq, 4H, 2×OCH_2), 5.57~5.74 (dd, 1H, $J^3_{H\text{-}H}$=16.7Hz, $J^2_{P\text{-}H}$=18.8Hz, CH=), 27~6.40 (dd, 1H, CH=), 6.65~6.72 (m, 3H, 3×CH=), 7.12~7.31 (m, 5H, C_6H_4+ CH=)
30~1.34 (t, 6H, 2×CH_3), 4.06~4.13 (dq, 4H, 2×OCH_2), 5.60~5.78 (dd, 1H, $J^3_{H\text{-}H}$=16.7Hz, $J^2_{P\text{-}H}$=18.8Hz CH=), 6.30~6.43 (dd, 1H, C 55~6.78 (m, 3H, 3×CH=), 7.12~7.34 (m, 5H, C_6H_4+ CH=)
27~1.34 (t, 6H, 2×CH_3), 4.02~4.10 (dq, 4H, 2×OCH_2). 5.56~5.73 (dd, 1H, $J^3_{H\text{-}H}$=16.7Hz, $J^2_{P\text{-}H}$=18.8Hz CH=), 5.94 (s, 2H, OCH_2O) 25~6.38 (d, 1H, CH=), 6.61~7.15 (m, 7H, 4×CH= + C_6H_3). ^{31}P NMR: 19.84
28~1.35 (t, 6H, 2×CH_3), 2.06 (s, 3H, CH_3), 4.00~4.15 (dq, 4H, 2×OCH_2), 5.62~5.80 (dd, 1H, $J^3_{H\text{-}H}$=16.7Hz, $J^2_{P\text{-}H}$=19.3Hz, CH=), 22~6.28 (d, 1H, $J^3_{H\text{-}H}$=15.5Hz, CH=), 6.61~6.69 (d, 1H, $J^3_{H\text{-}H}$=16.7Hz, CH=), 6.75~6.83 (d, 1H, $J^3_{H\text{-}H}$=16.6Hz, =CH- Ar), 7.24~7.3 H, C_6H_4+ CH=)
28~1.35 (t, 6H, 2×CH_3), 2.07 (s, 3H, CH_3-Ar), 2.32 (s,3H,CH_3 in C=C), 4.04~4.11 (dq, 4H, 2×OCH_2), 5.59~5.77 (dd, 1H, $J^3_{H\text{-}H}$=16. $_{P\text{-}H}$=19.3Hz, =CH-P), 6.21~6.27 (d, 1H, $J^3_{H\text{-}H}$=15.4Hz, CH=), 6.65~6.80 (q, 2H, CH=), 7.10~7.14 (d, 1H, $J^3_{H\text{-}H}$=15.8Hz, Ar-CH=), 24~7.37 (m, 4H, C_6H_4)

X-ray diffraction analysis indicated that the single crystal of **5d** is triclinic, space group $P\bar{1}$, cell parameter A=9.852(1), B=9.887(1), C=19.949(3) Å, α=83.161(4), β=87.012 (3), γ=66.085 (3), V=1763.7 (4) $Å^3$, Z=4, Dc=1.154 g/cm^3, F (000)=656, μ=0.163 mm^{-1} and final R=0.0785, wR=0.1854 for 2094 reflections ($I>2\sigma(I)$). X-ray analysis reveals that the three carbon-carbon double bonds of the molecule are all in E-configuration. The selected bond distances and angles are listed in Table III and Table IV.

TABLE III Selected Bond Lengths (Å)

Bond	*Dist.*	*Bond*	*Dist.*	*Bond*	*Dist.*	*Bond*	*Dist.*
P(1)-O(1)	1.450(4)	C(1)-C(2)	1.315(7)	C(6)-C(7)	1.439(8)	C(10)-C(11)	1.377(8)
P(1)-O(2)	1.533(5)	C(2)-C(3)	1.429(8)	C(7)-C(12)	1.401(7)	C(10)-C(13)	1.467(8)
P(1)-O(3)	1.579(7)	C(3)-C(4)	1.332(8)	C(7)-C(8)	1.410(7)	C(11)-C(12)	1.360(8)
P(1)-C(1)	1.725(7)	C(4)-C(5)	1.412(8)	C(8)-C(9)	1.372(8)	C(14)-C(15)	1.472(5)
O(2)-C(14)	1.426(5)	C(5)-C(6)	1.314(7)	C(9)-C(10)	1.388(8)	C(16)-C(17)	1.476(5)
O(3)-C(16)	1.347(5)						

TABLE IV Selected Bond Angles (°)

Angle	*(°)*	*Angle*	*(°)*	*Angle*	*(°)*
O(1)-P(1)-O(2)	112.3(3)	C(1)-C(2)-C(3)	129.0(6)	C(8)-C(9)-C(10)	124.2(7)
O(1)-P(1)-O(3)	116.2(4)	C(4)-C(3)-C(2)	126.7(6)	C(11)-C(10)-C(9)	114.5(7)
O(2)-P(1)-O(3)	102.5(3)	C(3)-C(4)-C(5)	128.4(7)	C(11)-C(10)-C(13)	124.0(8)
O(1)-P(1)-C(1)	117.8(3)	C(6)-C(5)-C(4)	125.5(6)	C(9)-C(10)-C(13)	121.4(8)
O(2)-P(1)-C(1)	103.8(3)	C(5)-C(6)-C(7)	128.8(7)	C(12)-C(11)-C(10)	123.4(6)
O(3)-P(1)-C(1)	102.4(3)	C(12)-C(7)-C(8)	115.6(6)	C(11)-C(12)-C(7)	122.1(6)
C(14)-O(2)-P(1)	118.1(5)	C(12)-C(7)-C(6)	121.0(6)	O(2)-C(14)-C(15)	108.7(8)
C(16)-O(3)-P(1)	114.6(8)	C(8)-C(7)-C(6)	123.5(6)	O(3)-C(16)-C(17)	103.1(11)
C(2)-C(1)-P(1)	125.9(5)	C(9)-C(8)-C(7)	120.2(6)		

The bioassays showed that compounds **5** possess plant growth regulating activity. Further tests are in progress.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a BRUKER AC-P200 spectrometer, while Mass spectra with a VG ZAB-HS spectrometer using the EI method. IR spectra were measured by a SHIMADZU-435 instrument system. Melting Points were determined with a Thomas-Hoover melting point apparatus and the thermometer is uncorrected.

The reagents and solvents were available commercially and purified according to conventional methods before use. α,β-unsaturated methyl ketones **1** were prepared according to the literature[5]. Bis(diethylphosphonyl) methane was synthesized in 52% yield by the reaction of sodium diethyl phosphite with dichloromethane[6].

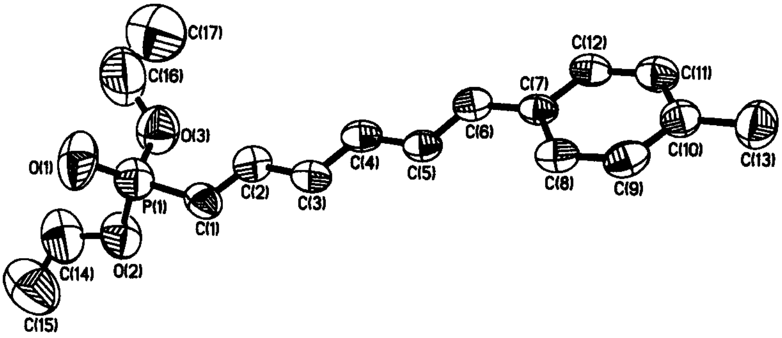


FIGURE 1 Structure of compound **5d**

1. Synthesis of 4-Aryl-3-butenols-2 (2a-f)[7]

To a solution of 70 mmol 4-Aryl-3-butenones-2 (**1**) in 120 ml anhydrous methanol was added slowly 70 mmol potassium borohydride in 1 h under cooling (-10°C to –5°C). Then the mixture was stirred for another hour and at room temperature for 2 h. The mixture was acidified by the slow addition of 2N aqueous hydrochloric acid. Then it was extracted with dichloromethane (2×70 ml), and the extract was washed with water, dried with sodium sulphate and concentrated under reduced pressure to give product **2**. yield: 86–95%.

2a. R=H, light yellow liquid, yield: 96%. ^{1}H NMR ($CDCl_3$): δ 1.35~1.36 (d, 3H, $^3J_{H\text{-}H}$=6.95Hz, CH_3), 2.47 (sb, 1H, OH), 4.40~4.53 (m,

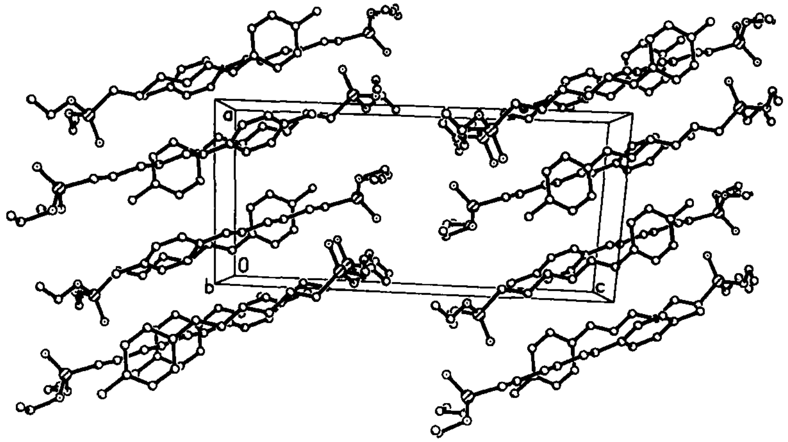


FIGURE 2 Packing of the molecules in the unit cell

1H, CH), 6.20~630 (dd, 1H, $^3J_{H-H}$=6.2, 15.6 Hz, =CH), 6.51~6.59 (d, 1H, $^3J_{H-H}$ =15.80 Hz, =CH-Ar), 7.28~7.39 (m, 5H, C_6H_5).

2e. R= p-Cl, white solid, m.p.: 54–56°C, yield: 92%. ^{1}H NMR ($CDCl_3$): δ 1.33~1.37 (d, 3H, $^3J_{H-H}$ =6.4 Hz, CH_3), 1.62 (sb, 1H, OH), 4.40~4.50 (m, 1H, CH), 6.16~6.27 (dd, 1H, $^3J_{H-H}$=6.2 and 15.9Hz, =CH), 6.47~6.55 (d, 1H, $^3J_{H-H}$=15.9Hz, =CH-Ar), 7.24~7.27 (m, 4H, C_6H_4).

2. Synthesis of 4-(4-chlorophenyl)-2-methyl-3-butenol-2 (2g)[8]

To the Grignard reagent prepared from magnesium (2.64 g, 0.11mol) and methyl iodide (16.5 g, 0.114mol) in dry ether (50 ml) is added dropwise a solution of **1g** (10.83 g, 0.06 mol) in ether (50 ml) under cooling (-10° to -5°C) and stirring during 1 h. The reaction mixture is allowed to stand overnight. It is heated under reflux for 2 h, and cooled to 0°C. The complex formed is decomposed by the slow addition of ice-cold water (45 ml), and saturated aqueous ammonium chloride (100 ml). The mixture is extracted with ether (2×50 ml), the extract washed with water, dried with sodium sulphate, and concentrated under reduced pressure at <30°C to give the product **2g**, which is recrystallized from benzene/hexane; yield: 88%; m.p. 65–66 °C.

3. Synthesis of 5-Aryl-2(E), 4(E)-pentadienals (3a-f) and 5-Aryl-3-methyl-2(E), 4(E)-pentadienal (3g), 3h[8]

Compounds **3** were obtained by Vilsmeier reaction of 4-Aryl-3-butenols-2 (**2a-f**) or 4-(4-chlorophenyl)-2-methyl-3-butenol-2 (**2g**) with $POCl_3$ and DMF.

Compounds **3**

3a. R=H, light yellow crystal, m.p.: 46–48°C, yield: 76%. ^1H NMR ($CDCl_3$): δ 6.19~6.31 (dd, 1H, $^3J_{H\text{-}H}$=7.3 and 15.1 Hz, =CH-C(O)), 6.97~7.00 (m, 2H, =CH-CH=), 7.24~7.34 (m, 1H, =CH), 7.36~7.51 (m, 5H), 9.58~9.62 (d, 1H, $^3J_{H\text{-}H}$= 8.1Hz, CHO)

3f. R=3,4-OCH_2O-, red-brown solid, m.p., 92–94°C, yield: 88%. ^1H NMR ($CDCl_3$): δ 5.97 (s, 2H, -OCH_2O-), 6.13~6.25 (dd, 1H, $^3J_{H\text{-}H}$=7.3 and 15.1 Hz, =CH-C(O)), 6.79~6.99 (m, 4H), 7.13~7.26 (m, 2H), 9.54–9.58 (d, 1H, $^3J_{H\text{-}H}$= 8.3Hz, CHO)

3g. R= 4-chloro, m.p. 136–137 °C (from benzene/hexane), yield: 89%. m.p., 136–138 °C[8].

4. Synthesis of product 5

To a suspension of 0.06 g (2 mmol) of 80% sodium hydride in 15 ml of anhydrous benzene was added dropwise a mixture of equimolecular amounts of bisphosphonate **4** in 5 ml of anhydrous benzene under N_2 atmosphere. The mixture was stirred at room temperature and allowed to stand for 1 h until no more hydrogen gas was evolved. Then the solution of dienal **3** (2 mmol) in 5 ml of anhydrous benzene was added dropwise with cooling in ice-bath. The mixture was stirred at room temperature for 2–4 h, and then 20 ml of water was added. The aqueous solution was extracted with 20 ml of benzene, and the extract was dried over anhydrous $MgSO_4$. After the removal of the solvent by evaporation under reduced pressure, the residue was purified by column chromatography on silica gel using petroleum ether – ethyl acetate (1:1 V/V) as the eluent. The physical data are listed in **Table I**, and 1H NMR, ^{31}P NMR data in **Table II**.

IR, MS and ^{13}C NMR for some compounds **5**:

5d (^{13}C NMR, $CDCl_3$, ppm) δ 16.396, 21.258, 61.655, 76.368, 77.005,77.648, 114.065, 117.879, 126.704, 129.419, 130.171, 130.713, 133.817, 136.772, 138.458, 140.248, 148.515

5d (IR, KBr, cm^{-1}) 2980 (m, =C-H), 1599(m), 1508, 1248(s, P=O, P-C), 1056(s), 1022(s), 950(s, P-O-C), 854, 800

5f (IR, KBr, cm^{-1}) 2972 (m, =C-H), 1598(m), 1497, 1455, 1252 (s, P=O, P-C), 1195 (s), 1097, 1050(s), 1016(s), 964 (s, P-O-C), 850(s), 808, 567

5b (EI-MS, m/e) 322 (M$^+$, 35%), 321 (100%), 293, 265, 247, 229, 184, 141, 115, 77, 65, 29

5g (EI-MS, m/e) 340 (20%), 342 (M$^+$, 3:1), 202, 167 (100%), 152, 138, 125,111, 82, 65, 29

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