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Synthesis and Stereoselectivity of a New Type of Unsaturated Phosphonates

De-Qing Shi, Yan-Ming Wang, and Ru-Yu Chen

Research Institute and State Key Laboratory of Elemento-Organic Chemistry, NanKai University, Tianjin 300071, Peoples Republic of China

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ABSTRACT: *A series of unsaturated phosphonates 2, 3, 4 with structures similar to that of abscisic acid (ABA) were synthesized by the Wittig-Horner reactions of bisphosphonylmethane* **1** *with β-substituted propenals, propargyl aldehydes or α,β-unsaturated methyl ketones. Compounds* **5** *were prepared by the Michaelis-Becker reactions of ω-bromodienes* **7** *with sodium phosphites. Compounds* **7** *were obtained by the phase transfer Wittig reactions of ω-bromobutylphosphonium salt* **6** *with β-substituted propenals. The structures of all new compounds prepared were characterized by ^1H NMR, ^{31}P NMR, IR spectra, and elemental analysis or MS. The stereochemistry of the Wittig reactions was studied.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:261–266, 2000

INTRODUCTION

2-*cis*, 4-*trans*-abscisic acid (ABA) is one of the plant hormones that was isolated from young cotton fruits in 1963 [1]. The compound ABA not only inhibits plant growth but also protects plants against deprivation of water during drought days [2]. However, so far only limited reports concerning the synthesis of this compound were available, but many articles about the synthesis of the analogs of ABA have been published [2–4]. In an attempt to discover new plant growth regulators, we designed and synthesized a number of new compounds **2, 3, 4**, and **5** with structures similar to that of ABA, but with a phosphonyl group present. The synthetic routes are shown in Schemes 1, 2, and 3.

Correspondence to: Ru-Yu Chen.
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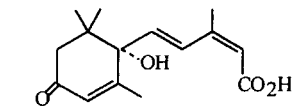
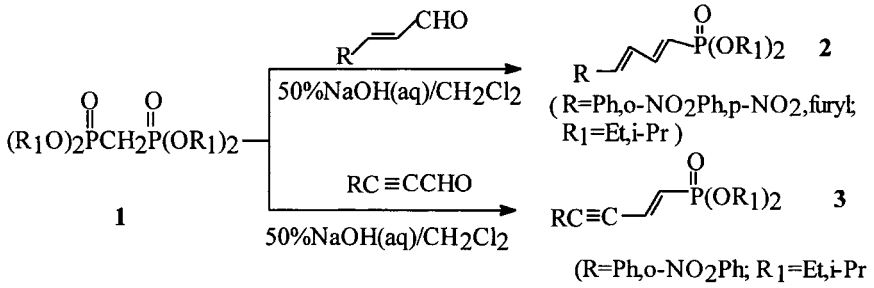
RESULTS AND DISCUSSION

Preparation of Compounds **2, 3,** *and* **4**

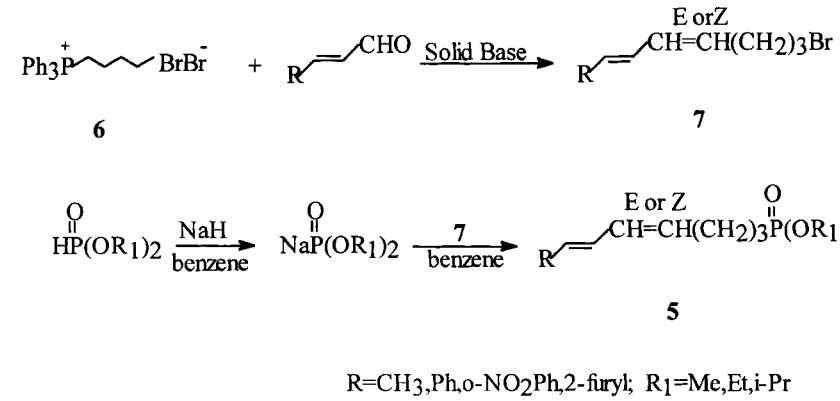
The application of the two-phase catalytic system in organic synthesis has been a subject of increasing interest in the past few years [5,6]. Recently, this approach of the two-phase catalytic system has been found to be very convenient for the synthesis of unsaturated compounds by the Wittig [7,8] and Wittig-Horner reactions [9,10]. These reactions were performed under typical two-phase reaction conditions (dichloromethane/50% aqueous sodium hydroxide), quaternary ammonium salts and crown ethers being used as phase-transfer catalysts. It is interesting to note that, in some cases, the Wittig reaction does not require the use of these catalysts since the starting materials—phosphonium salts—contain the active "onium" center and act themselves catalytically. Recently, Mikolajczyk et al. (1976) reported that the Wittig-Horner reaction might also be carried out in a two-phase system in the absence of a typical phase-transfer catalyst [11]. This fact may be considered as an indication that the starting phosphonates are able to catalyze the two-phase reactions [12], although the mechanism of their catalytic action must be different from that of the "onium" salts. Compounds **2** and **3** can also be easily obtained as the pure (*E*)-isomers by phase-transfer Wittig-Horner reactions of bisphosphonyl methane **1** with *β*-substituted pro-



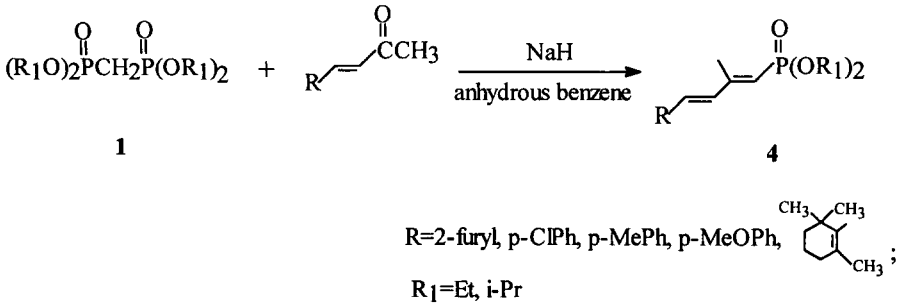
ABA



SCHEME 1



SCHEME 2



SCHEME 3

penals or propargyl aldehydes in the presence of 50% aqueous sodium hydroxide, as shown in Scheme 1. However, compounds **4** can not be synthesized under similar conditions, because the electrophilicity of α,β-unsaturated ketones is much lower than that of α,β-unsaturated aldehydes. However, when a strong base such as sodium hydride was used in anhydrous benzene, compounds **4** were obtained in high yields as the pure (*E*)-isomers, and no by-products were detected. The synthetic route is shown in Scheme 2.

Preparation of ω-Bromodienes **7** *[21]*

The simplified Wittig reaction under the solid/liquid conditions has been applied in organic synthesis as

a useful method [13]. ω-Bromoalkenes are important intermediates of some pharmaceutical products, insect sex hormones, and other natural products [14,15]. They are usually synthesized by multistep reactions [16]. The Wittig reaction of the accessible ω-bromoalkyltriphenylphosphonium salts with an aldehyde is a practical method. However, an early study on this reaction using RONa as a base resulted in a complex mixture of alkenes because of the partial elimination of HBr or the occurrence of a cyclization reaction [17]. This method, used to synthesize ω-unsaturated bromides under mild conditions, has been reported previously [18]. Herein we report the method of a direct Wittig reaction of an ω-bromoalkyltriphenyl phosphonium salt **6** with α,β-unsaturated aldehydes to produce ω-bromodienes **7**, as shown in Scheme 2. Our approach represents a one-pot reaction carried out under mild conditions, with good regioselectivity and high yields of ω-bromodienes.

It was shown that reactions of phosphonium salt **6** with α,β-unsaturated aldehydes led to very poor yields when anhydrous potassium carbonate was used as a base with CH_2Cl_2 as a solvent, even after refluxing for 20 hours. However, when the NaOH/tetrahydrofuran (THF) system was applied, the elimination of HBr occurred. However, when K_2CO_3/THF or NaOH/CH_2Cl_2 was utilized, the reaction took place smoothly, and ω-bromodienes were obtained in high yields without any by-product being detected by gas chromatography/mass spectrometry GC-MS. Still, the reaction of 3-bromopropyltriphenylphosphonium salt with α,β-unsaturated aldehydes, even in the presence of a weak base such as K_2CO_3, gave no ω-bromodienes but only the more stable trienes ($RCH=CHCH=CHCH=CH_2$) because of the elimination of HBr. The polarity of the solvent appears to play an important role in the stereoselectivity of the reaction. When THF was used as the solvent, the reaction showed Z-selectivity. However, when CH_2Cl_2 was used, the stereoselectivity of the products differed from that reported for Le Bigot's experiments [19,20]. The stereoselectivity of the reactions is listed in Table 3.

Preparation of Compounds **5**

We tried to prepare compounds **5** by Michaelis-Arbuzov reactions of ω-bromodienes **7** with trialkyl phosphites, but the reactions did not take place even under reflux for 24 hours in xylene. This was probably due to the low reactivity of ω-bromodienes. When a new route (Scheme 3) was adopted, compounds **4** were easily obtained in high yields, and no by-product was found.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a BRUKER AC-P200 spectrometer. Mass spectra were recorded with a VG ZAB-HS spectrometer using the EI method. IR spectra were measured by a SHIMADZU-435 instrument. GC were recorded with a HEWLETT PACKARD G1800A GCD (Gas Chromatograph Electron Ionization Detector) system. Melting Points were determined with a Thomas-Hoover melting point apparatus and are uncorrected.

The reagents and solvents were available commercially and purified according to conventional methods before use. β-Substituted propenals, propargyl aldehydes, and α,β-unsaturated methyl ketones were prepared according to procedures in the literature [22,23]. *Bis*(diisopropylphosphonyl) methane was obtained in 94% yield by reacting triisopropyl phosphite with dibromomethane [24]. *Bis*(diethylphosphonyl)methane was synthesized in 52% yield by the reaction of sodium diethyl phosphite with dichloromethane [25]. Phosphonium salt **6** was prepared in 95% yield from Ph_3P and 1, 4-dibromobutane in refluxing toluene [26].

Preparation of Compounds **2** *and* **3**

A mixture of bisphosphonate 1 (2 mmol), β-substituted propenal, or propargyl aldehyde (2 mmol), 5 mL of 50% aqueous sodium hydroxide, and 15 mL of dichloromethane was stirred at room temperature for 4 to 10 hours (reaction monitored by TLC), and the aqueous solution was extracted with dichloromethane. The dichloromethane solutions were combined and washed with saturated sodium chloride aqueous solution, then dried over $MgSO_4$. The solvent was removed by evaporation under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether and ethyl acetate as the eluent. The physical data are given in Table 1 and Table 2.

^{1}H NMR, ^{31}P NMR, IR for some of compounds **2** and **3**:

2a. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2–7.4 (m, 5H), 5.6–7.0 (m, 4H), 4.64 (m, 2H), 1.30 (q, 12H); IR (cm^{-1}) 1620, 1580, 1380, 1240, 1000.

2d. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.3–7.8 (m, 4H), 5.5–6.0 (m, 4H), 4.5 (m, 2H), 1.2(q, 12H); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 200 MHz) δ18.06; IR (cm^{-1}) 1620, 1600, 1580, 1520, 1340, 1240, 1000.

2g. ^{1}H NMR ($CDCl_3$, 200 MHz) δ7.2–7.4 (d, 1 H), 7.0–7.2 (m, 1H), 6.4–6.8 (m, 2H), 6.4 (s, 2H), 5.6–5.8 (t, 1H, $^3J_{H\text{-}H}$ = 16.2 Hz), 4.0–4.1 (d q, 4H), 1.24–1.31 (t, 6H).

3a. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2–7.5 (m, 5H), 5.95–6.95 (q, 2H), 4.6 (m, 2H), 1.25 (q, 12H); ^{31}P

TABLE 1 The Physical Data of Compounds **2** and **4**[a]

					Elemental Analysis/Found (*Cacld.*) *or MS Data* (*m/e*)		
Compd.	*R*	*R1*	*State* (*m.p.*)	*Yield* (%)	*C* (%)	*H* (%)	*N* (%)
2a	Ph	i-Pr	Colorless crystal (62–64)	52.4	65.24 (65.31)	7.95 (7.82)	
2b	Ph	Et	Colorless liq.	68.5	63.29 (63.16)	7.21 (7.14)	
2c	*o*-NO_2Ph	Et	Red liq.	59	54.34 (54.01)	5.85 (5.79)	4.66 (4.50)
2d	*o*-NO_2Ph	i-Pr	Light yellow crystal	55	56.41 (56.64)	6.67 (6.49)	3.91 (4.13)
2e	p-NO_2Ph	Et	Red liq.	58.2	54.15 (54.01)	5.70 (5.79)	4.42 (4.50)
2f	p-NO_2Ph	i-Pr	Yellow crystal (74–76)	54.2	56.95 (56.64)	6.77 (6.49)	4.27 (4.13)
2g	2-furyl	Et	Red liq.	78	56.38 (56.25)	6.69 (6.64)	
4a	2-furyl	i-Pr	Red liq.	57	60.76 (60.40)	7.71 (7.72)	
4b	p-MePh	i-Pr	Red liq.	60.5	322(M^+), 238, 223, 208, 128, 136, 104, 77		
4c	p-ClPh	i-Pr	Red liq.	58	342, 344 (M^+, 3:1), 302, 260, 223, 208, 128, 104, 43		
4d	p-MeOPh	i-Pr	Red liq.	53.5	338 (M^+), 254, 223, 208, 128, 104		
4e	2-furyl	Et	Red-brown liq.	68	270 (M^+), 213, 196, 132, 104, 77, 65, 29		
4f		Et	Light yellow liq.	56	326 (M^+), 311, 269, 203, 173, 132, 119, 91		

[a]The stereoselectivity of the reactions in Table 1 shows that all of the compounds are in the E,E-form from the ^{1}H NMR data of the compounds.

TABLE 2 The Physical Data of Compounds **3**

					Elemental Analysis/Found (*Calcd.*) *or MS Data* (*m/e*)		
Compd.	*R*	*R1*	*State*	*Yield* (%)	*C* (%)	*H* (%)	*N* (%)
3a	Ph	i-Pr	Red liq.	51	65.83 (65.75)	6.85 (7.19)	
3b	Ph	Et	Red liq.	47	264 (M^+), 235, 208, 191, 155, 126, 111, 79		
3c	*o*-NO_2 Ph	Et	Red liq.	52	309 (M^+), 263, 217, 137, 113, 89		

NMR ($CDCl_3$, 85% H_3PO_4, 200 MHz) δ 18.03; IR (cm^{-1}) 1600, 1360, 1355, 1240, 1000.

3b. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (m, 5H), 5.7–6.9 (q, 2H), 3.9 (m, 4H), 1.2 (t, 6H); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 200 MHz) δ 16.68; IR (cm^{-1}) 2200, 2100, 1600, 1580, 1370, 1360, 1240, 1000.

Preparation of Compounds **4**

To a suspension of 0.12 g (4 mmol) of 80% sodium hydride in 15 mL of anhydrous benzene was added dropwise a mixture of equimolecular amounts of bisphosphonate **1** in 5 mL of anhydrous benzene under an N_2 atmosphere. The mixture was stirred at room temperature and allowed to stand for 1 hour until no more hydrogen gas was evolved. Then the solution of α,β-unsaturated methyl ketones (4 mmol) in 5 mL of anhydrous benzene was added dropwise with cooling with an ice bath. The mixture was stirred at room temperature for 2 to 4 hours, then 20 mL of water was added. The aqueous solution was extracted with 20 mL of benzene and the extract was

TABLE 3 The Physical Data and MS Data of ω-Bromodienes **7**

Compd.	*R*	*Solvent/Base*	*state*	*Yield* (%)	*E,Z-isomer* (%)[a]	*MS Data* (*m/e*)
7a	Ph	THF/K_2CO_3	Light yellow liq.	86	60.2	250, 252 (M^+, 1:1), 171, 143, 129, 115, 91, 77
7a′	Ph	CH_2Cl_2/NaOH	Light yellow liq.	83	27.5	250, 252 (M^+, 1:1), 171, 143, 129, 115, 91, 77
7b	*o*-NO2Ph	THF/K_2CO_3	Yellow liq.	81	86.8	250, 252 (M^+, 1:1), 171, 143, 129, 115, 91, 77
7b′	*o*-NO2Ph	CH_2Cl_2/NaOH	Yellow liq.	89	66.1	250, 252 (M^+, 1:1), 171, 143, 129, 115, 91, 77
7c	2-furyl	THF/K_2CO_3	Red-brown liq.	78	79.4	240, 242 (M^+, 1:1), 161, 133, 119, 105
7c′	2-furyl	CH_2Cl_2/NaOH	Red-brown liq.	85	36.7	240, 242 (M^+, 1:1), 161, 133, 119, 105
7d	Me	THF/K_2CO_3	Colorless liq.	63	79.5	188, 190 (M^+, 1:1), 109, 95, 81, 67
7d′	Me	CH_2Cl_2/NaOH	Colorless liq.	58	77.9	188, 190 (M^+, 1:1), 109, 95, 81, 67

[a]The contents of E, Z and E, E isomers of the products were determined by GC and ^{1}H NMR.

TABLE 4 The Physical Data and MS Data of Compounds **5**

						Elemental Analysis/Found (*Calcd.*) *or MS Data* (*m/e*)		
Compd.	*R*	*R1*	*state*	*Yield* (%)	*E,Z-isomer* (%)[a]	*C* (%)	*H* (%)	*N* (%)
5a, 5a′	Ph	Me	Light yellow Liq	78	60.2(5a), 27.5(5a′)	280 (M^+), 189, 124, 94, 79, 65		
5b, 5b′	Ph	Et	Light yellow Liq	82	60.2(5b), 27.5(5b′)	308 (M^+), 169, 152, 125, 108, 97, 91		
5c, 5c′	Ph	i-Pr	Light yellow Liq	75	60.2(5c), 27.5(5c′)	65.90 (66.23)	7.71 (8.12)	
5d, 5d′	2-furyl	Me	Red-brown liq.	63	79.4(5d), 36.7(5d′)	270 (M^+), 160, 124, 94, 79, 65		
5e, 5e′	2-furyl	Et	Red-brown liq.	66	79.4(5e), 36.7(5e′)	298 (M^+), 269, 159, 152, 125, 108, 97, 81		
5f, 5f′	2-furyl	i-Pr	Red-brown liq.	58	79.4(5f), 36.7(5f′)	326 (M^+), 241, 159, 133, 96, 81, 43		
5g, 5g′	*o*-NO_2Ph	Et	Yellow liq.	45	86.6(5g), 66.1(5g′)	57.95 (57.79)	6.68 (6.80)	3.65 (3.97)
5h, 5h′	Me	Et	Colorless liq.	58	79.5(5h), 77.9(5h′)	246 (M^+), 165, 152, 125, 108, 97, 79, 65		

[a]The contents of E, Z and E, E-isomers of the products were determined by GC and ^{1}H NMR and are consistent with those of compounds **7**.

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 (1:2–3 V/V) as the eluent. The physical data are listed in Table 1.

^{1}H and ^{31}P NMR for some of compounds **4**:

4b. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.0–7.6 (m, 4H), 6.0–6.4 (m, 3H), 4.68 (m, 2H), 3.0–3.8 (q, 3H); 2.38 (s, 3H), 1.28 (q, 12H); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 200 MHz) δ 22.07.

Preparation of ω-Bromodienes **7**

A mixture of phosphonium salt **6** (24 mmol), α,β-unsaturated aldehydes (20 mmol), sodium hydroxide powder (50 mmol), and 45 mL dichloromethane [or anhydrous potassium carbonate (80 mmol) and tetrahydrofuran 50 ml] was stirred under reflux for 12 to 24 hours (reaction monitored by TLC), filtered, and purified by column chromatography on silica gel using petroleum ether:ethyl ether (10:1 V/V) as the eluent. The results are shown in Table 3.

^{1}H NMR, IR for some of compounds **7**:

7a. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.95–2.02 (m, 2H), 2.31–2.47 (m, 2H), 3.41–3.47 (t, 2H), 5.39–5.52 (q, 1H, J = 7.3, 18.76 Hz), 6.16–6.28 (t, 1H, J = 10.44, 11.46 Hz), 6.50–6.58 (d, 1H, J = 15.64 Hz), 7.02–7.15 (m, 1H), 7.24–7.40 (m, 5H); IR (cm^{-1}) 3137 (m), 3012, 1592, 1488, 1458, 980 (s), 727 (s), 688 (s), 562 (m).

7b. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.95–2.02 (m, 2H), 2.02–2.48 (m, 2H), 3.41–3.47 (t, 2H), 5.51–5.64 (q, 1H), 6.23–6.33 (t, 1H), 7.03–7.10 (m, 2H), 7.36—7.90 (m, 4H); IR (cm^{-1}) 3049 (m), 2919, 1630 (m), 1603 (m), 1516 (s), 1341 (s), 980, 728, 560.

Preparation of Compounds **5**

To a suspension of 0.15 g (5 mmol) of 80% sodium hydride in 15 mL of anhydrous benzene was added dropwise a solution of dialkyl phosphite (5 mmol) in

5 mL of anhydrous benzene at room temperature with stirring under the protection with anhydrous nitrogen for 1 hours. Then the solution of ω-bromodienes **7** (4 mmol) in 5 mL of anhydrous benzene was added dropwise with stirring for 6 hours at room temperature, under reflux for 8 to 12 hours, and then 25 mL water was added. The aqueous solution was extracted with 20 mL of benzene, and the extract was dried over anhydrous sodium sulfate. 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 (1:2.5 V/V) as the eluent. The physical data are listed in Table 4.

^{1}H NMR, ^{31}P NMR, IR for some of compounds **5**:

5a. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26–7.38 (m, 5H), 6.99–7.05 (q, 1H), 6.45–6.53 (d, 1H, J = 15.6 Hz), 6.11–6.22 (t, 1H), 5.34–5.47 (q, 1H), 3.65–3.71 (d, 2H, J = 11.1 Hz), 2.29–2.39 (q, 2H), 1.63–1.75 (m, 4H); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4 , 200 MHz) δ 34.95; IR (cm^{-1}) 1620, 1580, 1380, 1240, 1010.

5e. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32 (s, 1H), 6.78–6.92 (m, 2H), 6.02–6.50 (m, 4H), 4.04–4.11 (m, 4H), 2.25–2.35 (q, 2H), 1.70–1.73 (m, 4H), 1.23–1.33 (m, 6H); ^{31}P NMR ($CDCl_3$, 85% H_3PO_4, 200 MHz) δ 32.40.

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