Heteroatom Chemistry
Volume 11, Number 4, 2000

Synthesis and Biological Activity of O, O′-Dialkyl-5-Aryl-1-hydroxy-2E,4E-pentadienylphosphonates

De-Qing Shi, Ru-Yu Chen, and Gui-Qing Huang

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

Received 29 October 1999; revised 1 March 2000

ABSTRACT: *A series of O,O-dialkyl-5-aryl-1-hydroxy-2E,4E-pentadienylphosphonates with structures similar to that of abscisic acid were synthesized by the reactions of dialkyl phosphites with 5-aryl-2E,4E-pentadienaldehydes. The structures of all new compounds have been confirmed by ^1H NMR, ^{31}P NMR, and IR spectroscopy and by elemental analysis or MS. The configurations of carbon-carbon double bonds were determined by X-ray diffraction analyses. The bioassays showed that some of these compounds exhibit inhibitory activity on the elongation of wheat coleoptile.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:303–307, 2000

INTRODUCTION

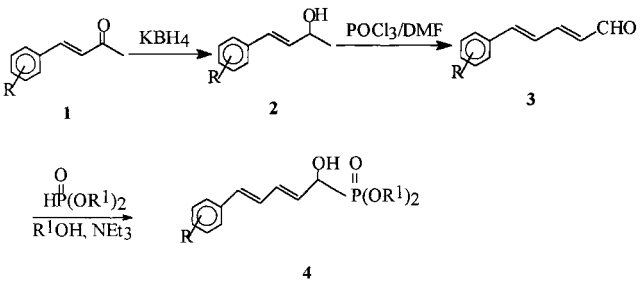
Abscisic acid (ABA) is one of the plant hormones that was isolated from young cotton fruits in 1963 [1]. It not only inhibits plant growth, but also keeps plants from deprivation of water during drought days [2]. We have reported the synthesis of the unsaturated phosphonates, analogues to ABA, some of which exhibit plant growth–regulating activity [3]. Hydroxyalkylphosphonic acids and their derivatives appear to be very important for their wide biological activities in the inhibition of enzymes [4,5], fungicides [6], and plant growth regulation [7,8]. In an attempt to discover new plant growth regulators, we designed and synthesized a number of new title compounds **4.** The synthetic route is shown in Scheme 1. Preliminary bioassays indicate that some of these compounds have inhibitory activity on the elongation of wheat coleoptile.

The structures of all products were confirmed by ^{1}H NMR, ^{31}P NMR, and IR spectroscopy and by MS and elemental analysis, and one of them was analyzed by X-ray diffraction.

RESULTS AND DISCUSSION

Synthesis of 5-Aryl-1-hydroxy-2E,4E-pentadienylphosphonates **4**

The reaction of dialkyl phosphites with aldehydes is a convenient method used to synthesize α-hydroxy-



R=H, *o*-Cl, p-Cl, p-OCH_3, 3,4-dioxymethylene; R^1=Me, Et, i-Pr.

SCHEME 1

Correspondence to: Ru-Yu Chen
Contract Grant Sponsor: National Natural Science Foundation of China.

phosphonates. There are some reports on the synthesis of hydroxyalkenylphosphonates [9,10]. However, there are few reports on the reaction of dialkyl phosphites with dienylaldehydes. Herein we report the reaction of dialkyl phosphites with 5-aryl-2*E*,4*E*-pentadienaldehydes to produce *O,O′*-dialkyl-5-aryl-1-hydroxy-2*E*,4*E*-pentadienylphosphonates, the phosphonate analogues of ABA. One-pot reactions under mild conditions resulted in high yields of the products as shown in Scheme 1.

The reaction of dialkyl phosphites with 5-aryl-2*E*,4*E*-pentadienals **3** was remarkably affected by the steric effects of the R groups in the phosphites (see Table 1). Data in Table 1 indicate that the use of large alkyl groups of dialkyl phosphites require a higher reaction temperature and a prolonged reaction time.

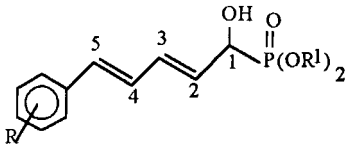
However, the addition of a base (triethylamine) was essential to the addition reaction. Without the use of the triethylamine as a catalyst, the reaction is greatly slowed and the yield is also very low.

We found that the products were racemic mixtures by the determination of their optical activities ($[\alpha]_D^{25}$).

However, the addition reaction of dialkyl phosphites to *β*-lonone did not take place in the presence of triethylamine under reflux for 12 hours. This was probably due to the low reactivity of *β*-lonone.

The Structures of the Title Compounds **4**

The molecular structures of all new compounds obtained were confirmed by ^{1}H NMR, ^{31}P NMR, and IR spectra, also MS and elemental analyses. All results are listed in Table 2.



For ^{1}H NMR spectra, when R^1 was Me, the hydrogens of the *O*Me displayed one set of double peaks. But when it was Pr^i, the hydrogens of the two methyl groups of the *O*Pr^i remained in different magnetic environments, giving different chemical shifts and displayed two sets of double peaks. The hydrogen of the hydroxyl group of all compounds displayed one wide single peak. The hydrogen of C_1 gave one set of equivalent quartet peaks, and three hydrogens of the two carbon-carbon double bonds gave undistinguished chemical shifts. If the R group was H and *p*-Cl, the hydrogens of the phenyl group displayed one set of multiple peaks. However, if the R group was *o*-Cl and *p*-*O*CH$_3$, the hydrogens of the phenyl group showed two sets of peaks.

For ^{31}P NMR spectra, the phosphorus atom of all compounds displayed a single peak, giving chemical shifts between 19 and 24 ppm.

The EI mass spectra of all compounds gave the anticipated molecular ion peaks.

The IR spectra of all compounds showed normal stretching absorption bands indicating the existence of the OH($\sim$3250cm^{-1}), P=O ($\sim$1180 cm^{-1}), C=C ($\sim$1630 cm^{-1}) and phosphonate diester groups ($\sim$1100, 1000 cm^{-1}).

A single crystal of compound **4e** was cultured from a mixture of ether and petroleum ether. X-ray diffraction analysis proved the molecular structure of **4e** (see Figure 1). The single crystal of **4e** is triclinic, space group P$\bar{1}$, cell parameter A = 7.948, B = 10.487, C = 13.101Å, α = 68.22, β = 78.00, γ = 77.31°, V = 9779.4Å^3, Mr = 357.77, Z = 2, Dc = 1.213 g/cm^3, μ = 0.292 mm^{-1}, F (000) = 378, R = 0.079, Rw = 0.222. The molecular structure of **4e** shows that the two carbon-carbon double bonds have *E*-configurations (see Figure 1). Obviously it is consistent with the previous conclusion. The selected bond distances and angles are listed in Tables 3 and 4.

TABLE 1 Reaction Conditions and Experimental Data

Compound	*R*	*R*^{1}	*state*	*m.p.* (°*C*)	*Reaction Temp.* (°*C*)	*Reaction Time* (*h*)	*Yield* (%)
4a	H	Et	light yellow crystal	54–56	25 ± 1	24	83
4b	H	Me	light gray solid	106–108	25 ± 1	16	88
4c	*p*-Cl	Et	colorless crystal	58–60	25 ± 1	24	80
4d	*p*-Cl	Me	colorless crystal	96–98	25 ± 1	16	85
4e	*p*-Cl	Pr^i	light gray crystal	62–64	reflux	8	75
4f	*o*-Cl	Et	colorless crystal	115–116	25 ± 1	24	82
4g	*o*-Cl	Pr^i	light yellow syrup		reflux	8	68
4h	*p*-*O*CH$_3$	Et	light yellow solid	74–76	25 ± 1	24	78
4i	*p*-*O*CH$_3$	Me	colorless crystal	124–125	25 ± 1	16	92
4j	3,4-*O*CH$_2$*O*-	Et	light gray crystal	102–104	25 ± 1	24	86
4k	3,4-*O*CH$_2$*O*-	Me	light gray crystal	120–122	25 ± 1	16	91

TABLE 2 The Data of Compounds **4**

Compound	^1H NMR and ^{31}P NMR (*ppm*)	IR (cm^{-1})	*Elemental Analysis* (%) *or MS Data* (*m/e*)		
			C	*H*	*N*
4a	1.28–1.36 (m,6H,2CH_3), 4.05 (sb,1H,OH), 4.14–4.21 (dq,4H,2CH_2), 4.53–4.63 (q,1H,C_1-H), 5.84–5.97 (m,1H,C_2-H), 6.50–6.85 (m,3H,C_3-H,C_4-H,C_5-H), 7.24–7.35 (m,5H)	3250 (sb, OH), 3010, 2980, 1630, 1230 (s, P=O)	296(M^+), 267, 159, 129, 111, 91(100%), 81, 65, 29		
4b	3.21 (sb,1H,OH), 3.49–3.84 (d,6H, $J^3_{P\text{-}H}$ = 10.43Hz, 2OCH_3), 4.57–4.68 (q,1H,C_1-H), 5.83–5.97 (m,1H,C_2-H), 6.48–6.83 (m,3H,C_3-H,C_4-H,C_5-H), 7.2–7.39 (m,5H)	3244 (sb, OH), 3000, 1642, 1235 (s, P=O)	58.12 (58.21)	6.15 (6.34)	
4c	1.28–1.35 (t, 6H, 2CH_3), 3.69 (s, b, H1, OH), 4.09–4.24 (dq,4H,2CH_2), 4.53–4.63 (q,H1,C_1-H), 5.84–5.98 (m,1H,C_2-H), 6.40–6.78 (m,3H,C_3-H,C_4-H,C_5-H), 7.21–7.28 (m, 4H). ^{31}P NMR: 21.498	3262 (mb, OH) 3010, 2998, 1640, 1238 (s, P=O), 1056 (s)	54.26 (54.46)	5.97 (6.05)	
4d	3.63 (sb,1H,OH), 3.76–3.82 (d, 6H, $J^3_{P\text{-}H}$ = 10.41Hz, 2OCH_3), 4.55–4.65 (q, 1H, C_1-H), 5.84–5.98 (m, 1H, C_2-H), 6.43–6.75 (m, 3H, C_3-H, C_4-H, C_5-H), 7.19–7.24 (m, 4H). ^{31}P NMR: 23.649	3259 (mb, OH) 3023, 2958, 1635, 1236 (s, P=O), 1058 (s)	51.48 (51.57)	5.23 (5.29)	
4e	1.29–1.33 (q, 12H, 4CH_3), 3.62 (sb, 1H, OH), 4.52–4.69 (q,1H,C_1-H), 4.70–4.74 (m, 2H, 2CH of isopropyl), 5.82–5.96 (m, 1H, C_2-H), 6.50–6.78 (m,3H,C_3-H,C_4-H,C_5-H), 7.21–7.27 (m, 4H). ^{31}P NMR: 19.883	3252 (mb, OH) 3035, 2995, 1642, 1235 (s, P=O), 1062 (s)	56.75 (56.95)	6.42 (6.69)	
4f	1.27–1.33 (1, 6H, 2CH_3), 3.40 (s b, 1H, OH), 4.12–4.20 (dq,4H,2CH_2), 4.55–4.64 (q,1H,C_1-H), 5.89–6.02 (m,1H,C_2-H), 6.58–6.91 (m,3H,C_3-H,C_4-H,C_5-H), 7.13–7.22 (m, 4H). ^{31}P NMR: 21.591	3273 (s b, OH) 3040, 2985, 1632, 1238 (s, P=O), 1050 (s)	54.36 (54.46)	6.03 (6.05)	
4g	1.31–1.34 (q, 12H, 4CH_3), 2.35 (sb, 1H, OH), 4.50–4.68 (q,1H,C_1-H), 4.70–4.81 (m,2H,2CH of iso-propyl), 5.83–5.96 (m,H1,C_2-H), 6.50–6.92 (m,3H,C_3-H,C_4-H,C_5-H), 7.17–7.42 (m,4H).	3258 (mb, OH) 3020, 2960, 1634, 1235 (s, P=O), 1058 (s)	358,360 (M^+, 3:1), 316, 256, 245, 220, 193, 125, 109, 82, 43 (100%), 81, 65, 29		
4h	1.28–1.35 (t, 6H, 2CH_3), 3.29 (sb, 1H, OH), 3.78 (s, 3H, OCH_3), 4.10–4.22 (dq,4H,2CH_2), 4.50–4.61 (q,1H,C_1-H), 5.78–5.91 (m,1H,C_2-H), 6.48–6.78 (m,3H,C_3-H,C_4-H,C_5-H), 6.80–6.84 (d, 2H, *J* = 8.4Hz), 7.24–7.32 (t, 2H). ^{31}P NMR: 21.77	3270 (sb, OH) 3002, 2982, 1630, 1240 (s, P=O)	58.67 (58.90)	7.15 (7.06)	
4i	2.66 (sb, 1H, OH), 3.79 (s, 3H, OCH_3), 3.80–3.84 (d, 6H, $J^3_{P\text{-}H}$ = 9.94Hz, 2OCH_3), 4.54–4.64 (q, 1H, C_1-H), 5.77–5.91 (m, 1H, C_2-H), 6.50–6.71 (m, 3H, C_3-H, C_4-H, C_5-H), 6.81–6.85 (d, 2H, *J* = 8.99Hz), 7.24–7.33 (t, 2H). ^{31}P NMR: 23.75	3250 (sb, OH) 3010, 2950, 1635, 1230 (s, P=O), 1050 (s)	56.23 (56.38)	6.42 (6.38)	
4j	1.28–1.35 (t, 6H, 2CH_3), 2.87 (sb, 1H, OH), 3.78 (s, 3H, OCH_3), 4.10–4.22 (dq,4H,2CH_2), 4.51–4.61 (q,1H,C_1-H), 5.80–5.92 (m,1H,C_2-H), 5.93 (s, 2H-OCH_2O-), 6.49–6.73 (m,3H,C_3-H,C_4-H,C_3-H), 6.74–6.909 (m, 3H). ^{31}P NMR: 21.71	3276 (sb, OH) 3030, 2995, 1631, 1240 (s, P=O), 1035 (s)	56.30 (56.47)	5.98 (6.18)	
4k	3.54 (sb,1H,OH), 3.73–3.79 (d, 6H, $J^3_{P\text{-}H}$ = 10.42Hz, 2OCH_3), 4.51–4.61 (q, 1H, C_1-H), 5.78–5.87 (m, 1H, C_2-H), 5.88 (s, 2H-OCH_2O-), 6.45–6.68 (m, 3H, C_3-H, C_4-H, C_5-H), 6.69–6.85 (m, 3H).	3255 (mb, OH) 3045, 2995, 1638, 1235 (s, P=O), 1060 (s), 750 (s)	53.71 (53.85)	4.96 (5.35)	

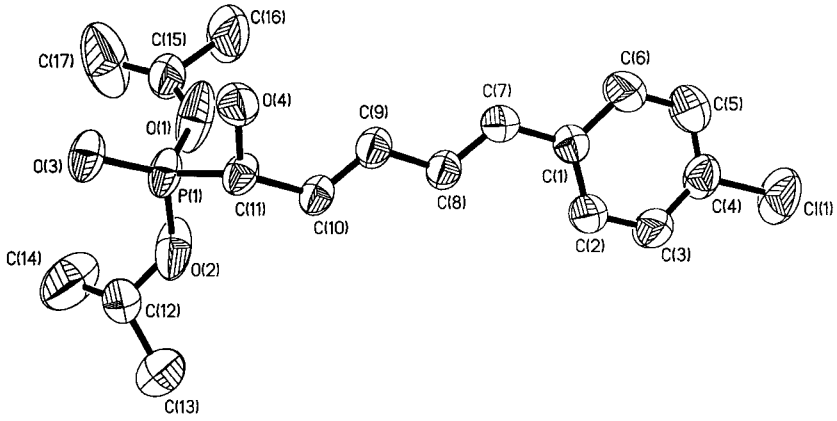


FIGURE 1 Crystal structure of **4e**.

TABLE 3 Selected Bond Lengths (Å) of **4e**

Bond	*Distance*	*Bond*	*Distance*
P(1)–O(3)	1.459(3)	C(2)–C(3)	1.374(6)
P(1)–O(2)	1.536(4)	C(3)–C(4)	1.341(7)
P(1)–O(1)	1.564(4)	C(4)–C(5)	1.348(8)
P(1)–C(11)	1.822(4)	C(5)–C(6)	1.384(7)
Cl(1)–C(4)	1.735(5)	C(7)–C(8)	1.338(6)
O(4′)–C(11)	1.287(6)	C(8)–C(9)	1.440(5)
O(4)–C(11)	1.303(6)	C(9)–C(10)	1.315(6)
O(2)–C(12)	1.378(6)	C(10)–C(11)	1.502(5)
O(1)–C(15)	1.290(8)	C(12)–C(14)	1.358(8)
C(1)-C(6)	1.376(6)	C(12)–C(13)	1.520(7)
C(1)–C(2)	1.378(6)	C(15)–C(17)	1.276(9)
C(1)–C(7)	1.459(6)	C(15)–C(16)	1.524(9)

TABLE 4 Selected Bond Angles (°) of **4e**

Angle	(°)	*Angle*	(°)
O(3)–P(1)–O(2)	115.8(2)	C(1)–C(6)–C(5)	121.7(5)
O(3)–P(1)–O(1)	115.5(2)	C(8)–C(7)–C(1)	126.9(4)
O(2)–P(1)–O(1)	102.6(3)	C(7)–C(8)–C(9)	124.8(4)
O(3)–P(1)–C(11)	113.34(16)	C(10)–C(9)–C(8)	125.0(4)
O(2)–P(1)–C(11)	104.33(19)	C(9)–C(10)–C(11)	126.1(4)
O(1)–P(1)–C(11)	103.8(2)	O(4′)–C(11)–O(4)	102.8(4)
C(12)–O(2)–P(1)	131.6(3)	O(4′)–C(11)–C(10)	111.2(4)
C(15)–O(1)–P(1)	136.3(4)	O(4)–C(11)–C(10)	115.5(4)
C(6)–C(1)–C(2)	116.5(4)	O(4′)–C(11)–P(1)	108.0(3)
C(6)–C(1)–C(7)	120.0(4)	O(4)–C(11)–P(1)	105.6(3)
C(2)–C(1)–C(7)	123.5(4)	C(10)–C(11)–P(1)	112.9(2)
C(3)–C(2)–C(1)	121.3(5)	C(14)–C(12)–O(2)	120.6(6)
C(4)–C(3)–C(2)	120.8(5)	C(14)–C(12)–C(13)	115.5(5)
C(3)–C(4)–C(5)	120.0(5)	O(2)–C(12)–C(13)	109.2(4)
C(3)–C(4)–Cl(1)	120.4(5)	O(1)–C(15)–C(17)	138.9(7)
C(5)–C(4)–Cl(1)	119.6(4)	O(1)–C(15)–C(16)	105.7(6)
C(4)–C(5)–C(6)	119.8(5)	C(17)–C(15)–C(16)	115.1(7)

Plant Growth Regulating Activities

The results of preliminary tests for the plant growth regulating activities indicated that some of the title compounds exhibit inhibitory activity on the elongation of wheat coleoptile. The data for the bioassays are listed in Table 5.

Preliminary tests indicated that some of the compounds **4** exhibit a certain extent of inhibitory activity on the elongation of wheat coleoptile (see Table 5). The substituents R of the phenyl group have some effects on the biological activity. When R is *p*-Cl, the compounds **4c** and **e** exhibits better inhibitory activity, whereas the ester groups have little effect.

EXPERIMENTAL

Instruments

^{1}H NMR and ^{31}P NMR spectra were recorded with a BRUKER AC-P200 spectrometer with TMS and 85% H_3PO_4 as the internal and external reference respectively and with $CDCl_3$ as the solvent. Mass spectra

TABLE 5 The Plant Growth Regulating Activities of Some New Compounds **4**[a]

Compound	*100 ppm* (%)	*10 ppm* (%)
4a	−10.62	−7.96
4c	−38.05	−8.85
4d	−24.34	−8.40
4e	−32.74	−7.08
4f	−17.70	−1.33
4i	−15.04	−3.54
4j	−7.08	−2.65

*Wheat coleoptile tests, inhibition %.

were recorded with a VG ZAB-HS spectrometer using the EI method. The IR spectra were measured by a SHIMADZU-435 instrument. Elemental analyses was performed with a Yanaco-CHN CORDER MT-3 elementary analyzer. Melting Points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Column chromatography was performed on silica gel GF_{254} (Qing dao Hai yang Chemical Group Co. of China).

The reagents and solvents were available commercially and purified according to conventional methods before use. 4-Aryl-3-butenones-2 (**1**) were prepared by aldol condensation of substituted benzaldehydes with acetone according to the literature [11].

4-Aryl-3-butenols-2 (**2**)

General Procedure. To a solution of 70 mmol of 4-Aryl-3-butenones-2 (**1**) in 120 mL of anhydrous methanol was added 70 mmol of potassium borohydride during 1 hour under cooling (−10°C to −5°C) and stirring for another hour. The reaction mixture was stirred at room temperature for 2 hours, cooled to 0°C, and the mixture was acidified by the slow addition of 2N aqueous hydrochloric acid. The mixture 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: 86–96%).

Data of Compounds **2a** *&* **2c**. **2a**: R = H, light yellow liquid, yield: 96%. ^{1}H NMR ($CDCl_3$): 1.35–1.36 (d, 3H, J = 6.95Hz, CH_3), 2.47 (sb, 1H, OH), 4.40–4.53 (m, 1H, CH), 6.20–630 (q, 1H, CH=), 6.51–6.59 (d, 1H, J = 15.80Hz), 7.28–7.39 (m, 5H).

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

5-Aryl-2E,4E-pentadienals (**3**)

Compounds 3 [2] were obtained by the Vilsmeier reaction of 4-Aryl-3-butenols-2 (2) with $POCl_3$ and DMF.

Data of Compounds **3a** *and* **3e.** **3a:** R = H, light yellow crystal, m.p.: 46–48°C, yield: 76%. ^{1}H NMR ($CDCl_3$): 6.19–6.31 (q, 1H, CH=), 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,J = 8.1Hz, CHO)

3e: R = 3,4-di*oxy*methylene, red-brown solid, m.p.:92–94°C, yield: 88%. ^{1}H NMR($CDCl_3$): 5.97 (s, 2H, -OCH_2O-) 6.13–6.25 (q, 1H, CH=), 6.79–6.99 (m, 4H), 7.13–7.26 (q, 2H), 7.36–7.51 (m, 5H), 9.54–9.58 (d, 1H, J = 8.3Hz, CHO).

O,O′-Dialkyl-5-aryl-1-hydroxy-2E,4E-pentadienylphosphonates (**4**)

General Procedure. 2 mmol of dienal (**3**), 8 mmol of triethylamine, and 4 mmol of dimethyl phosphite in 10 mL of anhydrous methanol (diethyl phosphite in ethanol or diisopropyl phosphite in 2-propanol, respectively) were added into a 25 mL reaction flask. The mixture was then stirred at room temperature or under reflux (see Table 1). The phosphite diester was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether-ethyl acetate (1:2–3, v/v) as the eluent.

A single crystal (**4e**) was cultured from ether-petroleum ether (60–90°C)(2:1, v/v), and its molecular structure was determined by X-ray diffraction (see Figure 1).

REFERENCES

[1] Ohkuma, K.; Lyon, T. L.; Addicott, F. T. Science 1963, 142, 1592.
[2] Parameswara Reddy, M.; Krishna Rao, G. S. Synthesis 1980, 815.
[3] Shi, D. Q.; Wang, Y. M.; Chen, R. Y. Heteroat Chem (In press).
[4] Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. Tetrahedron Lett 1990, 31, 5587.
[5] Stowasser, B.; Budt, K.-H.; Li, J. Q. et al. Tetrahedron Lett 1992, 33, 6625.
[6] Maier, L.; Spoerri, H. Phosphorus Sulfur Silicon Relat Elem 1992, 70, 49.
[7] He, H. W.; Wang, J.; Liu, Z. J. Chin J Appl Chem 1994, 11, 21.
[8] Vassilev, G. N.; Petrova, J.; Momchilova, S.; Vassilev, N. G. Dokl Blug Akad Nauk 1992, 45, 87.
[9] Fulvia, O. Tetrahedron Lett 1998, 39, 1425.
[10] Tsutomu, Y.; Takehiro, Y.; Shiroshi, S. Synlett 1995, 1035.
[11] Gilman, H.; Blatt, A. H. Org Synth Coll 1 1941, 77.