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Studies on Organophosphorus Compounds 81. A Novel Synthetic Approach to Substituted Cyclopentane-1,1-diylbisphosphonates via Pd(0) Catalyzed Enyne Cyclization

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ABSTRACT

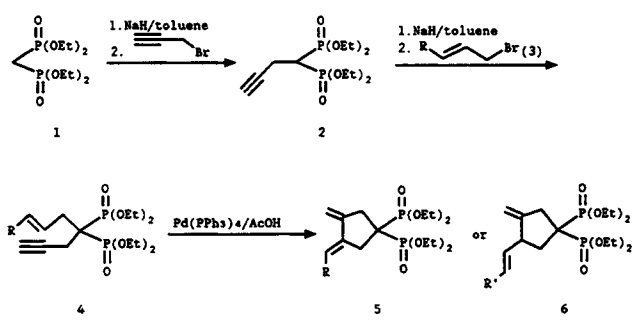
Intramolecular enyne cycloisomerization reactions catalyzed by $Pd(PPh_3)_4$ gave 4-substituted 3-methylenecyclopentane-1,1-diylbisphosphonates in good yield.

INTRODUCTION

Methylenebisphosphonic acid and its derivatives are of considerable interest because of their important biological activities. They can act as antivirus agents [1], as calcium metabolism regulators [2], and as ligands in ^{99m}Tc radiopharmaceuticals [3]. These biological properties appear to be related to their abilities to chelate metal ions. Alicyclic bisphosphonates offer an important means to modify coordination aptitutes and therefore may impose significant effects on their biological properties. Hence, their synthesis is of interest. Unfortunately, only a few methods have been reported in the literature [4–7]. Ebetino and co-workers reported the synthesis of cyclopentane-1,1-diylbisphosphonates by the dialkylation reaction of methylenebisphosphonate with 1,4-dibromo-butane [4]. This method, however, suffered from the difficult purification of products caused by the contamination of monoalkylated by-products, the excess methylenebisphosphonate, and the unavailability of appropriate 1,4-dihalides. Nasser et al. also reported similar results [5]. Herein, we wish to report a novel method for the synthesis of substituted cyclopentane-1,1-diylbisphosphonates **5** and **6** via palladium(0) catalyzed enyne cyclizations [8].

RESULTS AND DISCUSSION

As shown in Scheme 1, reaction of the methylenebisphosphonate **1** with propargyl bromide gave the alkylation product **2** which, by further alkylation with allyl bromide derivatives **3**, led to the corresponding 1,6-enyne-4,4-diylphosphonates **4**.



Scheme 1

Dedicated to Prof. Antonino Fava on the occasion of his seventieth birthday.

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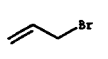
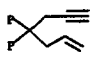
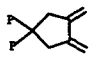
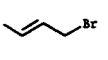
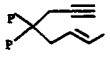
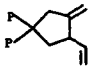
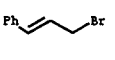
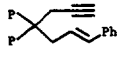
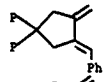
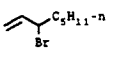
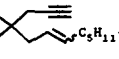
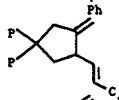
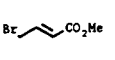
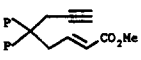
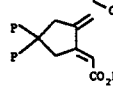
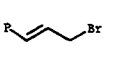
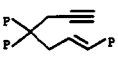
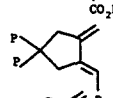
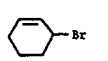
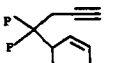
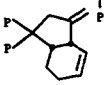
TABLE 1 Synthesis of Compounds **4**, **5**, and **6**

Entry	3	4	5,6	Time (h)	Yield (%)[a]
a				6	90
b				8	85
c				10	82
d				12	83
e				12	63
f				15	76
g				10	83

[a]Isolated yields based on the corresponding **4**. P=P(O) $(OEt)_2$.

The palladium catalyzed 1,6-enyne cycloisomerization is the key step in the formation of cyclopentane derivatives. As indicated in the literature, both palladium(2+) and palladium(0) can catalyze this kind of reaction. In our experiments, we chose the readily available Pd $(PPh_3)_4$ as the catalyst and AcOH as the solvent. When heated at 80°C for 6–15 hours, compounds **4** isomerized readily to the corresponding cyclopentane-1,1-diylbisphosphonate derivatives **5**, **6** in good yields. The isomerizations proceeded smoothly with excellent regio- and stereoselectivity. Substrates **4** containing methyl or methylene groups in the allylic position underwent the isomerization, yielding exclusively 1,4-dienes. Otherwise, 1,3-dienes were produced as the sole products. In the reactions of **4c, d, e, f**, only the E-configurational olefins were obtained. For the case of **4g**, only the cis-configurational isomer was isolated, its structure being proven by its ^1H NMR spectra.

Although the reaction mechanisms have not been satisfactorily solved and are still the subject of continued research, the reaction mechanism may best be rationalized by the hydropalladation pathway rather than by the cyclopalladation pathway, based on Trost's discussions [8]. Hydridopalladium acetate, "PdHX," might be formed in situ and catalyzes the isomerization. The configurations of the products served as evidence for the proposed hydropalladation pathway [8].

As shown in Table 1, the $Pd(PPh_3)_4$-catalyzed cycloisomerization of compounds **4** proceeded smoothly with either electron-rich alkenes or electron-deficient alkenes (entries e and f) without the presence of an additional coordinating ligand or a co-catalyst. Although the second alkylation step with allyl bromide derivatives gave relatively low yields due to the poor reactivity of the anion of **2**, caused by the presence of the two bulky phosphonate groups, this method was proven to be an efficient route to cyclopentane derivatives **5** or **6**, which are of potential use in the preparation of other bisphosphonate derivatives. For example, compounds **5** may act as dienes in Diels-Alder reactions. By further transformations of the double bonds, compounds **5** or **6** can be transferred to the corresponding cyclopenta-3-none-1,1-diylbisphosphonate derivatives. By subsequent hydrolysis using standard procedures with hydrochloric acid or trimethylbromosilane, compounds **5** or **6** can be readily converted to the corresponding free acids, which are of potential biological interest.

EXPERIMENTAL

Tetraethyl methylenebisphosphonate **1** was prepared by the method described by us recently [9]. 3-Bromooct-1-ene (**3d**), methyl 4-bromocrotonate (**3e**), and 2-bromocyclohex-1-ene (**3g**) were prepared according to the literature [10]. Diethyl (E)-4-bromobut-2-en-1-ylphosphonate (**3f**) was synthesized by Hashimoto et al.'s method [11]. Toluene was dried over Na and distilled prior to use. Propargyl bromide was purchased from Aldrich Chemical Co., Milwaukee, WI. Other reagents were obtained from a local source (Shanghai Chemical Co.). ^1H and ^{31}P NMR spectra were recorded on an AMX-300 NMR spectrometer with TMS as the internal standard and 85% H_3PO_4 as the external standard for ^{31}P NMR. The coupling constant J is given in Hertz. EIMS spectra were taken on a Finnigan-4021 mass spectrometer. IR spectra were measured on an IR-440 infrared spectrometer.

Tetraethyl But-3-yn-1,1-diylbisphosphonate (**2**)

A mixture of NaH (0.30 g, 10 mmol) and toluene (40 mL) was placed in a 100 mL three-necked flask under nitrogen placed in an ice-cooled bath. Tetraethyl methylenebisphosphonate (**1**, 2.88 g, 10 mmol) was added dropwise to the solution at 0°C. After the complete addition, the solution was stirred at r.t. for 2 hours. Propargyl bromide (1.32 g, 11 mmol) was added dropwise. The mixture was then heated at 60°C for 4 hours. Hydrochloric acid (1 N) was added until the pH was slightly acidic. The mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After the removal of the solvents, the resulting crude product was purified through column chromatography on silica with the eluent of petroether/acetone (1/1, v/v) to give the pure product **2** as a colorless oil. Yield: 2.28 g (70%).

IR (film) ν 1240, 1020. EIMS: m/z 327 (M^++H), 189. ^{1}H NMR ($CDCl_3$) δ 1.30 (12H, t, J = 7, CH_3), 1.90 (1H, br, CH), 2.20–2.60 (3H, m, CHP + CH_2), 4.10 (8H, m, CH_2O). ^{31}P NMR ($CDCl_3$)δ 23.59. Anal. calcd for $C_{12}H_{24}O_6P_2$: C, 44.18; H, 7.42. Found: C, 44.32; H, 7.23.

Tetraethyl Hept-1-yn-6-en-4, 4-diylbisphosphonate (**4a**)

General Procedure. The mixture of NaH (30 mg, 1 mmol) and toluene (20 mL) was placed in a 100 mL three-necked flask under nitrogen with use of an ice-cooled bath. Tetraethyl but-3-yn-1, 1-diyl-bisphosphonate (**2**, 0.326 g, 1 mmol) was added dropwise to the solution at 0°C. After the complete addition, the solution was stirred at r.t. for 2 hours. Allyl bromide (0.17 g, 1.4 mmol) was added dropwise. The mixture was then refluxed for 2 hours. Hydrochloric acid (1 N) was added until the pH was slightly acidic. The mixture extracted with ether (4 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After the removal of the solvent, the resulting crude product was purified by column chromatography on silica, the eluent being petroether/acetone (1.5/1, v/v), to give the pure product **4a** as a colorless oil. Yield: 0.14 g (38%).

IR (film) ν 1240, 1020, 970. EIMS: m/z 367 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.35 (12H, t, J = 7, CH_3), 1.88 (1H, t, J = 6, $CH_2C\equiv$), 2.13 (1H, dt, J = 28, 3, $CH_2C\equiv$), 2.80 (3H, m, CH_2–C= + ≡CH), 4.18 (8H, q, J = 7, CH_2O), 5.10 (2H, m, CH_2=), 6.02 (1H, m, CH=). ^{31}P NMR ($CDCl_3$) δ 24.70. Anal. calcd for $C_{15}H_{28}O_6P_2$: C, 49.19; H, 7.71. Found: C, 49.02; H, 7.78.

Tetraethyl (E)-Oct-1-yn-6-en-4,4-diylbisphosphonate (**4b**)

Yield: 35%. Colorless oil. IR (film) ν 1240, 1020, 965. EIMS: m/z 381 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.32 (12H, t, J = 7, CH_3CH_2O), 1.68 (3H, d, J = 4, CH_3), 1.78 (2H, m, $CH_2C\equiv$), 2.50–3.00 (3H, m, CH_2C= + ≡CH), 4.19 (8H, m, CH_2O), 5.60 (2H, m, CH=CH). ^{31}P NMR ($CDCl_3$) δ 24.59. Anal. calcd for $C_{16}H_{30}O_6P_2$: C, 50.53; H, 7.95. Found: C, 50.69; H, 7.67.

Tetraethyl (E)-1-Phenylhept-6-yn-1-en-4,4-diylbisphosphonate (**4c**)

Yield: 30%. Colorless oil. IR (film) ν 1600, 1240, 1020, 970. EIMS: m/z 443 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.30 (12H, t, J = 7, CH_3), 2.12 (1H, m, $CH_2C\equiv$), 2.82–3.05 (4H, m, CH_2C= + ≡CH + $CH_2C\equiv$), 4.15 (8H, m, J = 7, CH_2O), 6.20–6.60 (2H, m, CH=CH), 7.30 (5H, m, C_6H_5). ^{31}P NMR ($CDCL_3$) δ 24.04. Anal. calcd for $C_{21}H_{32}O_6P_2$: C, 57.02; H, 7.29. Found: C, 57.32; H, 7.14.

Tetraethyl Dodec-1-yn-6-en-4,4-diylbisphosphonate (**4d**)

Prepared by the reaction of 3-bromooct-1-ene (**3d**) with **2**. Yield: 25%. Colorless oil. IR (film) ν 1240, 1020, 970. EIMS: m/z 437 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7, CH_3), 1.32 (16H, t, J = 7, $C\underline{H}_3CH_2O$ + $CH_3C\underline{H}_2C\underline{H}_2$), 2.05 (4H, m, 3, 9-H), 2.78 (5H, m, 1, 5, 8-H), 4.17 (8H, m, CH_2O), 5.55 (2H, m, CH=CH). ^{31}P NMR ($CDCl_3$) δ 24.41. Anal. calcd for $C_{20}H_{38}O_6P_2$: C, 55.04; H, 8.78. Found: C, 55.03; H, 8.51.

Tetraethyl (E)-1-Methoxycarbonylhept-6-yn-1-en-4,4-diylbisphosphonate (**4e**)

Yield: 30%. Colorless oil. IR (film) ν 1725, 1240, 1020, 970. EIMS: m/z 425 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.30 (12H, t, J = 7, $C\underline{H}_3CH_2O$), 2.10 (2H, m, $CH_2C\equiv$), 2.85–3.05 (3H, m, CH_2C= + ≡CH), 3.75 (3H, s, CH_3O), 4.15 (8H, q, J = 7, CH_2O), 5.95 (1H, m, CH=), 7.10 (1H, m, CH=). ^{31}P NMR ($CDCl_3$) δ 22.70 (s), 23.10 (s). Anal. calcd for $C_{17}H_{30}O_6P_2$: C, 48.12; H, 7.13. Found: C, 48.25; H, 7.04.

Hexaethyl (E)-Hept-6-yn-1-en-1,4,4-triyltrisphosphonate (**4f**)

Yield: 27%. Colorless oil. IR (film) ν 1250, 1025. EIMS: m/z 503 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.32 (18H, m, CH_3), 1.90 (2H, m, $CH_2C\equiv$), 2.70–3.00 (3H, m, ≡CH + CH_2C=), 4.18 (12H, m, CH_2O), 5.50–6.40 (2H, m, CH=CH). ^{31}P NMR ($CDCl_3$) δ 15.50 (=CHP), 24.25 (CP_2). Anal. calcd for $C_{19}H_{37}O_9P_3$: C, 45.43; H, 7.42. Found: C, 45.21; H, 7.59.

*Tetraethyl 1-(Cyclohex-2'-en-1'-yl)*but-3-yn-1,1-diylbisphosphonate (**4g**)

Yield: 32%. Colorless oil. IR (film) ν 1235, 1025, 965. EIMS: m/z 407 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.32 (16H, t, J = 7, $C\underline{H}_3CH_2O$ + 5', 6'-H), 1.85–2.10 (3H, m, 2, 4-H), 3.00 (3H, m, 1', 4'-H), 4.15 (8H, m, CH_2O), 5.70 (2H, m, CH=CH). ^{31}P NMR ($CDCl_3$) δ 24.72. Anal. calcd for $C_{18}H_{32}O_6P_2$: C, 53.20; H, 7.94. Found: C, 53.40; H, 7.67.

Tetraethyl 3,4-Dimethylenecyclopentane-1,1-diylbisphosphonate (**5a**)

General Procedure. A mixture of compound **4a** (0.184 g, 0.5 mmol), $Pd(PPh_3)_4$ (29 mg, 5% of 0.5 mmol) and acetic acid (20 mL) was stirred at 80°C under nitrogen for 6 hours. The mixture was concentrated under reduced pressure, and the resulting crude product was purified by column chromatography on silica, the eluent being petroether/acetone (2/1, v/v), to give the pure product **5a** as a colorless oil. Yield: 0.165 g (90%).

IR (film) ν 1240, 1020, 965. EIMS: m/z 367 (M^+

+ H). ^{1}H NMR ($CDCl_3$) δ 1.30 (12H, t, J = 7, CH_3), 3.10 (4H, tt, J = 2, 17, CH_2C=), 4.15 (8H, m, CH_2O), 4.92 (2H, s, CH_2=), 5.38 (2H, s, CH_2=). ^{31}P NMR ($CDCl_3$) δ 27.07. Anal. calcd for $C_{15}H_{28}O_6P_2$: C, 49.19; H, 7.71. Found: C, 49.02; H, 7.89.

Tetraethyl 3-Methylene-4-vinylcyclopentane-1, 1-diylbisphosphonate (**6b**)

Colorless oil. IR (film) ν 1240, 1020, 970. EIMS: m/z 381 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.31 (12H, t, J = 7, CH_3), 1.67 (2H, d, J = 6, $C\underline{H}_2CH$), 2.60 (2H, m, CH_2–C=), 2.98 (1H, m, CH), 4.15 (8H, m, CH_2O), 4.85 (1H, dd, J = 1.6, 4.5, CH_2=), 5.10 (1H, m, CH_2=), 5.53 (2H, m, CH_2=), 6.25 (1H, m, CH=). ^{31}P NMR ($CDCl_3$) δ 27.22 (d, J = 12.5), 27.69 (d, J = 12.5). Anal. calcd for $C_{16}H_{30}O_6P_2$: C, 50.53; H, 7.95. Found: C, 50.77; H, 7.81.

Tetraethyl (E)-3-Methylene-4-phenylmethylenecyclopentane-1,1-diylbisphosphonate (**5c**)

Colorless oil. IR (film) ν 3010, 1600, 1250, 1025. EIMS: m/z 443 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.31 (12H, t, J = 7, CH_3), 3.10–3.30 (4H, m, CH_2), 4.15 (8H, m, CH_2O), 4.95 (2H, m, CH_2=), 5.90 (1H, m, CH), 7.35 (5H, m, C_6H_5). ^{31}P NMR ($CDCl_3$) δ 27.80. Anal. calcd for $C_{21}H_{32}O_6P_2$: C, 57.02; H, 7.29. Found: C, 56.83; H, 7.22.

Tetraethyl (E)-3-Methylene-4-(hex-1'-enyl)cyclopentane-1,1-diylbisphosphonate (**6d**)

Colorless oil. IR (film) ν 1250, 1020, 970. EIMS: m/z 437 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7, CH_3), 1.32 (14H, t, J = 7, $C\underline{H}_3CH_2O$ + CH_3–$C\underline{H}_2$), 1.60–1.80 (4H, m, 5-H + $C\underline{H}_2CH_2C$=), 2.30–2.80 (5H, m, 2,4-H + $C\underline{H}_2$–CH=), 4.10 (8H, m, CH_2O), 4.90–5.00 (2H, m, CH=), 5.60 (2H, m, CH=CH). ^{31}P NMR ($CDCl_3$) δ 27.35. Anal. calcd for $C_{20}H_{38}O_6P_2$: C, 55.04; H, 8.78. Found: c, 55.29; H, 8.60.

Tetraethyl (E)-3-Methylene-4-methoxycarbonylmethylenecyclopentane-1,1-diylbisphosphonate (**5e**)

Colorless oil. IR (film) ν 1720, 1240, 1020, 965. EIMS: m/z 425 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.32 (12H, t, J = 7, CH_3), 3.20–3.80 (4H, m, CH_2), 3.70 (3H, s, CH_3O), 4.20 (8H, m, CH_2O), 5.00 (2H, m, CH_2=), 6.20 (1H, m, CH=). ^{31}P NMR ($CDCl_3$) δ 26.61 (s), 27.09 (s). Anal. calcd for $C_{17}H_{30}O_8P_2$: C, 48.12; H, 7.13. Found: C, 48.02; H, 7.42.

Tetraethyl (E)-3-Methylene-4-diethoxyphosphorylmethylenecyclopentane-1,1-diylbisphosphonate (**5f**)

Colorless oil. IR (film) ν 1250, 1020. EIMS: m/z 503 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.32 (18H, t, J = 7, CH_3), 3.40–3.60 (4H, m, CH_2), 4.15 (12H, m, CH_2O), 4.95 (2H, m, CH_2=), 6.40 (1H, m, CH=). ^{31}P NMR ($CDCl_3$) δ 15.40 (=CHP), 27.35 (CP_2). Anal. calcd for $C_{19}H_{37}O_9P_3$: C, 45.43; H, 7.42. Found: C, 45.43; H, 7.71.

Tetraethyl 9-Methylenebicyclo [4,3,0]nona-2-ene-7, 7-diylbisphosphonate (**6g**)

Colorless oil. IR (film) ν 1240, 1025, 965. EIMS: m/z 407 (M^+ + H). ^{1}H NMR ($CDCl_3$) δ 1.32 (15H, m, $C\underline{H}_3CH_2O$ + 5,6-H), 2.80–3.10 (4H, m, 4,8-H), 3.45 (1H, dd, J = 6, 8, 1-H), 4.15 (8H, m, CH_2O), 4.75 (1H, d, J = 1.5, CH_2=), 4.95 (1H, d, J = 1.5, CH_2=), 5.75 (2H, m, CH=CH). ^{31}P NMR ($CDCl_3$) δ 25.93 (d, J = 8.6), 28.42 (d, J = 8.6). Anal. calcd for $C_{18}H_{32}O_6P_2$: C, 53.20; H, 7.94. Found: C, 53.45; H, 7.81.

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