Synthesis of Ethenylidenebis(phosphonic acid) and Its Tetraalkyl Esters

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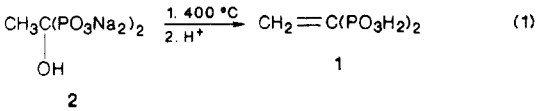
A new method for the preparation of tetraalkyl ethenylidenebis(phosphonates) has been developed. This two-step procedure involves the base-catalyzed reaction of a methylenebis(phosphonate) ester with paraformaldehyde followed by acid-catalyzed elimination of methanol. The effects of variations in the reaction conditions of the first step of this process are described. Ethenylidenebis(phosphonate) esters can be converted to the free acid by reaction with bromotrimethylsilane.

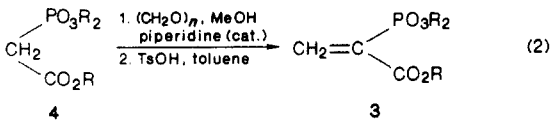
Ethenylidenebis(phosphonic acid) (1) and its esters have found utility as sequestering agents,[1] in the development of polymeric flame retardants,[2] and in certain pharmaceutical applications.[3] Currently, ethenylidenebis(phosphonic acid) is prepared via the thermal dehydration of tetrasodium (1-hydroxyethylidene)bis(phosphonate) (2) at high temperature (eq 1).[1] Disadvantages of this procedure



(1)

include the need for precise control of temperature during the dehydration step and a lengthy and time-consuming purification process. Tetraalkyl esters of ethenylidenebis(phosphonate) can be prepared by the reaction of free acid 1 with trialkyl orthoformates.[4]

We wish to report a two-step, single-flask method of preparing tetraalkyl ethenylidenebis(phosphonates) which is both convenient and efficient. Furthermore, these esters can be readily converted to free acid 1. This new method for producing esters of 1 is derived from a procedure originally developed by Pudovik and co-workers to prepare α-phosphonoacrylate esters 3 from the corresponding phosphonoacetates 4 (eq 2).[5] Reaction of the phosphonoacetate in methanol with paraformaldehyde and a catalytic amount of piperidine followed by an acid-catalyzed elimination step afforded the desired esters 3 in good overall yield.



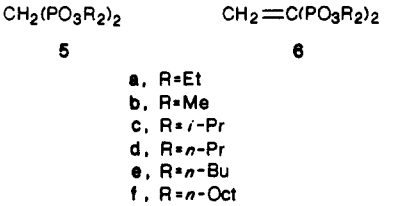
(2)

An initial attempt to directly apply this procedure to the conversion of tetraethyl methylenebis(phosphonate) (**5a**) to ethenylidenebis(phosphonate) **6a** presented two practical problems. First, under these reaction conditions (catalytic piperidine), the reaction of **5a** with paraformaldehyde proved to be considerably slower than that of triethyl α-phosphonoacetate (4, R = Et). Several days of refluxing gave conversions of **5a** in only the 20–40% range. The incompleteness of this reaction presented a second difficulty, namely, the separation of the final product (**6a**) from unreacted **5a**. Since distillation proved ineffective, purification of **6a** required repeated chromatography on silica gel. These difficulties thus rendered the large-scale synthesis of ester **6a** impractical.

Table I. Reaction of Tetraethyl Methylenebis(phosphonate) (5a) with Paraformaldehyde and Piperidine[a]

entry	concn of **5a** (M)	concn of piperidine (M)	concn of paraformaldehyde (M)	half-life of **5a** (h)
1	0.116	0.059	0.578	47
2	0.116	0.117	0.578	31.5
3	0.116	0.347	0.578	14
4	0.116	0.694	1.16	7
5	0.347	0.347	1.74	15

[a] Reactions were monitored by ^{31}P NMR. Half-lifes of **5a** were determined from a plot of % reaction vs. time.



A detailed study of the effects of changes in the reaction conditions of **5a** with paraformaldehyde was undertaken to overcome these problems. It was observed that increasing the concentration of paraformaldehyde in the reaction afforded only a slight improvement in reaction rate. Varying the structure of the amine produced no improvement in the reaction at the catalytic level. However, a significant increase in reaction rate was observed at higher concentrations of base. For example, at a 1:1 molar ratio of piperidine:**5a**, the reaction was 50% complete in 31.5 h (Table I, entry 2). Higher concentrations of piperidine relative to **5a** produced further rate increases but also tended to generate several additional products during the reaction. This problem was particularly severe when the initial concentration of piperidine exceeded that of paraformaldehyde. Additional rate increases could also be achieved by increasing the overall concentrations of the reactants (Table I, entry 5). The results of these studies are summarized in Table I.

While increasing the concentration of piperidine relative to that of **5a** greatly enhanced the reaction rate, concentration of the reaction mixture during workup (see Experimental Section) afforded a number of byproducts which were not observed at lower base levels. These byproducts substantially reduced the yield and purity of the final product **6a**. This problem was overcome by replacing piperidine with a lower boiling amine. Diethylamine

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proved to be particularly effective, producing little or none of the byproducts observed with piperidine as well as providing a further increase in reaction rate.

As a result of these studies it was concluded that the reaction of **5a** with paraformaldehyde could be efficiently conducted by using a 1:1:5 molar ratio of **5a**:diethylamine:paraformaldehyde with the initial concentration of **5a** being about 0.35 M. Under these conditions, the reaction is complete in 21 h, producing mainly an intermediate product which we assign structure **7** based on NMR

$$CH_3OCH_2CH(PO_3Et_2)_2$$
7

and mass spectral data. Refluxing intermediate **7** in toluene with a catalytic amount of *p*-toluenesulfonic acid effects elimination of methanol and affords ester **6a** which can be purified by distillation. This ester can be readily converted to free acid **1** by reaction with bromotrimethylsilane.[6]

The procedure discussed above also provides a means for converting other tetraalkyl methylenebis(phosphonates) (**5b–f**) to the corresponing ethenylidenebis(phosphonate) esters (**6b–f**). A considerable difference in the rates of reaction of **5b–f** with paraformaldehyde was observed depending on the steric bulk of the ester group. For example, tetramethyl ester **5b** reacted completely in less than 1 h, while tetraisopropyl ester **5c** required approximately 5 days.

In summary, a convenient and efficient method has been developed for the synthesis of tetraalkyl ethenylidenebis(phosphonates). This procedure can be readily adapted to large-scale preparations without decrease in product yield or purity. Furthermore, these esters can be readily dealkylated to afford the corresponding free acid **1**.

Experimental Section

Proton and carbon-13 NMR spectra were obtained on a JEOL FX-90Q spectrometer at 89.6 MHz and 22.5 MHz, respectively, using tetramethylsilane as an internal reference. Phosphorus-31 spectra were obtained on the JEOL FX-90Q spectrometer at 36.2 MHz using 85% phosphoric acid as an external standard with an internal deuterium lock. Positive shifts are downfield and negative shifts upfield. Broadband proton decoupling was employed on all carbon-13 and phosphorus-31 NMR spectra. All coupling constants (*J* values) are given in hertz. Chemical ionization mass spectra were obtained on an AEI/Kratos MS-30 spectrometer. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN.

Tetraethyl methylenebis(phosphonate) was purchased from Strem Chemicals and distilled prior to use. The other methylenebis(phosphonate) esters were obtained from Alfa Products or prepared by reaction of methylenebis(phosphonyl dichloride) with the appropriate alcohol and pyridine in toluene.

Tetraethyl Ethenylidenebis(phosphonate) (6a). General Procedure. Paraformaldehyde (104.2 g, 3.47 mol) and diethylamine (50.8 g, 0.69 mol) were combined in 2 L of methanol and the mixture was warmed until clear. The heat was removed and **5a** (200.0 g, 0.69 mol) was added. The mixture was refluxed for 24 h, then an additional 2 L of methanol was added, and the solution was concentrated under vacuum at 35 °C. Toluene (1 L) was added and the solution again concentrated. This last step was repeated to ensure complete removal of methanol from the product (**7**) which was obtained as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 4.02 (m, 8 H, OCH_2CH_3, J = 7.3), 3.63 (overlapping m, 2 H, CH_3OCH_2, J = 5.4 and 15.6), 3.20 (s, 3 H, CH_3O), 2.52 (tt, 1 H, PCHP, J = 6.0 and 24.0), 1.18 (t, 12 H, CH_2CH_3, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 67.8 (t, CH_3OCH_2, J = 4.4), 62.2 (d, OCH_2CH_3, J = 4.4), 58.3 (s, CH_3O), 38.5 (t, PCP, J = 132.4), 16.0 (d, OCH_2CH_3, J = 7.4); ^{31}P NMR ($CDCl_3$) δ +21.0; ammonia CI mass spectrum, m/e 350 $(M + NH_4)^+$.

Intermediate **7** was dissolved in 1 L of dry toluene. *p*-Toluenesulfonic acid monohydrate (0.50 g) was added and the mixture refluxed. Methanol was removed from the reaction mixture either by collection in a Dean–Stark trap or by adsorption into 4A molecular sieves contained in a Soxhlet extractor. After 14 h, the solution was concentrated. The crude product was diluted with 1 L of chloroform and washed with water (2 × 150 mL). The chloroform solution was dried over $MgSO_4$ and concentrated. Distillation afforded 158.3 g (79%) of **6a** as a clear liquid: bp 115–116 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 6.98 (distorted dd, 2 H, H_2C=, J = 33.8 and 37.7), 4.32–4.00 (m, 8 H, OCH_2CH_3), 1.32 (t, 12 H, CH_2CH_3, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 148.8 (s, H_2C=), 132.3 (t, PCP, J = 166), 62.5 (d, OCH_2CH_3, J = 2.9), 16.2 (d, OCH_2CH_3, J = 2.9); ^{31}P NMR ($CDCl_3$) δ +12.8.

An analytical sample of **6a** was obtained by flash chromatography on silica gel using 1:1 acetone/hexane eluent. Anal. Calcd for $C_{10}H_{22}O_6P_2$: C, 40.00; H, 7.39; P, 20.63. Found: C, 39.68; H, 7.29; P, 20.34.

Tetramethyl Ethenylidenebis(phosphonate) (6b). Ester **5b** (4.03 g, 17.4 mmol), paraformaldehyde (2.60 g, 86.7 mmol), and diethylamine (1.27 g, 17.4 mmol) were combined as above and refluxed for 2 h. Elimination of methanol and workup as before afforded 3.05 g (72%) of **6b** as a clear liquid following distillation: bp 113–118 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 6.99 (distorted dd, 2 H, H_2C=, J = 33.9 and 37.7), 3.77 (distorted dd, 12 H, OCH_3, J = 5.1 and 6.1); ^{13}C NMR ($CDCl_3$) δ 150.2 (s, H_2C=), 130.2 (t, PCP, J = 168), 53.2 (s, OCH_3); ^{31}P NMR ($CDCl_3$) δ +15.5. Anal. Calcd for $C_6H_{14}O_6P_2$: C, 29.52; H, 5.78; P, 25.38. Found: C, 29.26; H, 6.01; P, 25.19.

Tetraisopropyl Ethenylidenebis(phosphonate) (6c). Ester **5c** (11.95 g, 34.7 mmol), paraformaldehyde (5.2 g, 173.5 mmol), and diethylamine (2.54 g, 34.7 mmol) were combined as above and refluxed for 117 h. Elimination of methanol and workup as before afforded 3.00 g (55%) of **6c** as a clear liquid, following medium pressure liquid chromatography (silica gel, 1:1 acetone/hexane): ^{1}H NMR ($CDCl_3$) δ 6.78 (distorted dd, 2 H, H_2C=, J = 33.9 and 37.8), 4.74–4.47 (m, 8 H, OCH), 1.21 (dd, 12 H, CH_3, J = 2.93 and 6.10); ^{13}C NMR ($CDCl_3$) δ 147.2 (s, H_2C=), 135.1 (t, PCP, J = 168), 71.2 (d, OCH, J = 2.9), 24.0 (d, CH_3, J = 4.4); ^{31}P NMR ($CDCl_3$) δ +10.9. Anal. Calcd for $C_{14}H_{30}O_6P_2$: C, 47.19; H, 8.49; P, 17.39. Found: C, 47.25; H, 8.53; P, 17.39.

Tetra-*n*-propyl Ethenylidenebis(phosphonate) (6d). Ester **5d** (5.97 g, 17.4 mmol), paraformaldehyde (2.61 g, 86.8 mmol), and diethylamine (1.27 g, 17.4 mmol) were combined as above and refluxed for 46 h. Elimination of methanol and workup as before afforded 4.46 g (72%) of **6d** as a clear oil following distillation: bp 130–133 °C (0.01 mm); ^{1}H NMR ($CDCl_3$) δ 6.81 (distorted dd, 2 H, H_2C=, J = 34.1 and 37.5), 4.13–3.90 (m, 8 H, $-OCH_2-$), 1.90–1.51 (m, 8 H, $-OCH_2CH_2-$), 0.95 (t, 12 H, CH_3, J = 6.8); ^{13}C NMR ($CDCl_3$) δ 148.6 (s, H_2C=), 132.2 (t, PCP, J = 168), 68.0 (s, $-OCH_2-$), 23.8 (s, $-OCH_2CH_2-$), 10.0 (s, CH_2CH_3); ^{31}P NMR ($CDCl_3$) δ +13.0; ammonia CI mass spectrum, m/e 374 $(M + NH_4)^+$, 357 $(M + H)^+$. Anal. Calcd for $C_{14}H_{30}O_6P_2$: C, 47.19; H, 8.49; P, 17.39. Found: C, 46.92; H, 8.74; P, 17.15.

Tetra-*n*-butyl Ethenylidenebis(phosphonate) (6e). Ester **5e** (6.95 g, 17.4 mmol), paraformaldehyde (2.61 g, 86.8 mmol), and diethylamine (1.27 g, 17.4 mmol) were combined as above and refluxed for 46 h. Elimination of methanol and workup as before afforded 4.72 g (66%) of **6e** as a clear liquid following distillation: bp 155–158 °C (0.01 mm); ^{1}H NMR ($CDCl_3$) δ 6.77 (distorted dd, 2 H, H_2C=, J = 33.9 and 37.6), 3.91–3.77 (m, 8 H, $-OCH_2-$), 1.63–1.10 (br m, 16 H, $-OCH_2CH_2CH_2-$), 0.74 (t, 12 H, CH_3, J = 6.6); ^{13}C NMR ($CDCl_3$) δ 148.7 (s, H_2C=), 132.1 (t, PCP, J = 168), 66.2 (s, $-OCH_2-$), 32.4 (s, $-OCH_2CH_2-$), 18.7 (s, CH_2CH_3), 13.5 (s, CH_3); ^{31}P NMR ($CDCl_3$) δ +13.1; ammonia CI mass spectrum, m/e 430 $(M + NH_4)^+$, 413 $(M + H)^+$. Anal. Calcd for $C_{18}H_{38}O_6P_2$: C, 52.42; H, 9.29; P, 15.02. Found: C, 52.23; H, 9.75; P, 15.28.

Tetra-*n*-octyl Ethenylidenebis(phosphonate) (6f). Ester **5f** (5.95 g, 10.0 mmol), paraformaldehyde (1.50 g, 50.0 mmol), and diethylamine (0.73 g, 10.0 mmol) were combined as above and refluxed for 50 h. Elimination of methanol and workup as before

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afforded 3.88 g (64%) of **6f** as a clear liquid following medium pressure liquid chromatography (silica gel, 3:1 hexane/acetone eluent): ^{1}H NMR ($CDCl_3$) δ 6.94 (distorted dd, 2 H, H_2C=, J = 33.7 and 37.1), 4.06–3.99 (m, 8 H, $-OCH_2-$), 1.66–1.50 (m, 8 H, $-OCH_2CH_2-$), 1.26 (br s, 40 H, $-OCH_2CH_2(CH_2)_5CH_3$), 0.85 (br t, 12 H, CH_3, J = 5); ^{13}C NMR ($CDCl_3$) δ 148.9 (s, H_2C=), 132.3 (t, PCP, J = 166), 66.6 (s, $-OCH_2-$), 31.9, 30.5, 29.2, 25.6, 22.7 (all s, $OCH_2(CH_2)_6CH_3$), 14.1 (s, CH_3); ^{31}P NMR ($CDCl_3$) δ +13.2; ammonia CI mass spectrum, m/e 637 $(M + H)^+$, 654 $(M + NH_4)^+$. Anal. Calcd for $C_{34}H_{70}O_6P_2$: C, 64.12; H, 11.08; P, 9.73. Found: C, 63.95; H, 10.87; P, 9.96.

Dealkylation of 6a. Bromotrimethylsilane (61.4 g, 0.40 mol) was added via syringe to a solution of ester **6a** (15.0 g, 0.05 mol) in 300 mL of dry CCl_4. The mixture was stirred for 72 h and then concentrated under vacuum. Methanol (200 mL) was added and the solution again concentrated. The crude product was dissolved in methanol (150 mL) and precipitated by addition of methanolic KOH solution. The mixture was filtered and the precipitate washed with methanol and then dried under vacuum. The white solid product was dissolved in 75 mL of water and stirred overnight with excess Rexyn 101(H) resin (Fisher Scientific). The ion-exchange resin was removed by filtration and the solution freeze-dried to afford 8.49 g (90%) of acid **1** as a white, hygroscopic solid: ^{1}H NMR (D_2O) δ 6.44 (t, H_2C=, J = 36.1); ^{13}C NMR (D_2O) δ 146.9 (s, H_2C=), 138.2 (t, PCP, J = 162); ^{31}P NMR (D_2O) δ +11.1.

Registry No. **1**, 34162-79-3; **5a**, 1660-94-2; **5b**, 16001-93-7; **5c**, 1660-95-3; **5d**, 28254-31-1; **5e**, 6997-56-4; **5f**, 13088-08-9; **6a**, 37465-31-9; **6b**, 67293-68-9; **6c**, 48074-47-1; **6d**, 103457-07-4; **6e**, 103457-08-5; **6f**, 103457-09-6; **7**, 103457-10-9.

Asymmetric Lignan Synthesis: Isolariciresinol Dimethyl Ether

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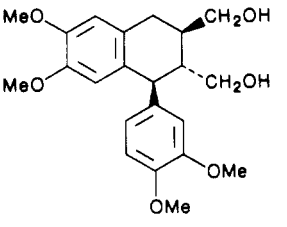
An asymmetric synthesis of the lignan (+)-isolariciresinol dimethyl ether **1** in nine steps and 13% yield (83% optical purity) from veratraldehyde is described. Veratraldehyde was converted to 6-(3,4-dimethoxybenzyl)-veratraldehyde **3** by bromination, acetal formation, metalation, and coupling to 3,4-dimethoxybenzyl bromide. **3** was irradiated in the presence of SO_2 to give the 3-hydroxy-1-aryl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide **4**, which was converted to the (*R*)-1-phenylethoxy derivative **5b**. **5b** on heating with dimethyl fumarate gave a mixture of primarily two diastereomeric cycloadducts **7b** and **7b′**, both of which had the 1,2-trans, 2,3-trans, 3,4-cis stereochemistry. The major adduct **7b** was subsequently assigned the stereochemistry 1*S*,2*R*,3*S*,4*S*. Separation and hydrogenolysis of the major adduct gave the diester **8**, 1*S*,2*R*,3*R*, which was reduced with $LiAlH_4$ to give (+)-isolariciresinol dimethyl ether **1**. A racemic synthesis was also carried out via the methoxy sulfone **5a** and its trans isomer **5a′** in 33% yield.

Intra- and intermolecular cycloadditions of dienophiles to *o*-quinodimethanes (*o*-QDMs) have been successfully used in a variety of natural product syntheses.[1-9] In some instances asymmetric syntheses have been achieved by controlling the face selectivity of the addition step.[5,8-9] In recent publications we have shown that chiral groups in the α position of an *o*-QDM can control the face selectivity of the addition.[10,11] The face selectivity with respect to the dienophile (exo vs. endo) is controlled by secondary orbital effects between the substituent groups on the dienophile and the *o*-QDM to yield, in most cases, the endo product.[10,11] While this asymmetric cycloaddition appears suitable for natural product lignan syntheses, it was not known how other substituents on the *o*-QDM would affect the stereoselectivity of the cycloaddition step. In this paper we describe both the racemic and asymmetric synthesis of (+)-isolariciresinol dimethyl ether.



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The absolute stereochemistry of (+)-isolariciresinol dimethyl ether was first established by Schrecker and Hartwell in 1954 by synthesis from α-conidendrin whose structure was well established.[12] This was later repeated by Stevenson and Williams during their investigation of phyltetralin (the enantiomer of isolariciresinol tetramethyl ether).[13] More recently Mann has published a synthesis of both racemic isolariciresinol dimethyl ether and racemic phyltetralin.[14]

Results and Discussion

The general scheme for the synthesis is shown in Scheme I. The synthesis of the intermediate *o*-QDM **6** is accomplished via our recently developed photochemical route to the 1-hydroxydihydrobenzo[*c*]thiophene 2,2-dioxide.[15,16,11]

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