JOC Article

First General Approach to Cyclohex-3-ene-1,1-bis(phosphonates) by Diels−Alder Cycloaddition of Tetraethyl Vinylidenebis(phosphonate) to 1,3-Dienes

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Tetraethyl vinylidenebis(phosphonate) (VBP) reacts smoothly with substituted 1,3-dienes at 90−110 °C without solvent to give the corresponding cyclohex-3-ene-1,1-bis(phosphonates) in good yields (60−85%). With nonsymmetrically substituted dienes, mixtures of regioisomers are obtained, the regioisomeric ratio being exclusively controlled by electronic effects. Danishefsky's diene allows tetraethyl 4-oxocyclohex-2-ene-1,1-bis(phosphonate) to be obtained in an 81% overall yield after the acid-catalyzed hydrolysis of the Diels−Alder cycloadduct. With 2,3-dimethoxy-1,3-butadiene, a mixture of regioisomeric dimethoxycyclohexene-1,1-bis(phosphonates) is formed by the VBP-catalyzed isomerization of the normal Diels−Alder cycloadduct. The mixture converges into tetraethyl 3,4-dimethoxycyclohex-2-ene-1,1-bis(phosphonate) at prolonged reaction times.

Introduction

Because of their physiological properties, *gem*-diphosphonic acid derivatives[1] are now recognized as an important class of pharmacologically active molecules that are likely to be effective therapeutic options in several human pathologies,[2] such as osteoporosis. They are also effective in the treatment of cancer-related hypercalcemia,[3] in the treatment of rheumatoid arthritis,[4] and as potent anti-inflammatory drugs.[5] In this context, cycloalkyl- and cycloalkenylbis(phosphonates) have become increasingly important as an alternative strategy in attempting to provide more potent antiresorptive analogues without significantly increasing the mineralization defects formerly observed with the first-generation bis(phosphonates).[6]

Whereas cycloalkylbis(phosphonate) esters can be easily prepared by the base-induced double alkylation of tetraalkyl methanebis(phosphonate) with 1,ω-dibromoalkanes,[7] an effective method for preparing the more valuable cycloalkenylbis(phosphonates) is still lacking. The Diels−Alder cycloaddition of vinylphosphonates to 1,3-dienes, which would seem to be the most obvious synthetic approach to cyclohexenylbis(phosphonates), has not been exploited, and the few reported examples are limited to the synthesis of monophosphonate cyclohexenes.[8] As dienophiles, vinylphosphonates are much less reactive than α,β-unsaturated carbonyl compounds and nitriles,[9,10] although their dienophilicity can be substantially enhanced and good yields of cycloadducts

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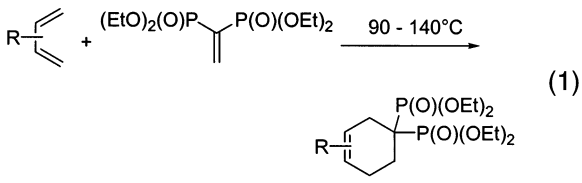
can be obtained in the presence of Lewis acids[9,11] or by introduction of a second electron-withdrawing substituent around the carbon−carbon double bond.[10] Data concerning the use of tetraalkyl vinylidene-1,1-bis(phosphonates) as dienophiles in Diels−Alder cycloaddition are anything but encouraging. Accordingly, the introduction of a second dialkyl phosphonyl group in the α position of dialkyl vinylphosphonate causes a drop in the reactivity of the resulting bis(phosphonate) dienophile even with electron-rich dienes. As a matter of fact, the reaction of tetraethyl vinylidenebis(phosphonate) (VBP) with *N*-buta-1,3-dienylsuccinimide was reported to give only 10% of the expected pseudo-ortho cycloadduct after 10 days in refluxing acetonitrile.[12] Although 1,3-dipolar cycloadditions of VBP to diazoketones were formerly exploited in the synthesis of the pharmacologically important pyrazoline bis(phosphonates),[13] to our knowledge, the above example is the sole report in the literature that deals with Diels−Alder reactions of 1,3-dienes involving VBP as a dienophile.

The importance of cycloalkenyl-1,1-bis(phosphonates) as valuable precursors in the synthesis of biologically active molecules and the lack of information about these kinds of processes induced us to reinvestigate the reaction of VBP with a variety of 1,3-dienes under quite different conditions (eq 1). Here, we report the results of this research.



(1)

Results and Discussion

A mixture of VBP and diene was reacted in a sealed steel reactor at a suitable temperature for varying times, depending on the nature of the diene. The crude oil was evaporated at reduced pressure to remove the excess diene, and the products were isolated, when possible, by column chromatography. Yields, regioisomeric ratios, and the conditions relative to the reaction of each diene are reported in Table 1.

Quantitative analysis of the regioisomeric mixture was performed by gas−liquid chromatography (GLC) and confirmed by ^{31}P NMR. Because of the relatively large values of the $^3J_{PC}$ coupling constants and their strong dependence on the P−C−C−C dihedral angle,[10,14] ^{13}C NMR turned out to be a valuable tool for the structural determination of the regioisomers obtained in the reactions involving nonsymmetrically substituted dienes. In the reaction with isoprene (**4a**), a 4.6:1 mixture of two inseparable isomeric cycloadducts was obtained in 79% yield. Among the other ^{13}C NMR signals, the triplet at δ 116.7 (J = 5.6 Hz) and the singlet at δ 133.3, attributed to the H- and CH_3-substituted olefinic carbons, respectively, allowed the structure of 4-methylcyclohex-3-ene-1,1-bis(phosphonate) to be assigned to the main regioisomer (**4b**; Chart 1). Conversely, the triplet at δ 129.6 (J = 5.6 Hz) and the singlet at δ 120.6, attributed to the CH_3- and H-substituted olefinic carbons, respectively, are compatible with the structure of 3-methylcyclohex-3-ene-1,1-bis(phosphonate) assigned to the minor regioisomer (**4c**).

As expected, the electron-releasing effect of the methyl group at C(2) of isoprene governs the regioselectivity of the cycloaddition process, orienting the attack of C(1) at the very electrophilic methylenic carbon of the VBP. The broad triplet of a relatively low J value (5.6 Hz), while stating the near magnetic equivalence of the two phosphorus atoms toward C(3), suggests a stable half-chair conformation for both the regioisomers **4b** and **4c** with a P−C−C−C(3) dihedral angle of about 120°.[15] In such way, the 1,3-diaxial interactions of the bulky phosphonate groups would be minimized.

Using the same criterion, the structure of 2-methylcyclohex-3-ene-1,1-bis(phosphonate) (**5b**) was assigned to the major regioisomer of the two obtained from the reaction of VBP with piperylene in a 3:1 molar ratio and in 60% yield. Interestingly, here the ^{13}C NMR signal attributed to C(3) appears as a doublet at δ 130.9 ($^3J_{PC(3)}$ = 10.2 Hz) and that of C(5) as a double-doublet at δ 22.1 ($^3J_{PC(5)}$ = 11.0 and 4.0 Hz), suggesting a quasi-chair conformation for **5b** with calculated dihedral angles P_1−C−C−C(3) and P_2−C−C−C(3) of 100 and 130°, respectively (Chart 1). Most probably, such a conformation allows the steric interaction of the two phosphonate groups at C(1) with the methyl group at C(2) to be minimized. The singlet at δ 18.4, assigned to the methyl carbon at C(2), suggests that it adopts a pseudoequatorial position. In fact, according to the Karplus equation,[15] a substantial coupling between the carbon of a pseudoaxial methyl group and the vicinal phosphorus in the anti position would be expected. Similar effects are also observed in the minor regioisomer to which the structure of 5-methylcyclohex-3-ene-1,1-bis(phosphonate) (**5c**) was assigned on the basis of its characteristic ^{13}C NMR signals.[16] Once again, the regioselectivity of the cycloaddition process is determined by the electron-releasing effect of the methyl group of piperylene, which favors the attack of C(1) at the methylenic carbon of the VBP with the predominant formation of the thermodynamically less-stable cycloadduct.

Analogous considerations were made to identify the two regioisomeric products obtained in nearly equimolar amounts, in 77% yield, from the reaction of 1-vinylcyclohexene (**6a**) with VBP. Chromatography of the crude

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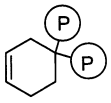
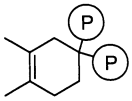
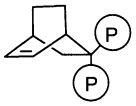
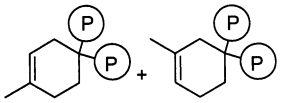
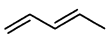
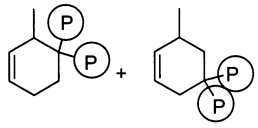
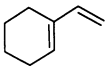
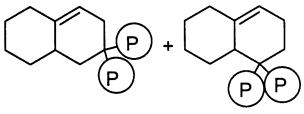
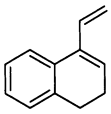
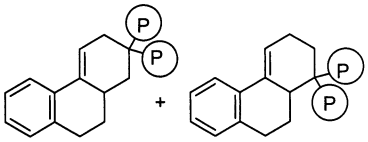
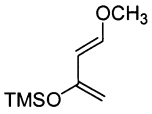
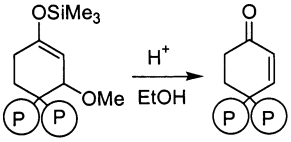
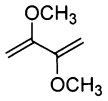
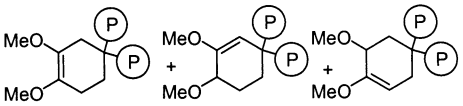
(15) The value was determined by applying the semiempirical equation $^3J_{PC} = 7.23 - 5.41 \cos\phi + 6.29 \cos 2\phi$ derived by Grossmann for diethyl cycloalkylphosphonates. For the sake of comparison, the calculated $^3J_{PC}$ values of 7.4, 0.9, and 19.0 Hz for the dihedral angles of 0, 90, and 180°, respectively, are reported.[14]

(16) The doublets at δ 122.2 ($^3J_{PC(3)}$ = 10.8 Hz) and 26.7 ($^3J_{PC(5)}$ = 11.9 Hz) attributed to C(3) and C(5), respectively, would suggest a quasi-chair conformation for this regioisomer with the methyl group taking on an equatorial position.

TABLE 1. Diels–Alder Cycloaddition Products from VBP and 1,3-Dienes

Diene (equiv.)	T, °C	Reaction time, h	Product	yield,%[a]	Isomeric Ratios[b]
 **1a** (10)	100	22	 **1b**	70	
 **2a** (10)	90	20	 **2b**	64	
 **3a**	140	12	 **3b**	73	--
 **4a** (1.1)	100	24	 **4b** **4c**	79	82:18
 **5a** (10)	110	54	 **5b** **5c**	60	75:25
 **6a** (1.3)	120	48	 **6b** **6c**	77	55:45
 **7a** (2)	100	27	 **7b** **7c**	74	93:7
 **8a** (2)	100	28	 **8b** **8c**	81[c]	--
 **9a** (3)	100	18 96 240	 **9b** **9c** **9d**	-- 80	46:28:26 12:74:14 1:93:4

[a] Calculated with respect to VBP after purification by column chromatography on neutral Al_2O_3 (eluent 9:1 petroleum ether and diethyl ether/EtOH). [b] Determined by GLC and ^{31}P NMR. [c] Calculated with respect to VBP after the acid-catalyzed hydrolysis of **8b** in EtOH.

reaction mixture allowed a small amount of the minor regioisomer to be isolated to which the structure of tetraethyl 3,5,6,7,8,8a-hexahydronaphthalene-1,1(2*H*)-bis(phosphonate) (**6c**) was assigned on the basis of the following ^{13}C NMR signals: the tight double-doublet at δ 138.0 (J = 6.8 and 3.4 Hz) assigned to the olefinic C(4a) and the singlet at δ 118.7 attributed to C(4) (Chart 2).

The main regioisomer was identified in the regioisomeric mixture as 3,5,6,7,8,8a-hexahydronaphthalene-2,2-(1*H*)-bis(phosphonate) (**6b**) by the presence of two doublets at δ 115.1 (J = 11.5 Hz) and δ 33.7 (J = 12.6 Hz) attributed to C(4) and C(8a), respectively.

The fact that the two regioisomers form in near-equimolar amounts supports the above statements about the important role of electronic effects on the regioselectivity of the cycloaddition process. Hence, the electron-releasing ability of the alkyl substitution at C(1) of **6a**, which would increase the coefficient on C(2) in the HOMO of the diene, is counterbalanced to nearly the same extent by the electron-releasing effect of the alkyl

CHART 1

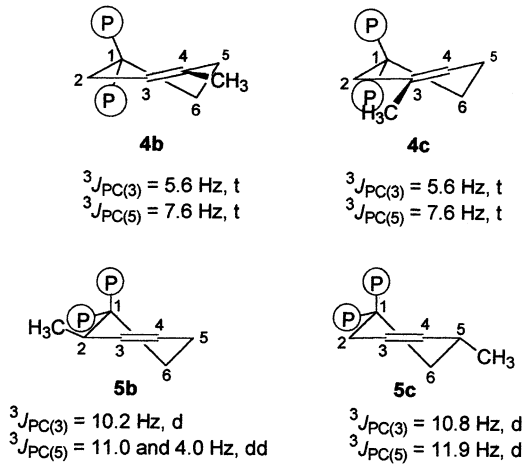
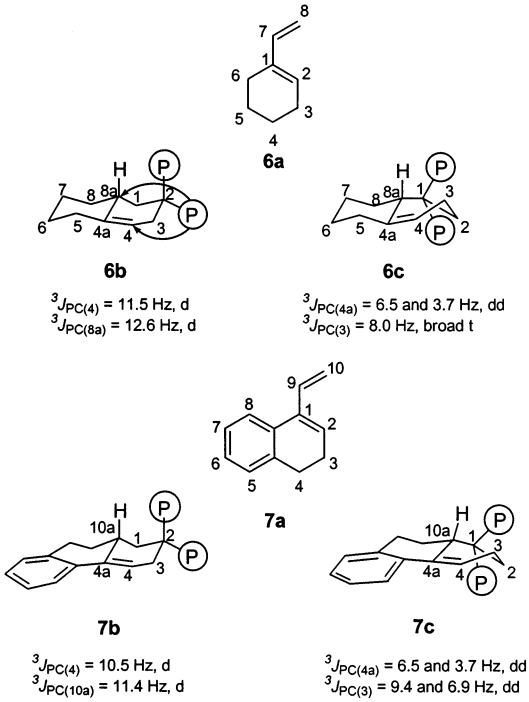


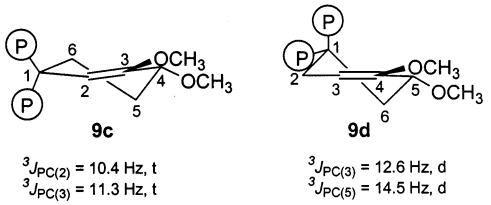
CHART 2



substitution at C(2) in **6a**, enhancing the coefficient on the vinylic carbon of CH_2.

In the same way, the structure of tetraethyl 3,9,10,-10a-tetrahydrophenanthrene-2,2(1*H*)-bis(phosphonate) (**7b**) and that of tetraethyl 3,9,10,10a-tetrahydrophenanthrene-1,1(2*H*)-bis(phosphonate) (**7c**) were assigned to the two regioisomers obtained in 74% overall yield from a reaction of VBP with 1-vinyl-3,4-dihydronaphthalene (**7a**). Once again, the regioisomeric distribution (93:7 **7b**/**7c**) is in good agreement with the prediction on the basis of the electronic effects of the substituents at C(1) and C(2) in the HOMO of **7a** (Chart 2). An aryl group at C(2) is expected to enhance the coefficient on C(1) of a 1,2-disubstituted 1,3-diene substantially more than an alkyl substituent at C(1) does on C(4). Thus, the attack at the methylenic carbon of the VBP by C(2) of **7a** is expected to be the preferred outcome of the cycloaddition process, leading to the preferential formation of the adduct **7b**, as was really observed.

CHART 3



In agreement with the latter considerations, the reaction of Danishefsky's diene **8a** with VBP gave exclusively the bis(phosphonate) adduct **8b** that was easily converted into the α,*β*-unsaturated cyclohexenone bis(phosphonate) (**8c**) in 81% overall yield by simple acid-catalyzed hydrolysis in refluxing ethanol.

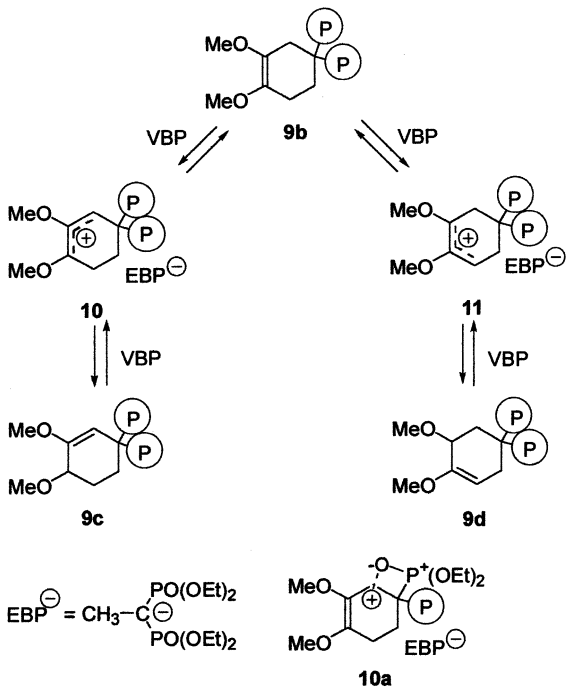
More intriguing results were obtained from the reaction of VBP with 2,3-dimethoxy-1,3-butadiene. After 18 h at 100 °C, the expected Diels−Alder cycloadduct 3,4-dimethoxycyclohex-3-ene-1,1-bis(phosphonate) (**9b**) turned out to be the main reaction product. However, it was accompanied by two minor isomeric species formed in nearly equimolar amounts (see Table 1).[17] At a longer reaction time (96 h), the amount of one isomer increased at the expense of both the adduct **9b** and the other isomer; after 240 h, it was the sole reaction product. Two characterizing triplets of its ^{13}C NMR spectrum at δ 158.4 (J = 11.3 Hz) and at δ 90.4 (J = 10.4 Hz) attributed to methoxy- and hydrogen-substituted olefinic carbons, respectively, and a doublet at δ 24.1 (J = 9.0 Hz) assigned to methoxy-substituted sp^3 carbon allowed the product to be identified as tetraethyl 3,4-dimethoxycyclohex-2-ene-1,1-bis(phosphonate) (**9c**; Chart 3).

The second regioisomer was unequivocally identified as tetraethyl 4,5-dimethoxycyclohex-3-ene-1,1-bis(phosphonate) (**9d**) by the doublet at δ 93.0 (J = 12.6 Hz) and the singlet at δ 154 and attributed to the hydrogen- and OCH_3-substituted olefinic carbons, respectively, in the spectrum of a 1:1 mixture with **9c**. In full agreement with these structural assignments, the absorption of the methoxy-bearing C(4) of **9c** appears as a singlet at δ 73.3, whereas the methoxy-substituted carbon C(5) in **9d** resonates as a clean doublet at δ 72.7 (J = 14.5 Hz), as expected for a $^3J_{PC}$ coupling with only the equatorial phosphorus atom.

A plausible explanation of this unexpected outcome could be found in the VBP-promoted isomerization of the previously formed cycloadduct **9b**. Accordingly, when a 1:0.7:0.7 mixture of **9b**, **9c**, and **9d** was heated to 100 °C for 96 h in the presence of an equimolar amount of VBP, the isomer **9c** was recovered in 95% yield as the only product. In contrast, under the same conditions, the composition of the above mixture remained unchanged either in the absence of VBP or in the presence of the starting diene. Most probably, because of the marked ability of the two phosphonate groups to stabilize a negative charge on the α carbon, VBP turns out to be an efficient hydride-trapping species which transforms itself into a relatively stable ethanide-1,1-bis(phosphonate) (EBP^-; Scheme 1).

(17) A pure sample of **9b** was obtained from the reaction of **9a** with VBP performed at 80 °C for 6 h, after chromatography on Al_2O_3, and identified on the basis of its spectroscopic and analytical characteristics (see Experimental Section).

SCHEME 1



In this case, the hydride abstraction from each isomer of the above mixture generates an allylic carbocation (**10** or **11**) whose positive charge is further stabilized by one α-methoxy group. The process, which probably generates a tight ion pair, would be reversible, allowing **9b** and **9d** to converge into the thermodynamically more stable **9c** through the ion pair **10** where the positive charge could take advantage of an additional stabilizing effect by the oxygen of the adjacent phosphonate group (**10a**).

Experimental Section

If not specified otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in a $CDCl_3$ solution using tetramethylsilane as an internal standard. ^{31}P NMR spectra were recorded at 81 MHz in a $CDCl_3$ solution using 85% H_3PO_4 as an external standard. IR spectra of neat samples were taken in the 4000−625-cm^{-1} range. Gas-chromatographic analyses were performed using 30-m × 0.32-mm capillary columns loaded with two different stationary phases: HP-5 MS (5% phenylmethylpolysiloxane) and HP-35 MS (35% phenylmethylpolysiloxane) at 70−310 °C. Mass spectra were obtained at 70 eV.

Reagents. 1,3-Butadiene, isoprene, piperylene, 2,3-dimethyl-1,3-butadiene, 2,3-dimethoxy-1,3-butadiene, 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene), and 1,3-cyclohexadiene of the highest grade of purity were used as purchased. 1-Vinylcyclohexene was prepared by the distillation of 1-vinylcyclohexanol in the presence of $KHSO_4$.[18] 3,4-Dihydro-1-vinylnaphthalene was prepared by the addition of vinylmagnesium bromide to 1-tetralone, followed by the $CuSO_4$-promoted dehydration of the resulting vinylcarbinol in refluxing benzene.[19] VBP was prepared in 82% yield by the condensation of tetraethyl methylenebis(phosphonate)[20] with formaldehyde in the presence of diethylamine in refluxing methanol, followed by TsOH-catalyzed elimination of methanol in refluxing toluene according to Degenhardt and Burdsall's protocol.[21]

Standard Procedure for the Synthesis of Cyclohexenyl-1,1-bis(phosphonates). A 2-mL steel reactor equipped with a Teflon gasket and filled with a mixture of VBP (4.0 mmol) and diene (1.1−10 equiv; see Table 1) was sealed with a steel cap fixed with six screws and immersed in an oil bath kept at the suitable temperature (see Table 1) for a certain time depending on the nature of the diene. After cooling, the reactor was opened and the crude oil was evaporated at a reduced pressure to remove any excess diene. Chromatography of the residue on neutral Al_2O_3 (activity grade V according to Brockman; eluent hexanes and 9:1 diethyl ether/ethanol) allowed pure or unresolvable regioisomeric mixtures of cycloalkenylbis(phosphonates) to be collected.

Tetraethyl cyclohex-3-ene-1,1-bis(phosphonate) (1b; 1.0 g, 70%): ^{1}H NMR δ 5.79−5.59 (br AB system, J = 10.6 Hz, 2H), 4.25−4.10 (m, 8H), 2.55 (br t, J = 16.2 Hz, 2H), 2.24−2.05 (m, 4H), 1.39−1.26 (m, 12H); ^{13}C NMR (100 MHz) δ 126.5, 123.0 (t, J = 5.5 Hz), 62.8 (quint, J = 3.3 Hz), 62.5 (quint, J = 3.3 Hz), 39.9 (t, J = 133.4 Hz), 25.6 (t, J = 4.4 Hz), 24.0 (t, J = 4.9 Hz), 21.8 (t, J = 7.5 Hz), 16.4; ^{31}P NMR δ 27.8; IR (film) ν_{max} 3027 (w), 2982−2860 (s), 1662 (w), 1246 (s), 1026 (s) cm^{-1}; MS (70 eV) m/z (%) 354 (M$^+$, 11), 308 (18), 217 (100), 189 (19), 161 (23), 79 (13). Anal. Calcd for $C_{14}H_{28}O_6P_2$: C, 47.46; H, 7.97. Found: C, 47.31; H, 8.01.

Tetraethyl 3,4-dimethylcyclohex-3-ene-1,1-bis(phosphonate) (2b; 0.98 g, 64%): ^{1}H NMR δ 4.2 (m, 8H), 2.42 (t, J = 16.0 Hz, 2H), 2.2−1.8 (m, 4H), 1.62 (s, 6H), 1.3 (m, 12H); ^{13}C NMR δ 125.2, 121.3 (t, J = 5.5 Hz), 62.5, 62.1, 40.9 (t, J = 133.2 Hz), 31.3 (t, J = 4.3 Hz), 28.2 (t, J = 7.6 Hz), 24.5 (t, J = 4.5 Hz), 18.7, 18.5, 16.2; ^{31}P NMR δ 27.98; IR (film) ν_{max} 2983−2864 (s), 1634 (w), 1243 (s), 1029 (s) cm^{-1}; MS (70 eV) m/z (%) 382 (M$^+$, 5), 245 (100), 217 (13), 189 (13), 107 (9), 91 (6). Anal. Calcd for $C_{16}H_{32}O_6P_2$: C, 50.26; H, 8.44. Found: C, 50.12; H, 8.49.

Tetraethyl bicyclo[2.2.2]oct-5-ene-2,2-bis(phosphonate) (3b; 1.0 g, 73%): ^{1}H NMR δ 6.36 (br tdd, J = 7.0, 2.7, and 1.2 Hz, 1H), 6.17 (t, J = 7.0 Hz, 1H), 4.1 (m, 8H), 3.02 (br s, 1H), 2.62 (br s, 1H), 2.6−2.1 (m, 3H), 1.9−1.5 (m, 3H), 1.3 (m, 12H); ^{13}C NMR δ 134.8 (dd, J = 14.2 and 2.1 Hz), 130.6, 61.9 (m), 44.8 (dd, J = 133.2 and 127.8 Hz) 32.0 (t, J = 2.8 Hz), 28.8, 23.9 (dd, J = 13.8 and 4.1 Hz), 21.7, 15.9, 15.8; ^{31}P NMR δ 28.21 (d, J = 7.4 Hz), 27.98 (d, J = 7.4 Hz); IR (film) ν_{max} 3049 (w), 2980 (s), 2941−2872 (m), 1651 (w), 1444 (m), 1392 (m), 1244 (s), 1032 (vs), 969 (s), 804 (m) cm^{-1}; MS (70 eV) m/z (%) 380 (M$^+$, 5), 379 (9), 301 (100), 273 (18), 243 (29), 189 (18), 171 (13), 105 (15). Anal. Calcd for $C_{16}H_{30}O_6P_2$: C, 50.52; H, 7.95. Found: C, 50.62; H, 7.91.

Tetraethyl 4-Methyl- and 3-Methylcyclohex-3-ene-1,1-bis(phosphonate) (4b and 4c; 1.2 g, 79% Overall Yield). 4b: ^{1}H NMR δ 5.29 (br s), 4.1 (m, 8H), 2.51 (br t, J = 16.1 Hz, 2H), 2.2−2.0 (m, 4H), 1.64 (br s, 2.5H), 1.3 (m, 12H); ^{13}C NMR δ 133.3, 116.7 (t, J = 5.6), 62.4, 62.2, 39.3 (t, J = 133.3 Hz), 26.5 (t, J = 7.7 Hz), 25.8 (t, J = 4.0 Hz), 24.4 (t, J = 4.4 Hz), 23.5, 16.2; ^{31}P NMR δ 28.06; MS (70 eV) m/z (%) 368 (M$^+$, 5), 231 (100), 203 (11), 175 (14), 93 (9). **4c**: ^{1}H NMR (characterizing signals in the 82:18 mixture of **4b** and **4c**) δ 5.43 (br s), 1.63 (br s); ^{13}C NMR δ 129.6 (t, J = 5.6 Hz), 120.6, 63.4, 61.7, 40.6 (t, J = 133.5 Hz), 39.8 (t, J = 4.3 Hz), 23.7 (t, J = 4.7 Hz), 23.3 (t, J = 7.5 Hz), 22.0, 16.2; ^{31}P NMR δ 27.97; MS (70 eV) m/z (%) 368 (M$^+$, 17), 231 (100), 203 (16), 175 (15), 93 (10); IR (82:18 mixture of **4b** and **4c**; film) ν_{max} 3059 (w), 2981−2909 (s), 1652 (w), 1444 (m), 1246 (s), 1028 (s), 966 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_6P_2$ (82:18 mixture of **4b** and **4c**): C, 48.91; H, 8.21. Found: C, 48.69; H, 8.22.

Tetraethyl 2-Methyl- and 5-Methylcyclohex-3-ene-1,1-bis(phosphonate) (5b and 5c; 0.88 g, 60% Overall Yield).

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5b: ^{1}H NMR δ 5.67 (br d, J = 10.1 Hz, 1H), 5.40 (br d, J = 10.1 Hz, 1H), 4.3−4.0 (m, 8H), 3.0−1.8 (m, 5H), 1.3 (m, 15H); ^{13}C NMR δ 130.9 (d, J = 10.2 Hz), 124.7, 63.2−61.3 (m), 45.6 (dd, J = 132.5 and 129.3 Hz), 32.1 (t, J = 3.9 Hz), 26.0 (t, J = 5.2 Hz), 22.1 (dd, J = 11.0 and 4.0 Hz), 18.4, 16.3 (m); ^{31}P NMR δ 28.26 (d, J = 9.2 Hz), 26.09 (d, J = 9.2 Hz); MS (70 eV) *m*/*z* (%) 368 (M^+, 4), 322 (12), 231 (100), 203 (10), 175 (12), 93 (13). **5c**: ^{1}H NMR (characterizing absorption in the 3:1 mixture of **5b** and **5c**) δ 5.57 (s, 2H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 132.9, 122.2 (d, J = 10.8 Hz), 62.5−61.3 (m), 40.6 (dd, J = 134.7 and 131.5 Hz), 32.7 (t, J = 4.2 Hz), 26.7 (d, J = 11.9 Hz), 25.5 (t, J = 4.0 Hz), 21.4, 16.3; ^{31}P NMR δ 28.20 (d, J = 6.0 Hz), 27.29 (d, J = 6.0 Hz); MS (70 eV) *m*/*z* (%) 368 (M^+, 2), 322 (19), 231 (100), 203 (14), 175 (16), 93 (15); IR (3:1 mixture of **5b** and **5c**; film) ν_{max} 3028 (w), 2980−2908 (s), 1661 (w), 1246 (s), 1047 (s), 1027 (s), 964 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_6P_2$ (3:1 mixture of **5b** and **5c**): C, 48.91; H, 8.21. Found: C, 48.79; H, 8.16.

Tetraethyl 3,5,6,7,8,8a-Hexahydronaphthalene-2,2(1*H*)- and -1,1(2*H*)-bis(phosphonate) (6b and 6c; 1.3 g, 77% Overall Yield). 6b: ^{1}H NMR (characteristic signals in a 1:1 mixture of **6b** and **6c**) δ 5.27 (br s), 4.1 (m, 8H), 3.0−1.5 (m, 13H), 1.3 (m, 12H); ^{13}C NMR δ 140.0, 115.1 (d, J = 11.5 Hz), 62.0 (d, J = 7.4 Hz), 61.5 (d, J = 7.4 Hz), 40.4 (dd, J = 134.3 and 131.3 Hz), 34.6, 33.7 (d, J = 12.6 Hz), 32.5 (t, J = 4.0 Hz), 27.2, 27.1, 26.1, 25.9, 16.3; ^{31}P NMR δ 28.33 (d, J = 8.0 Hz), 27.40 (d, J = 8.0 Hz); IR (1:1 mixture of **6b** and **6c**; film) ν_{max} 3053 (w), 2982 (s), 2929 (s), 2855 (m), 1654 (w), 1444 (m), 1245 (s), 1028 (vs), 967 (s), 732 (m) cm^{-1}; MS (70 eV) *m*/*z* (%) 408 (M^+, 3), 362 (2), 301 (3), 271 (100), 243 (11), 215 (13), 133 (7), 91 (14). Anal. Calcd for $C_{18}H_{34}O_6P_2$ (1:1 mixture of **6b** and **6c**): C, 52.94; H, 8.39. Found: C, 53.08; H, 8.40. Chromatography of the above mixture on Al_2O_3 (eluent 95:5 (v/v) diethyl ether/EtOH) was allowed to isolate pure **6c** (91 mg). **6c**: ^{1}H NMR δ 5.42 (br s, 1H), 4.2 (m, 8H), 2.7−1.4 (m, 13H), 1.3 (m, 12H); ^{13}C NMR δ 138.0 (dd, J = 6.8 and 3.4 Hz), 118.7, 63.0 (dd, J = 38 and 7.0 Hz), 62.2 (dd, J = 25.2 and 7.3 Hz), 46.7 (dd, J = 131.7 and 127.9 Hz), 39.9, 36.9, 30.8, 27.7, 27.2, 25.5 (t, J = 5.6 Hz), 22.3 (dd, J = 9.4 and 6.9 Hz), 16.4; ^{31}P NMR δ 28.36 (d, J = 8.3 Hz), 26.74 (d, J = 8.3 Hz); IR (film) ν_{max} 3049 (w), 2982 (s), 2930 (s), 2855 (m), 1443 (m), 1244 (s), 1029 (s), 965 (s), 732 (m) cm^{-1}; MS (70 eV) *m*/*z* (%) 408 (M^+, 15), 301 (5), 271 (100), 243 (9), 215 (9), 133 (8), 91 (13). Anal. Calcd for $C_{18}H_{34}O_6P_2$: C, 52.94; H, 8.39. Found: C, 52.75; H, 8.34.

Tetramethyl 3,9,10,10a-Tetrahydrophenanthrene-2,2-(1*H*)- and -1,1(2*H*)-bis(phosphonate) (7b and 7c; 1.3 g, 74% Overall Yield). Pure **7b** (90 mg) was obtained by chromatography of the above mixture on Al_2O_3 (eluent 95:5 (v/v) diethyl ether/EtOH). **7b**: ^{1}H NMR (400 MHz) δ 7.6 (m, 1H), 7.1 (m, 3H), 6.22 (br s, 1H), 4.2 (m, 8H), 3.0−2.6 (m, 4H), 2.7−2.4 (m, 2H), 2.1−1.7 (m, 3H), 1.3−1.2 (m, 12H); ^{13}C NMR (100 MHz) δ 136.4, 136.0 (d, J = 1.6 Hz), 133.7, 129.2, 126.7, 125.9, 123.1, 116.1 (d, J = 10.6 Hz), 63.3 (d, J = 7.1 Hz), 62.6 (d, J = 7.1 Hz), 62.5 (d, J = 7.1 Hz), 40.1 (dd, J = 135.3 and 132.0 Hz), 32.6 (t, J = 4.9 Hz), 32.3 (d, J = 12.6 Hz), 30.6, 29.6, 27.2 (t, J = 4.4 Hz), 16.4; ^{31}P NMR δ 28.17 (d, J = 8.1 Hz), 27.22 (d, J = 8.1 Hz); MS (70 eV) *m*/*z* (%) 411 ($M^+ - OC_2H_5$, 1), 347 (1), 319 (100), 291 (6), 261 (9), 179 (10). Anal. Calcd for $C_{22}H_{34}O_6P_2$: C, 57.89; H, 7.51. Found: C, 57.97; H, 7.49. **7c**: ^{1}H NMR (400 MHz; characterizing peaks in the 85:15 mixture of **7b** and **7c**) δ 6.40 (br s, 1H); ^{13}C NMR (100 MHz) δ 136.1, 135.0, 133.5 (d, J = 11.1 Hz), 128.9, 126.5, 125.6, 123.8, 119.9, 63.5 (d, J = 7.0 Hz), 62.6 (d, J = 7.0 Hz), 62.0 (d, J = 7.3 Hz), 61.3 (d, J = 7.5 Hz), 46.0 (dd, J = 133.0 and 129.0 Hz), 38.4 (t, J = 3.4 Hz), 30.9, 26.4 (d, J = 4.2 Hz), 26.2, (t, J = 5.5 Hz), 23.1 (dd, J = 12.5 and 3.2 Hz), 16.4; ^{31}P NMR δ 28.29 (d, J = 11.2 Hz), 26.30 (d, J = 11.2 Hz); MS (70 eV) *m*/*z* (%) 456 (M^+, 29), 319 (100), 301 (16), 261 (14), 179 (32), 141 (8); IR (85:15 mixture of **7b** and **7c**; film) ν_{max} 3050 (w), 2982−2821 (s), 1652 (w), 1246 (s), 1026 (s) cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_6P_2$ (85:15 mixture of **7a** and **7b**): C, 57.89; H, 7.51. Found: C, 57.74; H, 7.57.

Tetraethyl 2-methoxy-4-(trimethylsilyloxy)cyclohex-3-ene-1,1-bis(phosphonate) (8b): ^{1}H NMR δ 5.28 (dd, J = 3.7 and 1.8 Hz, 1H), 4.54 (ddd, J = 12.9, 11.3, and 4.1 Hz, 1H), 4.4−4.1 (m, 8H), 3.35 (s, 3H), 2.8−2.2 (m, 4H), 1.27−1.2 (m, 12H), 0.29 (s, 9H); ^{13}C NMR δ 153.6, 102.3 (t, J = 5.6 Hz), 76.5 (d, J = 6.4 Hz), 63.3−61.5 (m), 56.6, 48.9 (dd, J = 132.8 and 125.9 Hz), 28.1 (t, J = 8.1 Hz), 25.3 (t, J = 5.3 Hz), 16.6, 16.5, 0.4; ^{31}P NMR δ 25.1 (d, J = 1.5 Hz), 24.2 (d, J = 1.5 Hz); IR (film) ν_{max} 2981−2823 (m), 1669 (m), 1623 (m), 1254 (s), 1217 (s), 1030 (s), 848 (s) cm^{-1}; MS (70 eV) *m*/*z* (%), 472 (M^+, 1), 457 (3), 373 (8), 335 (68), 303 (100), 247 (21), 196 (16), 157 (19), 141 (10), 73 (16).

Tetraethyl 4-Oxocyclohex-2-ene-1,1-bis(phosphonate) (8c). A solution of crude **8b** (2.0 g) and *p*-toluenesulfonic acid (50 mg) in ethanol (50 mL) was refluxed for 1 h. Solid $NaHCO_3$ (0.1 g) was added, and the solvent was evaporated. Chromatography of the residual oil on neutral aluminum oxide (eluent 9:1 diethyl ether/EtOH) allowed pure **8c** (1.2 g, 81% overall yield with respect to VBP) to be collected: ^{1}H NMR δ 6.94 (dt, J = 10.3 and 6.3 Hz, 1H), 6.18 (dt, J = 10.3 and 4.1 Hz, 1H), 4.2 (m, 8H), 2.8−2.4 (m, 4H), 1.34 (td, J = 7.0 and 1.3 Hz, 12H); ^{13}C NMR δ 197.3, 142.3 (t, J = 9.8 Hz), 131.7 (t, J = 10.8 Hz), 64.2 (m), 63.8 (m), 46.1 (t, J = 131.1 Hz), 34.0 (t, J = 5.5 Hz), 25.1 (t, J = 3.9 Hz), 16.7; ^{31}P NMR δ 21.36; IR (film) ν_{max} 3060 (w), 2985 (s), 2934 (m), 1684 (s), 1446 (m), 1389 (m), 1250 (s), 1022 (vs), 973 (s), 775 (s) cm^{-1}; MS (70 eV) *m*/*z* (%) 368 (M^+, 11), 339 (43), 311 (26), 283 (25), 255 (46), 231 (100), 203 (28), 175 (49), 65 (27). Anal. Calcd for $C_{14}H_{26}O_7P_2$: C, 45.66; H, 7.12. Found: C, 45.59; H, 7.17.

Tetraethyl 3,4-Dimethoxycyclohex-3-ene-1,1-bis(phosphonate) (9b). A mixture of VBP (1.2 g, 4.0 mmol) and **9a** (1.4 g, 12 mmol) was heated at 80 °C for 6 h. After cooling, most of the unreacted diene was evaporated at a reduced pressure, and the residue was chromatographed on Al_2O_3 (eluent 9:1 (v/v) diethyl ether/EtOH) to collect **9b** (75 mg). The product was contaminated by traces of two isomeric products: ^{1}H NMR δ 4.2 (m, 8H), 3.62 (s, 3H), 3.60 (s, 3H), 2.61 (br t, J = 15.8 Hz, 2H), 2.4−2.0 (m, 4H), 1.36 (t, J = 7.0 Hz, 12H); ^{13}C NMR δ 138.3, 134.7 (t, J = 7.3 Hz), 62.6 (m), 57.6, 56.6, 41.0 (t, J = 133.4 Hz), 26.6, 24.6 (t, J = 4.3 Hz), 22.9 (t, J = 8.8 Hz), 16.2; ^{31}P NMR δ 27.05; IR (film) ν_{max} 2981 (s), 2934 (s), 2833 (m), 1652 (w), 1444 (m), 1391 (m), 1245 (s), 1025 (vs), 968 (s) cm^{-1}; MS (70 eV) *m*/*z* (%) 414 (M^+, 7), 276 (100), 233 (6), 205 (17), 139 (12), 109 (5). Anal. Calcd for $C_{16}H_{32}O_8P_2$: C, 46.38; H, 7.78. Found: C, 46.47; H, 7.71.

Tetraethyl 3,4-Dimethoxycyclohex-2-ene-1,1-bis(phosphonate) (9c). A mixture of VBP (1.2 g, 4.0 mmol) and **9a** (1.4 g, 12.2 mmol) was heated at 100 °C for 18 h. After cooling, most of the unreacted diene was evaporated at a reduced pressure, and the residue was passed through a short column of Al_2O_3 (eluent 9:1 (v/v) diethyl ether/EtOH). GLC and ^{31}P NMR analyses of the collected oil (1.3 g) showed the presence of **9b** and two other isomeric products in a 1.7:1:1 molar ratio. The latter mixture was divided into three portions (0.4 g each); one portion was heated at 100 °C without added reagents for 240 h. To the second and third portions were added respectively **9a** (0.11 g, 0.96 mmol) and VBP (0.29 g, 0.96 mmol), and the resulting mixtures were heated once again at 100 °C for 240 h. GC−MS and ^{31}P NMR analyses of the former two mixtures did not show any change in their composition, whereas those containing VBP showed the presence of one isomer of **9b** slightly contaminated (less than 2%) by a third isomeric species. A pure sample of the above product, obtained by chromatography of the mixture on Al_2O_3, using 95:5 (v/v) diethyl ether/EtOH as the eluent, exhibited the following spectroscopic and analytical characteristics compatible with the structure of **9c**: ^{1}H NMR δ 4.84 (dd, J = 6.9 and 4.9 Hz, 1H), 4.2 (m, 8H), 3.63 (br s, 1H), 3.62 (s, 3H), 3.39 (s, 3H), 2.5−1.8 (m, 4H), 1.3 (m, 12H); ^{13}C NMR δ 158.4 (d, J = 11.3 Hz), 90.5 (t, J = 10.4 Hz), 73.3, 63.4 (d, J = 7.0 Hz), 63.0 (d, J = 7.0 Hz), 62.8 (m), 56.9, 54.4, 43.4 (dd, J = 135.8 and 135.5 Hz), 24.1 (d, J = 9.0 Hz), 19.7 (t, J = 3.7 Hz), 16.2; ^{31}P NMR

δ 24.65 (d, J = 9.1 Hz), 23.67 (d, J = 9.1 Hz); IR (film) ν_{max} 3064 (w), 2980 (s), 2933 (s), 1655 (s), 1444 (m), 1391 (m), 1247 (s), 1021 (vs), 966 (s) cm^{-1}; MS (70 eV) m/z (%) 414 (M^+, 5), 276 (100), 245 (10), 189 (16), 161 (19), 109 (14). Anal. Calcd for $C_{16}H_{32}O_8P_2$: C, 46.38; H, 7.78. Found: C, 46.54; H, 7.81.

Tetraethyl 4,5-Dimethoxycyclohex-3-ene-1,1-bis(phosphonate) (9d). A mixture of VBP (1.2 g, 4.0 mmol) and **9a** (1.4 g, 12.2 mmol) was heated at 100 °C for 120 h. After cooling, most of the unreacted diene was evaporated at a reduced pressure, and the residue was passed through a short column of Al_2O_3 (eluent 9:1 (v/v) diethyl ether/EtOH). GLC and ^{31}P NMR analyses of the collected oil (1.1 g) showed the presence of **9c** and a second isomeric product in an 8:2 molar ratio. In the mixture, the latter was identified as **9d** on the basis of the following spectral characteristics: ^1H NMR δ 4.64 br s, 1H), 4.15 (m, 8H), 3.65 (br s, 1H), 3.56 (s, 4H), 3.46 (s, 3H), 2.8−1.8 (m, 4H), 1.3 (m, 12H); ^{13}C NMR δ 154.1, 93.0 (d, J = 12.6 Hz), 72.8 (d, J = 14.5 Hz), 62.7−62.4 (m), 56.9, 54.1, 40.7 (t, J = 131.9 Hz), 30.0 (t, J = 4.7 Hz), 24.8, 16.2; ^{31}P NMR δ 26.78 (d, J = 6.5 Hz), 26.56 (d, J = 6.5 Hz); IR (8:2 mixture of **9c** and **9d**; film) ν_{max} 3076 (w), 2982 (s), 2935 (s), 2826 (w), 1654 (w), 1445 (m), 1247 (s), 1026 (vs), 969 (s) cm^{-1}; MS (70 eV) m/z (%) 414 (M^+, 2), 276 (100), 245 (90), 217 (18), 189 (40), 109 (23). Anal. Calcd for $C_{16}H_{32}O_8P_2$ (8:2 mixture of **9c** and **9d**): C, 46.38; H, 7.78. Found: C, 46.42; H, 7.82.

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Supporting Information Available: ^1H, ^{13}C, and ^{31}P NMR spectra of all the reported products. This material is available free of charge via the Internet at http://pubs.acs.org.

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