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Generation of α-phosphonovinyl radicals and development of a new route to highly functionalized vinylphosphonates and vinylphosphonate-incorporated carbocyclic or heterocyclic compounds *via* a radical trapping sequence†

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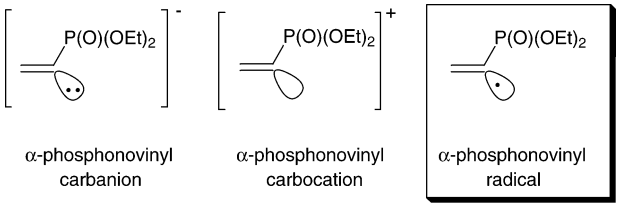
The first direct generation of synthetically useful α-phosphonovinyl radicals was achieved by treatment of α-phosphonovinyl halides with a tributyltin radical. The α-phosphonovinyl radicals **2a–d** were trapped with electron-rich olefins and an electron-deficient olefin to produce α-functionalized vinylphosphonates **3a–f** in 16–55% yields. The α-phosphonovinyl radicals **7e–g** containing the $YCH_2CH{=}CH_2$ (Y = O, CH_2, S) substituent at the β-position afforded mixtures of 5-*exo* and 6-*endo* cyclization products, **5e–g** and **6e–g**, in good yields. The 5-*exo*/6-*endo* product ratios increase in the following order of the β-substituent: $OCH_2CH{=}CH_2$ > $CH_2CH_2CH{=}CH_2$ > $SCH_2CH{=}CH_2$. The effects of the β-substituents upon the cyclization reaction were discussed. Radical cyclization of α-phosphonovinyl radicals bearing functional groups such as geranyloxy, geranylthio, and (2-cyclohexen-1-yl)thio groups at the β-position afforded 5-*exo*, 5-*exo* and 6-*endo*, and *cis*-fused-5,6-ring cyclization products incorporating an α,β-unsaturated phosphonate unit within the ring, respectively, in good yields. The α-phosphonovinyl radical **20** underwent tandem radical cyclization–radical cyclization to produce a mixture of two isomeric bicyclo[4.3.0]nonenes including a vinylphosphonate moiety in high yield.

Introduction

The synthesis and application of vinylphosphonates have recently attracted much interest to synthetic organic chemists and bioorganic chemists, since vinylphosphonates are often utilized as key intermediate reagents for the synthesis of synthetically useful products and biologically active compounds.[1–3] Accordingly, development of new synthetic methods of vinylphosphonates is one of the important subjects to organic chemists. Recently, a new synthesis of vinylphosphonates by trapping vinyl radicals with $(MeO)_3P$ has been developed by Jiao and Bentrude.[4] Furthermore, 3-(phosphonomethylene)oxacyclopentanes were derived from intramolecular cyclization of a 6-phosphono-3-oxa-5-hexynyl radical.[5] This synthetic method of vinylphosphonates is, to our knowledge, the first example *via* the α-phosphonovinyl radical intermediate. Although various free radicals involving vinyl radicals have been well studied and become useful intermediates in organic synthesis,[6] the studies on generation, synthetic application, and ring formation mode in cyclization reaction of the α-phosphonovinyl radical species have not been made so far, except for the above and a few related examples.[5,7] Accordingly, similar to α-phosphonovinyl carbanion[2p,u,8] and α-phosphonovinyl carbocation equivalent species,[2y] generation of a new type of reactive α-phosphonovinyl radical species and their synthetic application are expected to open a new promising field in the chemistry of vinylphosphonates.

We now report the first example of direct generation of the α-phosphonovinyl radicals *via* abstraction of an α-halogen atom from a wide variety of newly developed α-halovinylphosphonates with the tri-*n*-butyltin radical, and their application to the trapping reaction with various alkenes, intramolecular cyclization and tandem reaction. Furthermore, we discuss the cyclization mode in the intramolecular reaction of α-phosphonovinyl radicals.

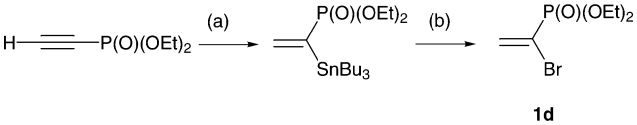


Results and discussion

Synthesis of the precursors, α-halovinylphosphonates 1a–g for α-phosphonovinyl radicals

Abstraction of a halogen atom of a C–X (X = halogen) bond with tri-*n*-butyltin radical has been known as the most commonly used method for the generation of free radicals.[6] To apply this method to the generation of α-phosphonovinyl radicals, synthesis of their precursors, α-halovinylphosphonates has been attempted first.

Of α-halovinylphosphonates, α-iodo- and α-bromophosphonoketene dithioacetals **1a,b** and α-iodo-β-ethoxyvinylphosphonate **1c** were prepared according to the reported procedures by us.[8] As shown in Scheme 1, α-bromovinylphosphonate



Scheme 1 The synthesis of α-bromovinylphosphonate **1d**. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, Bu_3SnH, benzene, r.t.; (b) Br_2, CCl_4, −5 °C, 75% over two steps.

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds and geometries and energies for all stationary points discussed in the paper. See http://www.rsc.org/suppdata/ob/b4/b416394j/

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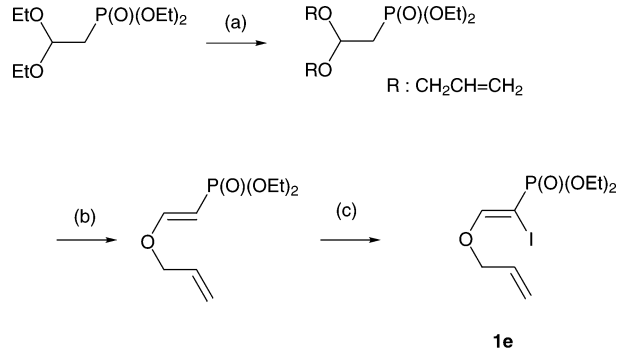
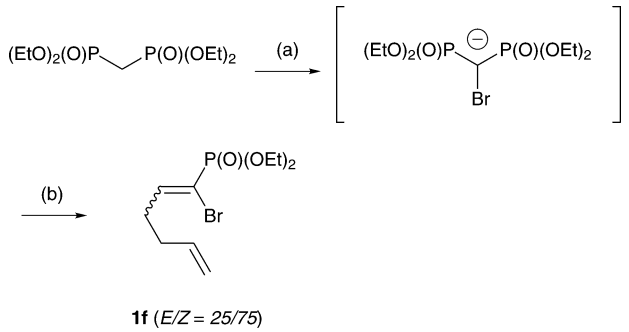
1d was synthesized by treatment of α-stannylvinylphosphonate, which was produced by the palladium-catalyzed hydrostannylation of diethyl ethynylphosphonate with tri-*n*-butyltin hydride, with bromine.

To examine the substituent effects on radical cyclization of the α-phosphonovinyl radicals, various types of α-halovinylphosphonates **1e–g** containing unsaturated functional groups such as allyloxy, homoallyl and allylthio at the β position were developed. Thus, the synthesis of β-allyloxy-α-iodovinylphosphonate **1e** was realized by acid-catalyzed transacetalization of diethylphosphonoacetaldehyde diethyl acetal with allyl alcohol into the corresponding diallyl acetal, followed by the similar procedures to those established in the preparation of **1c** (Scheme 2).



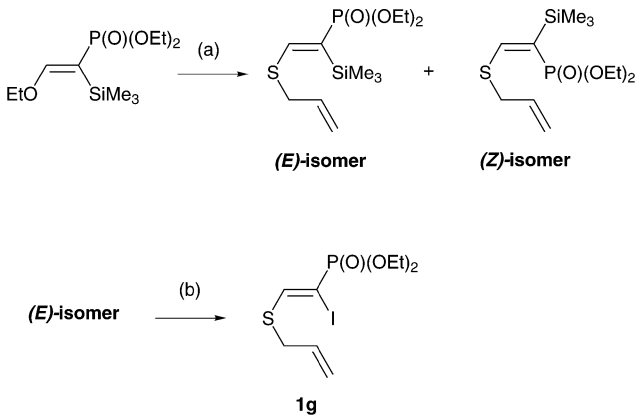
Scheme 2 The synthesis of β-allyloxy-α-iodovinylphosphonate **1e**. *Reagents and conditions*: (a) allyl alcohol, TsOH, benzene, reflux; (b) *n*BuLi, THF, −78 °C; (c) LDA, $CuBrSMe_2$, I_2, THF, −78 °C, 55% over three steps.

In addition, diethyl 1-bromo-hexa-1,5-dienylphosphonate (**1f**) was prepared by the Horner–Wadsworth reaction of tetraethyl α-bromomethylenediphosphonate with 4-pentenal (Scheme 3).



Scheme 3 The synthesis of α-bromo-1,5-hexadienylphosphonate **1f**. *Reagents and conditions*: (a) LDA, *N*-bromosuccinimide, THF, −78 °C to r.t.; (b) 4-pentenal, THF, −78 °C to r.t., 70%.

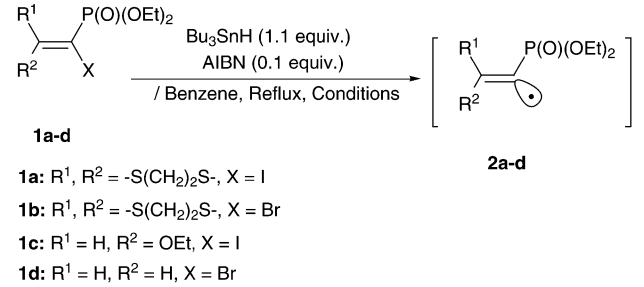
For the synthesis of the β-allylthio-α-iodovinylphosphonate derivative **1g**, a synthetic route *via* double transfunctionalization of β-ethoxy-α-(trimethylsilyl)vinylphosphonate[8] at the β- and α-positions was designed. On the basis of this synthetic design, the Michael addition of an allylthiolate anion to the vinylphosphonate expectedly resulted in β-allylthio-α-(trimethylsilyl)vinylphosphonate in 60% yield as a *E*- and *Z*-stereoisomeric mixture (*E*-isomer : *Z*-isomer = 76 : 24). Subsequent treatment of the *E*-isomer with NaI/*N*-chlorosuccinimide in acetonitrile led to the desired β-allylthio-α-iodovinylphosphonate **1g** in a stereospecific manner in good yield (Scheme 4).



Scheme 4 The synthesis of β-allylthio-α-iodovinylphosphonate **1g**. *Reagents and conditions*: (a) *n*BuLi, allyl mercaptan, THF, −78 °C to r.t., (*E* : *Z* = 76 : 24); (b) NaI, *N*-chlorosuccinimide, MeCN, r.t., 36% over two steps.

Intermolecular additions of α-phosphonovinyl radicals to alkenes

The carbon radicals used in the intermolecular addition reactions with alkenes have mostly been limited to alkyl radicals and the related application of vinyl radicals has remained still unexplored except for a few examples.[9] The generation of α-phosphonovinyl radicals **2** and their application to the intermolecular addition reaction with alkenes are, therefore, expected to furnish an efficient synthetic route to functionalized vinylphosphonates. When the reaction of α-iodophosphonoketene dithioacetal **1a** (0.2 M) with α-methylstylene (10 equiv.) was performed in benzene at reflux by addition of a benzene solution of Bu_3SnH (0.22 M, 1.1 equiv.) and AIBN (0.1 equiv.) over a period of 1 h, the desired addition product **3a** was obtained, albeit in low yield (28%), together with the reduction product **4a** (28%) (Scheme 5). To optimize the product yield, we examined the influence of the concentration and the addition time of Bu_3SnH, and of the radical precursors **1** upon the yield (entries 2–4 in Table 1). The highest yield (55%) of **3a** was obtained by slow addition (5 h) of a solution of

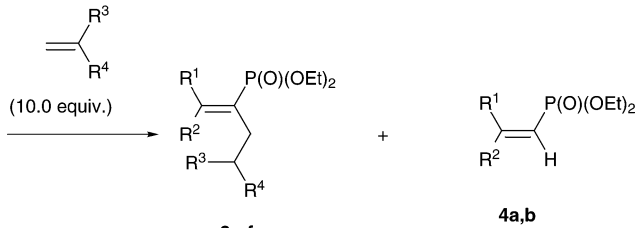


1a: R^1, R^2 = -S(CH$_2$)$_2$S-, X = I

1b: R^1, R^2 = -S(CH$_2$)$_2$S-, X = Br

1c: R^1 = H, R^2 = OEt, X = I

1d: R^1 = H, R^2 = H, X = Br



3a: R^1, R^2 = -S(CH$_2$)$_2$S-, R^3 = Me, R^4 = Ph

3b: R^1, R^2 = -S(CH$_2$)$_2$S-, R^3 = H, R^4 = SPh

3c: R^1, R^2 = -S(CH$_2$)$_2$S-, R^3 = OSiMe$_3$, R^4 = Ph

3d: R^1 = H, R^2 = OEt, R^3 = H, R^4 = SPh

3e: R^1 = H, R^2 = H, R^3 = H, R^4 = SPh

3f: R^1, R^2 = -S(CH$_2$)$_2$S-, R^3 = H, R^4 = CO_2Et

4a: R^1, R^2 = -S(CH$_2$)$_2$S-

4b: R^1 = H, R^2 = OEt

Scheme 5 Intermolecular additions of α-phosphonovinyl radicals **2a–d** with alkenes.

Table 1 Radical trapping reaction of α-phosphonovinyl radicals **2a–d** with alkenes

Entry	Vinylphosphonates **1**	Alkenes		Conditions[a]			Product[b] (Yield, %)	
		R^3	R^4	Concentration[c]/mol l^{-1}	Addition time/h	Total time/[d] h		
1	**1a**	Me	Ph	0.2	1	5	**3a** (28)	**4a** (28)
2	**1b**	Me	Ph	0.07	1	2	**3a** (35)	**4a** (33)
3	**1b**	Me	Ph	0.07	5	6	**3a** (38)	**4a** (24)
4	**1b**	Me	Ph	0.025	5	8	**3a** (55)	**4a** (33)
5	**1b**	H	SPh	0.07	2	4	**3b** (48)	**4a** (16)
6	**1b**	$OSiMe_3$	Ph	0.025	5	12	**3c** (47)	**4a** (41)
7	**1c**	H	SPh	0.07	2	3	**3d** (49)	**4b** (22)
8	**1d**	H	SPh	0.07	2	5	**3e** (30)	—
9	**1b**	H	CO_2Et	0.1	2	7	**3f** (16)	**4a** (24)[e]

[a] Reactions were carried out by slow addition of a solution of Bu_3SnH (0.22 mmol) and AIBN (0.02 mmol) in benzene (1 mL) for entries 1–3, 5, 7 and 8 and in benzene (2 mL) for entries 4, 6 and 9 through a syringe pump to a solution of **1** (0.2 mmol) in refluxing benzene (1–8 mL). [b] Isolated yields. [c] Each concentration was determined on initial concentration of **1**. [d] Total reaction time until starting material **1** was consumed completely. [e] **1b** was recovered unchanged in 44% yield.

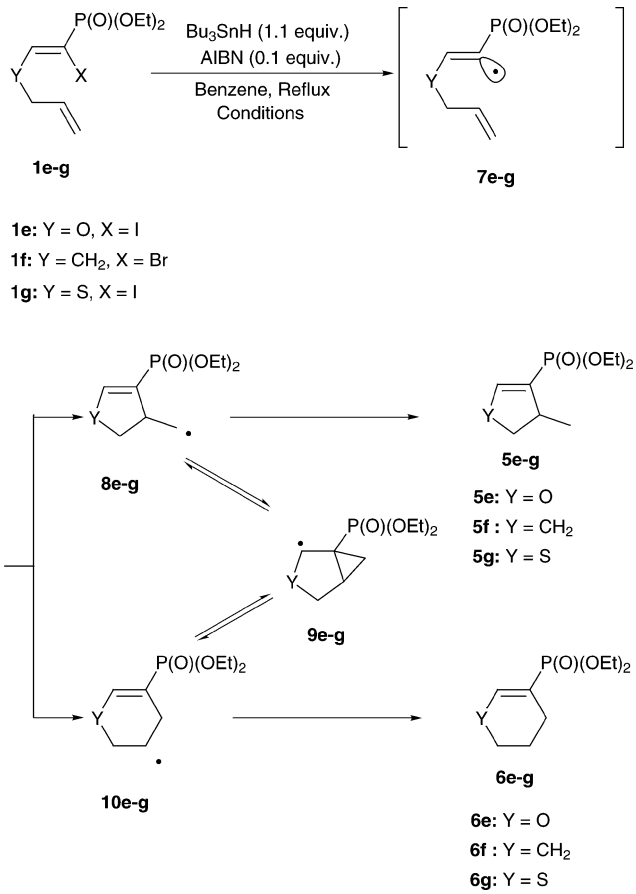
Bu_3SnH (0.11 M) and AIBN(0.01 M) in benzene to a solution of a mixture of **1b** (0.025 M) and α-methylstylene in benzene (entry 4), while the addition of a benzene solution of Bu_3SnH (0.22 M) and AIBN (0.02M) to the mixture of **1b** (0.07 M) and α-methylstylene in benzene over 1 or 5 h improved slightly the yield up to 35–38% (entries 2, 3). The similar tin-mediated reaction of **1b** with electron-rich olefins such as phenyl vinyl sulfide and 1-phenyl-1-(trimethylsilyloxy)ethylene successfully led to the corresponding radical adducts **3b,c** in 48 and 47% yields, respectively (entries 5 and 6).

To investigate the scope and limitations of this tin-mediated α-phosphonovinyl radical coupling reaction with olefins, the reaction of the radicals **2c,d**, generated from α-iodo-β-ethoxyvinyl- or α-bromovinylphosphonates **1c,d**, with phenyl vinyl sulfide was similarly conducted to give the corresponding coupling products **3d,e** in 30–49% yields (entries 7 and 8). The stereochemistry of **3d** was assigned as the *cis*-isomer on the basis of the coupling constant $^3J_{P-H}$ = 10.5Hz between vinylic H and phosphorus (see ESI†). The formation of the expected *trans*-isomer was negligible. This result indicates that the radical **2d** generated in the reaction system is configurationally stable during the trapping reaction. Similar treatment of **1b** with an electron-deficient alkene, ethyl acrylate, also led to the radical coupling product **3f** albeit in low yield (16%) together with recovered **1b** (44%) (entry 9). These results showed that the coupling reaction of α-phosphonovinyl radicals with olefins is essentially substrate independent, although electron-rich olefins are preferable to electron-deficient ones. Accordingly, this synthetic method suggests a new promising possibility for development of synthetically useful and biologically valuable vinylphosphonates.

Ring formation in radical cyclization of α-phosphonovinyl radicals

The synthesis of biologically active compounds and naturally occurring compounds[10] by radical cyclization of alkenyl and vinyl radicals as well as alkyl radicals has recently attracted great attention of synthetic organic chemists, due to various advantages such as high regio- and/or stereoselectivity,[11] simple procedures, good yield, *etc.* In contrast to alkenyl radicals which usually cyclize in the 5-*exo*-mode, the cyclization of vinyl radicals often affords 6-*endo*-mode products in substantial yields in addition to 5-*exo*-mode products.[12] Since the role that the α-phosphono group and β-heteroatom may play in the vinyl radical cyclization mode was not known, we examined the substituent effect of α-phosphonovinyl radicals with a $YCH_2CH{=}CH_2$ (Y = O, CH_2, S) substituent at the β-position on ring formation reaction and also aimed at developing a new synthetic method of hard-to-prepare heterocyclic or carbocyclic systems incorporating the vinylphosphonate unit.

Treatment of **1e** (0.1 M) with Bu_3SnH (1.1 equiv.) and AIBN (0.1 equiv.) in benzene at reflux for 3.5 h led in high yield (90%) to 5-*exo* radical cyclization product **5e**, along with a trace amount of 6-*endo* cyclization product **6e**, but no acyclic product was observed (Scheme 6, entry 1 in Table 2).



Scheme 6 Intramolecular cyclization of α-phosphonovinyl radicals **7e–g**.

We next examined the Bu_3SnH concentration dependence on the products.[13] Similar treatment of **1e** (0.025 M) by slow addition of a solution of Bu_3SnH (*ca.* 0.11 M, 1.1 equiv.) and AIBN (0.1 equiv.) in benzene over 5 h resulted in a 77 : 23 mixture of **5e** and **6e** in 79% yield (entry 2). The α-bromovinylphosphonate **1f** was similarly treated under the same conditions as above to produce 66 : 34 and 8 : 92 mixtures of 5-*exo* and 6-*endo* cyclization products, **5f** and **6f**, in 73% and 83% yields, respectively (entries 3 and 4). These results indicate

Table 2 Radical cyclization of α-halovinylphosphonates **1e–g**

Entry	Vinylphosphonates **1**	Conditions[a]				
		Concentration/mol l^{-1}	Addition time/h	Time[b]/h	Yield[c] (%) (**5** + **6**)	Ratio[d] of **5** : **6**
1	**1e**	0.1	0	3.5	90	**5e** : **6e** = 99 : 1
2[e]	**1e**	0.025	5	7.0	79	**5e** : **6e** = 77 : 23
3	**1f**	0.1	0	4.0	73	**5f** : **6f** = 66 : 34
4[e]	**1f**	0.025	5	8.0	83	**5f** : **6f** = 8 : 92
5	**1g**	0.1	0	3.5	76	**5g** : **6g** = 20 : 80
6[e]	**1g**	0.025	5	8.0	77	**5g** : **6g** = 5 : 95

[a] The reaction was carried out by using **1** (0.2 mmol), Bu_3SnH (0.22 mmol) and AIBN (0.02 mmol), unless otherwise noted. [b] Total reaction time until starting material **1** was consumed completely. [c] Isolated yields. [d] Based on ^1H NMR yield. [e] To a solution of **1** (0.2 mmol) in refluxing benzene (8 mL) was added a benzene solution (2 mL) of Bu_3SnH (0.22 mmol) and AIBN (0.02 mmol) through a syringe pump.

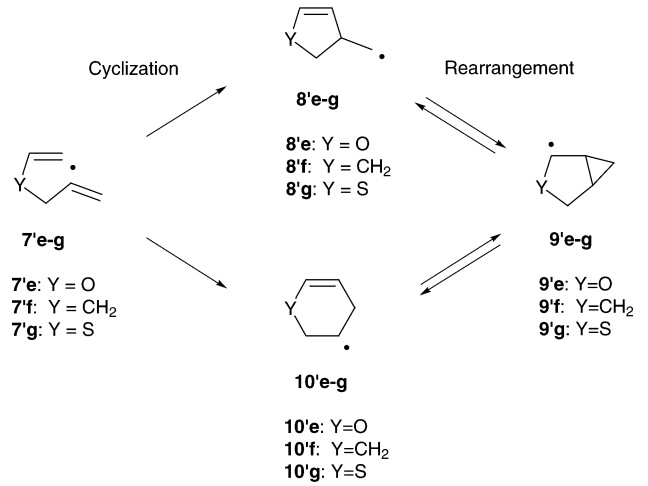
that, as observed in other vinyl radicals,[13] cyclization of α-phosphonovinyl radicals **7e,f** at higher concentration of Bu_3SnH predominantly gave kinetically controlled 5-*exo* products **5e,f**. However, it is of great interest that the α-iodovinylphosphonate **1g** on treatment with Bu_3SnH/AIBN under identical conditions with entry 1 afforded 5-*exo* and 6-*endo* products, **5g** and **6g**, in a 20 : 80 ratio, which is the reversed ratio when **1e,f** were used as substrates (entry 5). Application of *trans*-**1g** isomer to cyclization reaction was not attempted.

Treatment with slow addition of Bu_3SnH/AIBN increased the ratio of **6g** to **5g** up to 95 : 5 (entry 6). Thus, even at higher concentration of stannane, β-allylthio-α-phosphonovinyl radical **7g** strongly favored 6-*endo* cyclization over 5-*exo* cyclization. This data might not rule out the possibility that the product **6g** was formed *via* both of two different pathways, a direct 6-*endo* radical cyclization of **7g** to **10g** and a 5-*exo* radical cyclization to **8g**, followed by rearrangement into thermodynamically favorable 6-*endo* radical intermediate **10g** through **9g**, that is, *via* "formal 6-*endo* cyclization" (Scheme 6).

In order to investigate the reason which caused such high 6-*endo* selectivity in the competition between 5-*exo* and 6-*endo* cyclization, we next calculated the energy level diagram relevant to the two competing mechanism in the radical cyclization of simple vinyl radicals as model systems.

Theoretical calculations

The reactions were examined briefly by theoretical calculations to disclose the origin of highly dependent selectivity (5-*exo vs.* 6-*endo*) upon the substrates, **7e–g**, and reaction conditions, since there was no report of such a calculation to the best of our knowledge. The potential energy surfaces associated with cyclization and rearrangement reactions of vinyl radicals **7′e–g** were calculated as model systems (Scheme 7). Calculations were performed using the GAUSSIAN 98[14a] program packages, employing standard basis sets and theoretical methods as defined in these programs. Geometries were optimized at the Becke3LYP/6-31G* level of theory.[14b–d] All structures were characterized as minima (number of imaginary frequencies, NIMAG = 0) or transition structures (NIMAG = 1) by analytic energy second-derivative calculations of harmonic vibrational frequencies. The same method was used to establish the connection of saddle points with minima on both sides by intrinsic reaction coordinate (IRC) calculations. Relative energies are given in kJ mol^{-1}. Absolute energies and structures are provided as ESI.†



Scheme 7 Model systems for theoretical calculation cyclization/rearrangement reaction of vinyl radicals **7′e–g**.

A: Cyclization reaction

Cyclization reactions of vinyl radicals **7′e–g** with 5-*exo* and 6-*endo* fashion resulted in the formation of product radicals, **8′e–g** and **10′e–g**, respectively. The relative activation energies, $\Delta\Delta E_{rxn}^{\ddagger}$, in cyclization reactions show that transition structures of 5-*exo* cyclization reactions, **7′e/8′e**, **7′f/8′f** and **7′g/8′g**, are more stable than transition structures of 6-*endo* cyclization reactions, **7′e/10′e**, **7′f/10′f** and **7′g/10′g**, by −19.3, −12.1 and −5.0 kJ mol^{-1}, respectively. The cyclization reactions are all highly exothermic and the reaction energies ΔE_{rxn} are in the range between −112.6 and −152.4 kJ mol^{-1} (Fig. 1, Table 3). Relative reaction energies, $\Delta\Delta E_{rxn}$, show that 5-*exo* radicals **8′e–g** are less stable than 6-*endo* radicals **10′e–g** by 26.0, 28.5 and 25.1 kJ mol^{-1}, respectively. From these results it can be concluded that cyclization reactions of **7′e–g** almost exclusively (or predominantly in the case of **7′g**) take place with 5-*exo*

Table 3 Activation energies ($\Delta E_{rxn}^{\ddagger}$) and reaction energies (ΔE_{rxn}) of the intramolecular cyclizations of **7′e–g** into 5-*exo* and 6-*endo* radicals, **8′e–g** and **10′e–g**, and the rearrangement between the radicals **8′e–g** and **10′e–g** *via* the bicyclic radical **9′e–g**[a,b]

Reaction	Cyclization		Reaction	Rearrangement	
	$\Delta E_{rxn}^{\ddagger}$	ΔE_{rxn}		$\Delta E_{rxn}^{\ddagger}$	ΔE_{rxn}
7′e → **8′e**	4.2	−126.4	**8′e** → **9′e**	45.6	4.6
7′e→**10′e**	23.4	−152.4	**9′e** → **10′e**	45.2	−30.6
$\Delta\Delta E_{rxn}^{\ddagger} = -19.3^c$					
$\Delta\Delta E_{rxn} = 26.0^d$					
7′f→**8′f**	16.3	−112.6	**8′f** → **9′f**	43.5	10.0
7′f→**10′f**	28.5	−141.1	**9′f** → **10′f**	40.6	−38.5
$\Delta\Delta E_{rxn}^{\ddagger} = -12.1^c$					
$\Delta\Delta E_{rxn} = 28.5^d$					
7′g → **8′g**	16.3	−119.3	**8′g** → **9′g**	33.1	−9.6
7′g → **10′g**	21.4	−144.4	**9′g** → **10′g**	39.4	−15.5
$\Delta\Delta E_{rxn}^{\ddagger} = -5.0^c$					
$\Delta\Delta E_{rxn} = 25.1^d$					

[a] Becke3LYP/6-31G*. [b] kJ mol^{-1}. [c] $\Delta\Delta E_{rxn}^{\ddagger} = \Delta E_{rxn}^{\ddagger}$ (**7′** → **8′**) $-\Delta E_{rxn}^{\ddagger}$(**7′** → **10′**). [d] $\Delta\Delta E_{rxn} = \Delta E_{rxn}$ (**7′** → **8′**) $-\Delta E_{rxn}$(**7′** → **10′**).

fashion to give radicals **8′e–g**. The possibility of the formation of **8′e–g** *via* equilibrium between **8′e–g** and **10′e–g** can be excluded because of higher thermodynamic stability of **10′e–g** than **8′e–g**. The possibility of direct formation of **10′g** from **7′g** to some extent can not be ruled out because of a lower energy gap between 5-*exo* and 6-*endo* transition structures **7′g**/**8′g** and **7′g**/**10′g** ($\Delta\Delta E_{rxn}^{\ddagger} = -5.0$ kJ mol^{-1}).

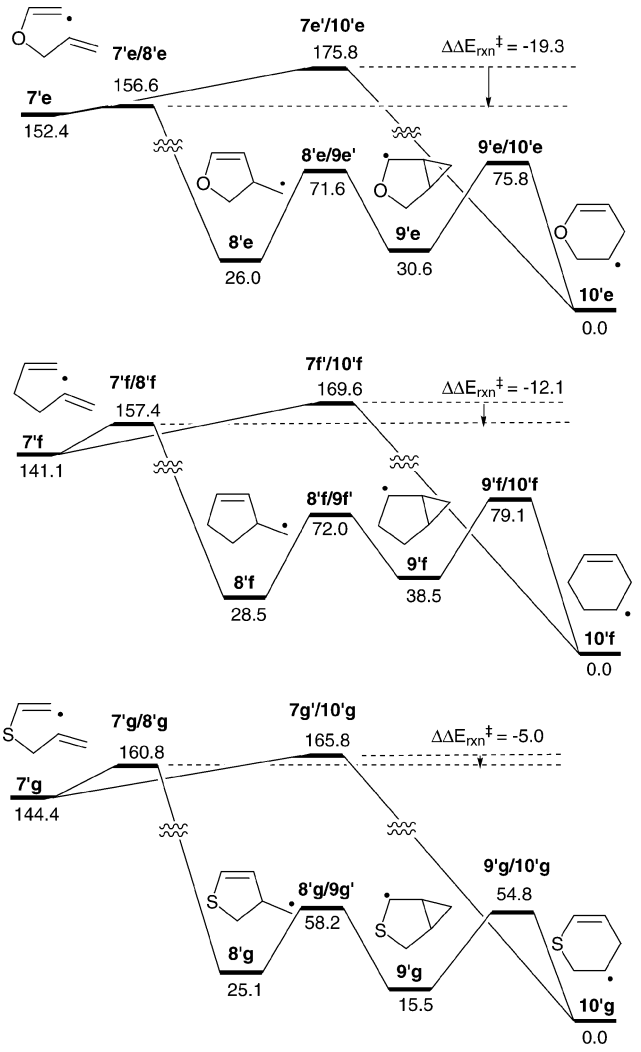


Fig. 1 Potential energy surfaces of the intramolecular cyclization of the model radicals **7′e–g** and of the rearrangement between the 5-*exo* and 6-*endo* radicals, **8′e–g** and **10′e–g** calculated at the B3LYP/6-31G* level of the theory (kJ mol^{-1}).

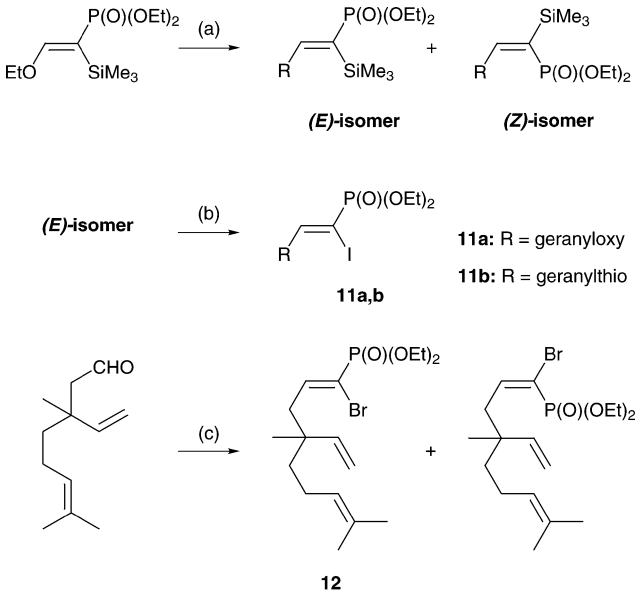
B: Rearrangement

Calculation of the rearrangement reactions of **8′e–g** to **10′e–g** *via* intermediate radicals **9′e–g** showed interesting features in activation and reaction energies, $\Delta E_{rxn}^{\ddagger}$ and ΔE_{rxn} (Table 3). The activation energy $\Delta E_{rxn}^{\ddagger}$ in rearrangement **8′e** → **9′e** is 45.6 kJ mol^{-1} and slightly larger than those of **8′f** → **9′f** (43.5 kJ mol^{-1}) and **8′g** → **9′g** (33.1 kJ mol^{-1}). The successive rearrangements **9′e** → **10′e**, **9′f** → **10′f** and **9′g** → **10′g** again show a similar trend indicating that the activation energies, $\Delta E_{rxn}^{\ddagger}$, are 45.2, 40.6 and 39.4 kJ mol^{-1}, respectively. From these results, it can be concluded that 5-*exo* radical **8′g** is considerably kinetically less stable in rearrangement reactions than **8′e** and **8′f**. It is noteworthy that reaction **8′g** → **9′g** is exothermic by −9.6 kJ mol^{-1}, although the reactions **8′e** → **9′e** and **8′f** → **9′f**, are slightly endothermic by 4.6 and 10.0 kJ mol^{-1}, respectively.

These calculations supported the following assumptions. (i) Cyclization reactions of intermediate radicals **7e–g** irreversibly take place with 5-*exo* fashion to give radicals **8e–g**, exclusively (or predominantly in the case of **7g**). (ii) The radicals **8e–g** are thermodynamically less stable than 6-*endo* radicals **10e–g**. (iii) Rearrangement reactions of **8e–g** take place with considerable rate to give **10e–g** and is competitive with radical trapping reaction by Bu_3SnH. Relative kinetic stabilities of the radicals **8e–g** in the rearrangement reactions are in the order of **8e** > **8f** ≫ **8g**. It is proposed that cyclization of **7g** takes place to form kinetically favored 5-*exo* **8g**, predominantly, which rearranges so rapidly to give **6g** in high yield even at higher concentrations of Bu_3SnH. Needless to say, at lower concentrations, the more rearrangement product **10g** would be formed. The possibility of some contribution of direct formation of **10g** can not be ruled out from the model calculations as already mentioned.

Synthetic application of α-phosphonovinyl radicals

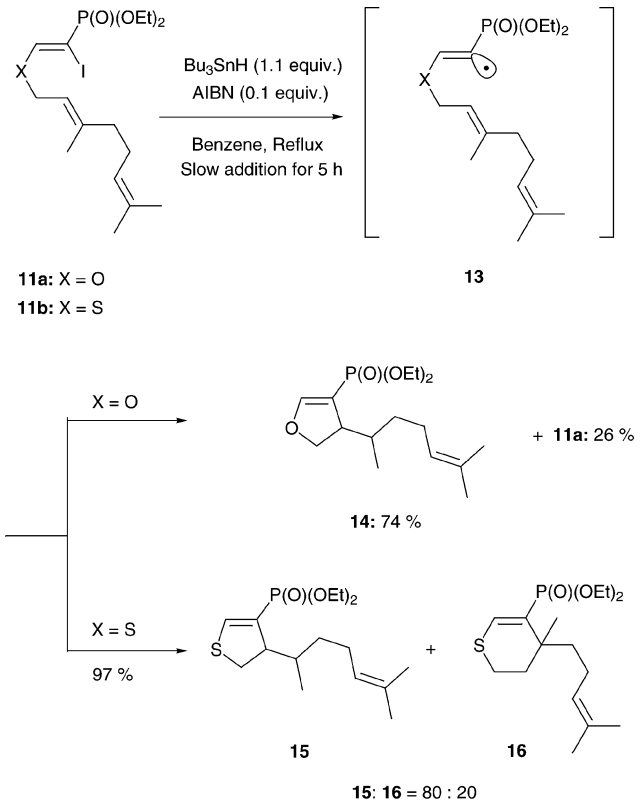
On the basis of above results, we expected that the synthesis of functionalized carbocyclic or heterocyclic compounds incorporating an α,β-unsaturated phosphonate moiety can be similarly realized by radical cyclization of functionalized α-phosphonovinyl radicals. So, we investigated radical cyclization of the terpenoid group-containing α-phosphonovinyl radicals to give the terpenoid-functionalized carbocyclic or heterocyclic compounds incorporating the vinylphosphonate moiety, which are expected to act as versatile building blocks for the synthesis of naturally occurring compounds and related derivatives or to exhibit useful biological activity. The synthesis of α-iodo-β-(geranyloxy)vinyl-**11a** and β-(geranylthio)vinylphosphonates **11b** as radical precursors was achieved in a similar manner as **1g** *via* double transfunctionalization of β-ethoxy-α-(trimethylsilyl)vinylphosphonates[8] (Scheme 8). Diethyl 1-bromo-4,8-dimethyl-4-vinylnona-1,7-dienylphosphonate (**12**) was prepared by the Horner–Wadsworth reaction of tetraethyl α-bromomethylenediphosphonate with 3,7-dimethyl-3-vinyl-6-octenal.



Scheme 8 Preparation of terpenoid group-containing α-bromovinylphosphonates **11a,b** and **12**. *Reagents and conditions*: (a) *n*BuLi, RH, −78 °C to r.t.; (b) NaI, *N*-chlorosuccinimide, MeCN, r.t.; (c) tetraethyl methylenediphosphonate, LDA, THF, −78 °C to r.t., and then NBS, THF, −78 °C to r.t.

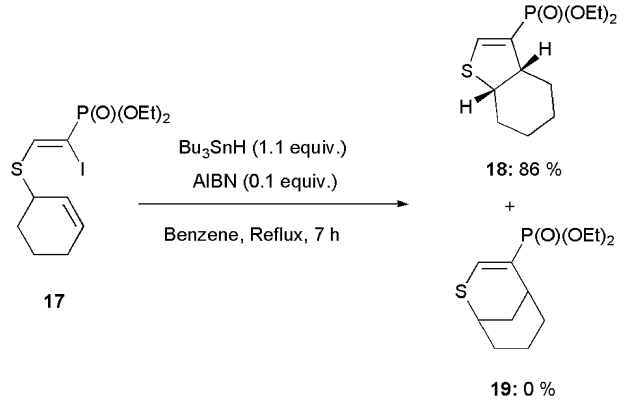
As expected, the tin-mediated reaction of α-iodo-β-(geranyloxy)vinylphosphonate **11a** produced exclusively 3-diethylphosphono-4-(6′-methyl-5′-hepten-2′-yl)-4,5-dihydrofuran (**14**) (74% yield), which is the 5-*exo* radical cyclization product of α-phosphonovinyl radical **13** (Scheme 9).

Neither product *via* 6-*endo* radical cyclization or *via* tandem cyclization was found. On the other hand, α-iodo-β-(geranylthio)vinylphosphonate **11b** on similar treatment led to



Scheme 9 Cyclization of α-phosphonovinyl radicals.

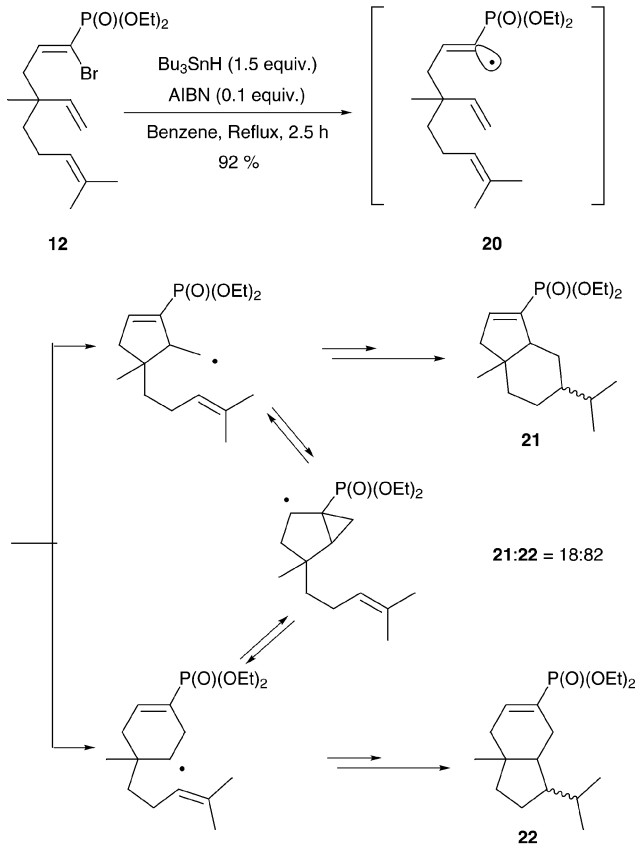
a 80 : 20 mixture of the 5-*exo* cyclization product, 3-diethylphosphono-4-(6′-methyl-5′-hepten-2′-yl)-4,5-dihydrothiophene (**15**) and the 6-*endo* cyclization product, 3-diethylphosphono-4-methyl-4-(4′-methyl-3′-penten-1′-yl)-4,5-dihydro-6*H*-thiopyran (**16**) in 97% yield. This tin-mediated radical cyclization reaction was applied to homologous α-iodo-β-(2-cyclohexenylthio)vinylphosphonate **17** to result in 3-phosphono-hexahydrobenzothiophene **18** (eqn. (1)).



(1)

We are, furthermore, interested in development of a synthetic route of fused bicyclic systems incorporating a vinylphosphonate moiety *via* a tandem radical cyclization process.[15,16] Similar treatment of the bromovinylphosphonate **12** with tin hydride led to 92% of a 18 : 82 mixture of desired two isomeric vinylphosphonate-incorporating bicyclo[4.3.0]nonene systems **21** and **22**, which are produced *via* tandem 5-*exo*-cyclization-6-*exo*-cyclization and 6-*endo*-cyclization-5-*exo*-cyclization processes, respectively (Scheme 10).

Thus, we revealed that α-phosphonovinyl radical species can be utilized for the synthesis of poly-functionalized vinylphosphonates and a wide variety of ring-size controlled carbocyclic or heterocyclic compounds incorporating an α,β-unsaturated phosphonate group within their rings.



Scheme 10 Tandem radical cyclization of α-phosphonovinyl radicals.

Conclusion

We note the following results from this investigation: (1) the first direct generation of α-phosphonovinyl radicals was achieved by treatment of α-halovinylphosphonates with Bu_3SnH/AIBN. (2) A new synthetic method of highly functionalized vinylphosphonates and vinylphosphonate-incorporated carbocyclic or heterocyclic compounds, which are not easily accessible by the established methods, was developed. (3) The influence of β-substituents upon radical cyclization mode of α-phosphonovinyl radicals was discussed on the basis of theoretical calculation of vinyl radicals as model compounds.

Experimental

General methods

^1H and ^{13}C NMR spectra were obtained in $CDCl_3$, ^1H NMR at 400.13 MHz, 500.00 MHz and ^{13}C NMR at 100.62 MHz, 125.65 MHz with Me_4Si as an internal standard. IR spectra were recorded on a JEOL JIR-WINSPEC50 spectrometer. Mass spectra were measured on a JEOL JMS-SX102A system.

General procedure for intermolecular additions of α-phosphonovinyl radicals derived from α-halovinylphosphonates 1a–d to alkenes. To a solution of α-halovinylphosphonate **1a–d** (0.2 mmol) and an alkene (2.0 mmol) in benzene (1–8 mL) at reflux was added Bu_3SnH (0.22 mmol) and AIBN (0.02 mmol) in benzene (1–2 mL) through a cannula using syringe pump for 1–5 h. After addition, the reaction mixture was heated at reflux for additional 1–7 h until starting material **1a–d** was completely consumed. After removal of the solvent, the residue was chromatographed on preparative TLC (AcOEt–hexane = 2 : 1 or 1 : 1) to give **3a–f**. The reaction conditions and yields of **3a–f** are summarized in Table 1. Representative spectral data are given for **3b** below.

Diethyl 3-(phenylthio)-1-(1,3-dithiolan-2-ylidene)propylphosphonate (3b). IR (neat) 792, 1041, 1390, 1243, 1438, 1538,

2981, 3451 cm^{-1}; ^1H NMR δ 1.31 (6H, t, J = 7.1 Hz), 2.64–2.73 (2H, m), 3.05–3.09 (2H, m), 3.36 (2H, t, J = 6.1 Hz), 3.41 (2H, m), 4.03–4.13 (4H, m), 7.17 (1H, t, J = 7.4 Hz), 7.29 (2H, t, J = 7.5 Hz), 7.40 (2H, d, J = 7.5 Hz); ^{13}C NMR (16.3 (d, $^3J_{P-C}$ = 6.4 Hz), 30.67, 35.9 (d, $^2J_{P-C}$ = 8.4 Hz), 36.8, 39.1, 61.6 (d, $^2J_{P-C}$ = 5.2 Hz), 110.2 (d, $^1J_{P-C}$ = 190.0 Hz), 125.7, 128.7, 128.9, 136.0, 159.9 (d, $^2J_{P-C}$ = 15.4 Hz); MS m/z 390 (M^+). Anal. Calc. for $C_{16}H_{23}PO_3S_3$: H, 5.94; C, 49.21. Found: H, 6.03; C, 49.17%.

General procedure for cyclization reaction of α-phosphonovinyl radicals derived from α-halovinylphosphonates 1e–g (Table 2, entries 1, 3, 5). A solution of α-halovinylphosphonate **1** (0.2 mmol), Bu_3SnH (0.22 mmol) and AIBN (0.02 mmol) in benzene (2 mL) was heated under reflux for 3.5–4.0 h, until starting material **1** was consumed completely. After removal of the solvent, the residue was chromatographed on preparative TLC (silica gel; AcOEt–hexane = 1 : 1) to give a difficultly separable mixture of **5** and **6**. The reaction conditions, and yields and ratios of the mixtures of **5e–g** and **6e–g** are summarized in Table 2.

General procedure for cyclization reaction of α-phosphonovinyl radicals derived from α-halovinylphosphonates 1e–g (Table 2, entries 2, 4, 6). To a solution of α-halovinylphosphonate **1** (0.2 mmol) in benzene (8 mL) at reflux was added a solution of Bu_3SnH (0.22 mmol) and AIBN (0.02 mmol) in benzene (2 mL) through a cannula using a syringe pump over 5 h. After addition, the reaction mixture was kept under reflux for 2.0–3.0 h, until starting material **1** was consumed completely. After similar workup, the residue was chromatographed on preparative TLC (silica gel; AcOEt–hexane = 1 : 1) to give a mixture of **5** and **6**. The reaction conditions, and yields and ratios of the mixtures of **5e–g** and **6e–g** are summarized in Table 2. The mixtures of **5e–g** and **6e–g** had the following properties.

The mixture of 3-(diethylphosphono)-4,5-dihydro-4-methyl-2*H*-furan (5e) and 3-(diethylphosphono)-4,5-dihydro-2*H*-pyran (6e) (entry 2, Table 2). IR (neat) 794, 1025, 1259, 1608, 2964, 3471 cm^{-1}; ^1H NMR δ 1.14 (3H, d, J = 6.8 Hz, for **5e**), 1.24–1.30 [(6 + 11/50 × 6)H, m, for **5e** and **6e**], 1.80–1.89 (11/50 × 2H, m, for **6e**), 2.04–2.05 (11/50 × 2H, m, for **6e**), 3.12–3.15 (1 H, m, for **5e**), 3.96–4.05 {[P(O)(OC$H_2$$CH_3$)$_2$ (4 + 11/50 × 4)H, m, for **5e** and **6e**], [OCHHCHMe, 1H, m, for **5e**], [OC$H_2$$CH_2$, 11/50 × 2H, m, for **6e**]}, 4.52 (OCHHCHMe, 1H, t, J = 9.8 Hz, for **5e**), 6.87 (1H, d, $^3J_{P-H}$ = 3.6 Hz, for **5e**), 7.10 (11/50 × 1 H, d, $^3J_{P-H}$ = 10.7 Hz, for **6e**); MS m/z 220 (M^+); HRMS: calc. for $C_9H_{17}O_4P$ 220.0864; found 220.0860.

The mixture of 1-(diethylphosphono)-5-methylcyclopentene (5f) and 1-(diethylphosphono)cyclohexene (6f) (entry 3, Table 2). ^1H NMR δ 1.09 (3H, d, J = 6.9 Hz, for **5f**), 1.23–1.28 [(6 + 1/2 × 6)H, m, for **5f** and **6f**], 1.47–1.50 (1/2 × 2H, m, for **6f**), 1.56–1.60 (2H, m, for **6f**), 2.1–2.15 [(2 + 1/2 × 2)H, m, for **5f** and **6f**], 2.39–2.44 (1/2 × 2H, m, for **6f**), 2.45–2.46 (1/2 × 2H, m, for **6f**), 2.80–2.90 (1H, m, for **5f**), 3.96–4.05 [(4 + 1/2 × 4)H, m, for **5f** and **6f**], 6.57 (1H, ddd, $^3J_{P-H}$ = 11.4 Hz, for **5f**), 6.69 (1/2 H, ddd, $^3J_{P-H}$ = 22.2 Hz, for **6f**); HRMS: calc. for $C_{10}H_{19}O_3P$ 218.1072; found 218.1072.

The mixture of 3-(diethylphosphono)-4,5-dihydro-4-methyl-2*H*-thiophene (5g) and 3-(diethylphosphono)-4,5-dihydro-2*H*-thiopyran (6g) (entry 5, Table 2). IR (neat) 786, 962, 1024, 1232, 1571, 2931, 3453 cm^{-1}; ^1H NMR δ 1.24 (6/25 × 3H, d, J = 6.8 Hz, for **5g**), 1.30–1.37 [(6 + 6/25 × 6)H, m, for **5g** and **6g**], 2.01–2.05 (2H, m, for **6g**), 2.26–2.31 (2H, m, for **6g**), 2.88–2.91 (2H, m, for **6g**), 3.53–3.58 (6/25 H, dd, J = 11.0 Hz, for **5g**), 4.01–4.11 {[P(O)(OC$H_2$$CH_3$)$_2$ (4 + 6/25 × 4)H, m, for **5g** and **6g**], (SCHHCHMe, 6/25 H, m, for **5g**)}, 7.11 (6/25 H, d, $^3J_{P-H}$ = 11.4 Hz, for **5g**), 7.22 (1H, d, $^3J_{P-H}$ = 21.6 Hz, for **6g**); MS m/z 236 (M^+); Anal. (as a mixture). Calc. for $C_9H_{17}O_3PS$: C, 45.75; H, 7.25. Found: C, 45.76; H, 7.15%.

3-(Diethylphosphono)-3a,4,5,6,7,7a-hexahydrobenzothiophene (18). IR (neat) 863, 960, 1238, 1392, 1448, 1540, 2933, 3486 cm^{-1}; ^1H NMR δ 1.33 (6H, t, J = 7.1 Hz), 1.53–1.54 (1H, m), 1.57–1.63 (4H, m), 1.75–1.80 (2H, m), 1.89–1.98 (1H, m), 2.88–2.91 (1H, m), 4.02–4.15 {[P(OC$H_2$$CH_3$)$_2$, 4H, m], [SC$H$($CH_2$)(CH), 1H, m]}, 7.16 (1H, d, $^3J_{P-H}$ = 11.8 Hz); ^{13}C NMR δ 16.3, 21.7, 22.8, 25.9, 27.2, 47.2, 54.3 (d, $^3J_{P-C}$ = 12.7 Hz), 61.7 (d, $^2J_{P-C}$ = 5.4 Hz), 128.7 (d, $^1J_{P-C}$ = 190.7 Hz), 145.2 (d, $^2J_{P-C}$ = 17.5 Hz); MS (FAB+) m/z 277 (M^+ + H); HRMS: calc. for $C_{12}H_{21}O_3PS$ 276.0949, Found 276.0959.

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