A new access to 2-phosphonothiophenes

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Graphical Abstract

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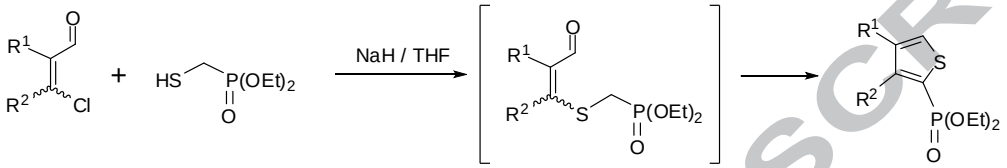

R^1 = Alk, Ar
R^2 = Alk, Ar

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A new access to 2-phosphonothiophenes

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ABSTRACT

2-Phosphonothiophenes are prepared via the reaction of β-chloroacroleins with diethyl mercaptomethylphosphonate.

Heterocycles bearing a phosphonyl group have found a wide range of applications in many research fields such as agricultural, medicinal, and materials chemistry. As a representative class, phosphonothiophenes are applied in medicine as potential antibacterial agents,[1] as antihypertensive agents, for asthma treatment,[2] as inhibitors of FBPase (inhibition of FBPase is considered a promising way to reduce hepatic gluconeogenesis, and therefore could be a potential approach to treat type 2 diabetes).[3] In addition, they find various applications in materials chemistry[4] and as ligands for catalysis.[5] Some synthetic approaches to phosphonothiophenes have already been reported.[6] The most commonly applied protocols include: the reaction of thienyl halides with trialkyl phosphites (Arbuzov reaction),[7] the reaction β-keto-phosphonates with active methylene nitriles and subsequent treatment of the resulting phosphonoalkylidenes with sulfur (Gewald reaction),[8] the phosphonylation of metalated thiophenes with dialkyl chlorophosphates,[9] and a very recent method based on a silver-catalyzed dehydrogenative cross-coupling reaction of substituted thiophenes with dialkyl phosphites.[10]

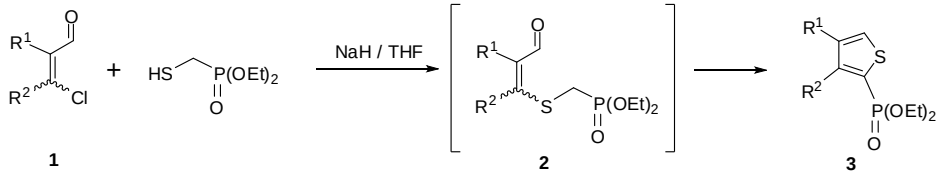
Considering the importance of heterocyclic phosphonates in medicinal[11] and coordination chemistry,[12] we recently reported a new strategy for the preparation of pyrazole-, thiazolidinone-, pyrrole- and phthalazine-phosphonic acids.[13] Herein, a convenient method for the synthesis of 2-phosphonothiophenes from easily available (via the Vilsmeier reaction) β-chloroacroleins[14] and diethyl mercaptomethylphosphonate[15] is reported.

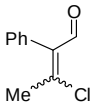
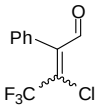
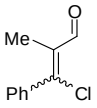
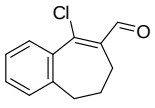
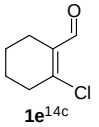
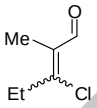
The synthetic route to 2-phosphonothiophenes **3a-f** is depicted in Table 1.[16]

The reaction of β-chloroacroleins and diethyl mercaptomethylphosphonate was performed in THF as the solvent and NaH as the base.[17] In some cases, we managed to isolate the aldehyde intermediate **2** (entries 3, 4 and 5). Attempts to transform this intermediate into **3** by prolonged heating (entry 4) ended mainly with excessive decomposition. The cyclization of aldehyde **2d** (entry 6) was conducted under similar conditions to those described for the reaction of compound **1d** with methyl mercaptoacetate,[18] using EtOH as the solvent and EtONa as the base. Thus, only the product of 3-*exo* trig cyclization **3d** was obtained, and in contrast to the nonphosphorylated variant,[18] no 5-*exo* trig cyclization products were found. However, when β-chloroacrolein **1e** was employed as the substrate (entry 7), two products were obtained: 2-phosphonothiophene **3e** and the known 4,5,6,7-tetrahydrobenzo[*b*]thiophene (**5**).[19] The phosphonothiophene **3e** results from 3-*exo* trig cyclization, while compound **5** is most likely formed by basic dephosphorylation[20] of intermediate **4,** which is itself the 5-*exo* trig cyclization product (but is not separated and is unstable in the reaction conditions) (Scheme 1).

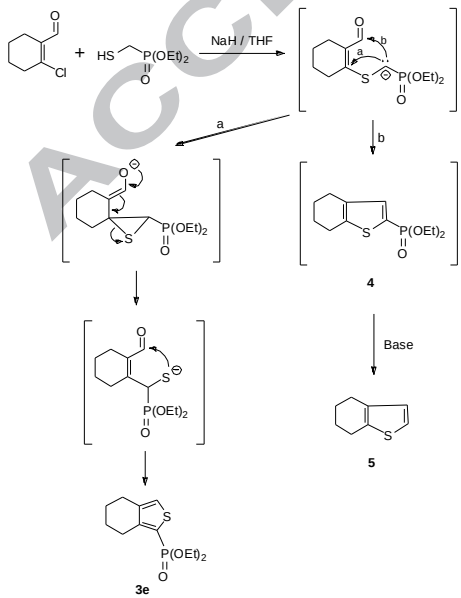
The structure of phosphonothiophene **3a** was confirmed by the heteronuclear multiple bond correlation (HMBC) experiment, in which the signal of the thiophene carbon atom C-2 correlates with the signal of the methyl protons of the methyl group attached to thiophene ring. In addition, the NOESY (nuclear Overhauser effect spectroscopy) spectrum displays a correlation between the protons of the methyl group attached to thiophene ring and the methyl protons of the ethyl group. We observed that the ^{13}C NMR spectra of **3a-f** exhibit four characteristic phosphorus-carbon coupling constants for the carbons of the thiophene ring: 209.5 ± 3.0 Hz, 6.3 ± 0.9 Hz, 17.0 ± 0.6 Hz and 11.5 ± 0.5 Hz, and based on the asigned structure of **3a** (Table 2, entry 1), they correspond to: $^{1}J_{PC}$, $^{2}J_{PCC}$, $^{3}J_{PCCC}$, and $^{3}J_{PCSC}$. The NMR (HMQC and HMBC) analysis, in particular the observation of typical coupling constants, and comparison with data obtained

Table 1
Synthesis of 2-phosphonothiophenes **3a-f**



Entry	Aldehyde	Conditions	Product	Yield[a] (%)
1	 **1a** (*Z* / *E*, 64 / 36)[14a]	NaH / THF, 4 h	**3a**	41
2	 **1b** (*Z* / *E*, 60 / 40)[14b]	NaH / THF, 38 h	**3b**	78
3	 **1c** (*Z* / *E*, 6 / 94)[14c]	NaH / THF, 4 h	**3c** (*E*)-**2c**	32 19
4	**1c**	NaH / THF, 19 h	**3c** (*E*)-**2c**	33 8
5	 **1d**[14d]	NaH / THF, 24 h	**2d** **3d**	92 6
6	**2d**	EtONa / EtOH, 14 h	**3d**	60
7	 **1e**[14c]	NaH / THF, 19 h	**3e** **5**	49 24
8	 **1f** (*Z* / *E*, 25 / 75)[14c]	NaH / THF, 19 h	**3f**	68

[a] Isolated pure product.



Scheme 1. The formation of **3e** by 3-*exo* trig cyclization (path a), and **5** by 5-*exo* trig cyclization (path b).

for **3a** and with an example in the literature (compound **6**, Table 2, entry 7),[7a] were useful tools for structural assignment of 2-phonothiophenes **3b-f** (Table 2, entries 2-6). For example, the characteristic coupling constant P-CH_{arom} for 3-*exo* trig cylization product **3f** , was 11.5 Hz instead of 6.3 ± 0.9 Hz, which would be expected for hypothetical 5-*exo* trig cylization product **7** (Figure 1).

In conclusion, a simple and convenient process for the preparation of 2-phosphonothiophenes from readily available starting materials has been developed. In addition, we have provided a simple method for determining the structures of 2-phosphonothiophenes, based on the values of the ^{31}P-^{13}C coupling constants.

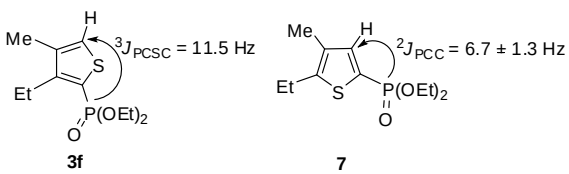
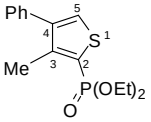
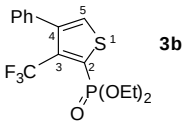
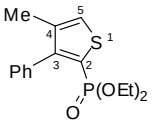
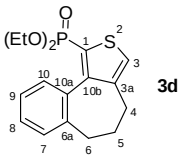
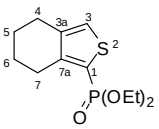
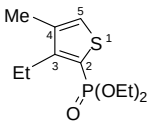
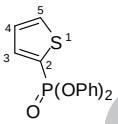


Figure 1. Determination of the structure of **3f** based on measurement of the P – CH_{arom} coupling constant.

Table 2
Coupling constants (P – C) of the carbons of the thiophene ring of 2-phosphonothiophenes **3a-f** and **6.**

Entry	2-Phosphonothiophene	P - C coupling constant (in bold)
1	 **3a**	123.5 (d, $^{1}J_{PC}$ = **211.6** Hz, C-2) 143.1 (d, $^{2}J_{PCC}$ = **5.4** Hz, C-3) 140.2 (d, $^{3}J_{PCCC}$ = **16.4** Hz, C-4) 138.8 (d, $^{3}J_{PCSC}$ = **11.1** Hz, C-5)
2	 **3b**	130.5 (d, $^{1}J_{PC}$ = **206.5** Hz, C-2) 132.2 (dq, $^{2}J_{PCC}$ = **7.2** Hz, $^{2}J_{FCC}$ = 36.4 Hz, C-3) 144.9 (dq, $^{3}J_{PCCC}$ = **16.6** Hz, $^{3}J_{FCCC}$ = 2.1 Hz, C-4) 139.1 (d, $^{3}J_{PCSC}$ = **11.0** Hz, C-5)
3	 **3c**	125.0 (d, $^{1}J_{PC}$ = **210.3** Hz, C-2) 146.4 (d, $^{2}J_{PCC}$ = **6.6** Hz, C-3) 134.4 (d, $^{3}J_{PCCC}$ = **16.5** Hz, C-4) 140.3 (d, $^{3}J_{PCSC}$ = **11.0** Hz, C-5)
4	 **3d**	125.0 (d, $^{1}J_{PC}$ = **211.0** Hz, C-1) 146.4 (d, $^{2}J_{PCC}$ = **6.9** Hz, C-10b) 139.9 (d, $^{3}J_{PCCC}$ = **16.4** Hz, C-3a) 139.2 (d, $^{3}J_{PCSC}$ = **11.9** Hz, C-3)
5	 **3e**	123.2 (d, $^{1}J_{PC}$ = **211.3** Hz, C-1) 144.9 (d, $^{2}J_{PCC}$ = **6.5** Hz, C-7a) 136.7 (d, $^{3}J_{PCCC}$ = **17.5** Hz, C-3a) 138.26 (d, $^{3}J_{PCSC}$ = **11.2** Hz, C-3)
6	 **3f**	122.1 (d, $^{1}J_{PC}$ = **212.4** Hz, C-2) 150.0 (d, $^{2}J_{PCC}$ = **6.5** Hz, C-3) 133.7 (d, $^{3}J_{PCCC}$ = **17.2** Hz, C-4) 139.8 (d, $^{3}J_{PCSC}$ = **11.5** Hz, C-5)
7	 **6**[7a]	125.9 (d, $^{1}J_{PC}$ = **218.15** Hz, C-2) 134.6 (d, $^{2}J_{PCC}$ = **8.0** Hz, C-3) 128.1 (d, $^{3}J_{PCCC}$ = **19.47** Hz, C-4) 138.3 (d, $^{3}J_{PCSC}$ = **13.06** Hz, C-5)

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16. *Reactions of β-chloroacroleins **1a-f** with diethyl mercaptomethylphosphonate*: To a suspension of NaH (0.024 g, 1.0 mmol) in THF (5 mL) at 0 °C was added diethyl mercaptomethylphosphonate (0.184 g, 1.0 mmol) and the resultant solution was stirred for 15 min. To the solution was added acrolein **1a-f** (0.9 mmol) and the mixture was stirred at room temperature under an argon atmosphere (time given in Table 1). In the case of **3b**, an additional portion of NaH (0.015 g, 0.6 mmol) was added after a period of 19 h and stirring was continued for an additional 19 h. The solution was poured into cold H_2O (or brine in the case of **3b**) / Et_2O mixture (1:4, v/v, 40 mL), the organic fraction was collected, and the aqueous fraction was extracted with Et_2O (2 x 30 mL).The combined organic fractions were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel (Et_2O, 100%) to afford **3a-f**, **2c,d**, and **5**.[19] *2-Diethoxyphosphoryl-3-methyl-4-phenylthiophene (**3a**)*: Yield: 41%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.36 (t, $^{3}J_{HH}$ = 7.3 Hz, 6H, $2CH_3$), 2.54 (s, 3H, CH_3), 4.10-4.22 (m, 4H, $2CH_2O$), 7.32-7.44 (m, 5H, C_6H_5), 7.59 (d, $^{4}J_{PH}$ = 8.6 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 14.5 (d, $^{3}J_{PC}$ = 2.0 Hz, CH_3), 16.3 (d, $^{3}J_{PC}$ =7.7 Hz, $2CH_3$), 62.6 (d, $^{2}J_{PC}$ = 4.4 Hz, $2CH_2$), 123.5 (d, $^{1}J_{PC}$= 211.6 Hz, C-2), 127.3 (CH_{arom}), 128.5 (CH_{arom}), 128.6 (CH_{arom}), 135.5 (C_{arom}), 138.8 (d, $^{3}J_{PC}$ = 11.1 Hz, C-5), 140.2 (d, $^{3}J_{PC}$ = 16.4 Hz, C-4), 143,1 (d, $^{2}J_{PC}$ = 5.4 Hz, C-3); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 11.96; HRMS (CI) Calcd for $C_{15}H_{19}O_3PS$:

310.0793. Found: 310.0785

2-Diethoxyphosphoryl-4-phenyl-3-(trifluoromethyl)thiophene ***(3b)***: Yield: 78%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.38 (t, $^{3}J_{HH}$ = 7.2 Hz, 6H, $2CH_3$), 4.15-4.27 (m, 4H, $2CH_2$), 7.42 (s, 5H, C_6H_5), 7.58 (dq, $^{5}J_{HF}$ = 1.4 Hz, $^{4}J_{PH}$ = 8.2 Hz, 1H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 16.3 (d, $^{3}J_{PC}$ = 6.6 Hz, $2CH_3$), 63.2 (d, $^{2}J_{PC}$ = 5.5 Hz, $2CH_2$), 122.0 (dq, $^{1}J_{FC}$ = 270.9 Hz, $^{3}J_{PC}$ = 2.7 Hz, CF_3), 128.5 (CH_{arom}), 128.7 (CH_{arom}), 130.5 (d, $^{1}J_{PC}$ = 206.5 Hz, C-2), 132.2 (dq, $^{2}J_{FC}$ = 36.4 Hz, $^{2}J_{PC}$ = 7.2 Hz, C-3), 133.4 (C_{arom}), 139.1 (d, $^{3}J_{PC}$ = 11.0 Hz, C-5), 144.9 (dq, $^{3}J_{PC}$ = 16.6 Hz, $^{3}J_{FC}$ = 2.1 Hz, C-4); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 9.01; HRMS (CI) Calcd for $C_{15}H_{16}F_3O_3PS$: 364.0510. Found: 364.0515.

2-Diethoxyphosphoryl-4-methyl-3-phenylthiophene ***(3c)***: Yield: 32%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.39 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, $2CH_3$), 2.35 (s, 3H, CH_3), 4.14-4.25 (m, 4H, $2CH_2O$), 7.38-7.51 (m, 6H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 151 MHz) : δ = 14.7 (CH_3), 16.3 (d, $^{3}J_{PC}$ = 6.7 Hz, $2CH_3$), 62.6 (d, $^{2}J_{PC}$ = 5.5 Hz, $2CH_2O$), 125.0 (d, $^{1}J_{PC}$ = 210.3 Hz, C_{arom}), 128.1 (CH_{arom}), 128.7 (CH_{arom}), 129.0 (CH_{arom}), 133.6 (d, $^{3}J_{PC}$ = 1.9 Hz, C_{arom}), 134.4 (d, $^{3}J_{PC}$ = 16.5 Hz, C-4), 140.3 (d, $^{3}J_{PC}$ = 11.0 Hz, C-5), 146.4 (d, $^{2}J_{PC}$ = 6.6 Hz, C-3); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 12.01; HRMS (CI) Calcd for $C_{15}H_{19}O_3PS$: 310.0793. Found: 310.0803.

(5,6-Dihydro-4H-2-thia-benzo[e]azulen-1-yl)phosphonic acid diethyl ester ***(3d)***: Yield: 6%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz): δ =1.38 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, $2CH_3$), 2.21-2.26 (m, 2H, CH_2), 2.67 (t, $^{3}J_{HH}$ = 6.6 Hz, 2H, CH_2), 2.69 (t, $^{3}J_{HH}$ = 7.2 Hz, 2H, CH_2), 4.14-4.25 (m, 4H, $2CH_2O$), 7.28-7.31 (m, 3H, CH_{arom}), 7.47-7.50 (m, 2H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 16.3 (d, $^{3}J_{PC}$ = 6.6 Hz, $2CH_3$), 27.0 (C-4), 32.1 (C-5), 33.0 (C-6), 62.6 (d, $^{2}J_{PC}$ = 5.5 Hz, $2CH_2O$), 125.0 (d, $^{1}J_{PC}$ = 211.0 Hz, C-1), 126.7 (CH_{arom}), 128.2 (CH_{arom}), 128.4 (CH_{arom}), 129.7 (CH_{arom}), 133.8 (d, $^{3}J_{PC}$ = 2.2 Hz, C-10a), 139.2 (d, $^{3}J_{PC}$ = 11.9 Hz, C-3), 139.9 (d, $^{3}J_{PC}$ = 16.4 Hz, C-3a), 140.8 (C-6a), 146.4 (d, $^{2}J_{PC}$ = 6.9 Hz, C-10b); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 12.22. HRMS (CI) Calcd for $C_{17}H_{21}O_3PS$: 336.0949. Found: 336.0958.

1-Diethoxyphosphoryl-4,5,6,7-tetrahydro-2-benzothiophene ***(3e)***: Yield: 49%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.35 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, $2CH_3$), 1.80-1.89 (m, 4H, CH_2), 2.64-2.66 (m, 2H, CH_2), 2.81-2.83 (m, 2H, CH_2), 4.07-4.20 (m, 4H, $2CH_2O$), 7.34 (d, $^{4}J_{PH}$ = 8.4 Hz, 1H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 16.3 (d, $^{3}J_{PC}$ = 6.7 Hz, $2CH_3$), 22.6 (CH_2), 23.3 (CH_2), 25.29 (CH_2), 25.31 (CH_2), 62.4 (d, $^{2}J_{PC}$ = 4.9 Hz, $2CH_2O$), 123.2 (d, $^{1}J_{PC}$ = 211.3 Hz, C-1), 136.7 (d, $^{3}J_{PC}$ = 17.5 Hz, C-3a), 137.8 (d, $^{3}J_{PC}$ = 11.2 Hz, C-3), 144.9 (d, $^{2}J_{PC}$ = 6.5 Hz, C-7a); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 13.00; HRMS (CI) Calcd for $C_{12}H_{19}O_3PS$: 274.0793. Found: 274.0791.

2-Diethoxyphosphoryl-3-ethyl-4-methylthiophene ***(3f)***: Yield: 68%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.31 (t, $^{3}J_{HH}$ = 7.5 Hz, 3H, CH_3), 1.34-1.37 (m, 6H, $2CH_3$), 2.18 (s, 3H, CH_3), 2.80 (q, $^{3}J_{HH}$ = 7.5 Hz, 2H, CH_2), 4.08-4.20 (m, 4H, $2CH_2O$), 7.37 (d, $^{4}J_{PH}$ = 8.4 Hz, 1H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 13.3 (CH_3), 15.3 (CH_3), 16.3 (d, $^{3}J_{PC}$ = 7.0 Hz, $2CH_3$), 21.7 (CH_2), 62.4 (d, $^{2}J_{PC}$ = 5.3 Hz, $2CH_2O$), 122.1 (d, $^{1}J_{PC}$ = 212.4 Hz, C-2), 133.7 (d, $^{3}J_{PC}$ = 17.2 Hz, C-4), 139.8 (d, $^{3}J_{PC}$ = 11,5 Hz, C-5), 150.0 (d, $^{2}J_{PC}$ = 6.5 Hz, C-3); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 12.77; HRMS (CI) Calcd for $C_{11}H_{19}O_3PS$: 262.0793 . Found: 262.0789.

(E)-3-(Diethoxyphosphorylmethylsulfanyl)-2-methyl-3-phenylprop-2-enal ***(2c)***: Yield: 8%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz) : δ = 1.32 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, $2CH_3$), 2.07 (s, 3H, CH_3), 2.56 (d, $^{2}J_{PH}$ = 14.7 Hz, 2H, CH_2), 4.08-4.13 (m, 4H, $2CH_2O$), 7.29-7.49 (m, 5H, C_6H_5), 9.18 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 12.6 (CH_3), 16.4 (d, $^{3}J_{PC}$ = 5.5 Hz, $2CH_3$), 25.8 (d, $^{1}J_{PC}$ = 146.4 Hz, CH_2P), 62.8 (d, $^{2}J_{PC}$ = 6.6 Hz, $2CH_2O$), 128.8 (CH_{arom}), 129.3 (C_{arom}), 129.5 (CH_{arom}), 130.3 (CH_{arom}), 133.5 (C-2), 159.9 (C-3), 189.9 (C-1); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 21.97; HRMS (CI) Calcd for $C_{15}H_{21}O_4PS$: 328.0898. Found: 328.0898. The *E* configuration was confirmed by a NOESY experiment in which a correlation between the aldehyde and aromatic protons was observed.

5-(Diethoxyphosphorylmethylsulfanyl)-8,9-dihydro-7H-benzo[7]anulene-6-carbaldehyde ***(2d)***: Yield: 92%; yellow oil: ^{1}H NMR ($CDCl_3$, 600 MHz): δ =1.29-1.39 (m, 6H, $2CH_3$), 2.11-2.16 (m, 2H, CH_2), 2.18-2.27 (m, 2H, CH_2) 2.61-2.71 (m, 4H, $2CH_2$), 4.05-4.22 (m, 4H, $2CH_2O$), 7.28-7.30 (m, 1H, CH_{arom}), 7.34-7.39 (m, 2H, $2CH_{arom}$), 7.72-7.74 (m, 1H, CH_{arom}), 10.53 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 16.4 (d, $^{3}J_{PC}$ = 5.6 Hz, $2CH_3$), 23.6 (C-7), 26.8 (d, $^{1}J_{PC}$ = 149.5 Hz, CH_2P), 31.6 (C-9), 34.8 (C-8), 62.6 (d, $^{2}J_{PC}$ = 6.6 Hz, $2CH_2O$), 126.9 (C-2), 128.7 (C-4), 129.7 (C-1), 130.1 (C-3), 135.9 (C-4a), 142.9 (C-6), 143.4 (C-9a), 153.9 (d, $^{3}J_{PC}$ = 3.3 Hz, C-5), 189.4 (d, $^{5}J_{PC}$ = 9.1Hz, CHO); ^{31}P NMR ($CDCl_3$, 243 MHz): δ = 22.44; HRMS (CI) Calcd for $C_{17}H_{23}O_4PS$: 354.1055. Found: 354.1042.

Cyclization of aldehyde ***2d***: To a solution of NaOEt in EtOH, prepared from Na (0.002 g, 0.09 mmol) and dry EtOH (1.0 mL), was added aldehyde **2d** (0.100 g, 0.28 mmol) and the resultant solution was stirred at room temperature under an argon atmosphere for 12 h. The solution was poured into ice H_2O (5 ml) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic fractions were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel (Et_2O, 100%) to afford **3d** (0.057 g, 60%).

17. Similar reaction conditions were applied to the preparation of thiophenes functionalized with carboethoxy- and trifluoromethyl-substituents: (a) Arnaud, R.; Bensadat, A.; Ghobsi, A.; Laurent, A.; Le Drean, I.; Lesniak, S.; Selemi, A. *Bull. Soc. Chim. Fr*. **1994**, *131*, 844-853; (b) Bartnik, R.; Bensadat, A.; Cal, D.; Faure, R.; Khatimi, N.; Laurent, A.; Laurent, E.; Rizzon, C. *Bull. Soc. Chim. Fr*. **1997**, *134*, 725-734.
18. De, A.; Bhattacharya, S.; Jash, S. S.; Mukherjee, S.; Saha, U.; Sen, P. K. *J. Heterocycl. Chem.* **1992**, *29*, 1213-1217.
19. Noe, C. R.; Knollmueller, M.; Wagner, E. *Monatsh. Chem.* **1986**, *117*, 621-630.
20. To the best of our knowledge, the dephosphorylation of phosphonothiophenes has not been reported yet. There are examples of basic decarboxylation of thiophene derivatives or basic dephosphorylation of phosphonopyrrole in the literature: (a) Lütjens, H.; Zickgraf, A.; Figler, H.; Linden, J.; Olsson, R. A.;Scammells, P. J.; *J. Med. Chem*.; **2003**, *46*; 1870-1877; (b) Griffin, C. E.; Peller, R. P.; Peters, J. A. *J. Org. Chem.* **1965**, *30*, 91–96.