Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01192 • Publication Date (Web): 13 Jul 2016

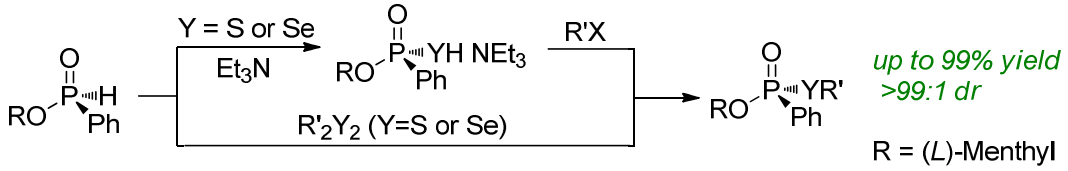
Stereospecific Preparations of *P*-Stereogenic Phosphonothioates and Phosphonoselenoates

Wei-Min Wang,[a] Li-Juan Liu,[a] Lan Yao,[a] Fan-Jie Meng,[a] Yong-Ming Sun,[a] Chang-Qiu Zhao,[a]* Qing Xu[b] and Li-Biao Han[c]*.

[a] *College of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng, Shandong 252059, China*

[b] *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang 325035, China*

[c] *National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan*



ABSTRACT: *P*-Stereogenic phosphonothioates and phosphonoselenoates were readily prepared utilizing R_P-menthyl phenylphosphite **1** by means of two methods. The first method used elemental sulfur or selenium to react with **1**, followed by alkylation of the intermediates with alkyl halides. The second used **1** to react with disulfide or diselenide. Both methods stereospecifically produced the title compounds in nearly quantitative yields under mild conditions. Stereospecific chalcogenation of the phosphoryl was proposed as the key step in these reactions.

Phosphonothioates and related compounds are widely used as agricultural pesticides due to their important biological activity such as acetylcholine esterase inhibitors.[1,2] These compounds are also famous neurotoxins, herbicides and insecticides. For the purpose to explore the metabolism and degradation of these substances in the organism or the nature, phosphonothioates and phosphinithioates, especially the *P*-stereogenic ones, are usually used as substrates.[3] Apart from the traditional agricultural, pharmacological and toxicological applications, *P*-stereogenic P-S species also are widely used as chemical-shift solvating reagent in the analysis of chiral substances. For example, (R_P)-*t*-BuPhP(S)OH was an efficient chemical shift reagent used to distinguish the enantiomers of chiral amines, alcohols and others with NMR spectroscopy.[4] In addition, P-S compounds can be used as precursors for

the preparation of *P*-stereogenic compounds via nucleophlic substitution, in inverting or retaining configuration on phosphorus, with alkoxide or alkyl anions as attacking reagents, respectively.[5]

Although the *P*-stereogenic phosphonothioates and their analogues have versatile applications, the preparation methods were quite limited, due to the difficulty to acquire *P*-stereogenic starting materials. On the other hand, H-P(O) compounds could be conveniently converted to P-S compounds by literature methods. For example, Mislow and coworker obtained diastereomerically enriched phosphonothioates from a mixture of two stereoisomers of chiral H-P(O) compounds.[6] The early preparation of (R_P)-*t*-BuPhP(S)OH was involved in the sulfurization of racemic H-P species and kinetic resolution of the products.[7] Recently, Kuo obtained two enantiomers of optically pure phosphonothioates by means of kinetic resolution.[3b] An effective preparation of the compounds was realized from the conversion of P-H bonds to the P-Cl bonds, followed by the reaction with thiols, affording phosphonothioates in high optical purity, as reported by Han.[8] However, to the best of our knowledge, a straightforward preparation of phosphonothioates from *P*-stereogenic H-P species has not been realized.

Recently, we reported a convenient synthesis of R_P-(-)-menthyl phenylphosphinate **1**.[9] Considering the usefulness of the P-S compounds and the deficiency of the effective method to acquire them, we pursued the steroeoselective formation of P-S bonds utilizing **1**. As discussed below, when **1** reacted with a dialkyldisulfides or elemental sulfur, the title compounds were stereospecifically produced in nearly quantitative yields under mild conditions.

The study was first carried out by treating a diastereomeric mixture of R_P-**1**/S_P-**1'** (46/54) with elemental sulfur in the presence of triethylamine. Two single peaks at 66.8 and 66.5 ppm, in the same ratio of 46/54, were observed in ^{31}P-NMR spectroscpy, which were assigned as the two stereoisomers of phenylphosphinothioate salt **2** and **2'** (Scheme 1). Subsequent addition of ethyl bromide to the mixture, the alkylation at sulfur took place, affording *S*-ethyl phenylphosphonothioate, also in a mixture of two stereoisomers. The two peaks at 43.4 and 43.3 ppm on ^{31}P NMR spectroscpy, in the same ratio to the original **1/1'**, were assigned as **3b** and **3b'**. In proton NMR spectroscpy, the multiplet at 4.43 ppm was assigned as the hydrogen on the α-carbon of menthoxy, and the signals of **3b** and **3b'** were coincided together.

Scheme 1. Reaction of 1 or 1/1' with sulfur followed by alkylation with EtBr and the ^{31}P-NMR spectroscopy.

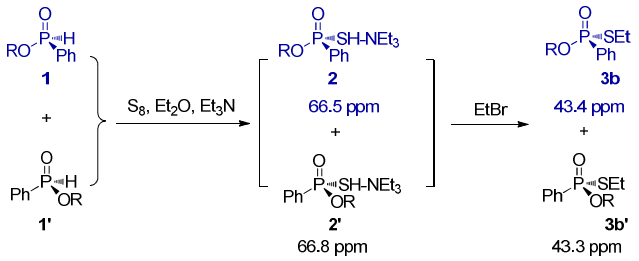
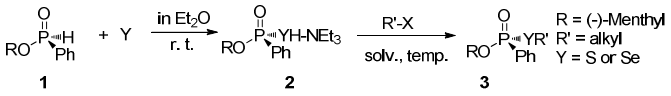


Table 1. Preparation of *P*-chalcogen derivatives 3 (Method A).



Entry	Y	R'	temp./time	Solvent	Yield % [a]
1	S	Me	rt/2h	ether	**3a**, 99 [b]
2	S	Et	rt/72h	ether	**3b**, 99
3	S	iPr	50°C/120h	neat	**3c**, 93
4	S	*s*Bu	55°C/72h	neat	**3d**, 89
5	S	*c*Hex	50°C/72h	neat	**3e**, 88
6	S	*t*Bu	60°C/72h	neat	**3f**, 83
7	S	Bn	rt/3h	ether	**3g**, 95
8	Se	Me	rt/2h	ether	**3k**, 99
9	Se	Et	rt/72h	ether	**3l**, 99

[a] Typicaly procedure of Method A: Reaction of **1** with sulfur or selenium powder in the presence of triethylamine, followed by alkylation with alkyl halides. The yields were calculated on $^{31}P\{H\}$NMR spectroscopy. [b] Methyl iodide was used in entry 1, and the alkyl bromide were used in other entries.

When optically pure (R_P)-**1** was used in the above reactions, only one stereoisomer was detected during the both steps (Scheme 1). At the first step, only the single peak at 66.5 ppm on ^{31}P-NMR spectroscpy was observed. After addition of ethyl bromide, another signal was observed at 43.4 ppm. The two peaks were assigned as **2** and **3b**, respectively, with an *R* configuration on phosphorus based on the results of single-crystal X-ray diffraction (vide infra). On the proton NMR spectroscpy, one *ddt* peak for **3b** was observed at 4.43 ppm. The formation of a sole stereoisomer for **2** and **3b** indicated the reaction of **1** with sulfur proceed in stereospecific manner. Therefore the alkylation on sulfur took place to afford **3b** as the sole product.

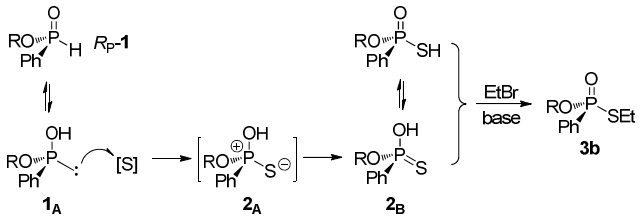
Various alkyl halides could be used for the *S*-alkylation of **2**, affording the sole R_P-stereoisomers. As observed in Table 1, aliphatic alkyl groups, as well as benzyl, were introduced into the molecules of **3** in excellent yields. The primary alkyl halides such as methyl iodide and ethyl bromide gave quantitatively **3a** and **3b**, respectively, at room temperature. The reactions of secondary and tertiary alkyl halides were performed at a slightly elevated temperature, affording **3c** to **3f** in good yields.

For 2-bromobutane (R = *s*-Bu), two stereoisomers of **3f** based on the *rac*-2-carbon were obtained in ca. 1:1 ratio, which was confirmed by the two groups of *qt* peaks of *sec*-hydrogen in 2-butyl, as observed at 3.26 and 3.19 ppm on proton NMR spectroscpy. No *C*-stereoselectivity was detected during the formation of the two isomers. The *Se*-alkyl *O*-menthyl phosphonoselenoate **3k** and **3l** were similarly prepared, also in quantitative yields, by reaction of **1** with elemental selenium, followed by alkylation. The similar configuration-retention mechanism was deducted for the formation of **3k** and **3l**.

The *R* configuration of **3** was unambiguously confirmed by X-ray diffraction of **3a**. The crystallographic information and cif file of **3a** can be found in the Supporting Information. Because alkylation of **2** took place at sulfur atom, the sulfurization of **1** or insertion of sulfur into P-H bond was thence conformed to proceed via *P*-retention mechanism.[6] As observed in Scheme 2, it was pro-

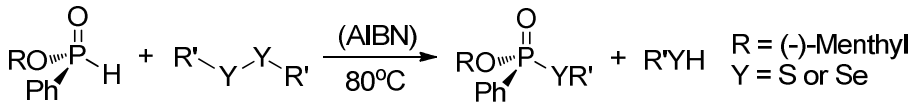
posed that the phosphorus atom attacked at sulfur with its lone pair electron, to form configuration-retention intermediate $\mathbf{2_A}$ that was converted to $\mathbf{2_B}$ and then to **3**.

Scheme 2. A proposed mechanism for the formation of 3.



On the other hand, Xu and Huang reported a reaction of $(RO)_2P(O)$-H with disulfides or diselenides, forming *S*-alkyl phosphonothioates or *Se*-alkyl phosphonoselenoates, respectively.[10] When this method was applied to R_P-**1**, as observed in Scheme 3 and Table 2), we found that the chirality on phosphorus was totally kept intact, also stereospecifically affording one stereoisomer of **3**. Both proton and ^{31}P-NMR spectroscopies confirmed that the compounds obtained herein were the same compounds to that obtained from Method A. Thus the same *P*-retaining products were obtained from the reaction.

Table 2. Preparation of *P*-chalcogen derivatives 3 (Method B).



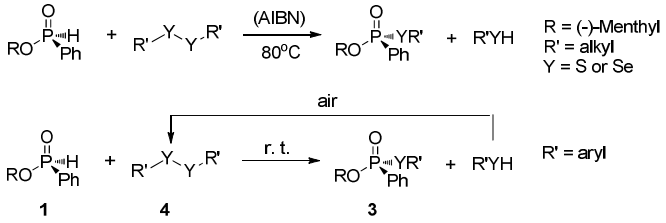
Entry	Y	R'	temp./time	Solvent	Yield % [a]
1	S	Me	rt/16h	neat	**3a**, 99
2	S	*c*Hex	rt/16h	neat	**3e**, 98
3	S	*t*Bu	rt/24h	neat	**3f**, 91
4	S	Bn	rt/24h	neat	**3g**, 98
5	S	Ph	rt/20h	ether	**3h**, 93 [b]
6	S	*p*-Tol	rt/20h	ether	**3i**, 83 [b]
7	S	2,4,5-$Cl_3C_6H_2$	rt/20h	ether	**3j**, 89 [b]
8	Se	Ph	rt/48h	ether	**3m**, 99 [b]

[a] Typical procedure for Method B: Dimethyl disulfide (0.225 g, 2.4 mmole) and **1** (0.560 g, 2 mmole) was heated at 80°C with stirring for 16 hours in the presence of AIBN (32.8 mg, 0.2 mmole). The yield was calculated on ^{31}P{H}NMR spectroscopy. [b] The reactions were carried out in ether in the absence of AIBN.

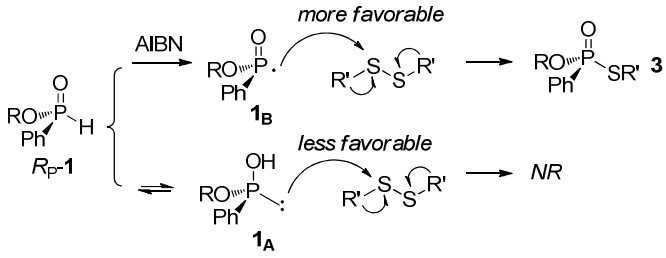
Noteworthy, with aromatic disulfides or diselenides, the above reactions of **1** efficiently took place under air, via simple stirring at room temperature (Scheme 3). Half an equivalent of the disulfide or diselenide **4** was enough to convert **1** to **3** because the generated benzenethiol or benzeneselenol could be oxidized back to **4** by air. The reaction of aliphatic disulfides did not readily proceed under similar conditions. However, in the presence of free radical initiator such as AIBN (2,2'-azobisisobutyronitrile) and at elevated temperature, they also reacted with **1** affording **3** as single stereoisomers in excellent yields.

It was assumed that aliphatic groups might have stronger electron-donating ability. The increased electron density on sulfur of aliphatic disulfides might raise the difficult approaching of phosphorus. On the other hand, the presence of AIBN was helpful to the cleavage of P-H bond by means of formation of free radical on phosphorus, which was less influenced by the electron-enrichment on sulfur atom, leading to an easy occurring reaction (Scheme 4).

Scheme 3. Preparation of 3 from disulfide or diselenide.



Scheme 4. A proposed free radical mechanism for the reaction of 1 with aliphatic disulfide.



In summary, the *P*-chalcogen derivatives, *S*-alkyl phosphonothioates and *Se*-alkyl phosphonoselenoates were prepared stereospecifically from two methods. The *S* or *Se*-alkylation with aliphatic alkyl groups was completed by the reaction of **1** with elemental sulfur or selenium, followed by reactions with alkyl halides. The reaction was confirmed to proceed in *P*-retaining mechanism by X-ray crystallography. When **1** directly reacted with disulfide or diselenide, the *S* or *Se*-alkylation products were also afforded stereo-specifically, via the same *P*-retaining mechanism. The present study provides a convenient method for the generation of *P*-chalcogen derivatives, which have extensive applications in both organic synthesis as precursors or auxiliaries, and in pharmacology as substrates to explore the metabolism.

Experimental section

All solvents when needed were freshly distilled prior to use. Except **1** that was prepared according to a literature,[9] all starting materials and catalysts are commercially available. The purity of the products was checked by TLC on pre-coated plates of Silica gel GF_{254} using as mobile phase a 3:1 mixture of petroleum ether and ethyl acetate. Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. ^{1}H NMR spectroscpies were recorded on a 400-MHz spectrometer. Chemical shift for ^{1}H NMR spectroscpy (in parts per million) relative to internal tetramethylsilane (Me_4Si, δ= 0.00 ppm) with $CDCl_3$ or DMSO. ^{13}C NMR spectroscpies were recorded at 101 mHz Chemical shifts for ^{13}C NMR spectroscpies are reported (in parts per million) relative to $CDCl_3$ (δ = 77.0 ppm). ^{31}P NMR spectroscpies were recorded at 162 MHz, and chemical shifts reported (in parts

per million) relative to external 85% phosphoric acid (δ= 0.0 ppm). TLC plates were visualized by UV. The ionization method of the high-resolution mass spectrum (HRMS) is electron impact (EI). The type of the mass analyzer is quadrupole.

Preparation of *(R_P)-S*-ethyl *O*-menthyl phenylphosphonothioate (3b) (Typical procedure for preparation of *S*-alkyl *O*-menthyl phenylphosphonothioates, Method A)

A mixture of **1** (1.01 g, 3.6 mmole), triethylamine (0.5 ml, 3.6 mmole) and sulfur powder (0.178 g, 5.4 mmole) in diethyl ether (5 ml) was stirred at room temperature for 24 h. The excess sulfur powder was filtered away and washed with ether (5 ml). The combined filtrate was evaporated in vacuo to afford **2** as a yellow solid (1.49 g) quantitatively which was used directly without further purification.

To the solution of **2** (0.413 g, 1 mmole) in ether (5 ml), ethyl bromide (0.150 ml, 2 mmole) was added. The mixture was stirred for 72 h at room temperature. The solid was filtered off and washed with ether for three times. The combined filtrated was evaporated in vacuo and the residue was purified with preparative TLC (silica gel, chloroform/methanol 20:1 as eluent) to afford the product as pale yellow oil (306 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.81 (m, 2H), 7.63 – 7.40 (m, 3H), 4.47 (ddd, J_{P-H}=19.4, *J*=10.6, *J*=4.5, 1H), 2.79 (dq, *J*=12.4, 7.4, 2H), 2.35 (d, *J*=12.3, 1H), 2.20 (dtd, *J*=13.8, 6.9, 2.2, 1H), 1.77 – 1.61 (m, 2H), 1.57 – 1.37 (m, 2H), 1.26 (dd, *J*=13.8, 6.3, 5H), 1.21 – 1.01 (m, 1H), 0.97 (d, *J*=7.0, 3H), 0.91 (t, *J*=6.7, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.97. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 134.3 (d, *J*=150.5), 132.1 (d, *J*=3.1), 131.1 (d, *J*=10.8), 128.3 (d, *J*=14.7), 48.67 (d, *J*=7.3), 43.5, 34.0, 31.6, 29.6, 29.6, 25.6, 24.8 (d, *J*=2.5), 22.9, 21.8, 21.1, 16.1 (d, *J*=5.8), 16.0. HRMS (ESI+) calculated for $C_{18}H_{29}O_2PS$: 340.1626, found: 340.1517.

***(R_P)-S*-methyl *O*-menthyl phenylphosphonothioate (3a)**

The compound was prepared by reaction of **2** with methyl iodide in ether for 2 h, isolated as a pale yellow solid (301 mg, 92% yield). Mp 75-76°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 – 7.77 (m, 2H), 7.60 – 7.38 (m, 3H), 4.45 (ddd, J_{P-H}=19.3, *J*=10.6, *J*=4.5, 1H), 2.31 (d, *J*=12.2, 1H), 2.24 – 2.06 (m, 3H), 2.06 – 1.82 (m, 1H), 1.67 (dd, *J*=21.0, 8.1, 2H), 1.42 (t, *J*=11.1, 2H), 1.30 – 1.13 (m, 2H), 1.04 (dd, *J*=13.0, 2.6, 1H), 0.95 (d, *J*=7.0, 3H), 0.87 (t, *J*=6.7, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.62. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 133.3 (d, *J*=150.4), 132.2 (d, *J*=2.9), 131.1 (d, *J*=10.7), 128.4 (d, *J*=14.8), 48.7 (d, *J*=7.2, 2.8), 43.5, 34.0, 31.6, 25.7, 22.9, 22.9, 21.8, 21.1, 15.9, 11.9. HRMS (ESI+) calculated for $C_{17}H_{28}O_2PS$ $[M + H]^+$: 327.1531, found: 327.1542.

***(R_P)-S*-isopropyl *O*-menthyl phenylphosphonothioate (3c)**

The compound was prepared by reaction of **2** with isopropyl bromide at 50°C for 120 h, isolated as a pale yellow solid from recrystallization with ether-hexane (262 mg, 74% yield). Mp 117-118°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (dd, *J*=13.8, 7.1, 2H), 7.53 (dd, *J*=23.0, 5.5, 3H), 4.61 – 4.31 (m, 1H), 3.57 – 3.29 (m, 1H), 2.35 (d, *J*=11.5, 1H), 2.21 (s, 1H), 1.81 – 1.55 (m, 3H), 1.53 – 1.36 (m, 4H), 1.34 – 1.16 (m, 5H), 1.15 – 1.02 (m, 1H), 0.98 (d, *J*=7.0, 3H), 0.92 (dd, *J*=6.5, 4.2, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.41. ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 132.0, 131.1 (d, *J*=10.8), 128.3 (d, *J*=14.7), 48.7 (d, *J*=7.3), 43.5, 37.4, 34.05, 31.6, 29.7, 25.5 (d, *J*=6.5), 22.9, 21.9, 21.1, 16.1, -0.1. HRMS (ESI+) calculated for $C_{19}H_{32}O_2PS[M + H]^+$: 355.1861, found: 355.1855

***(R_P)-S*-secbutyl *O*-menthyl phenylphosphonothioate (3d)**

The compound was prepared by reaction of **2** with *sec*butyl bromide at 55°C for 72 h, isolated as pale yellow oil (279 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (dd, *J*=13.8, 7.1, 2H), 7.53 (dd, *J*=23.0, 5.5, 3H), 4.61 – 4.31 (m, 1H), 3.57 – 3.29 (m, 1H), 2.35 (d, *J*=11.5, 1H), 2.21 (s, 1H), 1.81 – 1.55 (m, 3H), 1.53 – 1.36 (m, 4H), 1.34 – 1.16 (m, 5H), 1.15 – 1.02 (m, 1H), 0.98 (d, *J*=7.0, 3H), 0.92 (dd, *J*=6.5, 4.2, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.71. ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (*J*=33.8), 134.4 (*J*=33.7), 131.9 (*J*=3.0), 131.0 (*J*=5.4), 128.2 (*J*=11.5), 78.9 (*J*=3.8), 77.0 (*J*=32.2), 48.7 (*J*=7.7), 43.8, 43.5, 34.0, 31.5 (*J*=6.9), 25.4 (*J*=16.9), 23.0 (*J*= 4.5), 22.9, 22.8 (*J*=3.8), 21.9, 21.0 (*J*=16.9), 16.1, 11.2, 11.0. HRMS (ESI+) calculated for $C_{20}H_{33}O_2PS$: 368.1939, found: 368.1836.

***(R_P)-S*-cyclohexyl *O*-menthyl phenylphosphonothioate (3e)**

The compound was prepared by reaction of **2** with cyclohexyl bromide at 55°C for 72 h, isolated as pale yellow oil (295 mg, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89-7.85 (m, 2H), 7.54-7.50 (m, 1H), 7.48-7.44 (m, 2H), 4.46-4.40 (m, 1H), 3.28-3.23 (m, 1H), 2.34-2.29 (m, 1H), 2.21-2.14 (m, 1H), 2.08-2.05 (m, 1H), 1.80-1.15 (m, 14H), 1.09-1.00 (qd, *J* = 13.1 Hz, *J* = 4.6 Hz, 1H), 0.94 (d, *J* = 7.3 Hz, 3H), 0.90-0.80 (m, 7H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 135.2 (J_{CP} = 149.7 Hz), 132.0 (J_{CP} = 3.1 Hz), 131.0 (J_{CP} = 10.3 Hz), 128.3 (J_{CP} = 14.5 Hz), 78.9 (J_{CP} = 8.3 Hz), 48.7 (J_{CP} = 7.1 Hz), 45.1 (J_{CP} = 2.1 Hz), 43.5, 35.5 (J_{CP} = 4.1 Hz), 35.4 (J_{CP} = 4.1 Hz), 34.1, 31.6, 25.9 (J_{CP} = 15.5 Hz), 25.5, 25.3, 22.9, 21.9, 21.2, 16.1. ^{31}P NMR (201.9 MHz, $CDCl_3$): δ 42.2. HRMS for $C_{22}H_{35}O_2PS$, calcd: 394.2095, found: 394.2073.

***(R_P)-S*-tertbutyl *O*-menthyl phenylphosphonothioate (3f)**

The compound was prepared by reaction of **2** with tertbutyl bromide at 60°C for 72 h, isolated as pale yellow oil (262 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 – 7.67 (m, 2H), 7.65 – 7.31 (m, 2H), 4.58 – 4.21 (m, 1H), 2.34 (d, *J*=12.3, 1H), 2.17 (dtd, *J*=13.9, 6.9, 2.3, 1H), 1.74 – 1.57 (m, 1H), 1.45 (s, 9H), 1.39 – 1.24 (m, 2H), 1.15 (dd, *J*=23.3, 12.2, 2H), 1.09 – 0.97 (m, 1H), 0.93 (d, *J*=7.0, 3H), 0.88 (dd, *J*=6.6, 5.1, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.20. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.2 (d, *J*=150.0), 131.8 (d, *J*=3.1), 131.1 (d, *J*=10.8), 128.2 (d, *J*=14.7), 50.2 (d, *J*=3.4), 48.7 (d, *J*=7.4), 43.6, 34.1, 32.9 (d, *J*=5.1), 31.6, 25.4, 22.9, 21.9, 21.2, 16.1. HRMS (ESI+) calculated for $C_{20}H_{34}O_2PS[M + H]^+$: 369.2009, found: 369.2012.

***(R_P)-S*-benzyl *O*-menthyl phenylphosphonothioate (3g)**

The compound was prepared by reaction of **2** with benzyl chloride at rt for 3 h, isolated as pale yellow solid (326 mg, 81% yield). Mp 62-63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 – 7.74 (m, 2H), 7.58 – 7.38 (m, 3H), 7.26 – 7.13 (m, 5H), 4.42 (ddd, J_{P-H}=19.6, *J*=10.6, *J*=4.5, 1H), 4.20 – 3.86 (m, 2H), 2.35 (d, *J*=12.2, 1H), 2.17 (dq, *J*=6.8, 4.8, 1H), 1.68 (dd, *J*=17.7, 7.2, 2H), 1.42 (dd, *J*=15.6, 6.8, 2H), 1.22 (dd, *J*=23.3, 12.1, 2H), 1.03 (ddd, J_{P-H}=26.5, *J*=13.4, *J*=3.6, 1H), 0.94 (d, *J*=7.0, 3H), 0.88 (dd, *J*=10.8, 6.7, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.36. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.4 (d, *J*=2.3), 137.3 (d, *J*=2.3), 134.7 (d, *J*=6.4), 133.2 (d, *J*=6.5), 132.1 (d, *J*=3.0), 131.0 (d, *J*=10.9), 128.4 (d, *J*=0.9), 128.4 (d, *J*=1.5), 128.2 (d, *J*=1.5), 127.3 (d, *J*=1.5), 48.7,

48.6, 43.5, 34.6, 34.0, 31.6, 25.6, 22.9, 21.9, 21.2, 16.0. HRMS (ESI+) calculated for $C_{23}H_{32}O_2PS[M + H]^+$: 403.1844, found: 403.1855

Preparation of *(R_P)-Se*-ethyl *O*-menthyl phenylphosphonoselenoate (3l) (Typical procedure for preparation of *Se*-alkyl *O*-menthyl phenylphosphonoselenoates **3k-3l**, Method A)

Triethylamine (0.263 ml, 1.892 mmole) was added to the mixture of **1** (0.265 g, 0.946 mmole) and selenium powder (82.2 mg, 1.04 mmole, 1.1 eq.) with stirring. Ether (5 ml) was added to the mixture and the resulted suspension was stirred at room temperature for 24 h. Ethyl bromide (0.141 ml, 1.892 mmole, 2 eq.) was added and the mixture was stirred at room temperature for 72 h. Ether (10 ml) was added to the mixture and the solid was filtered away, washed with ether. The combined ether solution was washed with water, dried over magnesium sulfate. After evaporation of solvent, the residue was purified with preparative TLC (silica gel, chloroform/methanol 20:1 as eluent) to afford yellow oil as product (308 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 – 7.75 (m, 2H), 7.57 – 7.38 (m, 3H), 4.43 (ddd, *J*=20.2, 10.3, 4.5, 1H), 2.87 – 2.61 (m, 3H), 2.34 (d, *J*=12.2, 1H), 2.15 (dt, *J*=13.7, 6.9, 1H), 1.67 (dd, *J*=20.4, 8.0, 2H), 1.53 – 1.38 (m, 2H), 1.33 (q, *J*=7.3, 2H), 1.28 – 1.13 (m, 2H), 1.05 (ddd, *J*=16.7, 13.7, 3.6, 1H), 0.94 (d, *J*=7.0, 3H), 0.87 (t, *J*=6.2, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.24. ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 135.0, 132.0 (d, *J*=3.1), 130.7 (d, *J*=11.2), 128.3 (d, *J*=14.7), 48.7 (d, *J*=7.5), 43.5, 34.0, 31.6, 25.6, 22.9, 21.8, 21.2, 20.0 (d, *J*=3.1), 16.6 (d, *J*=4.7), 16.2. MS (ESI+) calculated for $C_{18}H_{29}O_2PSe$: 388.107, found: 388.1. Elemental analysis: calculated for $C_{18}H_{29}O_2PSe$: C, 55.81; H, 7.55; found: C, 55.75; H, 7.66.

***(R_P)-Se*-methyl *O*-menthyl phenylphosphonoselenoate (3k)**

The product was isolated as yellow oil (286 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (ddd, *J*=13.8, 8.2, 1.3, 2H), 7.58 – 7.40 (m, 3H), 4.44 (ddd, J_{P-H}=19.9, *J*=10.6, *J*=4.5, 1H), 2.34 (d, *J*=12.3, 1H), 2.17 (ddd, *J*=18.6, 9.3, 4.6, 1H), 2.07 – 2.02 (m, 3H), 1.68 (dd, *J*=20.7, 8.5, 2H), 1.43 (dd, *J*=16.7, 6.8, 2H), 1.22 (dd, J_{P-H}=23.3, *J*=12.1, 2H), 1.05 (ddd, *J*=16.7, 13.8, 3.8, 1H), 0.95 (d, *J*=7.0, 3H), 0.88 (t, *J*=7.2, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.74. ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4, 134.1, 132.2 (d, *J*=3.1), 130.8 (d, *J*=11.2), 128.4 (d, *J*=14.7), 48.7 (d, *J*=7.5), 43.5, 34.0, 31.6, 25.7, 22.9, 21.8, 21.2, 16.1, 4.5. Elemental analysis: calculated for $C_{17}H_{27}O_2PSe$: C, 54.69; H, 7.29; found: C, 54.75; H, 7.38.

Preparation of *(R_P)-S*-methyl *O*-menthyl phenylphosphonothioate (3a) (Typical procedure for preparation of *S*-alkyl *O*-menthyl phenylphosphonothioate; Method B).

Dimethyl disulfide (0.225 g, 2.4 mmole) and **1** (0.560 g, 2 mmole) was heated at 80°C with stirring for 16 hours in the presence of AIBN (32.8 mg, 0.2 mmole). After removing low boiling point substances, the residue was purified as above (for **3a**) and gave the same spectroscpy data to Method A in 85% isolated yield.

***(R_P)-S*-cyclohexyl *O*-menthyl phenylphosphonothioate (3e)**

The compound was prepared from **2** and dicyclohexyl disulfide in 98% yield, giving the same spectroscpy data to the compound obtained from method A.

***(R_P)-S*-tertbutyl *O*-menthyl phenylphosphonothioate (3f)**

The compound was prepared from **2** and ditertbutyl disulfide in 91% yield, giving the same spectroscpy data to the compound obtained from method A.

***(R_P)-S*-benzyl *O*-menthyl phenylphosphonothioate (3g)**

The compound was prepared from **2** and dibenzyl disulfide in 98% yield, giving the same spectroscpy data to the compound obtained from method A.

***(R_P)-S*-phenyl *O*-menthyl phenylphosphonothioate (3h)** (Typical procedure for preparation of *S or Se*-aryl *O*-menthyl phenylphosphonothioate, Method B).

To the solution of **1** (0.276 g, 0.984 mmole) in ether (1 ml), diphenyl diselenide (0.214 g, 0.984 mmole) was added, and the resulted solution was stirred open to air at room temperature for 24 h. the crude product was purified with preparative TLC (silica gel, chloroform/methanol 20:1 as eluent) to afford a pale yellow oil as product (324 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.69 (m, 2H), 7.53-7.49 (m, 1H), 7.41-7.38 (m, 4H), 7.31-7.27 (m, 1H), 7.24-7.21 (m, 2H), 4.58-4.51 (m, 1H), 2.27-2.17 (m, 2H), 1.74-1.68 (m, 2H), 1.50-1.43 (m, 2H), 1.23-1.16 (q, J = 11.9 Hz, 1H), 1.13-1.04 (qd, J = 11.3 Hz, J = 4.9 Hz, 1H), 0.97 (d, J = 6.1 Hz, 3H), 0.90 (d, J = 7.3 Hz, 3H), 0.87 (d, J = 8.6 Hz, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 135.4 (J_{CP} = 4.1 Hz), 133.2 (J_{CP} = 149.9 Hz), 132.2 (J_{CP} = 3.1 Hz), 131.4 (J_{CP} = 10.3 Hz), 129.0 (J_{CP} = 2.1 Hz), 128.7 (J_{CP} = 2.1 Hz), 128.1 (J_{CP} = 14.4 Hz), 126.7 (J_{CP} = 5.1 Hz), 79.8 (J_{CP} = 8.3 Hz), 48.7 (J_{CP} = 7.1 Hz), 43.4, 34.0, 31.6, 25.6, 22.9, 21.9, 21.2, 16.0. ^{31}P NMR (201.9 MHz, $CDCl_3$): δ 39.8. HRMS for $C_{22}H_{29}O_2PS$, calcd: 388.1626, found: 388.1604.

***(R_P)-S-p*-methylphenyl *O*-menthyl phenylphosphonothioate (3i)**

The compound was prepared from **2** and ditolyl disulfide, isolated as pale yellow oil (265 mg, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.70 (m, 2H), 7.51-7.47 (m, 1H), 7.41-7.37 (m, 2H), 7.27-7.25 (m, 2H), 7.02 (d, J = 7.6 Hz, 2H), 4.55-4.50 (m, 1H), 2.29 (s, 3H), 2.26-2.15 (m, 2H), 1.72-1.65 (m, 2H), 1.46-1.42 (m, 2H), 1.22-14 (q, J = 12.1 Hz, 1H), 1.11 (dq, J = 13.1 Hz, J = 3.4 Hz, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 138.9 (J_{CP} = 3.1 Hz), 135.3 (J_{CP} = 4.1 Hz), 133.4 (J_{CP} = 149.9 Hz), 132.1 (J_{CP} = 3.1 Hz), 131.4 (J_{CP} = 11.3 Hz), 129.8 (J_{CP} = 2.0 Hz), 128.1 (J_{CP} = 14.4 Hz), 122.8 (J_{CP} = 5.0 Hz), 79.7 (J_{CP} = 8.3 Hz), 48.7 (J_{CP} = 6.1 Hz), 43.4, 34.0, 31.6, 25.6, 22.9, 21.9, 21.2, 21.1, 16.0. ^{31}P NMR (201.9 MHz, $CDCl_3$): δ 39.9. HRMS for $C_{23}H_{31}O_2PS$, calcd: 402.1782, found: 402.1792.

***(R_P)-S*-(2,4,5-trichlorophenyl) *O*-menthyl phenylphosphonothioate (3j)**

The compound was prepared from **2** and ditolyl disulfide, isolated as pale yellow oil (366 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.75 (m, 3H), 7.58-7.55 (m, 1H), 7.48-7.44 (m, 3H), 4.62-4.55 (m, 1H), 2.25-2.14 (m, 2H), 1.75-1.67 (m, 2H), 1.51-1.46 (m, 2H), 1.25-1.18 (q, J = 11.5 Hz, 1H), 1.13-1.05 (qd, J = 13.4 Hz, J = 3.4 Hz, 1H), 0.99 (d, J = 7.4 Hz, 3H), 0.91 (d, J = 9.2 Hz, 3H), 0.88 (d, J = 7.4 Hz, 3H). ^{13}C NMR (125.4 MHz, $CDCl_3$): 132.2, 132.1, 131.4, 131.3, 131.2, 130.8, 130.7, 130.2, 129.1, 128.9, 128.4, 128.3, 48.6 (J_{CP} = 2.3), 43.1, 34.2, 31.7, 25.6, 23.0, 22.1, 21.1, 15.6, 0.1. ^{31}P NMR (201.9 MHz, $CDCl_3$): δ 38.0.

HRMS for $C_{22}H_{26}Cl_3O_2PS$, calcd: 490.0457, found: 490.0380. Elemental analysis: calculated for $C_{22}H_{26}Cl_3O_2PS$: C, 53.72; H, 5.33; found: C, 53.89; H, 5.41.

***(R_P)-Se*-phenyl *O*-menthyl phenylphosphonoselenoate (3m)**

To the solution of **1a** (0.276 g, 0.984 mmole) in ether (1 ml), diphenyl diselenide (0.309 g, 0.984 mmole) was added, and the resulted solution was stirred open to air at room temperature for 24 h. the crude product was purified with preparative TLC (silica gel, chloroform/methanol 20:1 as eluent) to afford a pale yellow solid as product (369 mg, 86% yield). Mp 34-35°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.65 (m, 2H), 7.51-7.45 (m, 3H), 7.41-7.37 (m, 2H), 7.31-7.28 (m, 1H), 7.21-7.18 (m, 2H), 4.55-4.50 (m, 1H), 2.29-2.15 (m, 2H), 1.74-1.66 (m, 2H), 1.50-1.44 (m, 2H), 1.25-1.18 (q, J = 11.6 Hz, 1H), 1.12-1.04 (qd, J = 12.8 Hz, J = 4.0 Hz, 1H), 0.98 (d, J = 5.2 Hz, 3H), 0.92-0.83 (m, 7H). ^{13}C NMR (125.4 MHz, $CDCl_3$): δ 136.3 (J_{CP} = 4.1 Hz), 135.5 (J_{CP} = 136.4 Hz), 132.2 (J_{CP} = 3.1 Hz), 131.0 (J_{CP} = 11.4 Hz), 129.1 (J_{CP} = 2.1 Hz), 128.5 (J_{CP} = 2.0 Hz), 128.1 (J_{CP} = 15.5 Hz), 124.2 (J_{CP} = 5.1 Hz), 80.1 (J_{CP} = 9.3 Hz), 48.7 (J_{CP} = 7.3 Hz), 43.4, 34.0, 31.6, 25.7, 23.0, 21.9, 21.2, 16.1. ^{31}P NMR (201.9 MHz, $CDCl_3$): δ 36.3. HRMS for $C_{22}H_{29}O_2PSe$, calcd: 436.1070, found: 436.1089.

AUTHOR INFORMATION

Corresponding Author

* E-mail: literabc@hotmail.com, libiao-han@aist.go.jp

Notes

The authors declare no competing financial interest..

ACKNOWLEDGMENT

The authors acknowledge the financial support of the Natural Science Foundation of China (grant no. 20772055)

ASSOCIATED CONTENT

Supporting Information

The Supporting Information, including crystallographic information and cif file of **3a**, photocopies of ^{1}H, ^{31}P, and ^{13}C NMR spectroscpies, is available free of charge on the ACS Publications website.

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