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Stereospecific Preparations of *P*-Stereogenic Phosphonothioates and Phosphonoselenoates

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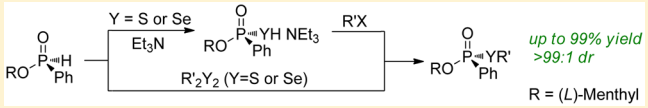
Supporting Information

ABSTRACT: *P*-Stereogenic phosphonothioates and phosphonoselenoates were readily prepared utilizing R_P-menthyl phenylphosphite **1** by 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.



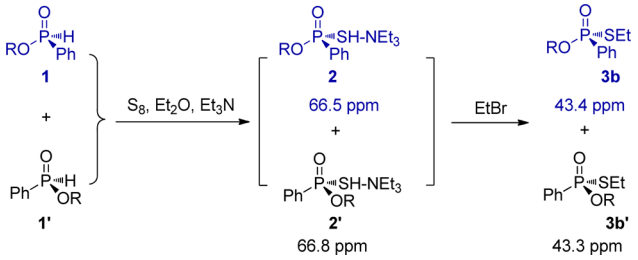
Phosphonothioates and related compounds are widely used as agricultural pesticides because of their important biological activity, acetylcholine esterase inhibitors, for example.[1,2] These compounds are also famous neurotoxins, herbicides, and insecticides. For the purpose of exploring the metabolism and degradation of these substances in an organism or 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 reagents 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 via 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 the 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, because of the difficulty in acquiring *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 a co-worker 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 P−Cl bonds, followed by the reaction with thiols, affording high-optical purity phosphonothioates, 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 for acquiring 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 conducted by treating a diastereomeric R_P-**1**/S_P-**1**′ mixture (46/54) with elemental sulfur in the presence of triethylamine. Two single peaks at 66.8 and 66.5 ppm, in the same ratio, were observed via ^{31}P NMR spectroscopy and were assigned as the two stereoisomers of phenylphosphinothioate salt **2** and **2**′, respectively (Scheme 1). Subsequent to addition of ethyl bromide to the mixture, the

Scheme 1. Reaction of 1 or the 1/1′ Mixture with Sulfur Followed by Alkylation with EtBr and ^{31}P NMR Spectroscopy



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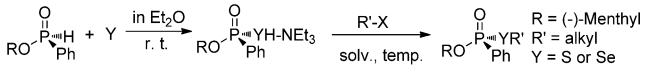
alkylation at sulfur took place, affording *S*-ethyl phenylphosphonothioate, also in a mixture of two stereoisomers. The two peaks at 43.4 and 43.3 ppm revealed via ^{31}P NMR spectroscopy, in the same ratio seen for the original **1**/**1′** mixture, were assigned as **3b** and **3b′**, respectively. In ^{1}H NMR spectroscopy, the multiplet at 4.43 ppm was assigned as the hydrogen on the α-carbon of menthoxy, and the signals of **3b** and **3b′** coincided together.

When optically pure R_P-**1** was used in the reactions described above, only one stereoisomer was detected during both steps (Scheme 1). During the first step, only the single peak at 66.5 ppm revealed via ^{31}P NMR spectroscopy 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). Via ^{1}H NMR spectroscopy, 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 proceeded in a 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,

Table 1. Preparation of *P*-Chalcogen Derivatives 3 (method A)



entry	Y	R′	temp/time (h)	solvent	yield (%)[a]
1	S	Me	rt/2	ether	**3a**, 99[b]
2	S	Et	rt/72	ether	**3b**, 99
3	S	*i*Pr	50 °C/120	neat	**3c**, 93
4	S	*s*Bu	55 °C/72	neat	**3d**, 89
5	S	*c*Hex	50 °C/72	neat	**3e**, 88
6	S	*t*Bu	60 °C/72	neat	**3f**, 83
7	S	Bn	rt/3	ether	**3g**, 95
8	Se	Me	rt/2	ether	**3k**, 99
9	Se	Et	rt/72	ether	**3l**, 99

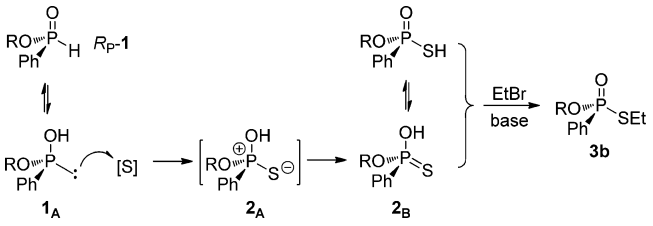
[a]Typical procedure for method A: reaction of **1** with sulfur or selenium powder in the presence of triethylamine, followed by alkylation with alkyl halides. The yields were calculated via ^{31}P{H} NMR spectroscopy. [b]Methyl iodide was used for entry 1, and the alkyl bromide was used for the other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

aliphatic alkyl groups, as well as benzyl, were introduced into the molecules of **3** in excellent yields. 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**−**3f** in good yields.

For 2-bromobutane (R = *s*Bu), two stereoisomers of **3f** based on the *rac*-2-carbon were obtained in an ∼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 via proton NMR spectroscopy. 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. A similar configuration−retention mechanism was deducted for the formation of **3k** and **3l**.

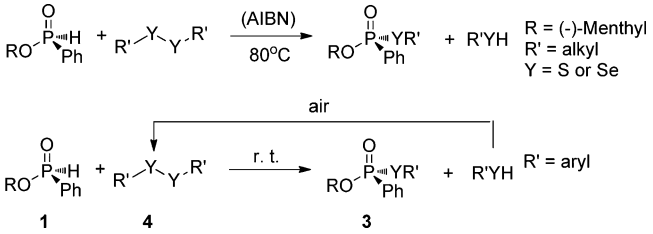
The *R* configuration of **3** was unambiguously confirmed by X-ray diffraction of **3a**. The crystallographic information and cif file of **3a** can be found in the Supporting Information. Because alkylation of **2** took place at the sulfur atom, the sulfurization of **1** or insertion of sulfur into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



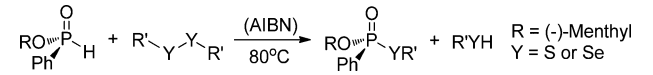
On the other hand, Xu and Huang reported a reaction of $(RO)_2P(O)H$ with disulfides or diselenides, forming *S*-alkyl phosphonothioates or *Se*-alkyl phosphonoselenoates, respectively.[10] When this method was applied to R_P-**1**, as shown in Scheme 3 and Table 2, we found that the chirality on

Scheme 3. Preparation of 3 from Disulfide or Diselenide



phosphorus was kept totally intact, also stereospecifically affording one stereoisomer of **3**. Both ^{1}H and ^{31}P NMR spectroscopies confirmed that the compounds obtained herein were the same compounds that were obtained via method A.

Table 2. Preparation of *P*-Chalcogen Derivatives 3 (method B)



entry	Y	R′	temp/time (h)	solvent	yield (%)[a]
1	S	Me	rt/16	neat	**3a**, 99
2	S	*c*Hex	rt/16	neat	**3e**, 98
3	S	*t*Bu	rt/24	neat	**3f**, 91
4	S	Bn	rt/24	neat	**3g**, 98
5	S	Ph	rt/20	ether	**3h**, 93[b]
6	S	*p*-Tol	rt/20	ether	**3i**, 83[b]
7	S	2,4,5-$Cl_3C_6H_2$	rt/20	ether	**3j**, 89[b]
8	Se	Ph	rt/48	ether	**3m**, 99[b]

[a]Typical procedure for method B: dimethyl disulfide (0.225 g, 2.4 mmol) and **1** (0.560 g, 2 mmol) heated at 80 °C while being stirred for 16 h in the presence of AIBN (32.8 mg, 0.2 mmol). The yield was calculated via ^{31}P{H} NMR spectroscopy. [b]Reactions performed in ether in the absence of AIBN.

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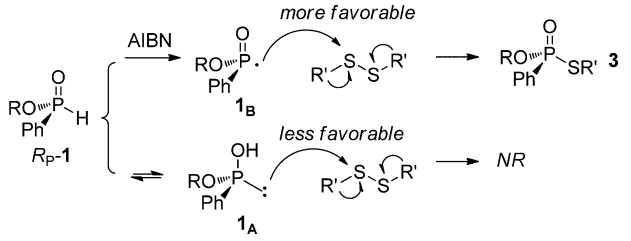
Thus, the same *P*-retaining products were obtained from the reaction.

It is noteworthy that, with aromatic disulfides or diselenides, the reactions of **1** described above 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 a free radical initiator such as AIBN [2,2′-azobis(isobutyronitrile)] and at elevated temperatures, they also reacted with **1**, affording **3** as a single stereoisomer in excellent yields.

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

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 via a *P*-retaining mechanism by X-ray crystallography. When **1** directly reacted with disulfide or diselenide, the *S*- or *Se*-alkylation products were also afforded stereospecifically, via the same *P*-retaining mechanism. This 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 pharmacology as substrates for exploring metabolism.

EXPERIMENTAL SECTION

All solvents when needed were freshly distilled prior to use. Except for **1** that was prepared according to a literature procedure,[9] all starting materials and catalysts are commercially available. The purity of the products was checked by TLC on precoated plates of silica gel GF_{254} using as a 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 spectroscopies were conducted on a 400 MHz spectrometer. The chemical shifts from ^{1}H NMR spectroscopy (in parts per million) were relative to internal tetramethylsilane (Me_4Si, δ 0.00) with $CDCl_3$ or DMSO. ^{13}C NMR spectroscopy was performed at 101 MHz. Chemical shifts for ^{13}C NMR spectroscopy are reported (in parts per million) relative to $CDCl_3$ (δ 77.0). ^{31}P NMR spectroscopy was performed at 162 MHz, and chemical shifts are reported (in parts per million) relative to external 85% phosphoric acid (δ 0.0). TLC plates were visualized by UV. The ionization method for high-resolution mass spectrometry (HRMS) is electron impact (EI). The type of 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 mmol), triethylamine (0.5 mL, 3.6 mmol), and sulfur powder (0.178 g, 5.4 mmol) 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 mmol) in ether (5 mL) was added ethyl bromide (0.150 mL, 2 mmol). The mixture was stirred for 72 h at room temperature. The solid was filtered off and washed three times with ether. The combined filtrate was evaporated in vacuo, and the residue was purified via preparative TLC (silica gel, 20/1 chloroform/methanol as eluent) to afford the product as a 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 Hz, J = 10.6 Hz, J = 4.5 Hz, 1H), 2.79 (dq, J = 12.4, 7.4 Hz, 2H), 2.35 (d, J = 12.3 Hz, 1H), 2.20 (dtd, J = 13.8, 6.9, 2.2 Hz, 1H), 1.77−1.61 (m, 2H), 1.57−1.37 (m, 2H), 1.26 (dd, J = 13.8, 6.3 Hz, 5H), 1.21−1.01 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 6.7 Hz, 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 Hz), 132.1 (d, J = 3.1 Hz), 131.1 (d, J = 10.8 Hz), 128.3 (d, J = 14.7 Hz), 48.67 (d, J = 7.3 Hz), 43.5, 34.0, 31.6, 29.6, 29.6, 25.6, 24.8 (d, J = 2.5 Hz), 22.9, 21.8, 21.1, 16.1 (d, J = 5.8 Hz), 16.0; HRMS (ESI+) calcd 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 Hz, J = 10.6 Hz, J = 4.5 Hz, 1H), 2.31 (d, J = 12.2 Hz, 1H), 2.24−2.06 (m, 3H), 2.06−1.82 (m, 1H), 1.67 (dd, J = 21.0, 8.1 Hz, 2H), 1.42 (t, J = 11.1 Hz, 2H), 1.30−1.13 (m, 2H), 1.04 (dd, J = 13.0, 2.6 Hz, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.87 (t, J = 6.7 Hz, 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 Hz), 132.2 (d, J = 2.9 Hz), 131.1 (d, J = 10.7 Hz), 128.4 (d, J = 14.8 Hz), 48.7 (d, J = 7.2, 2.8 Hz), 43.5, 34.0, 31.6, 25.7, 22.9, 22.9, 21.8, 21.1, 15.9, 11.9; HRMS (ESI+) calcd 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 and 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 Hz, 2H), 7.53 (dd, J = 23.0, 5.5 Hz, 3H), 4.61−4.31 (m, 1H), 3.57−3.29 (m, 1H), 2.35 (d, J = 11.5 Hz, 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 Hz, 3H), 0.92 (dd, J = 6.5, 4.2 Hz, 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 Hz), 128.3 (d, J = 14.7 Hz), 48.7 (d, J = 7.3 Hz), 43.5, 37.4, 34.05, 31.6, 29.7, 25.5 (d, J = 6.5 Hz), 22.9, 21.9, 21.1, 16.1, −0.1; HRMS (ESI+) calcd for $C_{19}H_{32}O_2PS$ $[M + H]^+$ 355.1861, found 355.1855

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

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(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 a 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*-*tert*-Butyl *O*-Menthyl Phenylphosphonothioate (3f). The compound was prepared by reaction of **2** with *tert*-butyl bromide at 60 °C for 72 h, isolated as a 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 Hz, 1H), 2.17 (dtd, J = 13.9, 6.9, 2.3 Hz, 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 Hz, 2H), 1.09−0.97 (m, 1H), 0.93 (d, J = 7.0 Hz, 3H), 0.88 (dd, J = 6.6, 5.1 Hz, 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 Hz), 131.8 (d, J = 3.1 Hz), 131.1 (d, J = 10.8 Hz), 128.2 (d, J = 14.7 Hz), 50.2 (d, J = 3.4 Hz), 48.7 (d, J = 7.4 Hz), 43.6, 34.1, 32.9 (d, J = 5.1 Hz), 31.6, 25.4, 22.9, 21.9, 21.2, 16.1; HRMS (ESI+) calcd 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 a 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 Hz, J = 10.6 Hz, J = 4.5 Hz, 1H), 4.20−3.86 (m, 2H), 2.35 (d, J = 12.2 Hz, 1H), 2.17 (dq, J = 6.8, 4.8 Hz, 1H), 1.68 (dd, J = 17.7, 7.2 Hz, 2H), 1.42 (dd, J = 15.6, 6.8 Hz, 2H), 1.22 (dd, J = 23.3, 12.1 Hz, 2H), 1.03 (ddd, J_{P-H} = 26.5 Hz, J = 13.4 Hz, J = 3.6 Hz, 1H), 0.94 (d, J = 7.0 Hz, 3H), 0.88 (dd, J = 10.8, 6.7 Hz, 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 Hz), 137.3 (d, J = 2.3 Hz), 134.7 (d, J = 6.4 Hz), 133.2 (d, J = 6.5 Hz), 132.1 (d, J = 3.0 Hz), 131.0 (d, J = 10.9 Hz), 128.4 (d, J = 0.9 Hz), 128.4 (d, J = 1.5 Hz), 128.2 (d, J = 1.5 Hz), 127.3 (d, J = 1.5 Hz), 48.7, 48.6, 43.5, 34.6, 34.0, 31.6, 25.6, 22.9, 21.9, 21.2, 16.0; HRMS (ESI+) calcd 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 and 3l, method A). Triethylamine (0.263 mL, 1.892 mmol) was added to the mixture of **1** (0.265 g, 0.946 mmol) and selenium powder (82.2 mg, 1.04 mmol, 1.1 equiv) while it was being stirred. Ether (5 mL) was added to the mixture, and the resulting suspension was stirred at room temperature for 24 h. Ethyl bromide (0.141 mL, 1.892 mmol, 2 equiv) 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 and washed with ether. The combined ether solution was washed with water and dried over magnesium sulfate. After evaporation of solvent, the residue was purified via preparative TLC (silica gel, 20/1 chloroform/methanol as the eluent) to afford yellow oil as the 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 Hz, 1H), 2.87−2.61 (m, 3H), 2.34 (d, J = 12.2 Hz, 1H), 2.15 (dt, J = 13.7, 6.9 Hz, 1H), 1.67 (dd, J = 20.4, 8.0 Hz, 2H), 1.53−1.38 (m, 2H), 1.33 (q, J = 7.3 Hz, 2H), 1.28−1.13 (m, 2H), 1.05 (ddd, J = 16.7, 13.7, 3.6 Hz, 1H), 0.94 (d, J = 7.0 Hz, 3H), 0.87 (t, J = 6.2 Hz, 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 Hz), 130.7 (d, J = 11.2 Hz), 128.3 (d, J = 14.7 Hz), 48.7 (d, J = 7.5 Hz), 43.5, 34.0, 31.6, 25.6, 22.9, 21.8, 21.2, 20.0 (d, J = 3.1 Hz), 16.6 (d, J = 4.7 Hz), 16.2; MS (ESI+) calcd for $C_{18}H_{29}O_2PSe$ 388.107, found 388.1. Elemental Anal. Calcd 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 a yellow oil (286 mg, 84% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (ddd, J = 13.8, 8.2, 1.3 Hz, 2H), 7.58−7.40 (m, 3H), 4.44 (ddd, J_{P-H} = 19.9 Hz, J = 10.6 Hz, J = 4.5 Hz, 1H), 2.34 (d, J = 12.3 Hz, 1H), 2.17 (ddd, J = 18.6, 9.3, 4.6 Hz, 1H), 2.07−2.02 (m, 3H), 1.68 (dd, J = 20.7, 8.5 Hz, 2H), 1.43 (dd, J = 16.7, 6.8 Hz, 2H), 1.22 (dd, J_{P-H} = 23.3 Hz, J = 12.1 Hz, 2H), 1.05 (ddd, J = 16.7, 13.8, 3.8 Hz, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 7.2 Hz, 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 Hz), 130.8 (d, J = 11.2 Hz), 128.4 (d, J = 14.7 Hz), 48.7 (d, J = 7.5 Hz), 43.5, 34.0, 31.6, 25.7, 22.9, 21.8, 21.2, 16.1, 4.5. Elemental Anal. Calcd 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 mmol) and **1** (0.560 g, 2 mmol) were heated at 80 °C while being stirred for 16 h in the presence of AIBN (32.8 mg, 0.2 mmol). After low-boiling point substances had been removed, the residue was purified as described above (for **3a**) and gave the same spectroscopy data that method A did 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 spectroscopy data as the compound obtained via method A.

(R_P)-*S*-*tert*-Butyl *O*-Menthyl Phenylphosphonothioate (3f). The compound was prepared from **2** and di-*tert*-butyl disulfide in 91% yield, giving the same spectroscopy data as the compound obtained via 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 spectroscopy data as the compound obtained via 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 mmol) in ether (1 mL) was added diphenyl diselenide (0.214 g, 0.984 mmol), and the resulting solution was stirred while open to air at room temperature for 24 h. The crude product was purified via preparative TLC (silica gel, 20/1 chloroform/methanol as eluent) to afford a pale yellow oil as the 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 a 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 a pale yellow oil (366 mg, 76% yield): ^{1}H NMR

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(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 Hz), 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 Anal. Calcd 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 mmol) in ether (1 mL) was added diphenyl diselenide (0.309 g, 0.984 mmol), and the resulting solution was stirred while open to air at room temperature for 24 h. The crude product was purified via preparative TLC (silica gel, 20/1 chloroform/methanol as eluent) to afford a pale yellow solid as the 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01192.

Copies of ^{1}H, ^{31}P, and ^{13}C NMR spectra (PDF)

Crystallographic information and cif file of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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