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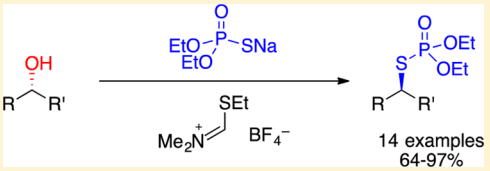
Conversion of Alcohols to Phosphorothiolates Using a Thioiminium Salt as Coupling Agent

Helen Grounds, Kristaps Ermanis, Sophie A. Newgas, and Michael J. Porter*

Department of Chemistry, University College London, Christopher Ingold Building, 20 Gordon Street, London WC1H 0AJ, U.K.

Supporting Information

ABSTRACT: We report a method for the direct and rapid conversion of primary and secondary alcohols to the corresponding phosphorothiolates in yields ranging from 64% to 97%, using as a coupling agent the iminium salt prepared from *N*,*N*-dimethylthioformamide and Meerwein's salt. Selective reaction of primary alcohols in the presence of secondary alcohols is possible. The reaction of secondary alcohols proceeds stereospecifically with inversion of configuration.



The phosphorothiolate linkage, $RSPO(OR')_2$, has found extensive use in the synthesis of nucleic acid analogues,[1,2] but until recently only a few examples of phosphorothiolates as synthetic intermediates were known. However, recent reports from the group of Wu have shown the utility of phosphorothioic acids as surrogates for H_2S in the synthesis of acylic and cyclic thioethers.[3,4] This group has also shown that the $-SPO(OR)_2$ moiety of allylic phosphorothiolates can be displaced by Grignard reagents[5] or, in a palladium-catalyzed process, by fluoride.[6]

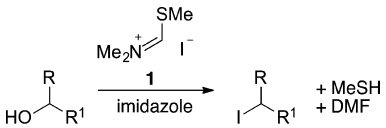
The most commonly used method for the synthesis of phosphorothiolate esters is the displacement of halide leaving groups by phosphorothiolate anions. Direct conversion of alcohols to phosphorothiolates under Mitsunobu conditions has also been reported.[7,8] Wu has reported a photochemical displacement of allylic hydroxy and methoxy groups by a phosphorothioic acid,[5] and a gallium triflate catalyzed substitution of allylic, benzylic, and tertiary alcohols.[9] More recently Han has reported a dehydrogenative palladium coupling of phosphonates with thiols.[10]

While the direct preparation of phosphorothiolates from alcohols without the need for prior activation is clearly advantageous, both the photochemical and gallium triflate methods suffer from both a lack of stereospecificity and a limited substrate scope (only allylic, benzylic, and tertiary alcohols react). Reported yields for the Mitsunobu reaction are only moderate (40−77%).[7]

In this paper, we describe a simple procedure for the one-pot conversion of primary and secondary alcohols to phosphorothiolates, using a sulfanyliminium salt as an activating agent. Aliphatic alcohols as well as allylic and benzylic alcohols undergo the substitution reaction, and the reaction with secondary alcohols proceeds stereospecifically with inversion of configuration.

Our interest in the use of sulfanyliminium salts as activating agents for alcohols stemmed from a protocol we developed for the preparation of alkyl iodides from primary and secondary alcohols using salt **1** (Scheme 1).[11] The presumed course of events in this iodination reaction involves attack of the alcohol on the iminium ion, expulsion of methanethiol, and displacement of *N*,*N*-dimethylformamide by an iodide ion. Selective conversion of primary alcohols to iodides in the presence of secondary alcohols was possible. We also showed that, with secondary alcohols, the initial displacement occurred with inversion of configuration, although the enantiomeric purity of the product was rapidly eroded by subsequent S_N2 reactions with further iodide ions.

Scheme 1. Conversion of Alcohols to Alkyl Iodides



Subsequently we modified this protocol by preparing a tetrafluoroborate analogue **2** of the iminium salt. Using this salt as an activating agent for a range of alcohols, we were able to use 1-phenyltetrazol-5-ylthiol as a nucleophile and to prepare the corresponding sulfides **3** directly.[12] In this paper we describe the use of iminium salt **2** as an activating agent for the formation of phosphorothiolates from alcohols.

Our test substrate for the preparation of phosphorothiolates was 4-methylbenzyl alcohol **4a**, and the conditions employed were analogous to those in Scheme 2. Reaction of alcohol **4a**

Scheme 2. Conversion of Alcohols to Tetrazolyl Sulfides

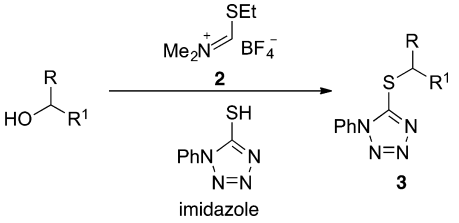


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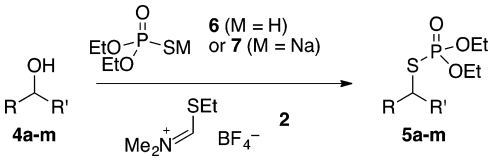
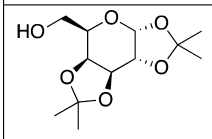
Table 1. Formation of *S*-Alkyl *O,O*-Diethyl Phosphorothiolates



Alcohol	R	R′	Conditions[a]	Time	Yield
4a	4-MeC$_6$H$_4$	H	A	1 h	94%
4a			B	0.5 h	91%
4b	Ph(CH$_2$)$_2$	H	A	1 h	84%
4b			B	0.5 h	97%
4c	*i*-Pr	H	B	0.5 h	88%
4d	THPOCH$_2$	H	B	0.5 h	88%
4e	BocNH(CH$_2$)$_2$	H	B	3 h	65%
(±)-**4f**	*n*-C$_6$H$_{13}$	Me	B	0.5 h	78%
(±)-**4g**	Ph	Me	B	0.5 h	75%
(±)-**4h**	Ph(CH$_2$)$_2$	Me	B	0.5 h	91%
4i	(*E*)-PhCH=CH	H	B	0.5 h	77%
(±)-**4j**	Ph	CH=CH$_2$	B	0.5 h	64%[b]
(±)-**4k**	(*E*)-PhCH=CH	Me	B	0.5 h	75%
(±)-**4l**	BnOCH$_2$CH(OH)CH$_2$	H	B	1 h	64%[c]
(±)-**4m**	PhCH(OH)(CH$_2$)$_2$	H	A	1.5 h	0%[d]
 **4n**			B	6 h	0%[e]

[a]Conditions A: (EtO)$_2$POSH (**6**) (1.1 equiv), Me$_2$NCHSEt$^+$ BF$_4^-$ (**2**) (1.1 equiv), imidazole (1.1 equiv), toluene, 90 °C; Conditions B: (EtO)$_2$POSNa (**7**) (1.1 equiv), Me$_2$NCHSEt$^+$ BF$_4^-$ (**2**) (1.1 equiv), toluene, 90 °C. [b]Total yield of a 1:4 mixture of secondary phosphorothiolate **5j** and the primary phosphorothiolate **5i** formed by an S$_N$2′ reaction. [c]Using **2** (1.0 equiv) and **7** (1.0 equiv). [d]2-Phenyltetrahydrofuran was formed in 72% yield. [e]EtSPO(OEt)$_2$ (**9**) formed in the reaction.

with diethyl phosphorothioic acid **6** (1.1 equiv), iminium salt **2** (1.1 equiv), and imidazole (1.1 equiv) in toluene at 90 °C (conditions A, Table 1) led, after 1 h, to a 94% yield of the desired phosphorothiolate **5a**. When 3-phenylpropan-1-ol **4b** was subjected to the same conditions, an 84% yield of **5b** was obtained.

For both of these reactions, it was found that two liquid phases formed and vigorous stirring was required in order for the reaction to proceed. However, when the acid **6** was replaced by its sodium salt **7**, the reaction proceeded in the absence of imidazole and without the formation of a second liquid phase. Under these conditions (conditions B) reactions were generally complete in 30 min, with **5a** and **5b** formed in 91% yield and 97% yield, respectively. These conditions were used to further explore the substrate scope of the reaction.

Three other primary alcohols, **4c**, **4d**, and **4e**, were converted smoothly to the corresponding phosphorothiolates; acid-sensitive functionalities in the form of a THP ether and a *tert*-butyl carbamate were unaffected. However, the reaction of the Boc-protected compound **4e** was markedly slower than that of other substrates. Secondary alcohols **4f**, **4g** and **4h** also underwent the reaction to the corresponding phosphorothiolates. (*E*)-Cinnamyl alcohol **4i** could be converted to the corresponding phosphorothiolate **5i** in 77% yield. However, when 1-phenylprop-2-en-1-ol **4j** was subjected to the reaction conditions, the major product was the same phosphorothiolate **5i** resulting from allylic rearrangement. Secondary allylic

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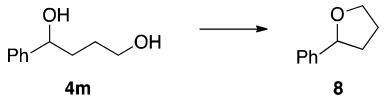
alcohol **4k** gave the expected phosphorothiolate **5k** without allylic rearrangement in 75% yield.

The reaction was found to be selective for a primary alcohol in the presence of a secondary alcohol (**4l**) when 1 equiv of **2** and **7** were used. However, when 1-phenyl-butane-1,4-diol (**4m**) was used tetrahydrofuran **8** was isolated as the major product (72%) (Scheme 3). In this case, it is presumed that

Scheme 3. Formation of 2-Phenyltetrahydrofuran[a]



4m **8**

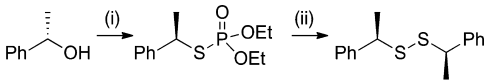
[a]Conditions: $(EtO)_2POSH$ (**6**) (1 equiv), $Me_2NCHSEt^+ BF_4^-$ (**2**) (1 equiv), imidazole (1 equiv), toluene, 90 °C, 72%.

cyclization of the secondary alcohol to the activated primary position is more rapid than the intermolecular reaction with the sulfur nucleophile. Indeed, when the reaction of **4m** with **2** was carried out in the absence of sulfur nucleophile **6**, the same tetrahydrofuran product **8** was obtained.

1,2:3,4-Di-*O*-isopropylidene-D-galactopyranose **4n** proved unreactive under the reaction conditions and was recovered unchanged. The low reactivity of leaving groups at the 6-position of galactopyranose derivatives has been noted previously,[13] although it should be noted that **4n** has been shown to react with several sulfur nucleophiles under Mitsunobu conditions[14] or with $PhSSPh/Bu_3P$.[15] In the present case, slow formation of $EtSPO(OEt)_2$ (**9**) was observed, presumably from direct reaction of thioiminium salt **2** with phosphorothiolate anion **7**.

The stereochemical course of the reaction was investigated through reaction of (*S*)-1-phenylethanol ((*S*)-**4g**, >99:1 er) with sodium salt **7** and iminium salt **2** (Scheme 4). The product

Scheme 4. Stereochemical Course of Reaction[a]



(*S*)-**4g** (*R*)-**5g** (*R,R*)-**10**

[a](i) $(EtO)_2POSNa$ (**7**), (1.1 equiv), $Me_2NCHSEt^+ BF_4^-$ (**2**) (1.1 equiv), toluene, 90 °C, 83%; (ii) KOH (4 equiv), THF, H_2O, 72%.

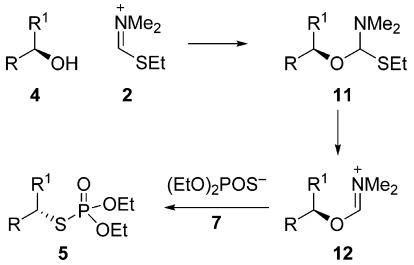
5g was obtained with 97:3 er. Upon hydrolysis of the sulfur–phosphorus bond,[9] spontaneous oxidation occurred to give the known[16] disulfide (*R,R*)-**10**, proving that the displacement had proceeded with inversion of configuration.

A similar selectivity was found when (*R*)-octan-2-ol ((*R*)-**4f**, > 98:2 er) was used: the product **5f** was obtained with 97:3 er. However, when enantiopure (*R*)-**4k** (prepared by enzymic resolution,[17] 98.5:1.5 er) was subjected to the reaction conditions erosion of enantiopurity was seen with the desired phosphorothiolate isolated with 61:39 er.

The proposed mechanistic course of phosphorothiolate formation is outlined in Scheme 5. Nucleophilic addition of alcohol **4** to iminium ion **2** leads to the formation of the adduct **11**, which can lose ethanethiolate (or, following protonation, ethanethiol) to give **12**. Nucleophilic displacement of the DMF leaving group by phosphorothiolate ion **7** then affords the desired product **5**.

In summary, a simple one-step method has been developed for the conversion of a wide range of primary and secondary

Scheme 5. Proposed Mechanism of Phosphorothiolate Formation



alcohols to the corresponding phosphorothiolates, with inversion of configuration. This methodology should facilitate the development of such compounds as synthetic intermediates.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under an inert atmosphere of N_2 or Ar. All reagents were used as received. Thin layer chromatography was carried out using Merck silica-aluminum plates, with UV light (254 nm), and potassium permanganate or anisaldehyde for visualization. Column chromatography column chromatography was carried out using Merck Geduran Si 60 silica gel or Sigma-Aldrich weakly acidic activated alumina. Chiral stationary phase HPLC was performed using Chiralcel OD or Chiralpak AD-H 25 cm analytical columns. Infrared spectra were recorded using a Bruker Alpha ATR spectrometer. NMR spectra were recorded in $CDCl_3$ using a Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz, or Bruker AVANCE III 600 MHz spectrometer. Reference values for $CDCl_3$ were taken as δ = 7.27 ppm for ^1H NMR spectroscopy and δ = 77.2 ppm for ^{13}C NMR spectroscopy. Coupling constants (J) are given in Hz. Where appropriate COSY and DEPT experiments were carried out to aid assignment. Mass spectrometry data were collected on a Waters Micromass LCT Premier XE time-of-flight instrument (ESI) or a Thermo Finnigan MAT900xp magnetic sector instrument (EI/CI). Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyzer. Optical rotations were obtained using a PerkinElmer 343 digital polarimeter and are reported in units of 10^{-1} deg cm^2 g^{-1}.

N-(Ethylsulfanylmethylene)-*N*,*N*-dimethylammonium tetrafluoroborate (**2**),[12] *O*,*O*-diethyl phosphorothioic acid (**6**),[5] sodium *O*,*O*-diethyl phosphorothioate (**7**),[4] 1-phenylprop-2-en-1-ol (**4h**),[18] (*R*)-4-phenylbut-3-en-2-ol ((*R*)-**4k**),[17] 4-benzyloxybutane-1,3-diol (**4l**),[19] and 4-hydroxy-1-phenylbutan-1-one (**4m**)[20] were synthesized according to reported literature procedures.

(*R*)-Octan-2-ol ((*R*)-**4f**) was purchased from Acros Organics, and its enantiomeric ratio was determined as >98:2 by Mosher's ester analysis.[21] (*S*)-1-Phenylethanol ((*S*)-**4g**) was purchased from Acros Organics, and its enantiomeric ratio was determined as >99:1 by chiral stationary phase HPLC (Chiralcel OD, 90:10 hexane/^{i}PrOH; flow rate 1.0 mL min^{-1}). The enantiomeric ratio of (*R*)-4-phenylbut-3-en-2-ol ((*R*)-**4k**) was determined as 98.5:1.5 by chiral stationary phase HPLC (Chiralcel OD, 90:10 hexane/^{i}PrOH; flow rate 1.0 mL min^{-1}).

General Procedure for the Synthesis of Phosphorothiolates. A solution of alcohol **4** (1.00 mmol) in toluene (2 mL) was treated with $(EtO)_2POSNa$ (**7**) (211 mg, 1.10 mmol) followed by iminium salt **2** (226 mg, 1.10 mmol) and heated using a silicone oil bath to 90 °C for 30 min (except where stated otherwise). The reaction was cooled to room temperature and concentrated *in vacuo*. Purification of the desired phosphorothiolates was achieved by flash column chromatography over SiO_2 (or Al_2O_3 where stated).

***O,O*-Diethyl *S*-(4-Methylbenzyl) Phosphorothioate (5a).** Eluent 30:70 EtOAc/hexanes; **5a** (249 mg, 91%) obtained as a colorless oil; R_f = 0.30 (20:80 EtOAc/hexanes); ν_{max}/cm^{-1} 2982, 1514, 1254, 1012, 969; ^1H NMR (600 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 7.7),

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7.13 (2H, d, J = 7.7), 4.17−4.01 (4H, m), 4.01 (2H, d, J = 13.6), 2.34 (3H, s), 1.35 (6H, t, J = 7.0); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 137.5 (C), 134.4 (d, J = 5.0, C), 129.4 (CH), 128.9 (CH), 63.6 (d, J = 5.0, CH_2), 34.9 (d, J = 2.5, CH_2), 20.9 (CH_3), 16.1 (d, J = 6.3, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.9; m/z (ESI+) 276 (10%), 275 ([M + H]$^+$, 100); HRMS (ESI+) m/z: [M + H]$^+$ calcd for $C_{12}H_{20}O_3PS$ 275.0879; found 275.0871. Anal. Calcd for $C_{12}H_{19}O_3PS$: C, 52.54; H, 6.98. Found: C, 52.48; H, 7.11.

_O,O_-Diethyl _S_-(3-Phenylpropyl) Phosphorothioate (5b). Eluent 30:70 EtOAc/hexanes; **5b** (280 mg, 97%) obtained as a colorless oil; R_f = 0.34 (40:60 EtOAc/hexanes); ν_{max}/cm^{-1} 2981, 1453, 1252, 1013, 967; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31−7.28 (2H, m), 7.22−7.18 (3H, m), 4.23−4.10 (4H, m), 2.89−2.81 (2H, m), 2.74 (2H, t, J = 7.4), 2.03 (2H, app. quintet, J = 7.5), 1.35 (6H, t, J = 7.1); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 140.9 (C), 128.6 (CH), 128.6 (CH), 126.2 (CH), 63.6 (d, J = 5.0, CH_2), 34.6 (CH_2), 32.3 (d, J = 3.8, CH_2), 30.3 (d, J = 2.5, CH_2), 16.2 (d, J = 6.3, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.0; m/z (EI) 288 (M$^+$, 47%), 118 ([M−$(EtO)_2POSH$]$^+$, 100), 91 ($PhCH_2^+$, 26); HRMS (EI) m/z: [M$^+$] calcd for $C_{13}H_{21}O_3PS$ 288.0944; found 288.0948. Anal. Calcd for $C_{13}H_{21}O_3PS$: C, 54.15; H, 7.34. Found: C, 54.36; H, 7.47.

_O,O_-Diethyl _S_-(2-Methylpropyl) Phosphorothioate (5c). Eluent 30:70 EtOAc/hexanes; **5c** (198 mg, 88%) obtained as a colorless oil; R_f = 0.29 (20:80 EtOAc/hexanes); ν_{max}/cm^{-1} 2960, 1388, 1258, 1163, 1014, 967; ^1H NMR (300 MHz, $CDCl_3$) δ 4.23−4.07 (4H, m), 2.73 (2H, dd, J = 13.1, 6.8), 1.90 (1H, app. nonet, J = 6.7), 1.36 (6H, t, J = 7.1), 1.01 (6H, d, J = 6.6); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 63.5 (d, J = 5.2, CH_2), 39.5 (d, J = 3.8, CH_2), 29.6 (d, J = 6.0, CH), 21.7 (CH_3), 16.2 (d, J = 6.8, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.5; m/z (CI) 227 ([M + H]$^+$, 100%); HRMS (CI) [M + H]$^+$ calcd for $C_8H_{20}O_3PS$ 227.0865; found 227.0865.

_O,O_-Diethyl _S_-(2-(Tetrahydro-2_H_-pyran-2-yloxy)ethyl) Phosphorothioate (5d). Eluent 25:75 EtOAc/hexanes; **5d** (262 mg, 88%) obtained as a colorless oil; R_f = 0.18 (25:75 EtOAc/hexanes); ν_{max}/cm^{-1} 2979, 1455, 1352, 1252, 1209, 1127, 1081, 1014, 967; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (1H, t, J = 3.4), 4.29−4.08 (4H, m), 3.98−3.82 (2H, m), 3.65 (1H, dt, J = 10.4, 6.5), 3.52 (1H, m), 3.00 (2H, dt, J = 15.1, 6.5), 1.83−1.60 (6H, m), 1.37 (6H, t, J = 7.1); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 98.9 (CH), 66.8 (d, J = 5.0, CH_2), 63.7 (d, J = 5.9, CH_2), 62.3 (CH_2), 30.7 (d, J = 3.9, CH_2), 30.6 (CH_2), 25.5 (CH_2), 19.4 (CH_2), 16.1 (d, J = 6.8, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.9; m/z (ES+) 299 ([M + H]$^+$, 100%); HRMS (ES+) [M + H]$^+$ calcd for $C_{11}H_{24}O_5PS$ 299.1082; found 299.1089. Anal. Calcd for $C_{11}H_{23}O_5PS$: C, 44.28; H, 7.77. Found: C, 44.21; H, 7.94.

***tert*-Butyl (3-((Diethoxyphosphoryl)thio)propyl)carbamate (5e).** Reaction conducted at 90 °C for 180 min. Purified by flash column chromatography on alumina (30:70 EtOAc/hexanes) to give _O,O,S_-triethyl phosphorothioate (28 mg, 14%) and **5e** (214 mg, 65%) as a colorless oil; R_f = 0.33 (50:50 EtOAc/hexanes); ν_{max}/cm^{-1} 3327, 2978, 2933, 1708, 1692, 1519, 1478, 1444, 1391, 1365, 1245, 1164, 1097, 967; ^1H NMR (600 MHz, $CDCl_3$) δ 4.94 (1H, br s), 4.24−4.12 (4H, m), 3.27−3.22 (2H, m), 2.87 (2H, dt, J = 15.7, 7.0), 1.88 (2H, quintet, J = 6.7), 1.43 (9H, s), 1.36 (6H, t, J = 7.1); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 156.1 (C), 79.4 (C), 63.8 (d, J = 6.2, CH_2), 38.7 (CH_2), 31.2 (CH_2), 28.5 (CH_3), 28.2 (CH_2), 16.2 (d, J = 7.2, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.1; m/z (ESI) 328 ([M + H]$^+$, 100%); HRMS (ESI) [M + H]$^+$ calcd for $C_{12}H_{27}NO_5PS$ 328.1348; found 328.1351. Anal. Calcd for $C_{12}H_{26}NO_5PS$: C, 44.03; H, 8.00; N, 4.28. Found: C, 44.30; H, 8.20; N, 4.49.

_O,O_-Diethyl _S_-Octan-2-yl Phosphorothioate (5f).[22] Eluent 0:100 to 20:80 EtOAc/hexanes; (±)-**5f** (220 mg, 78%) obtained as a colorless oil. The NMR data agree with those reported in the literature.[22]

Reaction repeated using (_R_)-octan-2-ol on a 0.82 mmol scale. Eluent 0:100 to 20:80 EtOAc/hexanes; (_S_)-**5f** (130 mg, 72%) obtained as a colorless oil. $[\alpha]_D^{20}$ +7 (_c_ 1.03, $^nBu_2O$) [lit.[22] +6.59 (no conc. reported, $^nBu_2O$)]; HPLC analysis (Chiralpak AD-H; 90:10 hexane/^{i}PrOH; flow rate 0.5 mL min^{-1}) er 97:3 [t_R (major) = 9.1 min, t_R (minor) = 8.6 min].

_O,O_-Diethyl _S_-(1-Phenylethyl) Phosphorothioate (5g).[23] Eluent 30:70 EtOAc/hexanes; (±)-**5g** (206 mg, 75%) obtained as a colorless oil. The NMR data agree with those reported in the literature.[23]

Reaction repeated using (_S_)-1-phenylethanol. Eluent 30:70 EtOAc/hexanes; (_R_)-**5g** (226 mg, 83%) obtained as a colorless oil. $[\alpha]_D^{20}$ +160.4 (_c_ 1.03, CH_2Cl_2); HPLC analysis (Chiralcel OD; 99:1 hexane/^{i}PrOH; flow rate 1.0 mL min^{-1}) er 97:3 [t_R (major) = 16.4 min, t_R (minor) = 22.2 min].

(±)-_O,O_-Diethyl _S_-(4-Phenylbutan-2-yl) Phosphorothioate (5h). Eluent 30:70 EtOAc/hexanes; **5h** (275 mg, 91%) obtained as a colorless oil; R_f = 0.41 (40:60 EtOAc/hexanes); ν_{max}/cm^{-1} 2981, 1453, 1252, 1016, 966; ^1H NMR (600 MHz, $CDCl_3$) δ 7.30−7.27 (2H, m), 7.21−7.19 (3H, m), 4.23−4.09 (4H, m), 3.37 (1H, app d.sextet, J = 13.3, 6.7), 2.83−2.70 (2H, m), 2.07−1.90 (2H, m), 1.49 (3H, d, J = 6.8), 1.36 (3H, t, J = 7.1), 1.34 (3H, t, J = 7.1); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 141.4 (C), 128.6 (CH), 128.5 (CH), 126.2 (CH), 63.60 (d, J = 5.0, CH_2), 63.58 (d, J = 5.0, CH_2), 42.6 (d, J = 2.5, CH), 40.2 (d, J = 7.5, CH_2), 33.3 (CH_2), 23.7 (d, J = 3.8, CH_3), 16.20 (d, J = 5.0, CH_3), 16.17 (d, J = 5.0, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.3; m/z (EI) 302 (M$^+$, 17%), 132 ([M−$(EtO)_2POSH$]$^+$, 100), 117 ($PhCH_2CHCH^+$, 68), 91 ($PhCH_2^+$, 34); HRMS (EI) [M]$^+$ calcd for $C_{14}H_{23}O_3PS$ 302.1106; found 302.1106. Anal. Calcd for $C_{14}H_{23}O_3PS$: C, 55.61; H, 7.67. Found C, 55.71; H, 7.80.

(_E_)-_O,O_-Diethyl _S_-(3-Phenylprop-2-enyl) Phosphorothioate (5i).[23] Eluent 30:70 EtOAc/hexanes; **5i** (219 mg, 77%) obtained as a pale yellow oil. The NMR data agree with those reported in the literature.[23]

(±)-_O,O_-Diethyl _S_-(1-Phenylprop-2-enyl) Phosphorothioate (5j). Eluent 30:70 EtOAc/hexanes; obtained **5i** (154 mg, 51%), and **5j** (39 mg, 13%) as a colorless oil; R_f = 0.42 (40:60 EtOAc/hexanes); ν_{max}/cm^{-1} 2979, 1450, 1389, 1249, 1160, 1096, 1008, 966; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.30 (5H, m), 6.18 (1H, ddd, J = 16.9, 10.1, 7.4), 5.26 (1H, dt, J = 16.9, 1.2), 5.20 (1H, dt, J = 10.1, 1.0), 4.99 (1H, ddt, J = 11.4, 7.4, 1.2), 4.11−3.95 (4H, m), 1.263 (3H, td, J = 7.1, 0.9), 1.258 (3H, td, J = 7.1, 0.9); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 140.6 (d, J = 4.0, C), 137.9 (d, J = 5.2, CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 117.0 (CH_2), 63.62 (d, J 6.0, CH_2), 63.58 (d, J = 5.8, CH_2), 53.1 (d, J = 3.3, CH), 16.0 (d, J = 7.4, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.3; m/z (EI) 286 (M$^+$, 19%), 117 ([M−$(EtO)_2POS$]$^+$, 100); HRMS (EI) [M]$^+$ calcd for $C_{13}H_{19}O_3PS$ 286.0787; found 286.0787.

(_E_)-_O,O_-Diethyl _S_-(4-Phenylbut-3-en-2-yl) Phosphorothioate (5k).[5] Eluent 20:80 EtOAc/hexanes; (±)-**5k** (225 mg, 75%) obtained as a colorless oil. The NMR data agree with those reported in the literature.[5]

Reaction repeated using (_R_)-**4k** (er 98.5:1.5)[17] to give **5k** (141 mg, 69%) as a colorless oil. HPLC analysis (Chiralcel OD; 97:3 hexane/^{i}PrOH; flow rate 1.0 mL min^{-1}) er 61:39 [t_R (major) = 11.2 min, t_R (minor) = 13.7 min].

_O,O_-Diethyl _S_-(4-Benzyloxy-3-hydroxybutyl) Phosphorothioate (5l). Reaction conducted at 90 °C for 60 min using 1.0 equiv of **2** and 1.0 equiv of **7**. Purified by flash column chromatography on alumina (30:70 EtOAc/hexanes) to give **5l** (222 mg, 64%) as a colorless oil; R_f = 0.31 (60:40 EtOAc/hexanes); ν_{max}/cm^{-1} 3397, 2983, 2905, 2862, 1453, 1237, 1162, 1010, 967; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38−7.28 (5H, m), 4.23−4.10 (4H, m), 3.99 (1H, ddt, J 8.8, 7.2, 3.7), 3.51 (1H, dd, J = 9.5, 3.4), 3.41 (1H, dd, J = 9.5, 7.0), 3.04−2.97 (2H, m), 1.89−1.78 (2H, m), 1.37−1.35 (6H, m); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 138.0 (C), 128.6 (CH), 128.0 (CH), 127.9 (CH), 74.2 (CH_2), 73.5 (CH_2), 68.3 (CH), 63.9 (d, J = 6.1, CH_2), 63.8 (d, J = 6.2, CH_2), 34.6 (d, J = 4.2, CH_2), 27.2 (d, J = 3.9, CH_2), 16.22 (d, J = 4.7, CH_3), 16.17 (d, J = 4.8, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.5; m/z (ES+) 349 ([M + H]$^+$, 100%); HRMS (ES+) [M + H]$^+$ calcd for $C_{15}H_{26}O_5PS$ 349.1239; found 349.1241. Anal. Calcd for $C_{15}H_{25}O_5PS$: C, 51.71; H, 7.23. Found: C, 51.72; H, 7.31.

2-Phenyltetrahydrofuran (8).[24] Purified by flash chromatography on alumina (5:95 EtOAc/hexanes) to give **8** (83 mg, 72%) as a colorless oil. The NMR data agree with those reported in the literature.[24]

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(*R*,*R*)-(+)-Di(1-phenylethyl) Disulfide (10).[16] A solution of (*R*)-**5g** (50 mg, 0.182 mmol) in THF (0.66 mL) was treated with a solution of KOH (41 mg, 0.731 mmol) in H_2O (0.34 mL) and stirred at rt for 6 h. After this time the solution was loaded directly onto a column and purified by flash column chromatography (0−10% EtOAc/Hexanes, SiO_2) to give (*R*,*R*)-**10** (18 mg, 72%) as a colorless oil. $[\alpha]_D^{20}$ +229 (*c* 0.65, EtOH) (lit.[16] $[\alpha]_D^{20}$ +277 (*c* 1.16, EtOH)). The NMR data agree with those reported in the literature.[16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01657.

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra for all compounds synthesized (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: m.j.porter@ucl.ac.uk.

ORCID

Michael J. Porter: 0000-0002-0376-5434

Notes

The authors declare no competing financial interest.

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