29 (100). Anal. Calcd for $C_{16}H_{22}F_{12}O_4$: C, 40.77; H, 4.18. Found: C, 40.87; H, 4.10.

4,4,5,5,6,6,7,7,8,8,9,9-Dodecafluoro-1,12-dodecanedioic Acid (5d). A mixture of $Co_2(CO)_8$ (1.64 g, 4.8 mmol), **3d** (14.64 g, 24 mmol), water (8.8 mL, 488 mmol), KF (5.58 g, 96.3 mmol), and *t*-BuOH (120 ml) in a 200-mL stainless steel autoclave was stirred at 80 °C under 50 atm of carbon monoxide pressure. To the cooled mixture was added concentrated aqueous HCl. The mixture was extracted with Et_2O. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized (Et_2O/hexane) to give **5d** in 94% (10.1 g) yield: mp 182 °C; ^1H NMR (acetone-d_6) δ 2.40 (m, 4 H), 2.7 (m, 4 H), 9.0 (br, 2 H); ^{19}F NMR (acetone-d_6) δ −114.1 (br, 4 F), −121.3 (br, 4 F), −123.2 (br, 4 F); IR (KBr) 3300–2800 (ν(OH)), 1710 (δ(C=O)) cm^{-1}; MS *m/e* 429 (M^+ − 17, 20), 402 (41), 139 (52), 131 (37), 123 (33), 109 (47), 103 (100), 77 (62), 59 (64), 55 (80), 47 (44), 45 (40). Anal. Calcd for $C_{12}H_{10}F_{12}O_4$: C, 32.30; H, 2.26. Found: C, 32.44; H, 2.29.

4,4,5,5-Tetrafluoro-1,8-octanedioic acid (5a): mp 204 °C; ^1H NMR (acetone-d_6) δ 2.10–3.00 (m, 8 H); ^{19}F NMR (acetone-d_6) δ −115.9 (br, 4 F); IR (KBr) 3450–3200 (ν(OH)), 1710 (ν(C=O)) cm^{-1}; MS *m/e* 229 (M^+ − 17, 7), 208 (8), 161 (10), 123 (37), 103 (100), 77 (40), 73 (40), 60 (58), 55 (78), 47 (47), 42 (42), 28 (34). Anal. Calcd for $C_{12}H_{10}F_{12}O_4$: C, 32.30; H, 2.26. Found: C, 32.44; H, 2.29.

4,4,5,5,6,6,7,7-Octafluoro-1,10-decanedioic acid (5b): mp 187–187.5 °C; ^1H NMR (acetone-d_6) δ 2.15–2.90 (m, 8 H), 11.0 (br, 2 H); ^{19}F NMR (acetone-d_6) δ −114.4 (br, 4 F), −123.3 (br, 4 F); IR (KBr) 3300–2800 (ν(OH)), 1720 (ν(C=O)) cm^{-1}; MS *m/e* 329 (M^+ − 17, 11), 302 (8), 123 (23), 109 (31), 103 (86), 77 (56), 73 (41), 59 (48), 55 (100), 47 (51), 45 (41). Anal. Calcd for $C_{10}H_{10}F_8O_4$: C, 34.70; H, 2.91. Found: C, 34.53; H, 2.85.

2,9-Dimethyl-4,4,5,5,6,6,7,7-octafluoro-1,10-decanedioic acid (5c): mp 1660168 °C; ^1H NMR (acetone-d_6) δ 1.33 (d, J = 8 Hz, 6 H), 1.60–3.10 (m, 6 H), 10.8 (br, 2 H); ^{19}F NMR (acetone-d_6) δ −113.4 (br, 4 F), −123.7 (br, 4 F); IR (KBr) 3300–2800 (ν(OH)), 1715 (ν(C=O)) cm^{-1}; MS *m/e* 357 (M^+ − 17, 3), 330 (7), 153 (27), 137 (17), 111 (23), 103 (16), 99 (17), 95 (18), 91 (67), 89 (52), 87 (34), 77 (24), 73 (68), 69 (41), 61 (27), 59 (22), 47 (65), 45 (45), 28 (60), 18 (100). Anal. Calcd for $C_{12}H_{14}F_8O_4$: C, 38.51; H, 3.77. Found: C, 38.38; H, 3.69.

2,11-Dimethyl-4,4,5,5,6,6,7,7,8,8,9,9-dodecafluoro-1,12-dodecanedioic acid (5e): mp 149.5–151 °C; ^1H NMR (acetone-d_6) δ 1.33 (d, J = 8 Hz, 6 H), 1.60–3.10 (m, 6 H), 11.0 (br, 2 H); ^{19}F NMR (acetone-d_6) δ −113.2 (br, 4 F), −121.6 (br, 4 F), −123.7 (br, 4 F); IR (KBr) 3300–2800 (ν(OH)), 1710 (ν(C=O)) cm^{-1}; MS *m/e* 457 (M^+ − 17, 2), 430 (14), 163 (21), 153 (22), 133 (22), 121 (32), 91 (60), 87 (30), 73 (75), 47 (100), 45 (37), 28 (34). Anal. Calcd for $C_{14}H_{14}F_{12}O_4$: C, 35.46; H, 2.98. Found: C, 35.56; H, 2.99.

3,3,4,4,5,5,6,6,7,7,8,8-Dodecafluoro-1,10-diisocyanatodecane (8c). A solution of **5d** (0.892 g, 2 mmol) and $SOCl_2$ (2 mL) was refluxed for 2 h under Ar. Excess $SOCl_2$ was then evaporated in vacuo to provide 4,4,5,5,6,6,7,7,8,8,9,9-dodecafluoro-1,12-dodecanedioyl dichloride (**6c**) in quantitative yield. To a toluene (2 mL) solution of **6c** was added a mixture of HN_3 (1.3 M, 3.1 mL, 4 mmol) and pyridine (0.33 mL, 4 mmol) in toluene (3 mL) at 0 °C. The solution was stirred for 15 min at 0 °C. The pyridine hydrochloride that precipitated was removed by filtration. Excess HN_3 was evaporated from the filtrate in vacuo (20 mmHg) over 1 h to give a toluene (~5 mL) solution of 4,4,5,5,6,6,7,7,8,8,9,9-dodecafluoro-1,12-dodecanedioyl diazide (**7c**). The toluene solution so obtained was heated at 95 °C for 1 h. After evaporation of the toluene, **8c** was obtained in 64% overall yield (0.565 g).

6c: ^1H NMR ($CDCl_3$) δ 2.45 (tt, J = 18 and 7 Hz, 4 H), 3.24 (t, J = 7 Hz, 4 H); IR (KBr) 1785 (ν(C=O)) cm^{-1}.

7c: IR (KBr fixed cell, toluene) 2145 ($\nu(N_3)$) and 1722 (ν(C=O)) cm^{-1}.

8c: ^1H NMR ($CDCl_3$) δ 2.40 (tt, J = 18 and 7 Hz, 4 H), 3.65 (t, J = 7 Hz, 4 H); ^{19}F NMR ($CDCl_3$) δ −114.7 (br, 4 F), −122.2 (br, 4 F), −124.1 (br 4 F); IR (KBr) 2270 (ν(N=C=O)) cm^{-1}; MS *m/e* 441 (M^+ + 1, 1), 384 (2), 56 (100). Anal. Calcd for $C_{12}H_8F_{12}N_2O_2$: C, 32.74; H, 1.83; N, 6.36. Found: C, 32.74; H, 1.83; N, 6.56.

3,3,4,4-Tetrafluoro-1,6-diisocyanatohexane(8a): ^1H NMR ($CDCl_3$) δ 2.37 (tt, J = 18 and 7 Hz, 4 H), 3.64 (t, J = 7 Hz, 4 H); ^{19}F NMR ($CDCl_3$) δ −115.2 (br, 4 F); IR (KBr) 2275 (ν(N=C=O)) cm^{-1}; MS *m/e* 241 (M^+ + 1, 1), 184 (16), 56 (100). Anal. Calcd for $C_8H_8F_4N_2O_2$: C, 40.01; H, 3.36; N, 11.66. Found: C, 40.19; H, 3.27; N, 11.36.

3,3,4,4,5,5,6,6-Octafluoro-1,8-diisocyanatooctane (8b): ^1H NMR ($CDCl_3$) δ 2.41 (tt, J = 18 and 7 Hz, 4 H), 3.66 (t, J = 7 Hz, 4 H); ^{19}F NMR ($CDCl_3$) δ −114.9 (br, 4 F), −124.1 (br, 4 F); IR (KBr) 2280 (ν(N=C=O)) cm^{-1}; MS *m/e* 341 (M^+ + 1, 1), 284 (2), 56 (100). Anal. Calcd for $C_{10}H_8F_8N_2O_2$: C, 35.31; H, 2.37; N, 8.24. Found: C, 34.95; H, 2.44; N, 8.63.

4,4,5,5,6,6,7,7,8,8,9,9-Dodecafluoro-*N*,*N*′-di-*tert*-butyl-1,12-dodecanediamide (9). To an Et_2O (4 mL) solution of **6c** (483 mg, 1 mmol) was added *t*-$BuNH_2$ (4 equiv). The solution was stirred for 30 min at room temperature. The solution was then washed with water and dried ($MgSO_4$). Purification by silica gel column chromatography ($CHCl_3$/EtOAc, 1:1) provided **9** in 77% yield: mp 163 °C; ^1H NMR ($CDCl_3$) δ 1.35 (s, 18 H), 2.10–2.70 (m, 8 H), 5.25 (br, 2 H); ^{19}F NMR ($CDCl_3$) δ −114.8 (br, 4 F), −122.3 (br, 4 F), −124.1 (br, 4 F); IR (KBr) 3340 (ν(NH)), 1650 (ν(C=O)) cm^{-1}; MS *m/e* 556 (M^+, 3), 485 (2), 58 (100), 57 (18). Anal. Calcd for $C_{20}H_{28}F_{12}N_2O_2$: C, 43.17; H, 5.07; N, 5.03. Found: C, 43.15; H, 5.16; N, 4.95.

Methanolysis of Phosphoramidates with Boron Trifluoride–Methanol Complex

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The synthesis of novel organophosphorus compounds remains important owing to their widespread use as agrichemicals,[1] biochemicals,[2] antisense oligonucleotides,[3] chemical reagents, and transition-state analogues.[4] Yet, the labile nature of certain functional groups appended to the phosphorus atom makes several classes of organophosphorus compounds difficult to prepare.

Phosphorothiolates **2** (Figure 1) are impurities that are found in commercial thiophosphoryl insecticides **1**.[5] Phosphorothiolates were found to be far more potent inhibitors of acetylcholinesterases than the parent phosphorothionates,[6] suggesting these materials could pose a risk to public health. A reliable and flexible synthesis of these impurities is needed to aid in the overall evaluation of their toxic action. Moreover, a method that would permit the preparation of chiral phosphorothiolates would be a worthy secondary aim. Several chiral phosphorus ester syntheses have been reported.[7]

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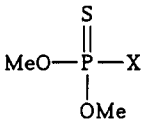
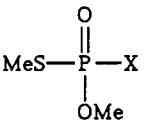
Table I. Conversion of PNR_1R_2 to $POCH_3$

entry	X	Y	Z	R_1	R_2	^{31}P (δ)	GC (min)	yield of 4 (%)[13,23]	^{31}P (δ)	GC (min)
3a	MeO	MeS	O	H	H	36.05	4.97	74	33.08	3.46
3b[19]	MeO	MeS	O	H	Bn	37.49	8.11	86	33.08	3.46
3c	MeO	MeS	O	Me	Me	39.18	4.21	80	33.08	3.46
3d	PhO	$N(Me)_2$	O	Me	Me	16.46	6.80	89[a]	-3.37	5.57
3e	EtO	$N(Me)_2$	O	Me	Me	20.08	4.14	54[a]	1.83	2.72
3f	PhO	Ph	O	Me	Me	23.55		84	17.42	
3g[21]	MeO	MeO	S	H	Bn	75.75	7.33	67	73.40	2.66
3h	MeO	MeO	S	Me	Me	81.25	3.44	62	73.40	2.66
3i[22]	EtO	EtO	S	Me	Me	77.08	4.26	70	69.85	3.55
3j[22]	EtO	EtO	S	H	Bn	71.71	7.92	65	69.85	3.55

[a] Y = MeO in product.



1: phosphorothionate



2: phosphorothiolate

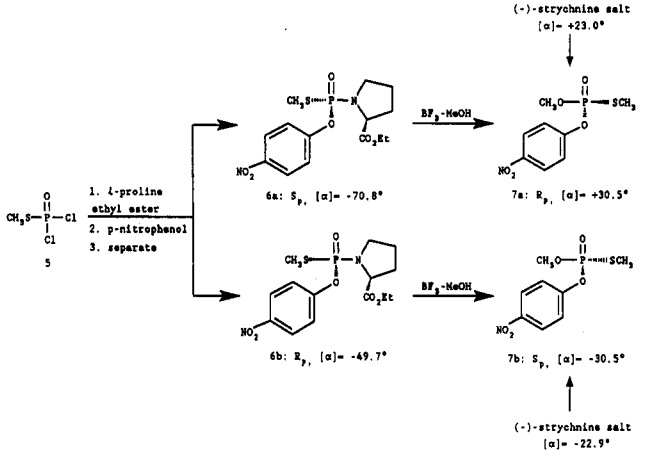
Figure 1.

Our work focused first upon the synthesis of *O,S*-dimethyl phosphorothiolates from the corresponding phosphoramidates. Methyl-containing phosphorothiolates represent a significant impurity class, and this transformation would offer an alternative to the alkylation of phosphorus thio acids, which may afford mixtures of O- and S-alkylation. However, acidic methanolysis[7c,i] of methylthio phosphoramides gave poor yields of the corresponding $POCH_3$ compounds. The evolution of methyl mercaptan indicated a nondiscriminate hydrolysis. The objective of this study was to find a new method for the conversion of sulfur-containing PNR_2 derivatives to the corresponding $POCH_3$ compounds.

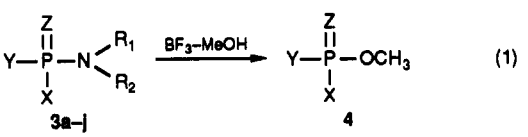
Results and Discussion

O,S-Dimethyl phosphoramidothiolate **3a** was prepared by reaction of ammonia with *O,S*-dimethyl phosphorochloridothioate.[8] Phosphoramidothiolates **3b** and **3c** were prepared by sequential dealkylation of the corresponding thionates with potassium ethyl xanthate and realkylation with dimethyl sulfate[6] in moderate yields. Two equivalents of potassium ethyl xanthate (PEX) and prolonged reflux times were required to achieve complete dealkylation. In certain cases, the first equivalent of PEX may deprotonate the amide, although this cannot explain the example with the tertiary amide. *N,N,N',N'*-Tetramethylphosphorodiamidates **3d** and **3e** were prepared by reaction of bis(dimethylamino) phosphorochloridate with the sodium salt of phenol or ethanol, respectively. Phosphonamidate **3f** was prepared in 66% yield by stepwise addition of phenylphosphonic dichloride and excess dimethylamine to sodium phenoxide in THF.[13] Phosphoramidothionates **3g–3j** were prepared in 64–85% yield by reaction of the corresponding phosphorochloridothionate with the requisite amines.[9] *p*-Nitrophenoxy *S*-methyl [(2*S*)-2-(carbethoxy)pyrrolidinyl]phosphorothioates (**6a/6b**) were prepared by sequential reaction of the *S*-methyl phosphorodichloridate (**5**) with *l*-proline ethyl ester and *p*-nitrophenol.[10] The 1,3,2-oxazaphospholidin-2-one **8** was prepared by reaction of **5** with (+)-ephedrine.[11] Phosphorus methyl ester products were prepared by reaction of the corresponding phosphorochloridate with sodium methoxide or methanol and base.[1,12,13]

Scheme I. Synthesis of Chiral Isoparathion-methyl 7a/7b



We were pleased to discover that boron trifluoride–methanol complex (BF_3–MeOH) reacted chemoselectively with many sulfur-containing phosphoramidates at room temperature in quantitative conversion to form the corresponding phosphate methyl ester as determined by NMR and GC (eq 1; Table I). Chromatographed mixtures



(1)

varied in yield from 54 to 89%. Product identity was confirmed by spectral analysis and by comparison to au-

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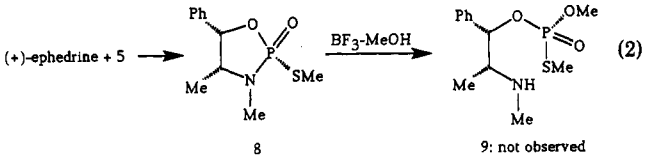
thentic materials prepared by alternate routes.[6,13]

Both thiolate **3a–c** and thionate **3g–j** organophosphorus compounds were amenable to the process as well as a representative phosphonate **3f**. Thionates were examined because amide–ester interchange also had been problematic for this class owing to partial rearrangement to the thiolate under strongly acidic conditions. No evidence of this rearrangement with BF_3–MeOH was detected. Primary, secondary, and tertiary phosphoramides all were converted to the corresponding methyl ester. Diamidates **3d** and **3e** were converted to the dimethyl esters but the triamide HMPA did not react after 96 h.

Next, we turned to the problem of chiral phosphorothiolate synthesis. Stepwise reaction of the dichloridate **5** with *l*-proline ethyl ester and *p*-nitrophenol gave an 81% yield of a mixture of diastereomers **6a/6b** (Scheme I). The diastereomers **6a/6b** were purified to greater than 99% homogeneity as determined by HPLC and ^{31}P NMR. Reactions of **6a** or **6b** with methanolic HCl led to a enantiomerically enriched ($[\alpha]^{22}_D = \pm 24°$) mixture of chiral isoparathion-methyl antipodes in low yield (10–20%). Exhaustive experimental control of the acid concentration (0.1–6.0 M), acid type (HCl, H_2SO_4, H_3PO_4, CF_3CO_2H), duration, temperature, cosolvent, and combinations of these variables did not have any profound effect on the outcome. Similarly, Casida and co-workers[14] reported a modest 20% yield for the acidic methanolysis of a related phosphoramidothiolate, additional evidence for the difficulty of this transformation.

Reaction of the individual diastereomers with BF_3–methanol complex gave the corresponding chiral isomers of isoparathion-methyl **7a** ($[\alpha]^{22}_D = +30.5°$, *c* 0.75, MeOH)/**7b** ($[\alpha]^{22}_D = -30.5°$, *c* 3.06, MeOH) in 75% yield. Comparison of **7a/7b** with chiral isoparathion-methyl prepared by the methanolic HCl method established that the reaction also had occurred with inversion of stereochemistry, although the isolated product had higher optical rotations when prepared by the BF_3-mediated process. Yet, the enantiomeric purity of both reactions was somewhat lower than material prepared from the diastereomeric strychnine salts (lit. $[\alpha]^{21}_D = +35.0°$).[7a] Intrigued by this outcome, we reexamined this prior report in detail. Reaction of parathion-methyl (**1**; X = *p*-nitrophenoxy) with an equimolar amount of (–)-strychnine in refluxing methanol led to the dealkylated, diastereomeric thioacid salts ($[\alpha]^{26}_D = +23°$, *c* 0.1, MeCN; $[\alpha]^{26}_D = -22.9°$, *c* 0.45, MeCN). Repeated fractional crystallization (MeOH and MeCN) yielded individual diastereomer salts that were at least 98% pure (limit of signal/noise detectability) by ^{31}P NMR doping experiments. Reaction of the individual salts with dimethyl sulfate directly or through the free acid afforded chiral isoparathion-methyl **7a** ($[\alpha]^{26}_D = +30.2°$, *c* 1.15, MeOH) and **7b** ($[\alpha]^{26}_D = -30.7°$, *c* 1.85, MeOH) with rotations sufficiently similar to those obtained by methanolysis (H^+ or BF_3) of diastereomeric amides. These results indicate that the stereochemical integrity of products derived from the BF_3–MeOH method is preserved. We were unable to effect satisfactory separation of **6a/6b** or **7a/7b** with lanthanide shift ($Eu(hfc)_3$; $Yb(fod)_3$) reagents at either 60- or 300-MHz field strengths. Additional studies are underway to clarify further the discrepancies in rotation with the prior report, although this minor conflict may simply be due to concentration differences.[15]

Ephedrine-based, diastereomeric oxazaphospholidin-2-ones also continue to be important precursors in chiral phosphorus preparations.[11,16] It was hoped that the BF_3-mediated methanolysis would also be applicable to this system. We reacted the single less polar diastereomer of the cyclic phosphoramidothiolate **8**[11b] with BF_3–methanol complex. Instead of the chiral, ring-opened product **9** (eq 2), ephedrine was obtained in 95% yield.



8 9: not observed (2)

Presumably, initial ring opening at the phosphoramide bond occurs, followed by O- to N-migration. The resultant product then undergoes a second methanolysis.[17]

In summary, BF_3–MeOH complex is an effective and useful alternative to acidic methanolysis of thiono and thiol esters with the exception of ephedrine-based 1,3,2-oxazaphospholidin-2-ones. Higher yields, ease of reaction manipulation, the commercial availability of reagent, hydrolytic control, and the successful preparation of chiral phosphorus thiol esters suggest this reagent to be superior to methanolic HCl for the conversion of phosphoramidates to the corresponding methyl esters.

Experimental Section

General Methods. Melting points are uncorrected. ^{31}P NMR chemical shifts are relative to phosphoric acid (H_3PO_4 in $CDCl_3$). Elemental analyses were conducted at Midwest Microlab, Indianapolis, IN.

Analytical thin-layer chromatography (TLC) was conducted with aluminum-backed silica plates. Visualization was accomplished with an ultraviolet lamp and/or anisaldehyde stain (a 2% solution of *o*-anisaldehyde in 95:4:1 absolute ethanol–concentrated sulfuric acid–glacial acetic acid) with heating and/or DBQ (5% 2,6-dibromoquinone-4-chloroimide) stain or phosphomolybdic acid (PMA). Flash chromatography[18] was conducted with Kieselgel 60, 230–400 mesh.

Reversed-phase, high-performance liquid chromatography (RPHPLC) was conducted on 10-μm ODS (30-cm) column utilizing a 55:45 CH_3OH/H_2O solvent system at a flow rate of 1.5 mL/min with detection at 270 nm. Capillary gas chromatography (GC) was performed on a 15-m, DB-1 capillary column at gas flow rates of 300 mL/min (air), 30 mL/min (hydrogen), and 15 mL/min (helium). The injector and detector temperatures were 250 and 275 °C, respectively. Ramped oven temperatures of 50–250 °C at 20 °C/min were used.

All reactions were conducted under a positive argon atmosphere utilizing standard techniques. *l*-Proline, boron trifluoride–methanol complex, (–)-strychnine, (+)-ephedrine, and all phosphorus-containing starting materials were purified by distillation or recrystallization prior to use. Racemic isoparathion-methyl was available from a prior study.[4]

Phenyl *N,N,N',N'*-Tetramethylphosphorodiamidate (3d).[13] Sodium hydride (6.0 mmol; 80% suspension) was added to a 25-mL THF solution of phenol (6 mmol) at 0 °C. After the solution was stirred for 15 min, dimethyl phosphorochloridate (5 mmol) was added and the ice bath removed. After being stirred for 2 h, the reaction mixture was filtered through a frit containing a 1-cm layer of Celite. The solution was concentrated in vacuo and purified by flash chromatography (100% ether) providing **3d** (1.18 g, 58%).

Ethyl *N,N,N',N'*-Tetramethylphosphorodiamidate (3e).[20]

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The same procedure as that for **3d** was used except ethanol was substituted for phenol. The reaction yield is 76%.

Phenyl *N,N*-Dimethylphenylphosphonamidate (3f).[13] Sodium hydride (5.5 mmol; 60% suspension) was added to a 25 mL THF solution of phenol (5 mmol) at 0 °C. Phenylphosphonic dichloride (5 mmol) was added dropwise and the mixture stirred for 3 h. Dimethylamine hydrochloride (10 mmol) was added followed by triethylamine (15 mmol). The mixture was warmed to room temperature and stirred an additional 2 h. The mixture was filtered, concentrated to a semisolid, and chromatographed to afford 66% of white crystals, mp 65–66 °C.

Synthesis of Phosphoramidothionates (3g–j). Triethylamine (9.6 mmol or 19.2 mmol for $Me_2NH_2^+Cl^-$) and benzylamine (8 mmol) or dimethylamine hydrochloride (8 mmol) were dissolved in 30 mL of THF and chilled to 0 °C. Dimethyl or diethyl phosphorochloridothionate (8 mmol) was added, and the reaction mixture was warmed to room temperature and monitored by TLC/GC for loss of starting material. Upon completion of the reaction, the mixture was diluted with 50 mL of ether, filtered through Celite, and evaporated to yield the crude product. The products were purified by flash chromatography using 1:1 petroleum ether–ether as eluent.

General Preparation of Phosphorus Methyl Esters from Phosphorus Amides. Method A. To an oven-dried flask under an argon atmosphere was added 2.5 mmol of a phosphoramide in 2 mL of anhydrous methanol. The solution was stirred at 0 °C for 20 min, at which point 25 mmol of BF_3–MeOH complex was added dropwise over 5 min. The temperature was maintained for 1 h and then stirred at rt overnight. The reaction mixture was added dropwise to a saturated solution of sodium bicarbonate and extracted thrice with ether. The ether extracts were combined, washed with saturated sodium bicarbonate and brine, and dried over sodium sulfate. Filtration, evaporation, and flash chromatography (100% ether) afforded the product.

Method B. As in method A, except with a modified workup. After being stirred overnight, the reaction mixture was diluted with 25 mL of ether and added to a stirred solution of 30 mmol of $NaHCO_3$ in 25 mL of ether. The heterogeneous mixture was stirred for 5 min and vacuum filtered through a 1-cm layer of Celite. The solvent was removed by rotary evaporation and the material purified by flash chromatography (ether).

***p*-Nitrophenoxy *S*-Methyl [(2*S*)-2-(Carbethoxy)-pyrrolidinyl]phosphorothioate (6a/6b).** *S*-Methyl phosphorodichloridate[8] (1.65 g, 10 mmol) was dissolved in 20 mL of anhydrous pyridine at −78 °C. *l*-Proline ethyl ester was added in a minimum of pyridine (resulting in a yellow color), and the reaction was monitored by TLC for consumption of starting material. When complete formation of the amidate was detected, *p*-nitrophenol (1.39 g, 10 mmol) was added and the mixture was stirred until the intermediate was consumed. The reaction was allowed to come to room temperature and diluted with 50 mL of ether, and the pyridinium hydrochloride was filtered. The filtrate was washed twice with saturated sodium bicarbonate, water, 10% HCl, and brine, dried over sodium sulfate, and concentrated to 3.04 g (81.4%) of an oil. The crude diastereomers were separated by column chromatography using 1:4 petroleum ether–ether as eluant. The purity of each diastereomer was determined by HPLC and ^{31}P NMR to be greater than 99%. The less polar diastereomer crystallized at 4 °C. Anal. Calcd for $C_{14}H_{19}N_2O_6PS$: C, 44.92; H, 5.12; N, 7.48. Found: C, 44.86; H, 5.04; N, 7.39.

6a (less polar): R_f = 0.18 (1:3 petroleum ether–ether); ^1H NMR δ 1.22 (t, J = 7.0 Hz, 3 H), 1.85–2.23 (m, 4 H), 2.37 (d, J = 16.0 Hz, 3 H), 3.36–3.44 (m, 1 H), 3.47–3.56 (m, 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 4.39–4.43 (m, 1 H), 7.39 (d, J = 9.3 Hz, 2 H), 8.2 (d, J = 9.3 Hz, 2 H); ^{13}C NMR δ 11.65 (d, J = 3.7 Hz), 14.1, 24.9 (d, J = 8.8 Hz), 31.5 (d, J = 8.2 Hz), 47.75 (d, J = 4.9 Hz), 60.36 (d, J = 4.9 Hz), 61.2, 121.0 (d, J = 5.4 Hz), 125.5, 144.6, 155.6 (d, J = 8.1 Hz), 173.1; ^{31}P NMR δ 30.67; HPLC t_R = 18.7 min; $[\alpha]^{22}_D$ = −70.8° (c = 3.25, MeOH).

6b (polar): R_f = 0.12 (1:3 petroleum ether–ether); ^1H NMR δ 1.24 (t, J = 7.0 Hz, 3 H), 1.91–2.11 (m, 3 H), 2.14–2.25 (m, 1 H), 2.29 (d, J = 15.6 Hz, 3 H), 3.40–3.52 (m, 2 H), 4.15 (q, J = 7.0 and 5.7 Hz, 2 H), 4.37–4.42 (m, 1 H), 7.42 (d, J = 9.2 Hz, 2 H), 8.21 (d, J = 9.2 Hz, 2 H); ^{13}C NMR δ 12.0 (d, J = 3.9 Hz), 14.1, 25.05 (d, J = 8.6 Hz), 31.4 (d, J = 8.2 Hz), 47.6 (d, J = 5.1 Hz), 60.5, 61.2, 121.2 (d, J = 5.3 Hz), 125.5, 144.7, 155.6 (d, J = 8.1 Hz), 173.0; ^{31}P NMR δ 30.46; HPLC t_R = 19.9 min; $[\alpha]^{22}_D$ = −49.7° (c = 1.35, MeOH).

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