^{31}P NMR (acetone-d_3, no decoupling) δ 26.6 (tq, J_{PH} = 9.1, 15.5).

B. Hydrolysis of *N*-(Methoxy(methyl)phosphinyl)-L-phenylalanine, Sodium Salt (13), To Give 11. *N*-(Methoxy(methyl)phosphinyl)-L-phenylalanine methyl ester **4** (4.9 mg, 0.018 mmol) was combined with 0.30 mL of D_2O and 10 μL (0.020 mmol) of 2.0 M NaOD in D_2O. After 15 min at 21 °C, the reaction mixture was diluted with 0.39 mL of D_2O and the ^1H NMR spectrum showed the presence of only methanol and **13**. A 0.10-mL (0.20 mmol) aliquot of 2.0 M NaOD in D_2O was added and the 250-MHz ^1H NMR spectrum was recorded at intervals. The initial rate of hydrolysis of **13** to give **11** was 8.1×10^{-5} M^{-1} s^{-1}.

C. Hydrolysis of *N*-(Methoxy(methyl)phosphinyl)-L-phenylalanine Amide (12) To Give 9. A 4.9-mg (0.019 mmol) sample of **12** was dissolved in 0.64 mL of D_2O, 10 μL (0.020 mmol) of 2 M NaOD in D_2O was added, and the 90-MHz ^1H NMR spectrum was recorded at 1-min intervals. The hydrolysis of **12** proceeded at a rate of 0.44 M^{-1} s^{-1} to give **9**.

***N*-(Methoxy(methyl)phosphinyl)-L-phenylalanine, Sodium Salt (13).** A solution of 8.1 mg (0.030 mmol) of *N*-(methoxy(methyl)phosphinyl)-L-phenylalanine methyl ester (**4**) in 2.1 mL of acetone/water (11:1) was treated with 35 μL (0.036 mmol) of 1.03 M NaOH. After 1.5 h at 21 °C, the solvent was removed at reduced pressure to give an oily residue: 250-MHz ^1H NMR see below for **13**R_P and **13**S_P. 63.1-MHz ^{13}C NMR (CD_3OD) δ 10.28 (d, J_{CP} = 133.1), 10.61 (d, J_{CP} = 133.0), 40.46 (d, J_{CP} = 8.1), 40.58 (d, J_{CP} = 7.4), 48.46 (d, J_{CP} = 6.7), 48.87 (d, J_{CP} = 6.7), 57.8, 58.1, 125.4, 127.3, 129.0, 138.4, 138.53, 178.36, 178.53.

Under the same conditions, saponification of **4**R_P (18:1 ratio of diastereomers) gave **13**R_P (12:1 ratio): 250-MHz ^1H NMR (CD_3OD) δ 0.91 (d, 3, J = 17.0), 2.69 and 3.13 (AB of ABXP, 2, J_{AB} = 13.3, $J_{AX} \approx 9.7$, $J_{BX} \approx J_{BP} \approx 3.2$), 3.43 (d, 3, J = 11.4), 3.64 (ddd, X of ABXP, 1, J_{HP} = 9.8, J_{HH} = 3.8, 9.8), 7.1–7.35 (m, 5); ^{31}P NMR (CD_3OD) δ 38.72.

Saponification of **4**S_P (5.9:1 ratio of diastereomers) gave **13**S_P (5.7:1 ratio): 250-MHz ^1H NMR (CD_3OD) δ 1.22 (d, 3, J = 16.8), 2.70 and 3.13 (AB of ABXP, 2, J_{AB} = 13.4, $J_{AX} \approx 9.6$, $J_{BX} \approx J_{BP} \approx 3.2$), 3.11 (d, 3, J = 11.3), 3.67 (ddd, X of ABXP, 1, J_{HP} = 9.6, J_{HH} = 4.1, 9.6), 7.1–7.35 (m, 5); ^{31}P NMR (CD_3OD) δ 37.78.

Hydrogenolysis of *N*-(Amino(methyl)phosphinyl)-L-phenylalanine Benzyl Ester (8). A. In H_2O/Acetone. A 35-μL aliquot of a solution of 21 mg (0.12 mmol) of K_2HPO_4 in 0.35 mL of H_2O/acetone (2:1) was added to 1.4 mg (0.0042 mmol) of **8** and 0.4 mg of 5% palladium on charcoal in a small vial. Hydrogen gas (1 atm) was introduced through a cannula and the reaction mixture was shaken for 45 min at 21 °C. After dilution with 0.5 mL of D_2O and filtration, only acetone and *N*-(hydroxy(methyl)phosphinyl)-L-phenylalanine, dipotassium salt (**11**), were observed by 250-MHz ^1H NMR spectroscopy.

B. In Methanol. A 35-μL aliquot of a solution of 12.7 mg (0.126 mmol) of *N*-methylmorpholine in 0.35 mL of anhydrous methanol was added to 2.0 mg (6.0 μmol) of **8** and 0.4 mg of 5% palladium on charcoal in a small vial. Hydrogen gas (1 atm) was introduced through a cannula and the reaction mixture was shaken at 21 °C for 30 min. After dilution with 0.4 mL of methanol-d_4 and filtration, only toluene, *N*-methylmorpholine, and *N*-(methoxy(methyl)phosphinyl)-L-phenylalanine, ammonium salt (**13**), were observed by 250-MHz ^1H NMR spectroscopy. Addition of 5 μL (10 μmol) of 2.0 M NaOD in D_2O followed by evaporation of the solvent gave a material identical by 250-MHz ^1H NMR spectroscopy in both methanol-d_4 and D_2O with the sodium salt **13** obtained by partial saponification of **4** (see above). Under the same conditions, hydrogenolysis of **8**S_P (>200:1 ratio of diastereomers) gave **13**S_P (>57:1 ratio) and hydrogenolysis of **8**R_P (5.2:1 ratio) gave **13**R_P (5.2:1 ratio).

Acknowledgment. Support for this research was provided by a grant from the National Institutes of Health (CA-22747). We would also like to express our appreciation to one of the referees for this paper, who pointed out some earlier work that we had overlooked.

Registry No. 1, 80556-17-8; **2**, 84558-47-4; **3**, 84558-48-5; **4** (isomer 1), 84558-46-3; **4** (isomer 2), 84558-49-6; **5** (isomer 1), 84558-49-6; **6**, 84558-51-0; **7** (isomer 1), 84558-52-1; **7** (isomer 2), 84558-53-2; **8** (isomer 1), 84621-23-8; **8** (isomer 2), 84621-24-9; **9**·Et_3N, 84621-25-0; **9**·Na, 84621-26-1; **10** (isomer 1), 84621-27-2; **10** (isomer 2), 84621-28-3; **11**·2(Et_3N), 84558-54-3; **11**·2Na, 84558-45-2; **12** (isomer 1), 84680-11-5; **12** (isomer 2), 84680-12-6; **13** (isomer 1), 84621-29-4; **13** (isomer 2), 84621-30-7; **14**, 84558-55-4; **16** (isomer 1), 84558-56-5; **16** (isomer 2), 84558-57-6; dimethyl methylphosphonate, 756-79-6; L-phenylalanine methyl ester, 2577-90-4; L-phenylalanine benzyl ester *p*-tosylate, 1738-78-9; methyl methylphosphonochloridate, 1066-52-0; L-phenylalanine amide, 5241-58-7; benzylamine, 100-46-9; **5** (isomer 2), 84558-58-7.

Cyclic Phosphonic–Carboxylic Imides and Anhydrides as Reactive Intermediates. 2. Solvolysis of *N*-(Hydroxy(methyl)phosphinothioyl)-L-phenylalanine Derivatives

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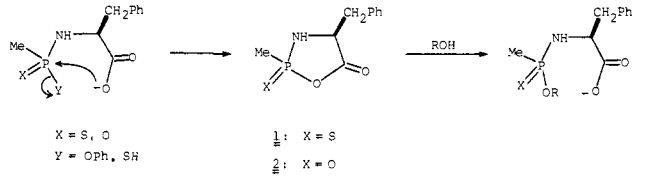
Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received August 5, 1982*

Abstract: Kinetic and stereochemical evidence is presented for the intermediacy of cyclic anhydrides Me-P(X)-L-Phe·O, **1** (X = S) and **2** (X = O), respectively, in the displacement of phenoxide from the phenyl ester **12** and H_2S from the dianion **10**. These substitution reactions both proceed with retention of configuration at phosphorus, indicating a clean, double inversion mechanism. In contrast, cleavage of the related methyl ester **11** takes place by direct attack of hydroxide on phosphorus in a simple inversion process. Analysis of the rates of appearance and disappearance of **12** during the course of alkaline hydrolysis of the diester precursor **5** indicates that the cyclic anhydride **1** is formed reversibly and that the relative rates at which it reacts with hydroxide, phenoxide, and water are 1.4×10^4, 7.6×10^3, and 1, respectively, at 22 °C.

In a continuation of our investigation of phosphonamidate peptide analogues as inhibitors of carboxypeptidase A,[1] we needed the diastereomers of phosphonamidothioates **10**R_P and **10**S_P (Scheme IV) in pure form. The hydrolytic behavior of these compounds and their precursors implicated the cyclic anhydrides **1** and **2** (Scheme I) as intermediates in a number of transformations, in analogy with our observations with the oxo derivatives described in the preceding paper.[2] For example, the diastereomers

Scheme I



(1) Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654. Jacobsen, N. E.; Bartlett, P. A. In "Phosphorus Chemistry"; Quin, L. D., Verkade, J., Eds.; American Chemical Society: Washington, DC; ACS Symp. Ser. No. 171, p 221.

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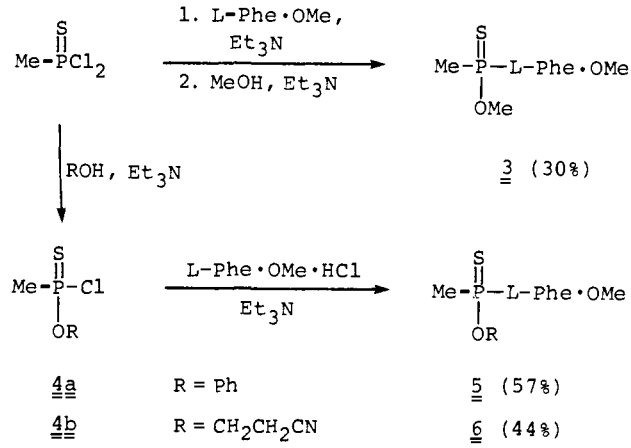
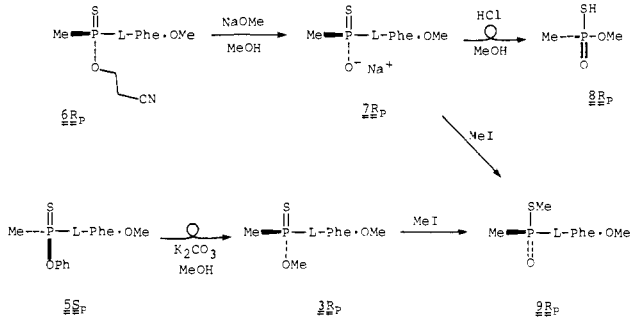
Scheme II



Scheme III



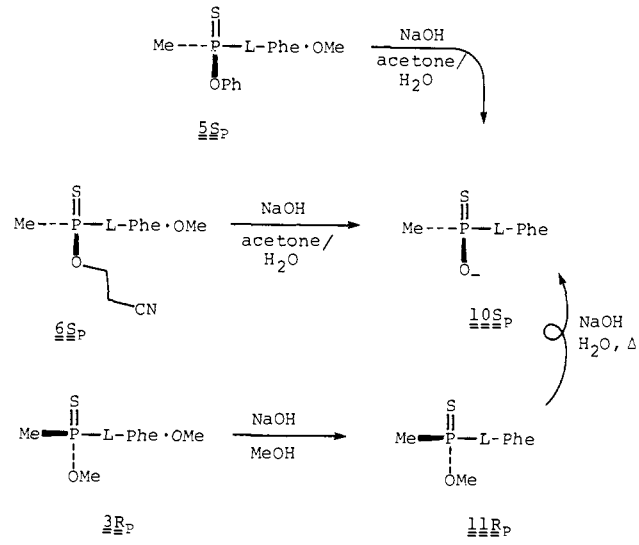
of **10** are prone to hydrolytic loss of sulfur at neutral pH, in contrast to the corresponding methyl esters **7** (Scheme VI). Moreover, hydrolysis of the phenyl esters **5** takes a different stereochemical course than hydrolysis of the methyl esters **3** (Scheme III). In this paper we present both stereochemical and kinetic evidence for the intermediacy of **1** and **2** in the reactions of *N*-(hydroxy(methyl)phosphinothioyl)-L-phenylalanine derivatives. The stereochemical consequences of reactions at the phosphorus center are readily discerned because of the incorporation of the chiral amino acid moiety, as indicated in the preceding paper.[2] With the thiophosphoryl group, the stereochemistry of hydrolysis itself can be readily investigated, because cleavage of the phosphorus ester does not destroy the chirality at that center. Furthermore, chemical correlation with simple phosphonothioic acid derivatives enables the absolute configuration to be determined.

Results

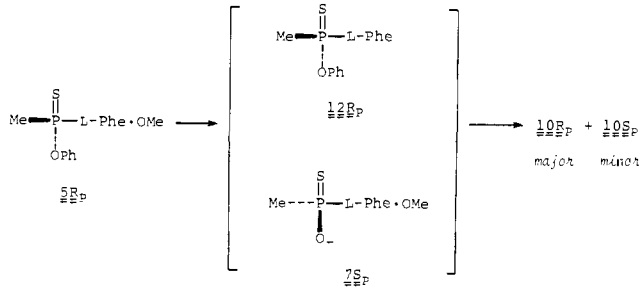
Synthesis of Diastereomeric Phosphonamidothioates. The methyl ester **3** was prepared by sequential addition of L-phenylalanine methyl ester and methanol to methylphosphonothioic dichloride (Scheme II). The phenyl ester **5** and cyanoethyl ester **6** were prepared by the reverse order of addition, with isolation and purification of the intermediate chloridates (**4**).[3a] The diastereomers of esters **3**, **5**, and **6** were separated by HPLC, the phenyl esters **5** being the easiest and the methyl esters **3** the hardest to resolve.

Determination of Absolute Configuration. The absolute configuration at phosphorus[3b] was determined for these esters by the chemical correlations depicted in Scheme III. Removal of the cyanoethyl group from the more polar diastereomer of **6** followed by acid-catalyzed methanolysis of the P–N linkage gives one of the enantiomers of *O*-methyl methylphosphonothioic acid (**8**). This material was shown to be greater than 95% the R_P enantiomer by the method of Mikolajczyk and Omelanczuk,[4] involving examination of the (−)-α-phenylethylamine salt by ^{1}H NMR spectroscopy. Since cleavage of the cyanoethyl ester does not alter the configuration at phosphorus and methanolysis of the acyclic phosphonothioamide bond is expected to occur with inversion of configuration, the more polar diastereomer of **6** and its elimination product ($7R_P$) must therefore have the R_P configuration at phosphorus.

Scheme IV



Scheme V



Methylation of $7R_P$ leads to the same *S*-methyl ester ($9R_P$) obtained from the Pitshchimuka rearrangement[5] of the less polar diastereomer of methyl ester **3**, indicating that the latter has the R_P configuration. Alkaline methanolysis of the more polar diastereomer of phenyl ester **5** gives $3R_P$ (stereoselectivity better than 85%). With the assumption that this ester exchange occurs with inversion, the configuration of the more polar phenyl ester diastereomer is established as S_P (Scheme III).

Alkaline hydrolysis of cyanoethyl ester $6S_P$ gives disodium salt $10S_P$ and acrylonitrile (Scheme IV). For the dimethyl esters **3**, the two hydrolytic steps clearly take place sequentially; loss of the carboxylic ester is rapid in NaOH/MeOH at room temperature, while cleavage of the phosphorus ester requires prolonged heating in aqueous NaOH. As indicated in Scheme IV, dianion $10S_P$ is obtained on hydrolysis of the dimethyl ester $3R_P$ (stereoselectivity better than 95%), indicating that this displacement occurs cleanly with inversion at phosphorus.

(2) Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1983**, *105* (preceding paper in this issue).

(3) (a) If **4b** is carried on to **6** without purification, the side product resulting from the addition of 2 mol of phenylalanine methyl ester to methylphosphonothioic dichloride is very difficult to separate from **6**. (b) For all phosphonamidothioate esters discussed in this paper (i.e., **3**, **5**, **6**, **11**, and **12**), the R_P isomer resonates at higher field in the ^{31}P NMR spectrum. This extends the correlation noted in the preceding paper[2] for the phosphonamidates, since the R_P isomers of this series correspond to the S_P isomers of the present series.

(4) Mikolajczyk, M.; Omelanczuk, J. *Tetrahedron Lett.* **1972**, 1539 (1972).

(5) Kabachnik, M. I.; Mastryukova, T. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1953**, 163; *Chem. Abstr.* **1954**, *48*, 3243. Kabachnik, M. I.; Mastryukova, T. A.; Kurochin, N. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1956**, 193; *Bull Acad. Sci., USSR Div. Chem. Sci. (Engl. Transl.)* **1956**, 185; *Chem. Abstr.* **1956**, *50*, 13727.

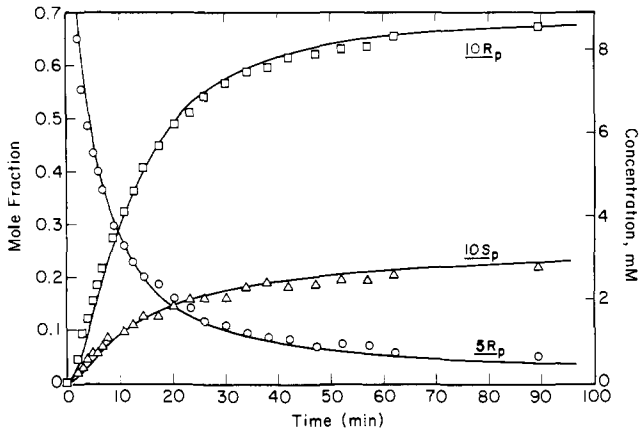


Figure 1. Time course of hydrolysis of $5R_P$ (see Experimental Section for details). Mole fraction of starting diester $5R_P$ (○), major product $10R$ (□), and minor product $10S_P$ (△) were determined by ^1H NMR peak heights. Curves were generated by computer simulation of Scheme VIII, using an iteration interval of 0.1 min and the following values for the rate constants: $k_1 = 0.0574\ M^{-1}\ s^{-1}$, $k_2 = 0.0235\ M^{-1}\ s^{-1}$, $k_3 = 0.00258\ s^{-1}$, $k_{-3} = 3.66\ M^{-1}\ s^{-1}$, $k_4 = 0.0617\ M^{-1}\ s^{-1}$, $k_5 = 6.58\ M^{-1}\ s^{-1}$, $k_w = 0.00891\ s^{-1}$. *Note*: only the relative values of k_{-3}, k_5, and k_w can be determined; increasing them all by the same factor serves only to decrease the steady-state concentration of $1S_P$, which so far has not been directly observable. By use of the rate constants given here, the mole fraction of $1S_P$ is predicted to reach a maximum of 0.004.

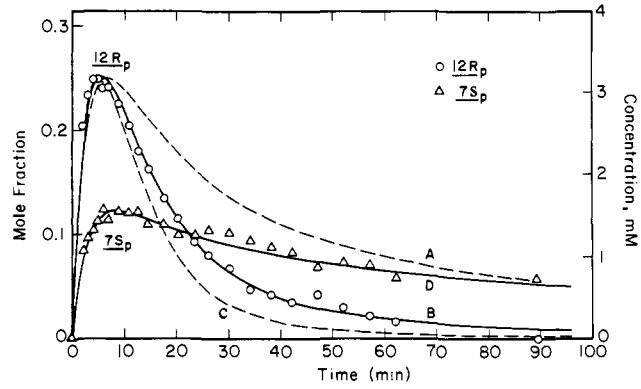


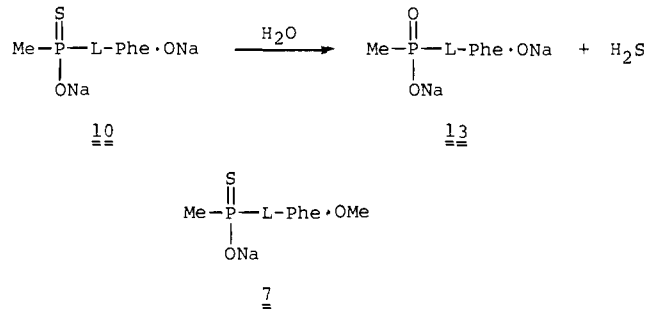
Figure 2. Time course of build-up and decay of the major intermediate $12R_P$ (○) and the minor intermediate $7S_P$ (△) in the hydrolysis of $5R_P$ (for details see Experimental Section). Curves were generated by computer simulation as for Figure 1, using either the full kinetic scheme (curves B and D), the full kinetic scheme with $k_{-3} = 0$ (curve C), or a simplified scheme in which it is assumed that $12R_P$ is hydrolyzed directly to give $10R_P$ with a second-order rate constant $k_3 = 0.0885\ M^{-1}\ s^{-1}$ (curve A).

The sequence of interconversions depicted in Scheme IV was carried out starting with the other diastereomers ($3S_P$, $5R_P$, and $6R_P$) as well, providing further confirmation of the configurational assignments.

Mechanism and Stereochemistry of Phenyl Ester Cleavage. In contrast to the methyl esters **3**, hydrolysis of the phenyl esters **5** with NaOH in aqueous acetone is rapid: the $5S_P$ diastereomer affords dianion $10S_P$ with 6.8:1 stereoselectivity, and $5R_P$ gives $10R_P$ (2.4:1 ratio). These hydrolyses therefore take place with predominant *retention* of configuration at phosphorus.

Since it is the least stereoselective, we studied the hydrolysis of phenyl ester $5R_P$ first, following the reaction by ^1H NMR and ^{31}P NMR spectroscopy (Figures 1 and 2, Scheme V). In addition to starting material and the products $10R_P$ and $10S_P$, two intermediates can be observed. The minor intermediate is assigned structure $7S_P$ by comparison with an authentic sample prepared from $6S_P$ (Scheme III). The major intermediate shows a coupling constant $^2J_{P\text{-}CH_3} = 15.0$ Hz and ^{31}P chemical shift δ 84.1, characteristic of intact phosphonamidothioic esters ($^2J_{P\text{-}CH_3} = 15.2$–$15.5$ Hz, δ 82–87) and significantly different from those observed for the phosphonamidothioate salts ($^2J_{P\text{-}CH_3} = 14.0$–$14.2$ Hz, δ 62–65)

Scheme VI



Scheme VII

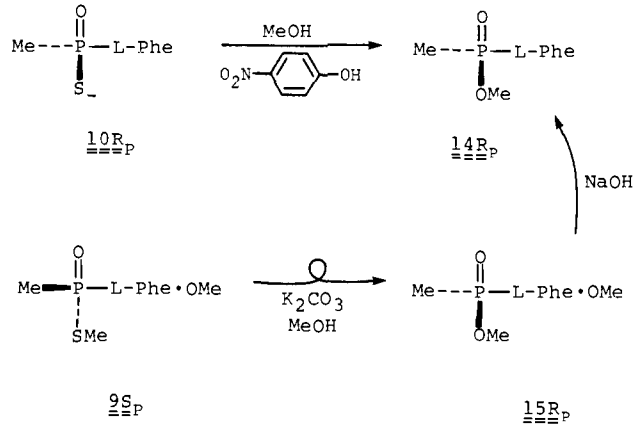


Table I. Rate of Desulfurization of Phosphonamidothioates, $K_{app} \times 10^4\ s^{-1}$ [a]

conditions[b]	substrate		
	$10S_P$	$10R_P$	7[c]
0.010 M NaOH	<0.01	0.02	
buffer, pH 10.5	<0.1	0.13	0.02
buffer, pH 8.5	0.27	1.04	<0.005
buffer, pH 7.5	3.09	9.39	<0.004
buffer, pH 6.0	56.4	151	<0.004
buffer, pH 4.0			0.05

[a] Pseudo-first-order rate constants. [b] 10% D_2O by volume, 22 °C; see Experimental Section for details. [c] Product(s) of decomposition of 7 not determined.

(see Experimental Section). The major intermediate is therefore $12R_P$. Consistent with Scheme V is the fact that there is a direct correlation between the mole fraction of methanol present ([MeOH]) and the sum of $[12R_P]$, $[10R_P]$, and $[10S_P]$, as well as between [phenol] and the sum of $[7S_P]$, $[10R_P]$, and $[10S_P]$ throughout the hydrolysis. It is also important to note that the ratio $([12R_P] + [10R_P])/([7S_P] + [10S_P])$ remains constant at 2.44 throughout the reaction.

Similar results are obtained with the diester $5S_P$, except that the steady-state concentration of the minor intermediate $7R_P$ is lower. For example, whereas the mole fraction of $7S_P$ reaches a maximum of 0.12 in the hydrolysis of $5R_P$ (Figure 2), for the isomer $5S_P$, $[7R_P]$ is never more than 0.07. This is consistent with the greater stereoselectivity of the latter hydrolysis (ratio of $([12S_P] + [10S_P])/([7R_P] + [10R_P]) = 6.8$).

Quenching the remaining hydroxide ion with excess phenol in the midst of the alkaline hydrolysis of $5R_P$ stops all processes except the conversion of $12R_P$ to $10R_P$. This goes to completion, albeit at a reduced rate (Figure 3).

Desulfurization. The dianions **10** are stable in aqueous solution at high pH, but are hydrolyzed at neutral pH to give H_2S and the oxo anion **13**[2] (Scheme VI). The pseudo-first-order rate constants for the decomposition of $10R_P$ and $10S_P$ in aqueous solution, as determined by ^{31}P NMR spectroscopy, are presented in Table I, along with the corresponding rate constants for the

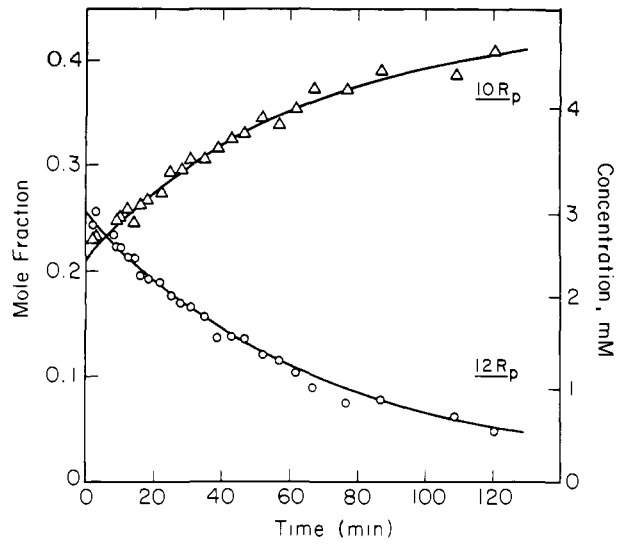
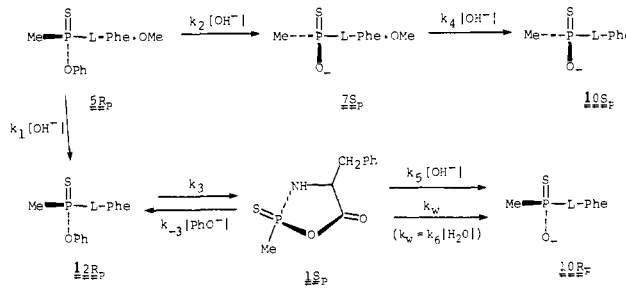


Figure 3. Time course of the conversion of the major intermediate **12**R_P (○) to the major product **10**R_P (△) following the addition of phenol to the reaction mixture of the hydrolysis of **5**R_P (for details, see Experimental Section). The mole fractions of **5**R_P, **7**S_P, and **10**S_P were unchanged during this time. The curves were generated by using the full kinetic scheme (as in Figure 1) but allowing for desulfurization of the products **10**. This process, which is significant after addition of phenol, was modeled by using the pseudo-first-order rate constants 7.65×10^{-6} s^{-1} and 2.55×10^{-6} s^{-1} for the desulfurization of **10**R_P and **10**S_P, respectively (see Table I). Consistent with the experimental data, the computer model predicts no significant change in the concentrations of **5**R_P, **7**S_P, and **10**S_P.

Scheme VIII



decomposition of the monoanion methyl esters **7**.

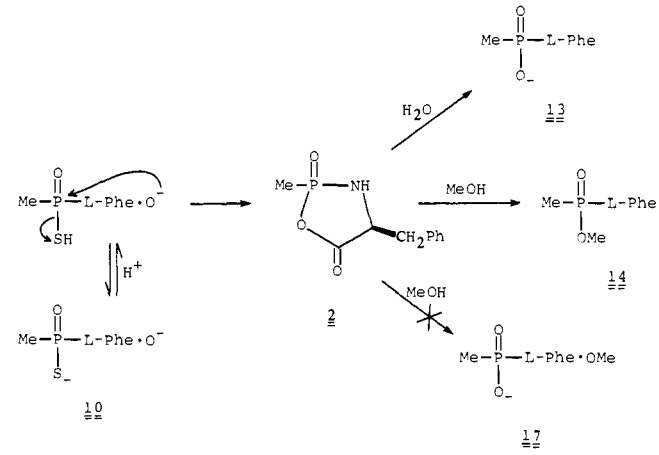
The dianions **10** are stable in methanol, but the addition of *p*-nitrophenol leads to rapid loss of H_2S with formation of the methyl esters **14**[2] (Scheme VII). This reaction was shown to proceed with retention of configuration at phosphorus by the correlations in Scheme VII. Alkaline methanolysis of thiol ester **9**S_P, followed by partial hydrolysis of the inverted diester **15**R_P, gives the same diastereomer obtained from the acid-catalyzed methanolysis of dianion **10**R_P. As described above for the transformations depicted in Scheme IV, these stereochemical correlations were performed in the diastereomeric series as well, starting with **9**R_P and **10**S_P.

Discussion

Mechanism of Phenyl Ester Hydrolysis. Our initial stereochemical studies on the hydrolysis of each of the phenyl esters **5** suggested that the carboxyl ester is cleaved first. This step is followed by cyclization to mixed anhydride **1**, which in turn rapidly undergoes P–O bond cleavage to give **10** with overall retention at phosphorus (Scheme VIII; illustrated for the **5**R_P diastereomer). We postulated that the minor, inverted product arises from initial attack of hydroxide directly on phosphorus to give **7** with inversion.

Although intermediates **7** and **12** accumulate and are readily observed by ^1H and ^{31}P NMR spectroscopy, the cyclic anhydride is never present at levels high enough to be detected by this technique. Nevertheless, the mechanism in Scheme VIII was confirmed by observing the progress of the overall reaction. The initial cleavage step is completely stereospecific: **5**R_P gives only **12**R_P and **7**S_P, and **5**S_P gives only **12**S_P and **7**R_P. Moreover, the fact that, for **5**R_P, the ratio $([\mathbf{12}R_P] + [\mathbf{10}R_P])/([\mathbf{7}S_P] + [\mathbf{10}S_P])$ remains constant throughout the reaction, even as the relative amounts of **12**R_P and **7**S_P change, indicates that the second cleavage step to give **10** is stereospecific in both cases. The same relationships hold true for hydrolysis of the **5**S_P isomer as well.

Scheme IX



In contrast to displacement of phenoxide from diester **5**, which occurs with inversion of configuration at phosphorus (e.g., **5**S_P → **7**R_P), hydrolysis of the major intermediate **12** to give dianion **10** proceeds with retention. The hydrolysis of **12** is kinetically anomalous as well. Knowing the rate at which **5** is consumed, the ratio with which **5** partitions to **7** and **12**, and the maximum concentration of **12** that accumulates during the course of the hydrolysis reaction, it is possible to predict the time course of the disappearance of **12** on the basis of various kinetic models. As the curves in Figure 2 indicate, hydrolysis of **12** takes place much faster than expected for direct, bimolecular displacement of phenoxide by hydroxide (curve A) but more slowly than predicted for a rate-limiting, irreversible cyclization (curve C). The full kinetic scheme (Scheme VIII), including reversibility of the cyclization step, is required to account for the observed rate of conversion of **12** to **10** (Figure 2, curve B).

In contrast, the conversion of the minor intermediate (**7**) to **10** is consistent with a simple displacement by hydroxide (Figure 2, curve D). This difference is even more dramatic after neutralization of the remaining hydroxide with phenol: hydrolysis of diester **5** and anion ester **7** ceases, but ester anion **12** continues to be converted to dianion **10**, giving exclusively the isomer resulting from retention (Figure 3). This confirms the stereospecificity of the final cleavage step and demonstrates the unique kinetic behavior of intermediate **12**. Hydrolysis of **12** continues even at very low concentrations of hydroxide, primarily because cyclization gives an intermediate (**1**) which is sufficiently reactive to be cleaved by water.

Examination of the rate constants obtained from the data in Figures 1–3 shows that **1** reacts with hydroxide, phenoxide, and water with relative rates of 1.4×10^4, 7.6×10^3, and 1, respectively. For comparison, the acyclic phosphonate ester dimethyl ethylphosphonate[6] and the cyclic carboxylic anhydride succinic anhydride[7] react 2.5×10^7 times and 3.1×10^8 times faster with hydroxide than water, respectively. The cyclic phosphonothioic carboxylic anhydride **1** is therefore considerably less selective, in keeping with the extraordinarily high reactivity of related five-membered cyclic phosphorus esters.[8]

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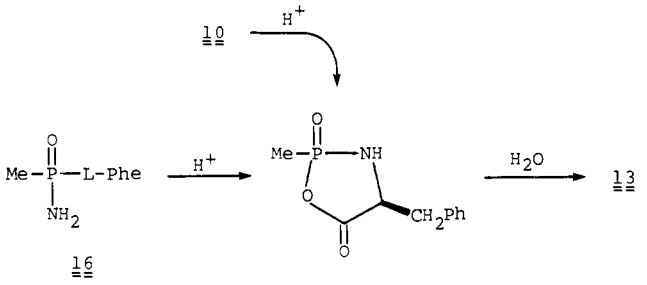
Scheme X



In contrast to the intramolecular mechanism for phenyl ester cleavage, hydrolysis of the corresponding methyl esters **11** involves intermolecular attack of hydroxide, with clean inversion of configuration. This result is logical in that methoxide is a significantly poorer leaving group than phenoxide and the weakly nucleophilic carboxylate is unable to displace it, even intramolecularly.

Desulfurization. Both our kinetic results (Table I) and stereochemical observations on the loss of sulfur from the dianions **10** require that these reactions also proceed via cyclic anhydride **2** (Scheme IX). The most compelling evidence is the fact that methanolysis occurs with retention of configuration at phosphorus and that desulfurization of the dianions is much faster than for the monoesters **7**. Loss of sulfur from the dianions **10** is therefore strictly analogous to the loss of ammonia from the related diamides **16** described in the preceding paper.[2] As before, none of the alternative anhydride cleavage product **17** was observed, confirming that **2** undergoes ring opening exclusively at phosphorus. The strong dependence of the rate of desulfurization on pH suggests that, as for the diamide **16**, protonation of the leaving group precedes or accompanies cyclization.

In further analogy to the hydrolysis of diamide **16**, the rate of desulfurization of the dianions **10** depends on the relative configuration of the two chiral centers: the reaction of $\mathbf{10}R_P$ via $\mathbf{2}S_P$ occurs about 3 times faster than $\mathbf{10}S_P$ loses sulfur via $\mathbf{2}R_P$ (Scheme X). This corresponds both in magnitude and stereochemical sense to the behavior observed with the diamides **16**, which decompose via the same intermediate (**2**), and we would advance arguments similar to those presented in the preceding paper to rationalize this phenomenon.[2]

Conclusion

Intramolecular nucleophilic catalysis by a neighboring carboxyl or hydroxyl group is a general phenomenon in the cleavage of phosphate esters.[9-11] As we have described here and in the preceding paper,[2] this mechanism extends to displacement of a variety of phosphorus substituents (phenoxide, HS^-, and NH_3) from L-phenylalanine phosphonamidate and -amidothioate derivatives. While previous studies of assisted displacement at phosphorus have focused on the kinetic properties of the reaction, for our substrates we were able to demonstrate unambiguously that the substitutions at phosphorus that proceed with intramolecular catalysis occur with the opposite stereochemistry than those which involve direct displacement. The sequence of interconversions is self-consistent if each individual step involving displacement at phosphorus proceeds with inversion of configuration. Any alternative stereochemical interpretation would appear to be extremely unlikely.

The classic demonstration by Westheimer of the existence of pseudorotation in phosphate ester hydrolysis involved five-membered ring cyclic phosphates.[8] However, the information available on the analogous cyclic esters, 1,3,2-oxazaphospholidine 2-oxides and 2-sulfides, indicates that ring opening by hydroxylic nucleophiles occurs with predominant inversion of configuration, without significant intervention of pseudorotation steps.[12] Our results, which indicate that the transiently formed cyclic anhydrides **1** and **2** (derivatives of 1,3,2-oxazaphospholidin-5-one 2-oxide and 2-sulfide, respectively) are also cleaved with inversion of configuration, are fully consistent with these observations. In our systems, the greater leaving group ability of the carboxylate anion precludes any of the P–N cleavage seen in previous studies of 1,3,2-oxazaphospholidine ring-opening reactions[12] and may account for the greater stereospecificity we observe as well.

Experimental Section

General Information. Ethanol-free chloroform was prepared as described in the preceding paper; reference standards for NMR spectroscopy and data presentation are also as reported in the preceding paper. ^1H NMR spectra were measured at 250 MHz unless otherwise indicated; spectra measured in acetone-d_6/D_2O (2:1 ratio) are referenced to residual CHD_2COCD_3 as 2.17 ppm. ^{13}C NMR spectra were acquired at 63.1 MHz unless otherwise indicated; spectra acquired in methanol-d_4 are referenced to CD_3OD solvent at 49.0 ppm. ^{31}P NMR spectra were measured at 72.9 MHz; chemical shifts in acetone-d_6/D_2O (2:1 ratio) are referenced to 0.05% internal trimethyl phosphate as 3.76 ppm. In addition to the solutions previously described,[2] the following buffer solutions were employed: pH 6.0 MES/NaOH, 0.025 M containing 0.5 M NaCl; pH 4.0 Radiometer (Copenhagen) Type S1316.

***N*-(Methoxy(methyl)phosphinothioyl)-L-phenylalanine Methyl Ester (3).** A solution of 0.39 mmol of L-phenylalanine methyl ester and 0.07 mL (0.50 mmol) of triethylamine in 2 mL of chloroform was added to a solution of 57 mg (0.39 mmol) of methylphosphonothioic dichloride in 2 mL of chloroform at 0 °C. After the mixture was stirred for 3 min at 0 °C and 1.25 h at 21 °C, a solution of 0.07 mL (0.50 mmol) of triethylamine in 1.5 mL of methanol was added and the reaction mixture was stirred at 21 °C for 3 h. After evaporation of solvent at reduced pressure, the residue was suspended in 5 mL of ether and filtered, and the filtrate was concentrated at reduced pressure and purified by preparative TLC on silica gel (ethyl acetate/hexane, 1:1) to give 33 mg (30% yield) of **3** as a syrup: ^1H NMR see below for $\mathbf{3}R_P$ and $\mathbf{3}S_P$; 25.1-MHz ^{13}C NMR ($CDCl_3$) δ 21.1 (d, J_{CP} = 107.3), 21.7 (d, J_{CP} = 107.4), 40.5 (d, J_{CP} = 5.8), 50.4 (d, J_{CP} = 7.1), 52.0, 56.1, 56.4, 126.9, 128.4, 129.3, 136.2, 173.2; ^{31}P NMR see below; IR (thin film) 3315, 2960, 1735, 1430, 1310, 1185, 1140, 910 cm^{-1}; HPLC (silica gel, ethyl acetate/hexane, 1:9), retention time in column volumes, 4.6 ($\mathbf{3}R_P$) and 4.8 ($\mathbf{3}S_P$); an analytical sample was obtained by bulb-to-bulb distillation (135 °C (0.15 torr)). Anal. ($C_{12}H_{18}NO_3PS$) C, H, N, P, S.

Separation of diastereomers by HPLC (silica gel, ethyl acetate/hexane, 1:19) gave pure $\mathbf{3}R_p$ as the first fraction and predominantly $\mathbf{3}S_p$ as the second fraction (2:1 ratio of diastereomers).

$\mathbf{3}R_P$: ^1H NMR ($CDCl_3$) δ 1.62 (d, 3, J = 15.2), 2.92 and 3.09 (AB of ABX, 2, J_{AB} = 13.6, $J_{AX} \approx$ 7.5, $J_{BX} \approx$ 5.5), 3.16 (br t, 1, J = 11), 3.34 (d, 3, J = 14.1), 3.74 (s, 3), 4.36 (dddd, 1, X of ABX, J_{HH} = 5.5, 7.5, 11.1, J_{PH} = 11.1), 7.1–7.4 (m, 5); ^{31}P NMR ($CDCl_3$) δ 85.78.

$\mathbf{3}S_P$: ^1H NMR ($CDCl_3$) δ 1.52 (d, 3, J = 15.2), 2.91 and 3.09 (AB of ABX, 2, J_{AB} = 13.7, $J_{AX} \approx$ 7.6, $J_{BX} \approx$ 4.8), 3.28 (dd, 1, J = 11, 7.7), 3.43 (d, 3, J = 14.1), 3.75 (s, 3), 4.26 (dddd, 1, X of ABX, J_{HH} = 4.8, 7.6, 11.3, J_{PH} = 11.3), 7.1–7.4 (m, 5); ^{31}P NMR ($CDCl_3$) δ 86.47.

***O*-Phenyl Methylphosphonochlorothioate (4a).** A solution of 0.64 g of phenol (6.8 mmol) in 3 mL of anhydrous ether was added slowly to a solution of 1.0 g (6.8 mmol) of methylphosphonothioic dichloride and 0.94 mL (6.7 mmol) of triethylamine in 3 mL of ether at 10 °C. After stirring for 2 h at 10 °C and 26 h at 21 °C, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure and bulb-to-bulb distilled (150 °C (0.13 torr)) to give 1.19 g (77% yield, based on 90% purity) of a colorless oil consisting of **4a** and diphenyl methylphosphonothioate in a ratio of 9:1 (w/w). 90-MHz ^1H NMR ($CDCl_3$) δ 2.47 (d, 3, J = 16.3), 7.1–7.5 (m, 5) (lit.[13] δ(P–CH_3) 2.26).

***O*-(2-Cyanoethyl) Methylphosphonochlorothioate (4b).** A solution of 142 mg (0.95 mmol) of methylphosphonothioic dichloride in 1.1 mL of chloroform was cooled to 0 °C, treated with 0.15 mL (0.95 mmol) of triethylamine and 68 mg (0.95 mmol) of 3-hydroxypropanenitrile, and warmed to 21 °C over a period of 3 h. After stirring for 2.5 h at 21 °C, the reaction mixture was diluted to 10 mL with chloroform, washed with 10 mL of 2 M H_2SO_4, dried ($MgSO_4$), concentrated under reduced pressure, and bulb-to-bulb distilled (160–170 °C (0.06 torr)) to give 131 mg (57% yield based on 76% purity) of a colorless oil consisting of **4b** and bis(2-cyanoethyl) methylphosphonothionate in the ratio 3:1 (w/w). ^1H NMR ($CDCl_3$) δ 2.39 (d, 3, J = 15.4), 2.82 (t, 2, J = 6.2), 4.31 (ddt,

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1, J_{PH} = 10.6, J_{HH} = 10.6, 6.2), 4.52 (ddt, 1, J_{PH} = 12.5, J_{HH} = 10.5, 6.3).

N-(Methyl(phenoxy)phosphinothioyl)-L-phenylalanine Methyl Ester (5). A solution of 1.19 g of *O*-phenyl methylphosphonochlorothioate (**4a**; 5.2 mmol based on 90% purity) in 18 mL of chloroform was added to a solution of 2.17 mL (15.6 mmol) of triethylamine and 1.23 g (5.7 mmol) of L-phenylalanine methyl ester hydrochloride in 18 mL of chloroform at 0 °C. The reaction mixture was warmed to 21 °C and stirred for 18 h, diluted to 50 mL with chloroform, washed successively with 40 mL of 1 M H_2SO_4 and 40 mL of H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. Column chromatography on silica gel (ethyl acetate/hexane, 1:3), followed by concentration and bulb-to-bulb distillation (230 °C (0.1 torr)) of the major fraction gave 1.36 g (57% overall yield from methylphosphonothioic dichloride) of **5** as a syrup: HPLC (silica gel, ethyl acetate/hexane, 1:9), retention time in column volumes, 3.6 (**5**R_P) and 4.4 (**5**S_P). The two diastereomers were separated by preparative HPLC (silica gel, ethyl acetate/hexane, 1:9).

5R_P: ^{1}H NMR ($CDCl_3$) δ 1.84 (d, 3, J = 15.1), 3.01 (AB of ABX, 2, J_{AB} = 14, $J_{AX} \approx$ 6.3, $J_{BX} \approx$ 6.1, $\Delta\delta \approx$ 0.01 ppm), 3.53 (t, 1, J = 10.3), 3.66 (s, 3), 4.52 (dddd, 1, X of ABX, J_{HH} = 10.3, 6.2, 6.2, J_{PH} = 12.4), 7.08–7.18 (m, 5), 7.24–7.34 (m, 5); 25.1-MHz ^{13}C NMR ($CDCl_3$, off-resonance ^{1}H-decoupled) δ 22.9 (dq, J_{CP} = 107.6), 40.6 (dt, J_{CP} = 4.6), 51.9 (q), 55.8 (d), 121.3 (dd, J_{CP} = 5.7), 124.7 (d), 126.9 (d), 128.4 (d), 129.1 (d), 129.4 (d), 135.8 (s), 150.6 (d, J_{CP} = 10.2), 172.8 (d, J_{CP} = 4.4); ^{31}P NMR ($CDCl_3$) δ 82.73. Anal. ($C_{17}H_{20}NO_3PS$) C, H, N, P, S.

5S_P: ^{1}H NMR ($CDCl_3$) δ 1.72 (d, 3, J = 15.1), 2.97 (AB of ABX, 2, J_{AB} = 13.3, $J_{AX} \approx$ 7.1, $J_{BX} \approx$ 5.4, $\Delta\delta \approx$ 0.02 ppm), 3.53 (dd, 1, J = 7.3, 10.5), 3.65 (s, 3), 4.39 (dddd, 1, X of ABX, J_{HH} = 11.2, 5.7, 5.7, J_{PH} = 11.2), 7.08–7.18 (m, 5), 7.24–7.34 (m, 5); 25.1-MHz ^{13}C NMR ($CDCl_3$) δ 22.6 (d, J_{CP} = 107.0), 40.7 (d, J_{CP} = 5.8), 52.1, 56.7, 121.2 (d, J_{CP} = 4.6), 124.7, 127.1, 128.6, 129.2, 129.4, 136.0, 150.7 (d, J_{CP} = 9.1), 172.9 (d, J_{CP} = 4.4); ^{31}P NMR ($CDCl_3$) δ 83.69. Anal. ($C_{17}H_{20}NO_3PS$) C, H, N, P, S.

N-((2-Cyanoethoxy)(methyl)phosphinothioyl)-L-phenylalanine Methyl Ester (6). A solution of 131 mg of *O*-(2-cyanoethyl) methylphosphonochlorothionate (**4b**; 0.54 mmol based on 76% purity) in 2 mL of chloroform was added to a solution of 0.23 mL (1.6 mmol) of triethylamine and 129 mg (0.60 mmol) of L-phenylalanine methyl ester hydrochloride in 2 mL of chloroform at 20 °C. After stirring for 3 h at 21 °C, the reaction mixture was diluted to 7 mL with chloroform, washed with 7 mL of 2 M H_2SO_4, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by preparative TLC (silica gel, ethyl acetate/hexane, 1:1) and bulb-to-bulb distillation (220 °C (0.1 torr)) of the major fraction gave 137 mg (44% overall yield from methylphosphonothioic dichloride) of **6** as a syrup: ^{1}H, ^{13}C, and ^{31}P NMR, see below for **6**R_P and **6**S_P. HPLC (silica gel, ethyl acetate/hexane, 3:17), retention time in column volumes, 7.0 (**6**S_P) and 7.8 (**6**R_P); IR (thin film) 3310, 2950, 2250, 1730, 1400–1450 cm^{-1}. Anal. ($C_{14}H_{19}N_2O_3PS$) C, H, N, P, S. The diastereomers **6**R_P and **6**S_P were separated by preparative HPLC (silica gel, ethyl acetate/hexane, 3:17 ratio).

6R_P: ^{1}H NMR ($CDCl_3$) δ 1.63 (d, 3, J = 15.3), 2.52 and 2.56 (AB of ABMX, 2, J_{AB} = 16.9, $J_{AX} \approx$ 5.9, $J_{AM} \approx$ 5.9, $J_{BX} \approx$ 6.0, $J_{BM} \approx$ 7.4), 2.88 and 3.13 (CD of CDY, 2, J_{CD} = 13.7, J_{CY} = 8.4, J_{DY} = 5.1, J_{DP} = 1.8), 3.20 (t, 1, J = 10.4), 3.48 (dddd, 1, M of ABMX, J_{HH} = 10.4, 7.4, 5.9, J_{PH} = 9.1), 3.77 (s, 3), 4.00 (dddd, 1, X of ABMX, J_{HH} = 10.2, 6.0, 6.0, J_{PH} = 10.2), 4.35 (dddd, 1, Y of CDY, J_{HH} = 11.2, 8.4, 5.1, J_{PH} = 11.2), 7.16–7.37 (m, 5); ^{13}C NMR ($CDCl_3$) δ 19.33 (d, J_{CP} = 8.7), 21.69 (d, J_{CP} = 106.9), 40.12 (d, J_{CP} = 6.4), 52.33, 56.28, 57.95 (d, J_{CP} = 6.5), 116.9, 127.0, 128.5, 129.4, 136.2, 173.1; ^{31}P NMR ($CDCl_3$) δ 85.76.

6S_P: ^{1}H NMR ($CDCl_3$) δ 1.57 (d, 3, J = 15.4), 2.48 and 2.56 (AB of ABMX, 2, J_AB = 17.0, $J_{AM} \approx$ 5.5, $J_{AX} \approx$ 5.5, $J_{BM} \approx$ 8.0, $J_{BX} \approx$ 5.7), 2.84 and 3.17 (CD of CDY, 2, J_{CD} = 13.7, J_{CY} = 9.0, J_{DY} = 4.6, J_{DP} = 2.0), 3.32 (dd, 1, J = 7.2, 10.9), 3.62 (dddd, 1, M of ABMX, J_{HH} = 10.4, 8.0, 5.5, J_{PH} = 9.5), 3.78 (s, 3), 3.97 (dddd, 1, X of ABMX, J_{HH} = 10.5, 5.5, 5.5, J_{PH} = 9.6), 4.32 (dddd, 1, Y of CDY, J_{HH} = 11.2, 9.0, 4.6, J_{PH} = 11.2), 7.18–7.38 (m, 5); ^{13}C NMR ($CDCl_3$) δ 19.35 (d, J_{CP} = 8.6), 21.16 (d, J_{CP} = 107.5), 40.22 (d, J_{CP} = 6.6), 52.46, 56.49, 58.09 (d, J_{CP} = 5.4), 116.9, 127.0, 128.5, 129.4, 136.2, 173.2; ^{31}P NMR ($CDCl_3$) δ 86.37.

(*R*$_P$)-N-(Methoxy(methyl)phosphinothioyl)-L-phenylalanine Methyl Ester (3*R*$_P$) by Methanolysis of 5*S*$_P$. A solution of 12.4 mg (0.036 mmol) of (S_P)-*N*-(methyl(phenoxy)phosphinothioyl)-L-phenylalanine methyl ester (**5**S_P; 17:1 ratio of diastereomers) in 0.87 mL of anhydrous methanol was stirred with 9.8 mg (0.071 mmol) of anhydrous K_2CO_3 for 1.45 h at 21 °C and applied directly to a preparative TLC plate (silica gel, ethyl acetate/hexane, 1:3) to give as the major fraction 9.7 mg (78% yield) of **3**R_P (4.6:1 ratio of diastereomers) as a syrup. In a similar manner, **5**R_P (single diastereomer) gave **3**S_P (5.6:1 ratio).

N-(Methyl(methylthio)phosphinyl)-L-phenylalanine Methyl Ester (9) by Rearrangement of 3. A solution of 74 mg (0.26 mmol) of *N*-(methoxy(methyl)phosphinothioyl)-L-phenylalanine methyl ester (**3**) in 4.5 mL of methyl iodide was heated at reflux for 24 h, solvent was evaporated at reduced pressure, and the residue was crystallized from 9 mL of ethyl acetate/hexane (2:1) to give 12.4 mg (17% yield) of white crystals consisting of nearly diastereomerically pure **9**S_P (65:1 ratio). Recrystallization (ethyl acetate/hexane, 1:1) gave fine white needles: mp 132–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (d, 3, J = 14.6), 2.15 (d, 3, J = 12.8), 3.08 and 3.11 (AB of ABX, 2, J_{AB} = 13.5, $J_{AX} \approx$ 6.1, $J_{BX} \approx$ 5.8), 3.32 (dd, 1, J = 11.0, 12.5), 3.73 (s, 3), 4.38 (dddd, 1, X of ABX, J_{HH} = 10.7, 5.9, 5.9, J_{PH} = 10.7), 7.15–7.35 (m, 5); ^{13}C NMR ($CDCl_3$, deduced from minor peaks in spectrum of mother liquor) δ 11.30 (d, J_{CP} = 3.3), 19.51 (d, J_{CP} = 97.3), 40.68 (d, J_{CP} = 4.7), 52.25, 54.20, 127.0, 128.4, 129.5, 135.8, 173.0; ^{31}P NMR ($CDCl_3$) δ 46.60; mass spectrum, m/z 287 (M^+), 228, 212, 196, 180, 162, 148, 118, 109 (base); exact mass calcd for $C_{12}H_{18}NO_3PS$, 287.0745; found, 287.0739. Anal. ($C_{12}H_{18}NO_3PS$) C, H, N, S. The mother liquors were concentrated at reduced pressure to give 53 mg (72% yield) of **9**R_P (1.6:1 ratio of diastereomers) as a syrup. HPLC (silica gel, ethanol/chloroform, 1:99), retention time in column volumes: 5.3 (**9**S_P) and 8.2 (**9**R_P). Preparative TLC (silica gel, ethanol/chloroform, 1:9) gave **9**R_P (4:1 ratio of diastereomers) and **9**S_P (9.5:1 ratio). Diastereomerically pure **9**R_P was obtained by preparative HPLC (silica gel, ethanol/chloroform, 1:99) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3, J = 14.5), 2.14 (d, 3, J = 12.5), 2.97 and 3.09 (AB of ABX, 2, J_{AB} = 13.5, $J_{AX} \approx$ 7.2, $J_{BX} \approx$ 5.5), 3.31 (br dd, 1, J = 8.9, 10.1), 3.74 (s, 3), 4.18 (dddd, 1, X of ABX, J_{HH} = 11.1, 7.3, 5.5, J_{PH} = 11.1), 7.15–7.35 (m, 5); ^{13}C NMR ($CDCl_3$, deduced from major peaks in spectrum of mother liquor) δ 10.75 (d, J_{CP} = 2.1), 18.98 (d, J_{CP} = 96.9), 40.5 (d, J_{CP} = 6.4), 52.32, 54.96, 127.0, 128.4, 129.5, 136.0, 173.2 (d, J_{CP} = 2.9); ^{31}P NMR ($CDCl_3$) δ 48.20; mass spectrum, m/z 288 (M + 1), 287 (M^+), 240, 228, 212, 196, 180, 162, 148, 118, 109 (base), 91.

By a similar procedure, heating **3**R_P (4.6:1 ratio of diastereomers) with methyl iodide produced **9**R_P (2.6:1 ratio), and **3**S_P (5.6:1 ratio) yielded **9**S_P (4.4:1 ratio).

N-(Hydroxy(methyl)phosphinothioyl)-L-phenylalanine Methyl Ester, Sodium Salt (7). *N*-((2-Cyanoethoxy)(methyl)phosphinothioyl)-L-phenylalanine methyl ester (**6**; 59 mg, 0.18 mmol) was treated with 0.73 mL (0.15 mmol) of 0.20 M sodium methoxide in methanol solution and the reaction mixture was stirred for 25 min at 21 °C. After removal of solvent at reduced pressure, the residue was partitioned between 5 mL of ether and 5 mL of water and the aqueous layer was lyophilized to give 43 mg (81% yield) of **7** as a glass. ^{1}H, ^{13}C, and ^{31}P NMR, see below for **7**R_P and **7**S_P.

In a similar manner, **6**R_P gave **7**R_P (>75:1 ratio of diastereomers) and **6**S_P gave **7**S_P (>100:1 ratio). **7**R_P: ^{1}H NMR (CD_3OD) δ 1.44 (d, 3, J = 14.2), 2.96 and 3.02 (AB of ABX, 2, J_{AB} = 13.2, $J_{AX} \approx$ 7.0, $J_{BX} \approx$ 6.2), 3.60 (s, 3), 4.23 (ddd, 1, X of ABX, J_{HH} = 6.6, 6.6, J_{PH} = 11.2), 7.13–7.30 (m, 5); ^{13}C NMR (CD_3OD) δ 26.32 (d, J_{CP} = 97.7), 42.04 (d, J_{CP} = 5.0), 52.38, 57.88, 127.6, 129.3, 130.5, 138.50, 176.49 (d, J_{CP} = 3.8); ^{31}P NMR (D_2O, ^{1}H decoupler off) δ 64.32 (dq, J_{PH} = 10.9, 14.0); (CD_3OD) δ 64.14.

7S_P: ^{1}H NMR (CD_3OD) δ 1.42 (d, 3, J = 14.2), 2.96 and 3.00 (AB of ABX, 2, J_{AB} = 13.2, $J_{AX} \approx$ 6.7, $J_{BX} \approx$ 6.2), 3.61 (s, 3), 4.25 (ddd, 1, X of ABX, J_{HH} = 6.5, 6.5, J_{PH} = 11.0), 7.13–7.30 (m, 5); ^{13}C NMR (CD_3OD) δ 26.03 (d, J_{CP} = 97.3), 42.12 (d, J_{CP} = 5.1), 52.38, 57.78, 127.6, 129.3, 130.5, 138.55, 176.55 (d, J_{CP} = 3.2); ^{31}P NMR (D_2O) δ 63.68; (CD_3OD) δ 64.14.

N-(Methyl(methylthio)phosphinyl)-L-phenylalanine Methyl Ester (9) by Alkylation of 7. *N*-(Hydroxy(methyl)phosphinothioyl)-L-phenylalanine methyl ester, sodium salt (**7**; 7.5 mg, 0.025 mmol, 1:1 ratio of diastereomers), was suspended in 0.6 mL of methyl iodide, heated for 2 h at 40 °C, and concentrated at reduced pressure. A solution of the residue in 10 mL of chloroform was washed successively with 10 mL of saturated $NaHCO_3$ and 10 mL of water, dried ($MgSO_4$), and concentrated at reduced pressure to give 5.6 mg (77% yield) of **9** (53:47 ratio of diastereomers S_P:R_P) as a white solid. By a similar procedure, **7**R_P (>75:1 ratio of diastereomers) gave **9**R_P (50:1 ratio) and **7**S_P (>75:1 ratio) gave **9**S_P (46:1 ratio).

***O*-Methyl Hydrogen Methylphosphonothioate (8) by Acidic Methanolysis of 7.** Acetyl chloride (0.04 mL, 0.6 mmol) was added to 0.35 mL of anhydrous methanol with stirring, and the resulting solution was combined with 15.5 mg (0.053 mmol) of *N*-(hydroxy(methyl)phosphinothioyl)-L-phenylalanine methyl ester, sodium salt (**7**; 1:1 ratio of diastereomers). After 1 h at 21 °C, the reaction mixture was applied to a cation-exchange column (Bio-Rad AG50W-X8, H^+ form, 1.0 mL resin bed) and eluted with methanol. The acidic fractions were concentrated at reduced pressure and bulb-to-bulb distilled (80 °C (0.15 torr)) to give 1.0 mg (15% yield) of **8** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.86 (d, 3, J = 15.7), 3.74 (d, 3, J = 13.9), 4.91 (br s, 1). Addition of 0.04 mL

(7.5 μmol) of a 0.188 M solution of (−)-α-phenylethylamine in $CDCl_3$ to the ^1H NMR sample in $CDCl_3$ gave doubling of the P–CH_3 and O–CH_3 signals: ^1H NMR ($CDCl_3$) δ 1.24 and 1.35 (two d, 3, J = 14.3), 1.63 (d, 3, J = 6.8), 3.44 and 3.45 (two d, 3, J = 13.1), 4.39 (q, 1, J = 6.8), 7.25–7.55 (m, 5).

Similar treatment of **7**S_P (10:1 ratio of diastereomers) gave the (−)-α-phenylethylamine salt of **8**S_P (6.8:1 ratio), as evidenced by the predominance of the lower-field P–CH_3 and O–CH_3 doublets; **7**R_P (75:1 ratio) gave the salt of **8**R_P (>20:1 ratio) as evidenced by the absence of the lower-field doublets. In both cases, increasing quantities of the (−)-α-phenylethylamine salt of racemic **8** were added to confirm the ^1H NMR peak assignments.

Hydrolysis of *N*-(Methoxy(methyl)phosphinothioyl)-L-phenylalanine Methyl Ester (3). A solution of 28 mg (0.095 mmol) of **3** (5:4 ratio of diastereomers S_P:R_P) in 0.25 mL of methanol was treated with 0.21 mL (0.37 mmol) of 1.8 M NaOH, and the solvent was removed at reduced pressure after 10 min. The residue was dissolved in D_2O and the hydrolysis reaction was monitored by 250-MHz ^1H NMR spectroscopy. After 1 day at 21 °C, no starting material was observed, and the conversion of the intermediate *N*-(methoxy(methyl)phosphinothioyl)-L-phenylalanine, sodium salt, **11**S_P (^1H NMR δ 1.43 (d, 3, J = 15.2), 3.38 (d, 3, J = 13.8); ^{31}P NMR δ 86.75), to *N*-(hydroxy(methyl)phosphinothioyl)-L-phenylalanine, disodium salt, **10**R_P (^1H and ^{31}P NMR spectra given below in description of hydrolysis of **6**), was 47% complete, while conversion of **11**R_P (^1H NMR δ 1.66 (d, 3, J = 15.1), 3.20 (d, 3, J = 13.9); ^{31}P NMR δ 86.20) to **10**S_P (^1H and ^{31}P NMR spectra given below) was only 37% complete. After 3 days at 21 °C, these two processes were 77% and 59% complete, respectively, and after 5 days at 21 °C and 5 h at 100 °C, both intermediates were gone, the desulfurization product *N*-(hydroxy(methyl)phosphinyl)-L-phenylalanine, disodium salt (**13**), comprised 14% of the product mixture, and the product ratio **10**S_P:**10**R_P was 46:40. By a similar procedure, **3**R_P (57:1 ratio of diastereomers) gave initially **11**R_P (26:1 ratio) and, after 2.5 h at 100 °C, **10**S_P (20:1 ratio, 89% yield) and **13** (5% yield).

***N*-(Hydroxy(methyl)phosphinothioyl)-L-phenylalanine, Disodium Salt (10), by Hydrolysis of 6.** A solution of 28 mg (0.085 mmol) of *N*-((2-cyanoethoxy)(methyl)phosphinothioyl)-L-phenylalanine methyl ester (**6**) in 5.5 mL of acetone was treated with 0.12 mL (0.24 mmol) of 2 M NaOH and the reaction mixture was periodically shaken vigorously. After 16 h at 21 °C, the reaction mixture was centrifuged and decanted and the pellet was dried under vacuum to give 15 mg (59% yield) of **10** as an unstable white powder. ^1H, ^{13}C, and ^{31}P NMR, see below for **10**R_P and **10**S_P. Similar treatment of **6**R_P (>93:1 ratio of diastereomers) gave **10**R_P (>100:1 ratio), and **6**S_P (>140:1 ratio) gave fine white needles of **10**S_P (>50:1 ratio).

10R_P: ^1H NMR (D_2O) δ 1.52 (d, 3, J = 14.0), 2.94 and 2.99 (AB of ABX, 2, J_{AB} = 13.3, $J_{AX} \approx$ 7.1, $J_{BX} \approx$ 6.4), 3.85 (ddd, 1, X of ABX, J_{HH} = 6.4, 6.4, J_{PH} = 11.2), 7.25–7.4 (m, 5); ^{13}C NMR (D_2O) δ 23.97 (d, J_{CP} = 94.0), 40.95 (d, J_{CP} = 5.8), 58.51, 126.4, 128.3, 129.6, 137.99, 181.1 (d, J_{CP} = 3.2); ^{31}P NMR (D_2O) δ 62.81.

10S_P: ^1H NMR (D_2O) δ 1.46 (d, 3, J = 14.1), 2.96 (d, 2, J = 6.4), 3.93 (dt, 1, J_{PH} = 12.1, J_{HH} = 6.1), 7.25–7.45 (m, 5); ^{13}C NMR (D_2O) δ 24.16 (d, J_{CP} = 96.0), 40.95 (d, J_{CP} = 5.8), 58.58, 126.4, 128.3, 129.6, 138.14, 181.1 (d, J_{CP} = 3.2); ^{31}P NMR (D_2O) δ 64.00.

Hydrolysis of *N*-(Methyl(phenoxy)phosphinothioyl)-L-phenylalanine Methyl Esters 5R_P **and 5**S_P**.** A solution of 2.7 mg (7.7 μmol) of **5**R_P in 0.40 mL of acetone-d_6 and 0.20 mL of D_2O was treated with 10 μL (20 μmol) of 2.0 M NaOD in D_2O, and the 200-MHz ^1H NMR spectrum was recorded at intervals for 1.5 h, maintaining the probe temperature at 22.0 ± 0.2 °C. As the starting material **5**R_P (^1H NMR δ 1.78 (d, 3, J = 15.5), 3.61 (s, 3); ^{31}P NMR δ 85.23) was consumed, the intermediates (R_P)-*N*-(methyl(phenoxy)phosphinothioyl)-L-phenylalanine, sodium salt, **12**R_P (^1H NMR δ 1.87 (d, 3, J = 15.0); ^{31}P NMR δ 84.10), and (S_P)-*N*-(hydroxy(methyl)phosphinothioyl)-L-phenylalanine methyl ester, sodium salt, **7**S_P (^1H NMR δ 1.50 (d, 3, J = 14.2), 3.64 (s, 3); ^{21}P NMR δ 63.65), increased to their maximum concentrations and the products **10**R_P (major product; ^1H NMR δ 1.41 (d, 3, J = 14.1); ^{31}P NMR δ 63.96) and **10**S_P (minor product; ^1H NMR δ 1.20 (d, 3, J = 14.2); ^{31}P NMR δ 62.44), appeared. The mole fractions of starting material, intermediates, and products as a function of time, determined from peak heights of the ^1H NMR P–CH_3 doublets, are displayed in Figures 1 and 2. The mole fractions of phenol and methanol were also determined by integration of the upfield phenoxide signals (^1H NMR δ 6.33 (tt, 1, J = 9.9, 1.7), 6.59 (dd, 2, J = 11.5, 1.8)) relative to the total aromatic absorbance and by integration of the methanol absorbance (δ 3.35 (s, 3)) relative to the total OCH_3 absorbance. The mole fraction of phenol correlates well with the total mole fraction of all species which have lost the phenyl ester (**7**S_P, **10**R_P, and **10**S_P); the analogous relationship holds for the mole fraction of methanol. For example, the mole fractions of phenol, **7**S_P + **10**R_P + **10**S_P, methanol, and **12**R_P + **10**S_P are 0.175, 0.145, 0.255, and 0.265, respectively, 2 min after the addition of NaOD, and 0.563, 0.593, 0.679, and 0.651 after 12.7 min. The ratio of R_P intermediates and products to S_P intermediates and products remains near 2.44 throughout the experiment with a standard deviation of 0.08.

By a similar procedure, **5**S_P (180-MHz ^1H NMR (acetone-d_6/D_2O, 2:1 ratio) δ 2.24 (d, 3, J = 15.4), 3.68 (s, 3); ^{31}P NMR δ 85.75) gave the intermediates **12**S_P (180-MHz ^1H NMR δ 1.53 (d, 3, J = 15.1); ^{31}P NMR δ 85.14) and **7**R_P (180-MHz ^1H NMR δ 1.48 (d, 3, J = 14.0), 3.64 (s, 3); ^{31}P NMR δ 63.42) and the products **10**S_P (major) and **10**R_P (minor). The time course of hydrolysis is analogous to that shown in Figures 1 and 2 for hydrolysis of **5**R_P, with the following exceptions: the minor intermediate **7**R_P reaches a maximum mole fraction of only 0.07 after 10 min; the major intermediate **12**S_P falls more rapidly from its maximum (0.23, 3.5 min) to a negligible level (<0.01, 40 min); and the ratio of S_P intermediates and products to R_P intermediates and products is higher (6.8 ± 1.1). The same relationship which was observed in the hydrolysis of **5**R_P between phenol and the species that have lost the phenyl ester and between methanol and the species that have lost the methyl ester holds for the hydrolysis of **5**S_P as well.

Partial Hydrolysis of 5R_P**, Interrupted by Addition of Phenol; Absolute Configuration of the Minor Intermediate (7).** A solution of 2.8 mg (8.0 μmol) of **5**R_P in 0.40 mL of acetone-d_6 and 0.20 mL of D_2O was treated with 10 μL (20 μmol) of 2.0 M NaOD in D_2O. After 6.3 min at 22 °C, 0.10 mL (58 μmol) of a 0.58 M solution of phenol in acetone-d_6/D_2O (2:1 ratio) was added and the 200-MHz ^1H NMR spectrum was recorded at intervals (probe at 22 ± 0.2 °C). The mole fractions of starting material **5**R_P, minor intermediate **7**S_P, and minor product **10**S_P remained constant at 0.35 ± 0.01, 0.11 ± 0.003, and 0.07 ± 0.01, respectively, and the mole fractions of the major intermediate **12**R_P and the major product **10**R_P as a function of time are shown in Figure 3. After 6.6 h the conversion of **12**R_P to **10**R_P was complete. Aliquots of a solution of **7** (1:1 ratio of diastereomers prepared by treatment of **6** with sodium methoxide) in acetone-d/D_2O (2:1) were added and the 200-MHz ^1H NMR spectrum was recorded. The absorbances assigned to **7**S_P (δ 1.50 (d, 3, J = 14.2), 3.64 (s, 3)) were augmented, while new absorbances (δ 1.49 (d, 3, J = 14.3), 3.65 (s, 3)) appeared which were attributed to **7**R_P. Separate experiments with **7**S_P (1.7:1 ratio of diastereomers) in the same solvent mixture demonstrated that the upfield P–CH_3 doublet and the downfield CO_2Me singlet are due to **7**R_P.

Stability of *N*-(Hydroxy(methyl)phosphinothioyl)-L-phenylalanine Methyl Ester, Sodium Salt (7), in Aqueous Solution. A solution of 6.3 mg (0.021 mmol) of **7** in 0.10 mL of water was combined with 0.16 mL of a 3% solution of trimethyl phosphate in D_2O and 1.00 mL of the appropriate buffer solution, and the ^1H-decoupled ^{31}P NMR spectrum was recorded at intervals, maintaining a temperature of 22 °C. Although no change was observed after 13 h at pH 6.0, 7.5, and 8.5, at pH 10.5 a small amount of conversion of **7** (^{31}P NMR δ 64.23, 63.63; 1:1 ratio) to **10** (δ 64.03, 62.57; 1:1 ratio) was apparent after 16.6 h. At pH 4.0, 22% of **7** was converted to a single unidentified product (δ 69.20) after 13.4 h, with equal quantities of **7**R_P and **7**S_P remaining. Pseudo-first-order rate constants calculated from these experiments are presented in Table I.

Stability of *N*-(Hydroxy(methyl)phosphinothioyl)-L-phenylalanine, Disodium Salt (10), in Aqueous Solution. A solution of 6.3 mg (0.021 mmol) of *N*-(hydroxy(methyl)phosphinothioyl)-L-phenylalanine methyl ester, sodium salt (**7**), in 0.10 mL of water was treated with 20 μL (0.021 mmol) of 1.025 M NaOH. After 20 min at 22 °C, the reaction mixture was diluted with 0.16 mL of a 3% solution of trimethyl phosphate in D_2O and 1.00 mL of the appropriate buffer, and the ^1H-decoupled ^{31}P NMR spectrum was recorded at intervals, maintaining a temperature of 22 °C. Below pH 10.5, the unreacted starting material **7** (18% of reaction mixture) remains unchanged, while the dianions **10**R_P (^{31}P NMR δ 62.73) and **10**S_P (δ 64.04) are converted to *N*-(hydroxy(methyl)phosphinyl)-L-phenylalanine, disodium salt, **13** (δ 26.23). At pH 10.5 and above, it was necessary to correct for the conversion of unreacted starting material **7** to **10** during the course of the desulfurization reaction. Plots of log [**10**R_P] and log [**10**S_P] vs. time were linear and yielded the pseudo-first-order rate constants listed in Table I.

***N*-(Methoxy(methyl)phosphinyl)-L-phenylalanine, Sodium Salt (14),[2] by Acid-Catalyzed Methanolysis of 10.** The white solid precipitate **10**R_P obtained by hydrolysis of 8.8 mg (0.027 mmol) of (R_P)-*N*-((2-cyanoethoxy)(methyl)phosphinothioyl)-L-phenylalanine methyl ester (**6**R_P) in acetone (see above) was dissolved in 0.73 mL of dry methanol and combined with 7.6 mg (0.055 mmol) of *p*-nitrophenol. After 1 h the solvent was removed at reduced pressure and the residue was shown to consist entirely of **14**R_P (>92:1 ratio of diastereomers) by ^1H NMR comparison in methanol-d_4 and in D_2O with an authentic sample obtained previously by a different route (see preceding paper[2]). By a similar procedure, **10** (1:1 ratio of diastereomers) was converted to **14** (1:1 ratio), and by use

of potassium dihydrogen phosphate in place of *p*-nitrophenol as the acid catalyst, **10**S_P was converted to **14**S_P. In the latter case it was necessary to add water (25% v/v) to solubilize the phosphate and as a result, the product consisted of **14**S_P (>15:1 ratio of diastereomers) and the dianion **13** in a ratio of approximately 2:1.

***N*-(Methoxy(methyl)phosphinyl)-L-phenylalanine Methyl Ester (15)[2] by Base-Catalyzed Methanolysis of 9.** A solution of 10.3 mg (0.036 mmol) of (S_P)-*N*-(methyl(methylthio)phosphinyl)-L-phenylalanine methyl ester (**9**S_P) in 1.75 mL of anhydrous methanol was stirred with 1.9 mg (0.014 mmol) of solid K_2CO_3 at 21 °C for 38 h. After removal of the solvent at reduced pressure, the residue was partitioned between 2 mL of chloroform and 2 mL of water. The aqueous layer was extracted with another 2-mL portion of chloroform, and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 8.8 mg (90% yield) of **15**R_P (4.2:1 ratio of diastereomers) as a white, crystalline solid, identical by ^1H NMR spectroscopy with a sample previously obtained by an alternate route (see preceding paper[2]). By a similar procedure, 10.9 mg (0.038 mmol) of **9**R_P produced 7.8 mg (76% yield) of **15**S_P (5.2:1 ratio of diastereomers) as a white, crystalline solid.

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Registry No. 1, 84558-28-1; **2**, 84558-47-4; **3** (isomer 1), 84558-29-2; **3** (isomer 2), 84558-30-5; **4a**, 14410-07-2; **4b**, 84558-31-6; **5** (isomer 1), 84558-32-7; **5** (isomer 2), 84558-33-8; **6** (isomer 1), 80556-19-0; **6** (isomer 2), 80565-18-0; **7** (isomer 1), 84558-34-9; **7** (isomer 2), 84558-35-0; (±)-**8**, 36585-69-0; **8**S^P·(−)-α-phenylethylamine, 84558-36-1; **8**R^P·(−)-α-phenylethylamine, 13889-55-9; **9** (isomer 1), 84558-37-2; **9** (isomer 2), 84558-38-3; **10** (isomer 1), 84558-39-4; **10** (isomer 2), 84558-40-7; **11** (isomer 1), 84558-41-8; **11** (isomer 2), 84558-42-9; **12** (isomer 1), 84558-43-0; **12** (isomer 2), 84558-44-1; **13**, 84558-45-2; **14** (isomer 1), 84621-21-6; **14** (isomer 2), 84621-22-7; **15** (isomer 1), 84558-46-3; **15** (isomer 2), 84558-49-6; L-phenylalanine methyl ester, 2577-90-4; methylphosphonothioic dichloride, 676-98-2; 3-hydroxypropanenitrile, 109-78-4; L-phenylalanine methyl ester·HCl, 7524-50-7.

Thermal Sigmatropic Rearrangements of Vinylallenes Leading to 11-*cis*-Retinoids and the Novel Properties of 9-*cis*,11-*cis*,13-*cis*-Retinal and 11-*cis*,13-*cis*-Retinal[1]

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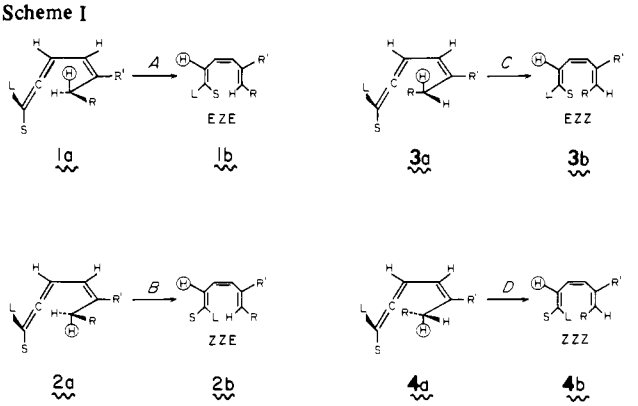
Abstract: The thermally induced [1,5] sigmatropic hydrogen shift of vinylallene **5** provided a route to highly hindered 11-*cis*-retinoids. The coupling of the hetero cuprate **14** with the propargyl benzoate **13b** gave the vinylallene **5**, which upon heating (69 °C, 2 h) gave three geometrically isomeric retinoids: 11-cis (**8**), 11-cis,13-cis (**9**), and 9-cis,11-cis,13-cis (**11**). The fourth possible geometric isomer, 9-cis,11-cis (**10**), was unstable to the conditions of thermolysis and underwent further electrocyclizations to the tricyclic compound **22**. The thermal rearrangement of the 9,10-allene **5**, though highly specific for the formation of 11-*cis*-retinoids, exhibits no selectivity in the formation of the Δ^9 and Δ^{13} double bonds. The highly hindered 11-*cis*,13-*cis*- and 9-*cis*,11-*cis*,13-*cis*-retinals, **9b** and **11b**, exhibit extraordinary electronic absorption spectra in that they exhibit their main maxima (302 nm) actually to the blue of the corresponding alcohols. The retinals **9b** and **11b** were very thermally unstable and underwent clean isomerization to 13-*cis*-retinal and 9-*cis*,13-*cis*-retinal, respectively.

Introduction

After a brief hiatus, there has been a resurgence of chemical interest in the retinoids (vitamin A). This can be attributed to the recent renaissance of the vision field[3] and the emergence of retinoids as compounds of importance in the areas of energy transduction,[4] cancer prophylaxis,[5] and acne therapy.[6] The availability of the various geometric isomers of retinoids and retinoid analogues in sufficient quantities for rigorous biological assay is crucial to the continued rapid progress in the retinoid field. In this light, the development of more efficient synthetic methods for preparing some of the difficult-to-obtain sterically hindered retinoids is highly desirable.

Scheme I



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