270-MHz NMR ($CDCl_3$) δ 7.40-7.20 (5 H, m), 5.91 (1 H, s), 4.16 (2 H, q, $J$ = 7.1 Hz), 2.86 (2 H, s), 1.29 (3 H, t, $J$ = 7.1 Hz), 1.16 (6 H, s).

**Ethyl (*E*)-5-phenyl-2-pentenoate (31b)**: oil; analytical TLC (silica gel F254) hexane/ether/$CH_2Cl_2$ 4:1:1, $R_f$ = 0.69; MS base peak = 91.0525; exact mass calcd for $C_{13}H_{16}O_2$ 204.115, found 204.1142, error = 3.9 ppm; IR (neat, $cm^{-1}$) C=O, 1720; 270-MHz NMR ($CDCl_3$) δ 7.28-7.08 (5 H, m), 6.93 (1 H, td, $J$ = 7.1, 14.1 Hz), 5.77 (1 H, td, $J$ = 1.3, 14.1 Hz); 4.11 (2 H, q, $J$ = 7.1 Hz); 2.70 (2 H, t, $J$ = 9.0 Hz), 2.44 (2 H, q, $J$ = 9.0 Hz), 1.21 (3 H, t, $J$ = 7.1 Hz).

**Ethyl (*E*)-4,4-dimethyl-5-phenyl-2-pentenoate (31d)**: oil; analytical TLC (silica gel F254), hexane/ether/$CH_2Cl_2$ 4:1:1, $R_f$ = 0.78; MS base peak = 91.0538; exact mass calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.146, error = 1.3 ppm; IR (neat, $cm^{-1}$) C=O, 1720; 270-MHz NMR ($CDCl_3$) δ 7.30-7.19 (3 H, m), 7.10-7.03 (2 H, m); 7.01 (1 H, d, $J$ = 15.9 Hz), 5.61 (1 H, d, $J$ = 12.9 Hz), 4.17 (2 H, q, $J$ = 7.1 Hz), 2.63 (2 H, s), 1.27 (3 H, t, $J$ = 7.1 Hz), 1.04 (6 H, s).

**Wittig Reactions of Phosphoniumn Ylides 1a and 1c. Standard Conditions.** The dry phosphonium salt (0.19 mmol) was dissolved in THF or EtOH (4 mL). The base (0.18 mmol) was added via a syringe, and the mixture was allowed to stir for 15 min. The aldehyde (0.18 mmol) was added neat and stirred for 4 h. Ether (20 mL) and 10% HCl (20 mL) were added, the organic layer was separated and dried ($MgSO_4$), and solvent was removed in vacuo. Purification via flash chromatography (Kieselgel 60) provided the olefins. Olefin product ratios were determined by integration of the vinyl region (enoates) or GLPC analysis (dienes or substituted styrenes) (Table IV).

**(*E*)-1-Phenyl-2-cyclohexylethene**: oil; analytical TLC (silica gel F254) hexane/ether/$CH_2Cl_2$ 4:1:1, $R_f$ = 0.81; MS base peak = 104.0613; exact mass calcd for $C_{14}H_{18}$ 186.1409, found 186.1413, error = 2.4 ppm; 270-MHz NMR ($CDCl_3$) δ 7.40-7.25 (4 H, m), 7.22-7.13 (1 H, m), 6.35 (1 H, d, $J$ = 16.08 Hz), 6.18 (1 H, dd, $J$ = 6.78, 15.98 Hz), 2.20-2.08 (1 H, m), 1.88-1.63 (4 H, m), 1.40-1.13 (6 H, m).

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**Registry No. 1a**, 1099-45-2; **1c**, 110223-71-7; **10**, 121192-38-9; **11a**, 121192-39-0; **11b**, 121192-40-3; **12**, 121192-37-8; **14a**, 121192-35-6; **15a**, 121250-46-2; **15b**, 121192-36-7; **16a**, 77131-98-7; **17a**, 83877-82-1; **17b**, 116544-25-3; **18a**, 121192-30-1; **19a**, 121192-32-3; **19b**, 121192-34-5; **19c**, 121192-54-9; **20** (anion), 72884-89-0; **22a**, 121192-47-0; $D_1$-**22a**, 121192-45-8; **22b**, 121192-56-1; $D_1$-**22b**, 121192-49-2; **22c**, 110223-70-6; $D_1$-**22c**, 121192-50-5; **22d**, 121192-58-3; $D_1$-**22d**, 121192-52-7; $D_1$-**30b**, 121192-59-4; **30c**, 18521-02-3; **30d**, 121192-60-7; $D_1$-**30d**, 121192-61-8; **31b**, 55282-95-6; **31d**, 121192-62-9; **33**, 121192-41-4; $C_6H_{11}CHO$, 2043-61-0; $Ph_3P$, 603-35-0; $MePh_2P$, 1486-28-8; PhCHO, 100-52-7; $PhCH_2CH_2CHO$, 104-53-0; $PhCH_2CMe_2CHO$, 1009-62-7; *trans*-1-cyclohexyl-1,3-butadiene, 25203-83-2; *cis*-1-cyclohexyl-1,3-butadiene, 25203-84-3; 5*H*-dibenzophosphole, 244-87-1; (*Z*)-2-cyclohexylstyrene, 40132-69-2; ethyl *trans*-phenylglycidate, 2272-55-1; ethyl (*Z*)-cinnamate, 4610-69-9; ethyl *cis*-phenylglycidate, 2272-49-3; *p*-chlorobenzaldehyde, 104-88-1; ethyl (*E*)-*p*-chlorocinnamate, 24393-52-0; ethyl (*Z*)-*p*-chlorocinnamate, 63757-30-2; ethyl (*E*)-cinnamate, 4192-77-2; ethyl (*E*)-2-cyclohexylacrylate, 17343-88-3; ethyl (*Z*)-2-cyclohexylacrylate, 18521-02-3; ethyl (diphenylphosphino)acetate-$d_2$, 121192-42-5; ethyl (diphenylphosphonium)acetate, 55552-24-4; *p*-(carbethoxymethyl)dibenzophosphole, 121192-43-6; ethyl bromoacetate, 105-36-2; (*E*)-2-cyclohexylstyrene, 18869-27-7.

# Kinetic Facial Selectivity in Nucleophilic Displacements at Tetracoordinate Phosphorus: Kinetics and Stereochemistry in the Reaction of Sodium Ethoxide with *O,S*-Dimethyl Phenylphosphonothioate

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**Abstract:** The reaction of ethoxide ion with *O,S*-dimethyl phenylphosphonothioate (**1a**) proceeds with competitive displacements of the methylthio and methoxy ligands. Each displacement occurs with complete inversion of configuration. The two products, ethyl methyl phenylphosphonate (**2ab**) and *O*-ethyl *S*-methyl phenylphosphonothioate (**1b**), respectively, react further with ethoxide ion to form diethyl phenylphosphonate (**2bb**). Displacement of the ethoxy ligand on **2ab** or **1b**, which leads to racemization, competes with formation of **2bb** in both of these reactions. The competitions favor displacement of methylthiolate over methoxide ion from **1a** (3/1), methoxide over ethoxide ion from **2ab** (6/1), and methylthiolate over ethoxide ion from **1b** (18/1). In addition, racemization of **1b** is 22 times faster than racemization of **2ab**, and displacement of methylthiolate ion from **1b** is 65 times faster than displacement of methoxide ion from **2ab**. The results rule out the possibility that methylthiolate ion is displaced in phosphonothioates with inversion stereochemistry simply because the retention pathway, seen in other related systems, is energetically blocked by the need for a high-energy isomerization process. The small preference for displacement of methylthiolate ion over methoxide ion from **1a** is identified to be the result of a methylthio ligand having a larger relative intrinsic kinetic affinity to occupy either an axial position or an equatorial position in a pentacoordinate intermediate or transition state, and these affinities partially cancel.

There has been and continues to be considerable interest in the mechanisms for nucleophilic displacement of a leaving group from phosphorus in tetracoordinate organophosphorus compounds. For associative processes with strong nucleophiles, it is generally assumed that the nucleophile approaches a trigonal face of the tetrahedral phosphorus center, forming a pentacoordinate intermediate (of idealized trigonal-bipyramidal geometry) with the nucleophile in an axial position (axial attack).[1] In systems with more than one potential leaving group, the particular face attacked (facial selectivity) would determine the positioning of the leaving groups in the resulting intermediate. If this intermediate then leads to a displacement, its structure may have an influence on determining which leaving group is displaced and will determine the resulting stereochemistry at phosphorus.[2] Therefore, we are

(1) Westheimer, F. *Acc. Chem. Res.* **1968**, *1*, 70.

(2) Mislow, K. *Acc. Chem. Res.* **1970**, *3*, 321.

(3) (a) De'ath, N. J.; Ellis, K.; Smith, D. J. H.; Trippett, S. *J. Chem. Soc., Chem. Commun.* **1971**, 714. (b) DeBruin, K. E.; Johnson, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 4675.

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**Scheme I**

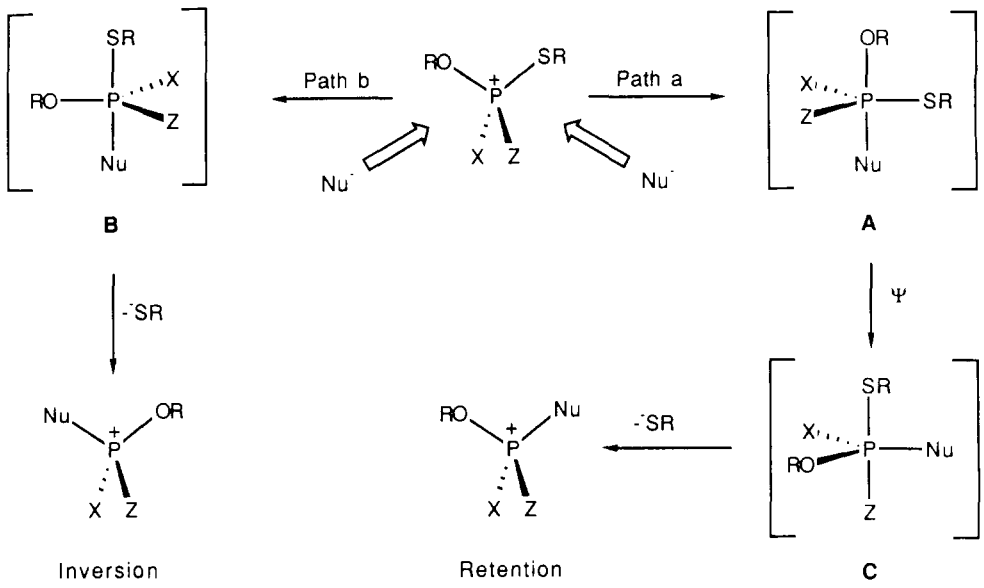


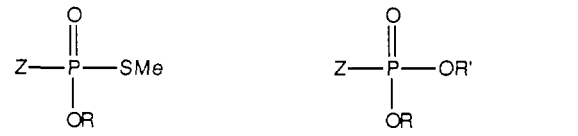

**Table I.** Stereochemistry of Carbanion and Oxyanion Displacements of an Alkylthiolate Ion from Acyclic Organophosphorus Compounds Containing both Alkoxy (OR) and Alkylthio (SR) Ligands

| Z(RO)P(X)SR | Z | X | nucleophile | stereochem | ref[a] |
|---|---|---|---|---|---|
| phosphonium salts | Ph | R | hydroxide ion | retention | 3 |
| phosphonothioates | R | $O^-$ | Grignard reagents | retention[b] | 4–7 |
| | | | alkoxide ions | inversion[c,d] | 8–15 |
| phosphonodithioates | R | $S^-$ | Grignard reagents | retention | 16 |
| | | | hydroxide ion | inversion[e] | 16, 17 |
| | | | alkoxide ions | inversion | 16 |
| phosphoramidothioates | RNH | $O^-$ | alkoxide ions | inversion[c] | 15, 18, 19 |
| phosphorothioates | RO | $O^-$ | alkoxide ions | retention | 12, 13 |

[a] Numbers refer to references in the text. [b] Inversion has been observed in one special case (ref 7). [c] Reactions are reported to proceed with less than 100% inversion. [d] (Dihalomethyl)phosphonothioates give retention (ref 15b). [e] Complete racemization has been reported (ref 17).

interested in elucidating the factors that determine these facial selectivities.

**Scheme II**




**1** (Z = Ph) **a** (R = Me)
**3** (Z = Me) **b** (R = Et)
**5** (Z = iPrO)

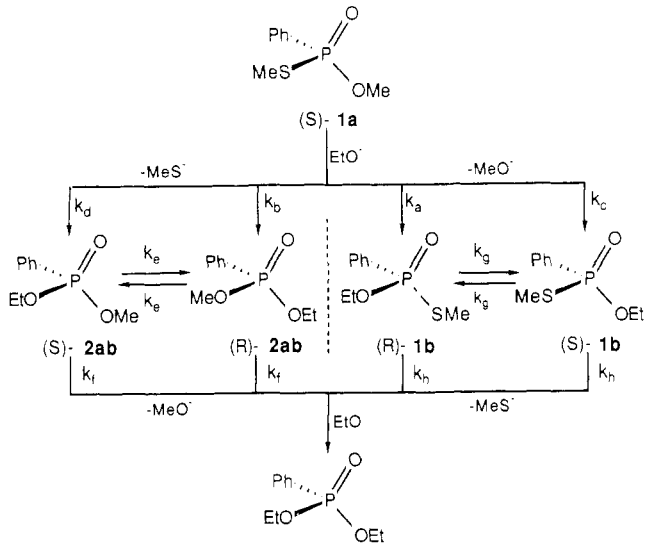
**2** (Z = Ph) **aa** (R = R' = Me)
**4** (Z = Me) **ab** (R = Me, R' = Et)
**6** (Z = iPrO) **bb** (R = R' = Et)

A number of researchers have looked at reactions involving carbanion or oxyanion displacements of an alkylthiolate ion from a phosphorus center containing both alkoxy (OR) and alkylthio (SR) ligands. This system is particularly interesting since nucleophilic attack could occur in the face opposite the more electronegative alkoxy ligand to give intermediate A (path a, Scheme I) or in the face opposite the more polarizable alkylthio ligand to give intermediate B (path b). The stereochemical results that have been reported for acyclic systems without ring constraints are summarized in Table I. Since retention stereochemistry implicates the formation of intermediate A, while inversion implicates B, it appears that the substitution on phosphorus and the nature of the nucleophilic system both have an influence on which face addition of the nucleophile occurs to give products. However, these results may not actually reflect varying kinetic facial selectivities.

A common feature of those reactions observed to proceed with retention of configuration is a relatively low barrier for the essential permutational isomerization of A to C which places the methylthio ligand in an axial position. For the Grignard and alkoxide ion reactions, the nucleophile (Nu) and ligand Z (which exchange positions) have similar electronegativities. A hydroxy ligand (Nu) in the phosphonium salt hydrolysis can deprotonate and become less apicophilic than the phenyl ligand (Z). In contrast, inversion of configuration was observed when the isomerization of A to C would be a relatively endothermic process (the nucleophile is more electronegative than ligand Z) and intermediate formation is potentially reversible (the nucleophile is an oxyanion). Thus, the possibility exists that *all* the reactions kinetically favor formation

(4) (a) Benschop, H. P.; van den Berg, G. R.; Boter, H. L. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 387. (b) Benschop, H. P.; Plantenburg, D. H. J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 1098. (c) van den Berg, G. R.; Platenburg, D. H. J. M.; Benschop, H. P. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 929.
(5) (a) Farnham, W. B.; Murray, R. K., Jr.; Mislow, K. *J. Chem. Soc., Chem. Commun.* **1970**, 605. (b) Donohue, J.; Mandel, N.; Farnham, W. B.; Murray, R. K., Jr.; Mislow, K.; Benschop, H. P. *J. Am. Chem. Soc.* **1971**, *93*, 3792.
(6) DeBruin, K. E.; Johnson, D. M. *J. Chem. Soc., Chem. Commun.* **1975**, 753.
(7) Moriyama, M.; Bentrude, W. G. *J. Am. Chem. Soc.* **1983**, *105*, 4727.
(8) Aaron, H. S.; Uyeda, R. T.; Frack, H. F.; Miller, J. I. *J. Am. Chem. Soc.* **1962**, *84*, 617.
(9) Michalski, J.; Okruszek, A.; Stec, W. *J. Chem. Soc., Chem. Commun.* **1970**, 1495.
(10) Farnham, W. B.; Mislow, K.; Mandel, N.; Donohue, J. *J. Chem. Soc., Chem. Commun.* **1972**, 120.
(11) Hall, C. R.; Williams, N. E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2746.
(12) (a) Cooper, D. B.; Hall, C. R.; Inch, T. D. *J. Chem. Soc., Chem. Commun.* **1975**, 721. (b) Hall, C. R.; Inch, T. D. *Tetrahedron Lett.* **1976**, 3645. (c) Cooper, D. B.; Hall, C. R.; Harrison, J. M.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1969.
(13) (a) Inch, T. D.; Lewis, G. J. *Carbohydr. Res.* **1975**, *45*, 65. (b) Inch, T. D.; Lewis, G. J.; Wilkinson, R. G.; Watts, P. *J. Chem. Soc., Chem. Commun.* **1975**, 500.
(14) Hall, C. R.; Inch, T. D.; Pottage, C.; Williams, N. *Tetrahedron* **1985**, *41*, 4909.
(15) (a) Hall, C. R.; Inch, T. D.; Williams, N. *Phosphorus Sulfur* **1983**, *18*, 213. (b) Hall, C. R.; Inch, T. D.; Peacock, G.; Pottage, C.; Williams, N. E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 669.
(16) (a) DeBruin, K. E.; Johnson, D. M. *Phosphorus* **1974**, *4*, 13. (b) DeBruin, K. E.; Johnson, D. M. *Phosphorus* **1974**, *4*, 17.
(17) Reiff, L. P.; Szafraniec, L. J.; Aaron, H. S. *J. Chem. Soc., Chem. Commun.* **1971**, 366.
(18) (a) Hall, C. R.; Inch, T. D. *Tetrahedron Lett.* **1977**, 3765. (b) Hall, C. R.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1646.
(19) DeBruin, K. E.; Ebersole, C. E.; Hughes, M. M.; Johnson, D. M. *ACS Symp. Ser.* **1981**, *171*, 543.

**Scheme III**



of A by facial attack opposite the more electronegative alkoxy ligand. When isomerization of A is energetically easy, retention stereochemistry would result; but, when the isomerization is difficult, product formation with inversion through intermediate B may be the overall lower energy pathway.

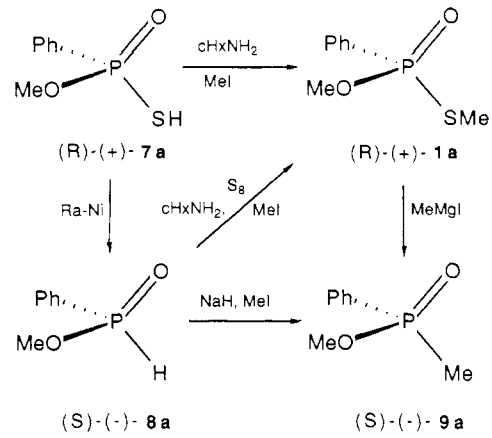
We decided to test this possibility on the phosphonothioate system (where both retention and inversion have been observed) by carrying out a kinetic, stereochemical, and product study on the reaction of sodium ethoxide in ethanol with *O,S*-dimethyl phenylphosphonothioate (**1a**, Z = Ph, X = O). Since ethoxide ion (Nu = EtO) is a poorer leaving group than methoxide ion (OR = OMe), the intermediacy of A would be detected by the appearance of *O*-ethyl *S*-methyl phenylphosphonothioate (**1b**) even if A does not form ethyl methyl phenylphosphonate (**2ab**) with retention of configuration at phosphorus. Our observations prove that formation of A does occur but also indicate that formation of B is the kinetically favored mode of reaction for this phosphonothioate. The results will be discussed in relationship to other studies on the reaction of alkoxide ions with methylphosphonothioate (**3** → **4**) and phosphorothioate (**5** → **6**) systems (Scheme II) and studies on other nucleophilic reactions in general.

## Results

A number of processes with various stereochemical results can occur in the reaction of sodium ethoxide with *O,S*-dimethyl phenylphosphonothioate (**1a**). These are shown in Scheme III, starting from **1a** of the *S* configuration at phosphorus. Sequential displacements of both methylthiolate and methoxide ions, with either occurring first, can occur to yield diethyl phenylphosphonate (**2bb**). Initial displacement of methylthiolate ion ($k_d$ and $k_b$) gives ethyl methyl phenylphosphonate (**2ab**) while displacement of methoxide ion ($k_a$ and $k_c$) gives *O*-ethyl *S*-methyl phenylphosphonothioate (**1b**) as intermediates. Either initial displacement can occur with inverstion ($k_b$ and $k_a$) or retention ($k_d$ and $k_c$) of configuration, and the products can undergo racemization ($k_e$ and $k_g$) in competition with formation of **2bb** ($k_f$ and $k_h$). Quantitatively establishing the degree to which each pathway is involved in the overall conversion of **1a** to **2bb** allows us to estimate kinetic facial selectivities of ethoxide ion toward **1a**, **1b**, and **2ab**. This requires relating the configuration of **2ab** and **1b** to that of **1a** and following enantiomeric purity and product ratios as a function of time.

**Stereochemical Correlations.** Our entrance into enantiomerically enriched compounds was accomplished by resolution of *O*-methyl and *O*-ethyl phenylphosphonothioic acids (**7a** and **7b**). The acid **7a** was easily resolved with methylbenzylamine[20] and

**Scheme IV**



the progress of the resolution followed by $^1$H NMR in benzene on the diastereomeric salts.[22] By use of (*S*)-(−)-methylbenzylamine, the salt with the more upfield chemical shift of the $POCH_3$ protons was obtained diastereomerically pure with a specific optical rotation of −16° (*c* 2–4, methanol).[23] The low-field diastereomer was not obtained in pure form but has a specific rotation of +6° (*c* 2–4, methanol) by extrapolation from various mixtures of the two diastereomeric salts (see Experimental Section). Conversion of these salts to free acid **7a** was accomplished by dissolution in a strongly basic solution to remove the unprotonated methylbenzylamine and then strong acidification to allow removal of the free acid. We have noticed the pure acid decomposes somewhat upon standing and gives nonreproducible optical rotations and therefore chose to convert it directly to its dicyclohexylammonium salt for further purification and storing. Thus, the high-field methylbenzylammonium salt of **7a** was converted to enantiomerically pure dicyclohexylammonium salt of **7a** with specific rotation of −11.8° (*c* 2–4, methanol). All attempts to resolve the thioacid **7b** with methylbenzylamine were unsuccessful[24] so a modification of the procedure of Ohkawa and co-workers[26] using brucine was adopted. The brucine salts obtained were converted to their dicyclohexylammonium salts, giving a material with maximum specific rotation of +9.1° (*c* 2–4, methanol) and presumed to be optically pure.

Synthesis of enantiomerically enriched **1a** (the starting material for our mechanistic study) and **1b** (one of the possible products) was accomplished by reaction of the dicyclohexylammonium salts of **7a** and **7b** with iodomethane in benzene.[27] The absolute configuration of **1b** has been established to be *R*-(+) by Benschop,[25] who chemically correlated (*S*)-(−)-ethyl phenylphosphinate (**8b**) to both (+)-**1b** and (−)-ethyl methylphenylphosphinate (**9b**),[28] known to have the *S* configuration.[29] We have utilized these reactions and others to complete the stereo-

(20) The resolution of **7a** with methylbenzylamine has been reported[21] with minimal experimental details.

(21) Allahyari, R.; Hollingshaus, J. G.; Lapp, R. L.; Timm, E.; Jacobson, R. A.; Fukuto, T. R. *J. Agric. Food Chem.* **1980**, *28*, 594.

(22) A shift difference between the two diastereomers has been reported, but no assignment of configuration to individual peaks was made. See: Mikolajczyk, M.; Omelanczyk, J.; Leitloff, M.; Drabowicz, J.; Ejchart, A.; Jurczak, J. *J. Am. Chem. Soc.* **1978**, *100*, 7003.

(23) A specific rotation for this salt of −17.68° (*c* 14.5) in methanol has been reported.[21]

(24) A footnote in ref 25 indicates those workers were successful in this resolution.

(25) Benschop, H. P.; van den Berg, G. R. *J. Chem. Soc., Chem. Commun.* **1970**, 1431.

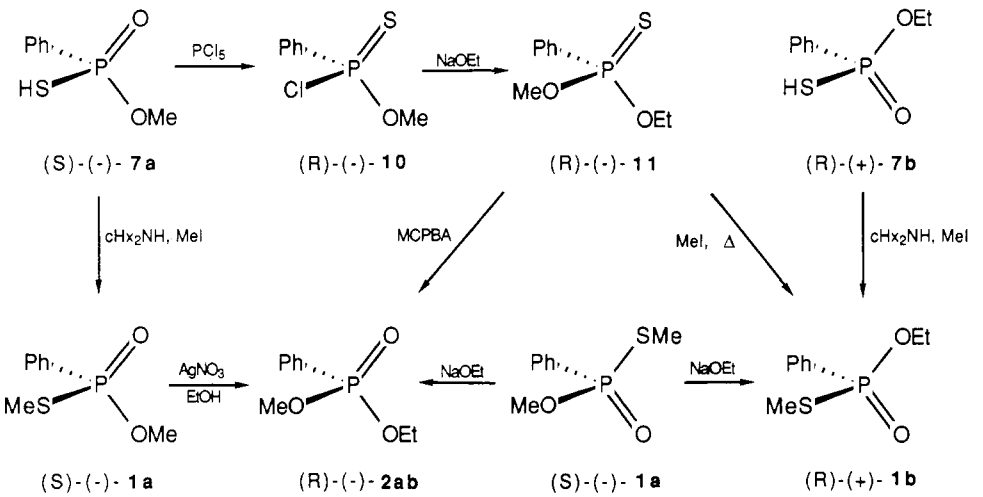
(26) Ohkawa, H.; Mikami, N.; Miyamoto, J. *Agric. Biol. Chem.* **1977**, *41*, 369. Other workers have also accomplished this resolution using brucine but provided little experimental detail. See: (a) Mikami, N.; Okawa, H.; Kasamatsu, N.; Okuno, Y. *Chem. Abstr.* **1978**, *89*, 163739. (b) Yoshitake, A.; Mohri, Z.; Kamada, T.; Yasuda, T.; Nakatsuka, I. *J. Labelled Compd. Radiopharm.* **1980**, *17*, 137. (c) Hirashima, A.; Eto, M. *Agric. Biol. Chem.* **1983**, *47*, 829.

(27) We noticed that carrying out the reaction in ether provided **1a** partially racemized. This may perhaps result from O-methylation, giving an achiral species (*O,O*-dimethyl phenylphosphonothioate) which then rearranges to racemic **1a**.

(28) van den Berg, G. R.; Platenburg, D. H. J. M.; Benschop, H. P. *J. Chem. Soc., Chem. Commun.* **1971**, 606.

(29) DeBruin, K. E.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7393.

**Scheme V**




chemical cycle shown in Scheme IV and thereby to establish the absolute configurations of both **1a**[30] and **7a** to be *R*-(+).[31] Raney nickel desulfurization[32] of (+)-**7a** provided (−)-**8a**, which, in turn, was resulfurized[10] and methylated to form (+)-**1a** and methylated to form (−)-**9a** by Benschop's method. The Grignard reaction of (+)-**1a**[5] closes the cycle to (−)-**9a**. Since the absolute configuration of **9a** is known to be *S*-(−)[33] and all these reaction types have been shown to proceed with retention stereochemistry, the absolute configurations are as shown.

The stereochemical cycles in Scheme V further relate the configuration of **1a** to that of **1b** and also to that of **2ab**, the other potential product from the reaction of sodium ethoxide with **1a**. *O*-Ethyl *O*-methyl phenylphosphonothioate (**11**) serves as a common precursor to both **1b** and **2ab**. We have synthesized **11** from **7a** by two inversion processes using phosphorus pentachloride[21] and sodium ethoxide[32] sequentially and carried out the conversion of **11** to **1b**, which must proceed with retention of configuration.[35] The conversion of **11** to **2ab** was reported by Koizumi[35] and also proceeds with retention of configuration. Thus, **2ab** must have the *R*-(−) configuration. This assignment[36] is supported by the direct conversion of **1a** to **2ab** using silver nitrate in ethanol, which promotes inversion of configuration.[12c]

Knowing the absolute configurations of **1a**, **1b**, and **2ab**, we were able to establish that the reaction of sodium ethoxide with **1a** displaces either the methoxy group or the methylthio group with net inversion of configuration as shown in Scheme V. The absolute stereochemistry and stereospecificity of these processes (see below) was most easily established by $^1$H NMR with the aid of the chiral contact-shift reagent Eu(tfc)$_3$. All three compounds show chemical shift nonequivalences between enantiomers in the presence of Eu(tfc)$_3$, with the *R* isomers of **1a**, **1b**, and **2ab** corresponding to the downfield PSMe, the downfield PSMe, and the upfield POMe proton signals, respectively. It is interesting to note that the SMe in (*R*)-**1a**, the SMe in (*R*)-**1b**, and the OMe in (*S*)-**2ab** all reside in a common stereo environment and are shifted more downfield in these isomers by the shift reagent.

**Determination of Competitive Pathway Ratios (Scheme III).** In a preliminary study, (*S*)-**1a** (70% ee) was reacted with a 0.63 M solution of sodium ethoxide in ethanol under pseudo-first-order conditions at room temperature. After 2 min, workup and analysis by NMR revealed that **1a**, **1b**, **2ab**, and **2bb** were all present in the reaction mixture in proportions of 1, 2, 10, and 1, respectively. Partial separation of the compounds by preparative chromatography gave samples enriched in **1b** or **2ab**, which could be analyzed by NMR for stereochemistry with a chiral shift reagent. Both compounds were formed with predominantly (>90%) inversion of configuration ($k_b \gg k_d$ and $k_a \gg k_c$; Scheme III).

A further evaluation of the stereochemistry in forming **2ab** and the competition in forming **1b** vs **2ab** was accomplished by kinetics with 0.36 M sodium ethoxide in ethanol at 20.0 °C under pseudo-first-order conditions. Beginning with **1a**, the reaction was allowed to proceed uninterrupted for an initial 2-h time interval. After this time interval, only **2ab** and **2bb** remain, and the ratios of **2ab** to **2bb** (as mol % **2ab**) and (*R*)-**2ab** to (*S*)-**2ab** (as % ee) were determined as a function of time. Two independent reactions were followed, beginning with (*S*)-**1a** having enantiomeric purities of 54% ee and 90% ee.

Both reactions gave nearly identical exponential curve fits of mole percent **2ab** against time ($r$ = 0.9999 and 0.9994, respectively) with an average pseudo-first-order rate constant ($k_f$) of 2.14 (±0.02) × $10^{-5}$ $s^{-1}$ and intercept corresponding to 77 (±2) mol% **2ab** (or 23% of **2bb**). Since formation of **2ab** from **1a** is much faster than conversion of **2ab** to **2bb**, the intercept implies that 23% (±2%) of **2bb** was formed by a reaction not proceeding through **2ab** but instead proceeding through **1b**. Thus, the ratio of rate constants for displacement of methylthiolate ion ($k_b$) vs methoxide ion ($k_a$) in the initial reactions of **1a** is approximately 3/1 (77%/23%) in favor of methylthiolate ion displacement. This is in excellent agreement with the ratio of **2ab**/(**1b** + **2bb**) found in the preliminary experiment (10/3).

The pseudo-first-order rate constant for racemization of **2ab** ($2k_e$) was obtained from an exponential curve fit of percent enantiomeric excess against time. Starting with (*S*)-**1a** of 54% ee, the **2ab** produced underwent racemization with a rate constant of 6.7 × $10^{-6}$ $s^{-1}$ ($r$ = 0.9902) and intercept corresponding to (*R*)-**2ab** of 55% (±1%) ee. The **2ab** produced from (*S*)-**1a** of 90% ee gave a similar rate constant of 6.9 × $10^{-6}$ $s^{-1}$ ($r$ = 0.9867) with intercept corresponding to (*R*)-**2ab** of 89% (±2%) ee. Since the intercepts are within error of initial percent enantiomeric excess values and (*R*)-**2ab** is in excess, the formation of **2ab** from **1a**, by displacement of methylthiolate ion, proceeds with *complete* inversion of configuration at phosphorus ($k_b \gg k_d$). Comparing the rate constant for formation of **2bb** from **2ab** ($k_f$) to that for racemization of **2ab** ($2k_e$) indicates the displacement of methoxide ion ($k_f$) is favored over displacement of ethoxide ion ($k_e$) by a ratio of approximately 6/1 [2.1 × $10^{-5}$ to (6.8 × $10^{-6}$)/2].

The conversion of **1b** to **2bb** by ethoxide ion was also studied kinetically with 0.19 M sodium ethoxide in ethanol at 20.0 °C. Following the reaction by UV–vis spectroscopy gave an average

(30) These reactions provided the information for footnote 5 in DeBruin, K. E.; Johnson, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 7921.

(31) The absolute configuration of **1a** has also been established[21] to be *S*-(−) by its synthesis from the ($S_CS_P$)-methylbenzylammonium salt of **7a** whose structure was determined by X-ray diffraction analysis. This salt shows the upfield POMe protons we observed in our resolution of **7a**.

(32) Szafraniec, L. J.; Szafraniec, L. L.; Aaron, H. S. *J. Org. Chem.* **1982**, *47*, 1936.

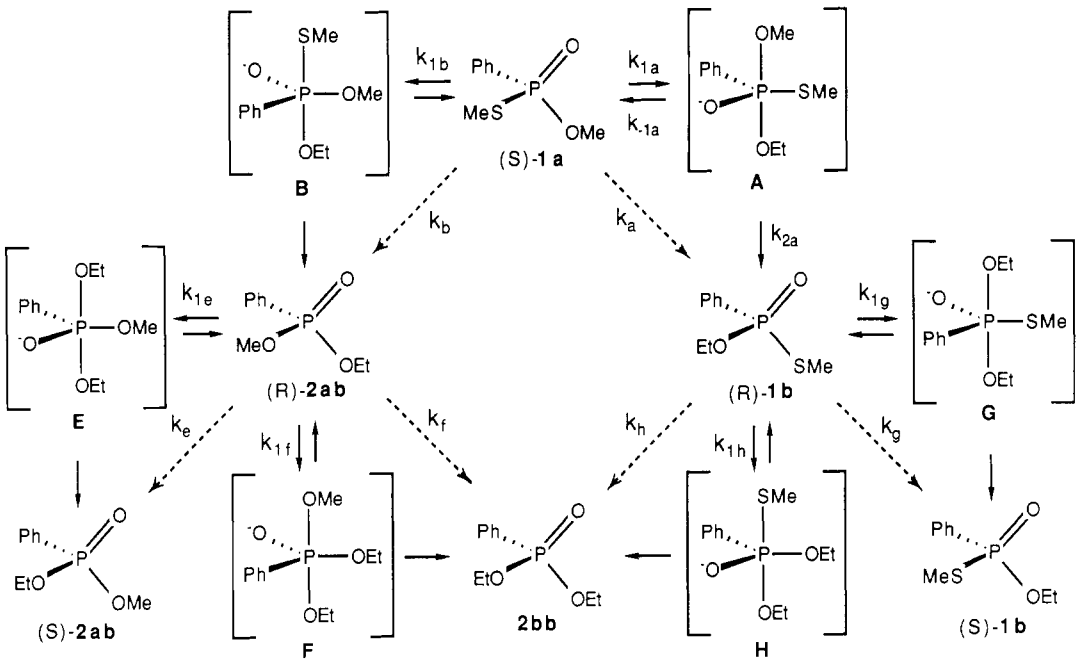
(33) DeBruin, K. E.; Petersen, J. R. *J. Org. Chem.* **1972**, *37*, 2272.

(34) Michalski, J.; Mikolajczak, J.; Skowronska, A. *J. Am. Chem. Soc.* **1978**, *100*, 5386.

(35) Koizumi, T.; Takagi, H.; Yoshii, E. *Chem. Lett.* **1980**, 1403.

(36) Koizumi[35] has also related the configurations of **1a** and **2ab** by synthesis from amide precursors.

**Scheme VI**




pseudo-first-order rate constant for methylthiolate ion displacement ($k_h$) of 7.3 (±0.1) × $10^{-4}$ $s^{-1}$. Correcting this rate constant to the same ethoxide ion concentration (0.36 M) used to study the reactions of **2ab** reveals that displacement of methylthiolate ion ($k_h$) from **1b** is faster than displacement of methoxide ion ($k_f$) from **2ab** by a factor of 65/1 (7.3 × $10^{-4}$ × 0.36/0.19 to 2.1 × $10^{-5}$).

In an independent large-scale experiment, (*S*)-**1b** (83% ee) was again allowed to react under the above reaction conditions. Two aliquots were taken at different times and determined by NMR analysis to consist of 77% (±2%) and 87% (±2%) **2bb**. The percent enantiomeric excess of the remaining **1b** in the two fractions was determined, with $Eu(tfc)_3$, to be 70% (±2%) and 67% (±2%), respectively, indicating that formation of **2bb** from **1b** ($k_h$) is approximately 9 (9.0 ± 0.5) times faster than racemization of **1b** ($2k_g$). Thus, displacement of methylthiolate ion ($k_h$) is favored over displacement of ethoxide ion ($k_g$) from **1b** by a factor of ca. 18/1. The calculated values (with errors) of all the above overall displacement ratios ($k_y/k_z$) are given in Table II.

**Calculation of Kinetic Facial Selectivities (Scheme VI).** If pentacoordinate intermediates are assumed to form in these displacement reactions by ethoxide ion, kinetic facial selectivities refer to relative rate constants for formation of these intermediates. The processes we observed and the structures of the various intermediates through which the displacements would occur are shown in Scheme VI.

A displacement reaction proceeding through a general intermediate Y which may return to starting material or proceed to product by loss of a leaving group (L) will have the form shown in eq 1. If steady-state conditions are assumed, the observed rate constant for an overall displacement reaction ($k_y$) is related to the rate constants of the individual steps by eq 2. Rearranging eq 2 gives eq 3, which relates the desired rate constant for intermediate formation ($k_{1y}$) to the rate constant of the overall displacement ($k_y$) and the ratio of rate constants for the intermediate returning to starting material ($k_{-1y}$) or proceeding to products ($k_{2y}$).

$$EtO^- + P\text{-}L \underset{k_{-1y}}{\overset{k_{1y}}{\rightleftharpoons}} [EtO\text{-}\underset{Y}{P}\text{-}L]^- \xrightarrow{k_{2y}} EtO\text{-}P + L^- \quad (1)$$

$$k_y = k_{1y}k_{2y}/(k_{-1y} + k_{2y}) = k_{1y}/[(k_{-1y}/k_{2y}) + 1] \quad (2)$$

$$k_{1y} = k_y[(k_{-1y}/k_{2y}) + 1] \quad (3)$$

**Table II.** Calculated Rate Constant Ratios[a] for Displacement of Various Leaving Groups (L) in the Reactions of **1a**, **1b**, and **2ab** with Sodium Ethoxide in Ethanol at 20.0 °C

| compd | L[b] | $k_y$ | compd | L[b] | $k_z$ | $k_y/k_z$[c] | $k_{1y}/k_{1z}$[d] |
|---|---|---|---|---|---|---|---|
| | | | Internal Ratios | | | | |
| **1a** | SMe | $k_b$ | **1a** | OMe | $k_a$ | 3.3 (±0.3) | 2 |
| **2ab** | OMe | $k_f$ | **2ab** | OEt | $k_e$ | 6.2 (±0.5) | 4.5 |
| **1b** | SMe | $k_h$ | **1b** | OEt | $k_g$ | 18 (±1) | 9 |
| | | | External Ratios | | | | |
| **1b** | SMe | $k_h$ | **2ab** | OMe | $k_f$ | 65 (±1) | 45 |
| **1b** | OEt | $k_g$ | **2ab** | OEt | $k_e$ | 22 (±2) | 22 |

[a] See Scheme VI for processes involved. At [NaOEt] = 0.36 M, $k_f$ = 2.14 × $10^{-5}$ $s^{-1}$. [b] Ligand being displaced in this process. [c] Rate constant ratios for overall displacement reactions. [d] Calculated rate constant ratios for formation of intermediates based on a $\beta_{LG}$ = 0.5 (see Results). For a $\beta_{LG}$ = 0.0, these values would equal $k_y/k_z$.

We estimated the ratios of $k_{-1y}/k_{2y}$ for the different leaving groups (L) by assuming loss of OEt or L from Y follows a Brønsted relationship with $\beta_{LG}$ = ca. 0.5. By definition, the ratio $k_{-1y}/k_{2y}$ for L = OEt must equal unity. Since methanethiol is considerably more acidic than ethanol, $k_{-1y}/k_{2y}$ for L = SMe would be near zero. Methanol is approximately 4 times more acidic than ethanol,[37] which gives a value for $k_{-1y}/k_{2y}$ when L = OMe of ca. 0.5. Thus, rate constants ($k_y$) for overall displacements of L = SMe, OMe, or OEt must be multiplied by factors of 1, 1.5, and 2, respectively, to obtain relative kinetic facial selectivities for formation of an intermediate in nucleophilic attack by an ethoxide ion.

The competitive processes shown in Scheme VI by which ethoxide ion reacts with a single substrate (internal ratios) involve the displacements of a methylthiolate ion ($k_b$) or a methoxide ion ($k_a$) from **1a** in a ratio of $k_b/k_a$ = 3/1, a methoxide ion ($k_f$) or an ethoxide ion ($k_e$) from **2ab** in a ratio of $k_f/k_e$ = 6/1, and a methylthiolate ion ($k_h$) or an ethoxide ion ($k_g$) from **1b** in a ratio of $k_h/k_g$ = 18/1. With the above corrections for reversibility, the approximation ratios for kinetic facial selectivities are $k_{1b}/k_{1a}$ = 2 (3/1 × 1/1.5), $k_{1f}/k_{1e}$ = 4.5 (6/1 × 1.5/2), and $k_{1h}/k_{1g}$ = 9 (18/1 × 1/2), respectively.

Our data also allow for a comparison of rate constants for reactions of ethoxide ion with two substrates (external ratios) which differ only in the nature of the ligands becoming axial or

(37) Determined in isopropyl alcohol. See: Hine, J.; Hine, M. *J. Am. Chem. Soc.* **1952**, *74*, 5266.

equatorial in the respective intermediates. Displacement of methylthiolate ion from **1b** ($k_h$) is favored over displacement of methoxide ion from **2ab** ($k_f$) by a ratio of 65/1. This corresponds to a kinetic ratio for intermediate formation with methylthio vs methoxy ligands becoming axial of $k_{1h}/k_{1f} = 43/1$ (65/1 × 1/1.5). Also, displacement of ethoxide ion from **1b** ($k_g$) is favored over displacement of ethoxide ion from **2ab** ($k_e$) by a ratio of 22/1, which gives a kinetic ratio for formation of intermediates with methylthio vs methoxy ligands becoming equatorial ($k_{1g}/k_{1e}$) also equal to 22/1 (22/1 × 2/2). These ratios of rate constants for intermediate formation ($k_{1y}/k_{1z}$) are also summarized in Table II for the processes defined in Scheme VI.

It should be pointed out that these ratios are dependent on the choice of $\beta_{LG}$ which determines the value of $k_{-1y}/k_{2y}$ (eq 3). If $\beta_{LG}$ is approximately equal to zero (very early transition states for decomposition of Y), all values of $k_{-1y}/k_{2y}$ become equal to unity and all values of $k_{1y}/k_{1z}$ become equal to the values directly calculated for $k_y/k_z$ given in Table II. The actual values are probably somewhere between these two extremes.

## Discussion

As described in the introduction, both retention and inversion stereochemistry at phosphorus has been observed in bimolecular nucleophilic displacements of an alkylthiolate ion from acyclic organophosphorus species containing alkoxy and alkylthio ligands. Assuming facial attack by the nucleophile, retention of configuration in alkylthiolate ion displacement requires that (1) the reaction proceeds by a stepwise mechanism ($A_N + D_N$) involving formation of a pentacoordinate TBP intermediate with a lifetime for isomerization, (2) kinetic control in formation of the intermediate parallels thermodynamic control with the less apicophilic alkylthio ligand[38] occupying an equatorial position, and (3) this intermediate is energetically able to undergo the isomerization essential for alkylthiolate ion departure from an axial position. If any of these conditions does not hold, inversion stereochemistry could result. We set out to determine whether inversion stereochemistry was observed in the reaction of alkoxide ions with phosphonothioates simply beause condition 3 cannot be energetically satisfied. In terms of the generic processes shown in Scheme I, this means intermediate A would be preferentially formed over B but would not undergo alkylthiolate ion disassociation since isomerization of A to C is energetically blocked.

The reaction of sodium ethoxide in ethanol with *O,S*-dimethyl phenylphosphonothioate (**1a**) was observed to proceed with competitive initial displacements of methylthiolate or methoxide ions ($k_b$ or $k_a$, Scheme VI) to form **2ab** or **1b**, respectively, in a ratio of 3/1 (Table II). Both displacements occurred with complete inversion of configuration at phosphorus, which implicates intermediates (or transition states) of structure B or A, respectively. Therefore, at least 25% of the reaction must have proceeded through an intermediate of structure A to give **1b**, but A can*not* be a precursor to methylthiolate ion dissociation. Measuring the amount of **1b** production underestimates the involvement of A if some of A could have returned to starting material (**1a**) by loss of ethoxide ion ($k_{-1a}$) and not shown up as product (**1b**). We corrected for this possibility by assuming methoxide ion is a 2-fold better leaving group (see Results). With this correction, there still remains a 2-fold (Table II) kinetic preference ($k_{1b}/k_{1a}$) for formation of B over A. Thus, in addition to the condition 3 above, conditions 2 and/or 1 are not met in this system and are the major reasons inversion stereochemistry is observed. In other words, *kinetic control does not favor nucleophilic attack in the face opposite the more apicophilic methoxy ligand*, and this may be due to the fact that one (or both) of these displacements does not proceed through an intermediate in a stepwise process ($A_N + D_N$ mechanism).

The rate constants for the further reactions (see Scheme VI) of ethoxide ion with the two initial products from **1a** provide additional insight. Both **1b** and **2ab** undergo racemization with displacement of an ethoxide ion ($k_g$ and $k_e$) in competition with formation of **2bb** with displacement of methylthiolate ion ($k_h$) and methoxide ion ($k_f$), respectively. Having determined approximate pseudo-first-order rate constants for all four displacements under similar conditions, we calculated rate constant ratios ($k_y/k_z$) for these displacements (Table II). Assuming these reactions proceed through intermediates as shown and correcting for reversibility in intermediate formation, we also estimated the rate constant ratios ($k_{1y}/k_{1z}$) for formation of these intermediates (Table II). Rate constant ratios are presented as either internal or external ratios depending on whether the ratio refers to competitive reactions on a single compound (kinetic facial selectivity) or refers to relative reactivities of two different compounds.

As already stated, the internal ratio ($k_{1b}/k_{1a}$) from the reaction of ethoxide ion with **1a** favors facial attack opposite a methylthio ligand to form B over a methoxy ligand to form A by a factor of 2. The internal ratio ($k_{1f}/k_{1e}$) from the reaction of ethoxide ion with **2ab** favors facial attack opposite a methoxy ligand to form F over an ethoxy ligand to form E by a larger factor of 4.5. The product of these two ratios equals the internal ratio ($k_{1h}/k_{1g}$) observed in the reaction of ethoxide ion with **1b**, which favors facial attack opposite a methylthio ligand to form H over an ethoxide ion to form G by a factor of 9. Thus, these ratios appear to be the result of intrinsic properties of the individual ligands. The general trend is for ethoxide ion to preferentially attack in a face opposite the better leaving group (MeS > MeO > EtO) and not the more electronegative group. The relative magnitude of the preferences, however, is not what one would expect if the facial selectivities are controlled by the stability of a negatively charged leaving group.

It should be pointed out that facial selectivities would not be determined simply by properties of one group becoming axial but also are affected by properties of the other group becoming equatorial. From a linear free energy relationship viewpoint, an internal ratio will reflect the relative "intrinsic affinities" for the two groups to occupy an axial position (axial substituent effect) over the relative intrinsic affinities for the two groups to occupy an equatorial position (equatorial substituent effect).[41] Our external ratios provide these intrinsic affinities. The ratio $k_{1h}/k_{1f}$ (45/1) for formation of H over F defines the kinetic affinity for a methylthio ligand (relative to a methoxy ligand) to occupy an axial position in the intermediate. The ratio $k_{1g}/k_{1e}$ (22/1) for formation of G over E defines the kinetic intrinsic affinity for a methylthio ligand (relative to a methoxy ligand) to occupy an equatorial position. Thus, formation of B from **1a** would be favored over formation of A by a ratio of these two intrinsic affinities, giving a factor of 45/22, in excellent agreement with the factor of 2 observed. Apparently, the small facial selectivity in the reaction of ethoxide ion with **1a** is the result of a methylthiolate ion (relative to a methoxide ion) having large but similar (45/22) intrinsic affinities for either an axial position or an equatorial position. A large relative intrinsic affinity for a methylthio ligand to occupy an axial position ($k_h/k_f$) seems to indicate concerted displacement mechanisms ($A_ND_N$) where negative charge is developing on the leaving group in the axial position.[43] However, it then becomes also necessary to explain the substantial relative intrinsic affinity ($k_g/k_e$) for a methylthio

(38) The apicophilicity of an OMe ligand was observed to be greater than that for an SMe ligand in processes involving isomerization of the ligand from an equatorial position to an axial position.[39] Also, the structure of a cyclic phosphorane with both oxygen and sulfur atoms attached to phosphorus within one ring contains the oxygen in an axial position.[40]

(39) Cavell, R. G.; Gibson, J. A.; The, K. T. *Inorg. Chem.* **1978**, *17*, 2880.

(40) Duff, E.; Russell, D. R.; Trippett, S. *Phosphorus* **1974**, *4*, 203.

(41) In systems where competitive modes of nucleophilic attack on a single compound are possible, the term "apical potentiality" has been suggested[42] "to relate the likelyhood, during nucleophilic attack at tetrahedral phosphorus, of a ligand being in-line with the nucleophile and therefore of occupying an apical position in the initially formed TBP". As defined, this would be a relative term and not exclusively an intrinsic property of the apical ligand. It is synonymous with our internal ratios.

(42) Hall, C. R.; Williams, N. E. *Tetrahedron Lett.* **1980**, 4959.

(43) For concerted processes, relative intrinsic affinities refer to external ratios of $k_x/k_y$ since intermediates are not involved.

(44) DeBruin, K. E.; Johnson, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 7921.

(45) Stec, W. J.; Okruszek, A.; Lesiak, K.; Uznanski, B.; Michalski, J. *J. Org. Chem.* **1976**, *41*, 227.

ligand to occupy an equatorial position. If no additional charge were developing on phosphorus, the effect is not inductive in the classical sense. The less electronegative methylthio ligand would better accommodate the resulting decrease in p character in the orbital on phosphorus which overlaps with the ligand becoming equatorial ($sp^3$ to $sp^2$). An equatorial methylthio ligand may also have relatively more stabilizing (less destabilizing) orbital interactions with the hypervalent-like orbitals on phosphorus. Until these effects are quantified, it seems more reasonable to suggest that the large equatorial substituent effect is indicative of the reaction being stepwise in nature ($A_N + D_N$) and reflects a decrease in positive charge occurring on phosphorus.

Since the external ratio ($k_h/k_f$) for forming H over F is consistent with a concerted mechanism while the external ratio ($k_{1g}/k_{1e}$) for forming G over E implicates an intermediate, we would like to suggest as a working hypothesis an alternative to the displacements being either concerted or stepwise. Presumably, there exists the potential for a continuum of mechanisms ranging from $A_N + D_N$, through $A_ND_N$, and on to $D_N + A_N$. The reactions of concern in this study most likely lie on the $A_N + D_N$ side of a truly synchronous process since we are dealing with a strong nucleophile. There is no reason why facial attack of a nucleophile opposite a methylthio ligand should have the same degree of bond formation or bond dissociation as attack opposite an alkoxy ligand. Of the two attacks, the former, with the better leaving group, should be less $A_N + D_N$ in character. If one assumes, for simplicity, that nucleophilic attack opposite an alkoxy ligand is stepwise ($A_N + D_N$) in all cases, situations that encourage concerted processes ($A_ND_N$) will predominantly proceed by nucleophilic attack opposite an alkylthio ligand and displace this ligand with inversion of configuration at phosphorus. Alternatively, situations that discourage concerted processes will predominantly proceed by nucleophilic attack opposite an alkoxy ligand to form the more stable intermediate. As a consequence, considerable amounts of alkoxide ion displacement with inversion or alkylthiolate ion displacement with retention of configuration at phosphorus will result. In terms of Scheme I, A would be an intermediate while B would represent a transition state.[46]

This dual-mechanism hypothesis goes a long way toward explaining our results, the stereochemical results in Table I, and other information in the literature. In the reaction of alkoxide ions with phosphonothioates (as well as phosphonodithioates and phosphoramidothioates), the polar solvent employed may encourage concerted processes and thus lead to methylthiolate ion displacement with inversion stereochemistry. Since alkoxide ion is also displaced in the phosphonothioate system, this would be a borderline situation. It has been reported[44] that the reaction of sodium methoxide in methanol with **1a** competitively displaces methylthiolate ion and methoxide ion in a ratio of 10/1. We found a ratio of 3/1 using sodium ethoxide in ethanol, consistent with a more polar protic solvent giving a higher ratio by favoring the concerted process of methylthiolate ion displacement. Hall, Inch, and co-workers[13] have similarly observed a low ratio in the reaction of bulky alkoxide nucleophiles in DMF and a high ratio in the reaction of methoxide ion in methanol with *O*-alkyl *S*-methyl methylphosphonothioates (**3a** and **3b**, PMe analogues of **1a** and **1b**).

Although the solvent is again quite polar, the reaction of hydroxide ion with a phosphonium salt[3] most likely proceeds through initial formation of a neutral pentacoordinate intermediate. Thus, attack opposite an alkoxy ligand to form A is favored and results in retention stereochemistry for methylthiolate ion displacement. Since Grignard reactions[4-6] were carried out in nonpolar solvents and magnesium coordination with phosphoryl oxygen[7] could increase the positive charge on phosphorus, concerted processes are discouraged, and formation of A with attack opposite an alkoxy ligand is favored and leads to retention stereochemistry.

The retention of configuration observed in the alkoxide ion displacement of methylthiolate ion from phosphorothioates (e.g., formation of **6ab** from **5a** or **5b**)[12] presents somewhat of a dichotomy since the solvent is again polar. It has been demonstrated[13b] that methylthiolate ion displacement from phosphorothioates is faster than from phosphonothioates while displacement of a halogen from analogues has the opposite order of reactivity. If halogen displacement from both substrates is occurring by the same mechanism ($A_ND_N$), methylthiolate ion displacement from phosphorothioates must be proceeding by a different mechanism ($A_N + D_N$), consistent with the retention stereochemistry observed. If our mechanistic hypothesis is assumed to be correct, compared to equatorial alkyl, aryl, or alkylamino ligands (ligand Z in Scheme I), an alkoxy ligand seems to encourage formation of an intermediate (which therefore would have structure A) over a transition state.

One other report in the literature seems to case some doubt on the dual-mechanism hypothesis. Displacement of methylthiolate ion from the phosphonothioate *O*-ethyl *S*-methyl ethylphosphonothioate by lithium anilide in the nonpolar solvent ether proceeded[45] with inversion of configuration at phosphorus. The yield, however, was only 19.5%, which still allows for predominant formation of intermediate A (as predicted for a nonpolar solvent) and subsequent displacement of ethoxide ion.

A number of alternatives or added considerations to a dual-mechanism hypothesis must be considered. Ligands on phosphorus or the nature of the nucleophile may simply have an effect on HOMO–LUMO interactions leading to varying facial selectivities.[48] Ion pairing of the nucleophile and selective complexation with the ligands on phosphorus may have a directing effect on facial attack.[7] Stereoelectronic effects[49] may also influence orientation of nucleophilic attack. We are proceeding with a systematic experimental and theoretical study to evaluate these and other possibilities in the hope of providing further fundamental information on displacement reactions at phosphorus containing multiple displaceable ligands.

## Summary

In this paper, we demonstrated that the ethoxide ion (in ethanol) displacement of methylthiolate ion from a phosphonothioate (**1a**) proceeds with *complete* inversion of configuration at phosphorus. The partial retention observed by other workers with analogous phosphonothioates[12] may be explained by our observation that the product of this displacement undergoes further racemization in competition with a second displacement.

The reaction of ethoxide ion with **1a** proceeds with a *low* kinetic facial selectivity which slightly favors placing the methylthio ligand, *not the methoxy ligand*, in an axial position of a pentacoordinate intermediate or transition state. This observation rules out the possibility that the preferred reaction of alkoxide ion with phosphonothioates is to place the more electronegative alkoxy ligand in an axial position but is prevented from leading to methylthioate ion displacement due to a required high-energy isomerization. Such a pathway is available and required in the reaction of Grignard reagents with phosphonothioates and alkoxide ions with phosphorothioates since retention stereochemistry is observed.

The facial selectivity in the reaction of ethoxide ion with **1a** (which puts a methylthio ligand axial and a methoxy ligand equatorial in B vs a methoxy ligand axial and a methylthio ligand equatorial in A) is identified to be the ratio of a relative intrinsic affinity for a methylthio ligand vs a methoxy ligand to be placed in an axial position and a relative intrinsic affinity of a methylthio ligand vs a methoxy ligand to be placed in an equatorial position. Thus, there is no ligand–ligand interaction between the methoxy

(46) One could also view this difference as methylthiolate ion displacement occurring via an "open" or "exploded" transition state with negative charge residing primarily on the nucleophile and leaving group and alkoxide ion displacement occurring via a "collapsed" transition state or intermediate with the negative charge being absorbed by the phosphorus atom.[47]

(47) (a) Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 7591. (b) Skoog, M. T.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 7597.

(48) Corriu, R. J. P.; Lanneau, G. F.; Leclercq, D. *Tetrahedron* **1986**, *42*, 5591, and references cited therein.

(49) (a) Fanni, T.; Taira, K.; Gorenstein, D. G.; Vaidyanathaswamy, R.; Verkade, J. G. *J. Am. Chem. Soc.* **1986**, *108*, 6311. (b) Gorenstein, D. *Chem. Rev.* **1987**, *87*, 1047, and references cited therein.

**Table III.** $^1$H NMR Spectral Data on Phenylphosphonothioates and Analogues

| Ph(Y)P(X)Z | | | | chem shifts, ppm ($J_{HP}$, Hz)[a] | | | |
|---|---|---|---|---|---|---|---|
| no. | X | Y | Z | $POCH_3$ | $POCH_2C$-$H_3$ | $POCH_2C$-$H_3$ | other |
| **1a** | O | OMe | SMe | 3.87 (12) | | | 2.15 (14)[b] |
| **1b** | O | OEt | SMe | | 4.30 (9) | 1.40 (0) | 2.16 (14)[b] |
| **2ab** | O | OMe | OEt | 3.80 (11) | 4.20 (8) | 1.39 (0) | |
| **2bb** | O | OEt | OEt | | 4.20 (8) | 1.40 (0) | |
| **7a** | O | OMe | SH | 3.75 (14) | | | |
| **7b** | O | OEt | SH | | 4.20 (10) | 1.31 (0) | |
| **8a** | O | OMe | H | 3.77 (12) | | | 7.62 (560)[c] |
| **8b** | O | OEt | H | | 4.13 (9) | 1.34 (0) | 7.62 (566)[c] |
| **10** | S | OMe | Cl | 3.92 (16) | | | |
| **11** | S | OMe | OEt | 3.70 (14) | 4.14 (10) | 1.29 (0) | |

[a] All $J_{HH}$ = 7 Hz. [b] $PSCH_3$ protons. [c] $PH$ proton.

**Table IV.** Stereochemistry in Conversions of Phenylphosphonate Analogues by the Reactions Shown in Schemes IV and V

| reactant | | | | product | | | |
|---|---|---|---|---|---|---|---|
| no. | config | $[\alpha]_D$, deg[a] | % ee | no. | config | $[\alpha]_D$, deg[a] | % ee |
| **7a** | *S* | −11.8[b] | 100 | **1a** | *S* | −123[c] | 100[d] |
| **7b** | *R* | +9.1[b] | 100 | **1b** | *R* | +120 | 100[d] |
| **7a** | *R* | +11.8[b] | 100 | **8a** | *S* | −42 | 100[e] |
| **8a** | *S* | −42 | 100 | **9a** | *S* | −30 | 58[f] |
| **8a** | *S* | −15 | 36 | **1a** | *R* | +44 | 36[d] |
| **7a** | *S* | −11.8[b] | 100 | **10** | *R* | −62 | 44[g] |
| **10** | *R* | −28.4 | 20 | **11** | *R* | −1.8 | 20[g] |
| **11** | *R* | −1.8 | 20 | **1b** | *R* | +24 | 20[d] |
| **1a** | *S* | −123 | 100 | **2ab** | *R* | −3.1[h] | 95[d] |

[a] Solvent benzene (*c* 2–4) except as noted. [b] Dicyclohexylammonium salt, solvent methanol (*c* 2–4). [c] $[\alpha]_D$ = −81° in methanol. [d] Determined by NMR in the presence of $Eu(tfc)_3$. [e] Determined by NMR in a chiral solvent [$PhCH(OH)CF_3$]. [f] Determined by comparison of optical rotation to the highest value reported in the literature (ref 33). [g] Established by the chemical correlation to **1b**. [h] Solvent carbon tetrachloride. In methanol, $[\alpha]_D$ = +0.64°.

ligand and the methylthio ligand which varies during the reaction. This suggests that kinetic facial selectivities in general can be predictable from a linear free energy treatment of isolated relative intrinsic affinities (axial and equatorial substituent constants).

## Experimental Section[50]

**General.** When similar reactions were performed on both methyl and ethyl derivatives, general procedures are given with specific results. All $^1$H NMR spectra are given in Table III, and Table IV lists the stereochemical results of chiral conversions.

**Synthesis of Methyl and Ethyl Phenylphosphinates (8a and 8b).** A solution of the appropriate alcohol (0.625 mol) and pyridine (30 g, 0.380 mol) in benzene (60 mL) was added dropwise over 1.5 h to a stirring, cooled solution of dichlorophenylphosphine (53.7 g, 0.30 mol) in benzene (350 mL). The pyridinium hydrochloride formed within 1 h was vacuum filtered from solution, and water (75 mL) was added dropwise to the filtrate. The organic layer was extracted with saturated sodium bicarbonate and water, and the aqueous phase was back-extracted twice with dichloromethane (150 mL). The combined organic phases were dried and concentrated. Kugelrohr distillation gave pure product.

With use of methanol, **8a** [bp 72 °C, 0.1 mmHg (lit.[51] bp 93 °C, 1 mmHg); IR ($cm^{-1}$) 2380 ($\nu_{PH}$), 1230 ($\nu_{P=O}$) (lit.[51] IR 2400, 1250)] was formed in 75% yield. Similarly, **8b** [bp 94 °C, 0.23 mmHg (lit.[51] mp 102–103 °C, 0.2 mmHg); IR ($cm^{-1}$) 2330, 2350 ($\nu_{PH}$), 1240 ($\nu_{P=O}$) (lit.[51] IR 2340, 1240)] was prepared from ethanol in 72% yield.

**Synthesis of Dicyclohexylammonium Salts of *O*-Methyl and *O*-Ethyl Hydrogen Phenylphosphonothioates (7a and 7b) from 8a and 8b.** Elemental sulfur (12 g, 0.375 mol) was slowly added to a stirring solution of **8** (0.375 mol) and dicyclohexylamine (68.0 g, 0.375 mol) in ether (500 mL) over a period of 1 h. After stirring for an additional 3 h, the mixture was filtered, and the crystalline solid was recrystallized from ethyl acetate to give the pure dicyclohexylammonium *O*-alkyl phenylphosphonothioate. Thus, the dicyclohexylammonium salts of **7a** [mp 161–162 °C (lit.[21] mp 155–156 °C). Anal. ($C_{19}H_{32}NO_2PS$) C, H] and **7b** [mp 152–153 °C. Anal. ($C_{20}H_{34}NO_2PS$) C, H] were prepared in 85% and 80% yields, respectively.

**Interconversions of Dicyclohexylammonium Salts with their *O*-Alkyl Hydrogen Phenylphosphonothioates (7a and 7b).** A solid sample of the dicyclohexylammonium *O*-alkyl phenylphosphonothioate (0.316 mol) was gradually added to a stirring solution (600 mL) of aqueous sodium hydroxide (1.5 M, 0.9 mol). After 30 min, the mixture was extracted with benzene (4 × 200 mL), and the aqueous layer was acidified with sulfuric acid (6 N, 200 mL), saturated with sodium chloride, and extracted with ether (5 × 400 mL). The combined ether extracts were dried and concentrated under reduced pressure to give *O*-alkyl hydrogen phenylphosphonothioate in 90–95% yield and pure by NMR. The acids were used directly without further purification.

Due to their apparent instability, when *O*-alkyl hydrogen phenylphoshonothioates were generated from other sources, they were converted and stored as their dicyclohexylammonium salts by the following general procedure. A solution of dicyclohexylamine (23.2 g, 0.127 mol) in ether (100 mL) was added to a solution of the *O*-alkyl hydrogen phenylphosphonothioate (0.127 mol) in ether (250 mL) and stirred for 1 h. Filtration gave the desired dicyclohexylammonium salt in 70–90% yield, purified as above.

**Resolution of *O*-Methyl Hydrogen Phenylphosphonothioate (7a).** A solution of (*S*)-(−)-methylbenzylamine (9.2 g, 0.076 mol; $[\alpha]_D$ = −39°, neat) in ether (50 mL) was added to a solution of racemic **7a** (14.2 g, 0.076 mol) in ether (200 mL) and stirred for 20 h. After this was allowed to stand without stirring an additional 24 h, the resulting salt (4.8 g) was filtered from solution. Two recrystallizations from ethyl acetate (100 mL) gave pure ($S_CS_P$)-methylbenzylammonium salt of **7a** [3.6 g, 0.012 mol; mp 145–146 °C (lit.[21] mp 142–144 °C); $[\alpha]_D$ = −15.9°, *c* 3, MeOH (lit.[21] $[\alpha]_D$ = −17.68°, *c* 14.5, MeOH)]. The diastereomeric ratio of $S_CS_P$ to $S_CR_P$ salts, and hence the degree of resolution, was followed by NMR spectroscopy in benzene of the POMe region. The $S_CS_P$ salt appeared at a higher field than the $S_CR_P$ salt. Analysis of additional samples of diastereomerically impure salts gave a linear plot of specific rotation vs percent $S_CR_P$ isomer with slope of 0.22 deg/% and intercept of −16 deg. Thus, by extrapolation, the pure $S_CR_P$ isomer would have $[\alpha]_D$ = +6.0° (±0.5°) in methanol.

**Resolution of *O*-Ethyl Hydrogen Phenylphosphonothioate (7b).** A warm solution of racemic **7b** (103 g, 0.51 mol) in acetone (250 mL) was added dropwise to a solution of brucine (201 g, 0.51 mol) in boiling acetone (3.3 L). After total addition, the mixture was allowed to cool to room temperature and left standing for 4 days. Filtration of the resulting solid (126 g) from solution and recrystallization from methanol (1.2 L) gave a white crystalline brucine salt of (*S*)-**7b** (107 g, 0.174 mol; mp 210–212 °C). The mother liquor was concentrated upon reduced pressure to an oil which immediately converted to solid upon the addition of methanol (800 mL). Heating this mixture to boiling and filtering gave the brucine salt of (*R*)-**7b** (147 g, 0.24 mol; mp 110–113 °C). The combined yield of brucine salts was 84%.

The higher melting brucine salt of (*S*)-**7b** (100 g, 0.16 mol) was dissolved in a solution of sodium hydroxide in 35% aqueous methanol (200 mL, 0.9 M) and diluted with water (250 mL). Extraction with dichloromethane (4 × 75 mL) removed the free brucine from solution. The aqueous layer was then acidified with hydrochloric acid (6 M, 32 mL) and extracted with dichloromethane (3 × 100 mL). Concentrating these organic extracts under vacuum gave the acid (*S*)-**7b** (33 g). Without purification, the acid was converted to its dicyclohexylammonium salt as above (50 g, 0.13 mol, 81% yield from brucine salt; mp 152–154 °C; $[\alpha]_D$ = −8.2°, methanol). A similar procedure converted the lower melting brucine salt to (*R*)-**7b** in 84% yield (mp 152.5–153.5 °C; $[\alpha]_D$ = +9.1°, methanol).

**Synthesis of *O*-Methyl *S*-Methyl and *O*-Ethyl *S*-Methyl Phenylphosphonothioates (1a and 1b) from the Dicyclohexylammonium Salts of 7a and 7b.** Excess iodomethane (6.3 mmol) was added to a stirring solution of the dicyclohexylammonium salt (2.7 mmol) in benzene (6 mL). After 6 h, the dicyclohexylammonium iodide precipitate was filtered from solution, and the filtrate was condensed under reduced pressure. Kugelrohr distillation afforded the desired *O*-alkyl *S*-methyl phenylphosphonothioate as a colorless oil. **1a** [bp 110–112 °C, 0.08 mmHg;

(50) Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter at concentrations of 2–4 g/100 mL in benzene unless noted otherwise. $^1$H NMR spectra were obtained on either a Varian A60A or a Varian T60 spectrometer, deuteriochloroform with 1% TMS being used as solvent. Mass spectra were obtained on an AEI MS-908 mass spectrometer. Elemental analyses were performed by Chemalytics, Inc., Tempe, AZ, and, in all cases, were within 0.3% of theoretical. Boiling points refer to Kugelrohr distillation temperatures, and melting points are uncorrected. A Lauda Model K-4/R constant-temperature bath was used to maintain temperatures to ±0.2 °C, and a Hewlett-Packard 5730A gas chromatograph was used to identify products and measure product ratios.

(51) Emmick, T. L.; Lestinger, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 3459.

IR ($cm^{-1}$) 1230; MS $m/z$ 202 ($M^+$). Anal. ($C_8H_{11}O_2PS$) C, H] and **1b** [bp 120 °C, 0.1 mmHg; MS $m/z$ 216 ($M^+$). Anal. ($C_9H_{13}O_2PS$) C, H] were obtained in 92% and 99% yields, respectively.

**Conversion of 7a to Methyl Phenylphosphinate (8a).** A solution of **7a** (5.6 g, 30 mmol) in methanol (5 mL) was added to a slurry of Raney nickel (25 g) in methanol (120 mL) and stirred for 10 min. Dichloromethane (100 mL) was then added; the mixture brought to reflux and filtered. The filtrate was washed twice with 3% aqueous sodium bicarbonate solution and once with water. The aqueous phases were back-extracted with dichloromethane, and the combined dichloromethane solutions were dried and concentrated. The resulting oil (1.7 g, 36% yield) was identified as pure **8a** by NMR comparison to authentic material prepared earlier by another route. For further stereochemical conversions, this material was used without purification due to its slow spontaneous racemization.

**Conversion of 8a to Methyl Methylphenylphosphinate (9a).** A solution of **8a** (0.40 g, 2.6 mmol) in dimethylformamide (5 mL) was added over a period of 10 min to a suspension of sodium hydride (0.065 g, 2.7 mmol) in dimethylformamide (5 mL) containing iodomethane (5.7 g, 40 mmol). After 40 min, water (10 mL) was added with stirring, the aqueous layer was separated and extracted with ether, and the combined organic phases were dried and concentrated under vacuum. The oil residue was Kugelrohr distilled to give a mixture (0.11 g), determined by NMR comparisons with authentic materials to contain only the desired **9a** (78%), dimethyl phenylphosphonate (**2aa**, 15%), and unreacted **8a** (7%). For stereochemical analysis, the optical rotation on a sample of the mixture was corrected for the presence of the achiral **2aa** and for **8a** by assuming it had retained its initial specific rotation.

**Conversion of 7a to *O*-Methyl Phenylphosphonochloridothioate (10).** A solution of **7a** (2.1 g, 11 mmol) in dichloromethane (2 mL) was added over a period of 10 min to a stirring suspension of phosphorus pentachloride (2.02 g, 11 mmol) in dichloromethane (10 mL) at ice-bath temperature.[52] After addition, the mixture was allowed to warm to room temperature, stirred for an additional 30 min, and then evaporated under reduced pressure to remove solvent and phosphorus oxychloride. Kugelrohr distillation (85 °C, 0.05 mmHg) afforded **10** (1.1 g, 5.5 mmol, 50% yield). The product was pure by NMR and used directly without further analysis.

**Conversion of 10 to *O*-Ethyl *O*-Methyl Phenylphosphonothioate (11).** A solution of **10** (0.765 g, 3.8 mmol) in hexane (2 mL) was added over 3 min to a stirring solution of sodium ethoxide in ethanol (3 mL, 2 M) in an ice bath. After 5 min, the mixture was added directly to aqueous hydrochloric acid (60 mL, 0.17 M) and extracted with dichloromethane. The organic layer was dried, concentrated, and Kugelrohr distilled (70 °C, 0.05 mmHg) to give pure **11** [0.7 g, 3.2 mmol, 85% yield; MS $m/z$ 186 ($M^+$). Anal. ($C_9H_{13}O_2PS$) C, H].

**Conversion of 11 to *O*-Ethyl *S*-Methyl Phenylphosphonothioate (1b).** Iodomethane (9.1 g, 64 mmol) and **11** (0.44 g, 2 mmol) were placed in a Fisher–Porter Airesol compatability tube pressure vessel and charged with 15 psi of nitrogen. The tube was placed in an oil bath at 113 °C and stirred for 6 h. After cooling, the contents were filtered and concentrated under reduced pressure. Kugelrohr distillation (120 °C, 0.1 mmHg) gave a product mixture (0.40 g) which was determined by NMR to contain the desired **1b** (88%), recovered **11** (8%), and *O,S*-dimethyl phenylphosphonothioate (**1a**, 4%). For optical rotation analysis, **11** was considered to be unracemized, and **1b** and **1a** were assumed to have the same optical purity but of opposite configurations.

(52) Ether and carbon tetrachloride are reported[53] to be better solvents for obtaining high optical purity in an analogous system. We found ether gave some unidentified side product.

(53) Michalski, J.; Mikolajczyk, M. *Tetrahedron* **1966**, *22*, 3055.

**Conversion of 1a to Ethyl Methyl Phenylphosphonate (2ab).** A sample of **1a** (1.0 g, 5 mmol) was added to a suspension of silver nitrate (1.68 g, 10 mmol) in ethanol (10 mL) at 0 °C and stirred for 15 h at room temperature. The mixture was then filtered and concentrated to 5 mL. After redilution with dichloromethane (50 mL), the solution was extracted with saturated aqueous sodium bicarbonate, dried, and reconcentrated. Kugelrohr distillation (71–73 °C, 0.05 mmHg) gave pure **2ab** [0.80 g, 81% yield. Anal. ($C_9H_{13}O_3P$) C, H].

**Synthesis of Diethyl Phenylphosphonate (2bb).** A solution of ethanol (17.5 mL, 0.30 mol) and pyridine (16.1 mL, 0.20 mol) in ether (100 mL) was added, over a period of 1 h to a stirring solution of phenylphosphonic dichloride (19.5 g, 0.10 mol) in ether (200 mL) at ice-bath temperature. After addition was completed, the mixture was stirred for 6 h at room temperature and filtered. Removal of solvent under vacuum and Kugelrohr distillation (110 °C, 0.25 mmHg) of the product gave pure **2bb** [19.6 g, 92% yield; MS $m/z$ 214 ($M^+$)].

**Kinetic Procedure for the Reaction of 1a with Sodium Ethoxide in Ethanol.** A solution of sodium ethoxide in ethanol (0.36 M, 100 mL), preequilibrated to 20.0 °C, was added to **1a** (0.93 g, 4.6 mmol). After rapid mixing, the kinetic solution was maintained at 20.0 °C in a constant-temperature bath. A 2-h period was allowed to pass until only **2ab** and **2bb** remained, and then, aliquots (10 mL) were removed at various time intervals over 36 h. Each aliquot was quenched by addition to a 50/50 mixture of water and dichloromethane in a separatory funnel and rapidly mixed. Separation of the organic layer, drying, and concentration under reduced pressure gave the crude sample for analysis. Product composition (**2ab** and **2bb**) was determined independently by gas chromatography (SE-30, 10-ft column, 200 °C) and NMR integrations with excellent agreement. Calibration curves indicated no correction was necessary for GC detector sensitivity variations. Enantiomer ratio for the ethyl methyl phenylphosphonate product (**2ab**) were determined by adding a chiral shift reagent [$Eu(tfc)_3$, 0.03–0.06 g] directly to the NMR sample and integrating the $POCH_3$ region. Independently prepared standards verified that integrations are a true measure of isomer ratios and that the *R* isomer corresponds to the upfield pair of signals. Pseudo-first-order rate constants were determined by an exponential curve fit of data for the conversion of **2ab** to **2bb** covering over four half-lives and of data for the racemization of **2ab** covering one half-life.

**Kinetic Procedure for the Reaction of 1b with Sodium Ethoxide in Ethanol.** A 10-μL sample of a solution of **1b** in ethanol (0.1 M) was added to a cell containing a solution of sodium ethoxide in ethanol (3 mL, 0.19 M) at 20.0 °C. After mixing, the kinetic solution was maintained at 20.0 °C and the UV–vis absorbance at 274 nm was followed as a function of time. A duplicate run was carried out under the same conditions. The resulting rate constants for the conversion of **1b** to **2bb** were determined by an exponential curve fit of data obtained over more than five half-lives.

In a separate large-scale reaction, (*S*)-**1b** (0.15 g, 83% ee) was dissolved in a solution of sodium ethoxide in ethanol (50 mL, 0.19 M). The reaction mixture was divided into two 25-mL parts. Each part was quenched after a different time interval by addition directly to a separatory funnel containing dichloromethane (25 mL) and an aqueous solution of hydrochloric acid (25 mL, 0.2 M). Following a normal workup, the resulting samples were analyzed by NMR for percent conversion to **2bb** and percent racemization with the chiral shift reagent $Eu(tfc)_3$.

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