Reaction of (*R*)-(+)-Isopropyl Methylphosphinate with Methyl Triflate. Stereospecific Synthesis of (*R*)-(+)-Isopropyl Methyl Methylphosphonite[1]

Leonard J. Szafraniec, Linda L. Szafraniec, and Herbert S. Aaron*

Research Division, Chemical Systems Laboratory, Aberdeen Proving Ground, Maryland 21010

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A new route for the stereospecific conversion of P^{IV} to P^{III} organophosphorus compounds has been developed from the reaction of methyl trifluoromethanesulfonate with a chiral resolved organophosphinate ester. Thus, (*R*)-(+)-isopropyl methylphosphinate (**1**) was alkylated in its preferred tetracovalent form to give a phosphonium salt (**2**), which yielded (*R*)-(+)-isopropyl methylphosphonite (**3**) on treatment with an ether or benzene solution of a tertiary amine. The neat product was stereochemically labile at ambient temperature but was relatively stable in benzene solution. It was converted on treatment with sulfur into (*S*)-(−)-isopropyl methyl methylphosphonothionate (**4**). All of the stated reactions take place with retention of configuration and appear to be highly, if not completely, stereospecific.

Methyl trifluoromethanesulfonate (methyl triflate) is a powerful alkylating agent, which methylates tetracovalent P=O, P=S, and P=Se systems at the oxygen, sulfur, and selenium atoms, respectively.[2,3] However, its reaction with phosphinylidene compounds,[4] that is, analogues which contain a hydrogen substituent, such as phosphinate RO(R)P(O)H, phosphonate $(RO)_2P(O)H$, or secondary phosphine oxide $R_2P(O)H$ species, appears not to have been reported.

We have studied the reaction of methyl triflate with phosphinate esters and find it is applicable to a new stereospecific synthesis of trivalent organophosphorus esters. The stereochemistry of trivalent organophosphorus compounds is currently being intensively studied,[3,5] and recently the stereospecific conversion of a resolved P^{IV} species into an optically active phosphinite ester (R_1R_2POR) was published.[3a] Optically active alkylphosphonites (e.g., **3**), however, have not been reported, although a (−)-*O*-trimethylsilyl analogue is known.[6]

Isopropyl methylphosphinate (**1**) reacted exothermically with methyl triflate at ambient temperatures, almost exclusively (if not solely, see below) in its preferred tetracovalent form (Scheme I), to produce a phosphonium salt (**2**), which gave isopropyl methyl methylphosphonite (**3**) when added to a benzene/triethylamine solution at −20 °C. After warming to room temperature, the product was obtained as a benzene/TEA solution, which separated from a heavier liquid layer that mainly consisted of amine salt byproducts in benzene/TEA. A study of the reaction under varying conditions revealed no advantage in using a solvent in the first step or a hindered amine such as 1,2,2,6,6-pentamethylpiperidine in place of TEA to preclude possible alkylation of the amine by **2** in the second step of the synthesis. For isolation of the neat product, however, a more volatile solvent/amine combination (ether/trimethylamine) seemed preferable for the second step, since **3** was not readily separated by distillation from benzene/TEA.

Scheme I

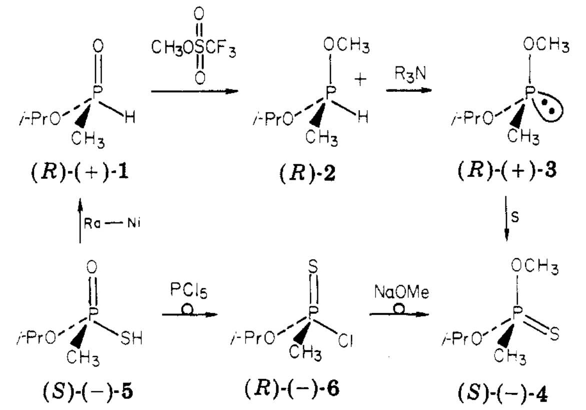

Table I. Distribution of Products from Reaction of (*R*)-(+)-Isopropyl Methylphosphinate (1) with Methyl Triflate[a]

product species	top layer mol %[b]	top layer δ	bottom layer mol %[b]	bottom layer δ	mol% total product[b]
(*R*)-(+)-3	60	176.6	9	175.9	69
other P^{III}	3[c]		<1		3
(*R*)-(+)-1	3	26.7	15	33.4	18
P^{IV} impurity[d]	0		2	39.3	2
P^{IV} impurity[e]	<1	46.0	8	53.4	8

[a] After addition to benzene/triethylamine. [b] Relative to original starting material (1) taken. [c] Observed in a molar ratio of 1/1/3, assigned as $MeP(OMe)_2$, MeP(OMe)(OEt), and $MeP(O\text{-}i\text{-}Pr)_2$ at δ 183.0, 180.0, and 173.0, respectively. [d] Assigned as Me(H)P(O)OMe. [e] Assigned as $Me_2P(O)O\text{-}i\text{-}Pr$.

When the reaction was run on (*R*)-(+)-**1**[7] (25% enantiomorphic excess), a 60 mol% yield of (*R*)-(+)-**3** was obtained as a benzene/TEA solution, 90 mol % pure with respect to its organophosphorus content. The total product composition and ^{31}P NMR chemical shift data are given in Table I. From the ^1H and ^{31}P NMR analyses a weight percent yield of each component was assigned (see Experimental Section), and from the observed rotation a value of $[\alpha]^{26}_D$ +67.7° was calculated for the specific rotation of the (*R*)-(+)-**3**, if optically pure starting material had been used.

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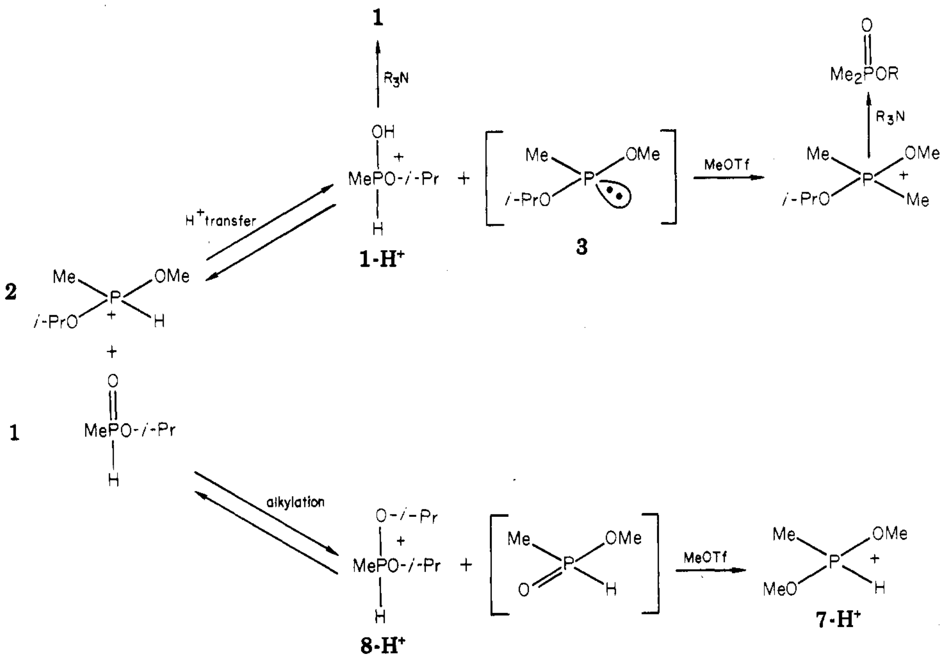
[7] Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 5275. The designation of the *R* configuration for (+)-**1** is a correction of the earlier assignment, due to subsequent results.[8]

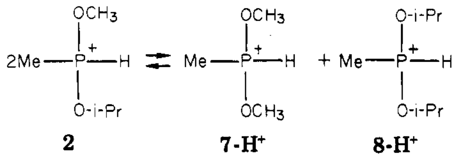
Scheme II



The NMR results (Table I) reveal that some dialkylphosphinate, assigned as $Me_2P(O)O$-*i*-Pr, was present in the bottom layer of the reaction product. It is uncertain whether this species was formed by direct alkylation of the trivalent tautomer of **1** or by some other mechanism, e.g., alkylation of the product (**3**) formed during the neutralization step and/or via a proton-transfer mechanism discussed below, as depicted in Scheme II. Thus, it is uncertain whether the starting material (**1**) is exclusively alkylated in its tetracovalent form or whether a small amount also reacts as the trivalent tautomer.

As summarized in Table I, the desired P^{III} product was found to contain small amounts of other P^{III} contaminants, assigned (NMR) as the two bis esters $MeP(OMe)_2$ (**7**) and MeP(O-*i*-Pr)$_2$ (**8**), plus (in this case) the extraneous MeP(OMe)(OEt) (**9**). The latter is believed to have formed from a little ethyl methylphosphinate contaminant in the starting material (**1**), apparently formed by ester interchange between **1** and traces of ethanol still present on the Raney nickel catalyst used for its synthesis (from **5**), even after the catalyst had been washed with isopropyl alcohol. This contaminant was eliminated in later runs by directly washing and storing the catalyst with isopropyl alcohol.

It was not possible, however, to eliminate completely bis ester contamination (**7** and **8**) from the desired product, since these are not only formed by thermal disproportionation of **3** but were already observed (in their protonated form) when the phosphonium salt (**2**) was first examined by NMR. When the latter was left to stand at room temperature for several hours, a decrease in the concentration of **2** was observed, accompanied by an increase in the percentage of (protonated) **7** and **8** (in unequal amounts, however,) together with other products.



$$2Me\!-\!\overset{\displaystyle OCH_3}{\underset{\displaystyle O\text{-}i\text{-}Pr}{\overset{+}{P}}}\!-\!H \rightleftarrows Me\!-\!\overset{\displaystyle OCH_3}{\underset{\displaystyle OCH_3}{\overset{+}{P}}}\!-\!H + Me\!-\!\overset{\displaystyle O\text{-}i\text{-}Pr}{\underset{\displaystyle O\text{-}i\text{-}Pr}{\overset{+}{P}}}\!-\!H$$

2 **7-H⁺** **8-H⁺**

Although depicted here as a simple ligand exchange, the mechanism of the actual process is unknown. The observed rate of decomposition of **2** would appear to be too slow, however, to account for the amount of **7-H**$^+$ and **8-H**$^+$ initially observed. We suggest, therefore, that the formation of the various byproducts observed in this reaction may be explained, at least in part, by a series of reactions that are summarized in Scheme II. That is, as the phosphonium salt (**2**) concentration begins to build up in the reaction mixture, it should compete with methyl triflate and react with the starting material (**1**), presumably via two possible pathways: proton transfer and alkylation. On proton transfer, a mixture of **1-H**$^+$ and **3** would be obtained. However, the latter would be rapidly alkylated by methyl triflate to give a phosphonium salt, which would be converted into an alkyl dimethylphosphinate after treatment with base. The **1-H**$^+$, on the other hand, would be recovered as starting material after the neutralization step. This scheme would account for the fact that unreacted starting material is always observed in the reaction product, even when an excess of methyl triflate is taken. An alkylation reaction (*i*-Pr group transfer between **1** and **2**, on the other hand, would account for the observed formation of the two protonated bis esters (before neutralization), as depicted in the scheme. For Me group transfer, of course, no apparent reaction would be observed, since the two reactants would merely be interconverted. Moreover, this postulated alkylation reaction would also account for the formation of the (assigned) methyl methylphosphinate, since a proton transfer (from **1-H**$^+$, for example) would preserve some of this intermediate until the neutralization step. This scheme was tested in the case of the ethyl methylphosphinate system, by adding the phosphinate to the methyl triflate and comparing (NMR) the resulting neat liquid phosphonium salt to that obtained by the reversed addition. Consistent with the postulated scheme, 2.5 mol % of each of the two protonated bis esters was observed in the former experiment, compared to 10 mol % in the latter. Unexpectedly, however, little difference in the amount of protonated starting material and dialkyl phosphonium intermediate $[Me(Et)P(OEt)(OMe)]^+$ was observed from either order of addition.

To determine the best conditions for isolation of the neat product, we studied a variety of solvent/amine combinations with racemic **1**, before proceding with resolved reagent. Thus, while benzene/TEA seemed to suppress the bis ester formation in comparison to ether/TMA, the product was not readily separated from the solvent/amine, even after distillation through a short packed column. Since the more volatile ether/TMA combination appeared to give the highest recovery of **3**, this procedure was followed with optically active **1** (20% ee). In this case, however, only a 27.5% yield of neat (*R*)-(+)-**3** was obtained after two distillations, 88 mol % pure by ^{31}P NMR, and considerably racemized in comparison to the product obtained in benzene/TEA solution (above). The optical rotation of this neat product was observed to decrease by 20% during 80 min at 27°. By comparison, that of the benzene/TEA solution, further diluted with benzene, decreased by only 14% during 70 h at ambient temperature. However, these data are not necessarily an accurate measure of the true optical stability of neat **3**, compared to that in benzene solution, since some disproportionation and hydrolysis products were also observed in both samples. Recent literature has suggested[9] that acidic impurities in trialkyl phosphites (hence, presumably, also **3**) catalyze disproportionation reactions. Since these impurities even include such weak acids as the dialkyl phosphonates, it is possible that the rate of disproportionation of **3** will differ for each sample, depending upon the amount of impurities or trace water that may be present. This suggestion was made to explain the results obtained in an earlier study of dialkyl alkylphosphonite disproportionation.[10] Attempts to stabilize the neat product by storing it over metallic sodium, as suggested,[9] actually resulted in a marked increase in the rate of racemization, possibly due to formation of alkoxide or hydroxide ions.

In the above-mentioned isolation experiments of neat **3** from racemic **1**, varying amounts of the bis esters **7** and **8** were observed as impurities in the distilled product. This result suggests that a redistribution reaction had taken place. To test this conclusion, we maintained a sample of neat racemic **3** at 80 °C for 10 h and examined it periodically by ^{31}P NMR. A disproportionation into **7** and **8** was indeed observed, according to an apparent first-order rate,[11] with a calculated half-life of 17 h.

Because of the chemical reactivity and stereochemical lability of optically active **3**, for stereochemical studies the product is best used directly in solution as obtained and not isolated as the neat material. Thus, excess sulfur was added directly to a portion of (+)-**3** in benzene/TEA, and (*S*)-(−)-isopropyl methyl methylphosphonothioate (**4**) was obtained. The distilled product, 92% pure by NMR, had an observed rotation (neat) of −0.384°, which corresponds to −1.55°, if optically pure starting material had been used. This result may be compared to a literature value of +1.50° for (+)-**4**, obtained (presumably with high if not complete stereospecificity) from the reaction of sodium methoxide with optically pure (+)-isopropyl methylphosphonothionochloridate (**6**).[12] Thus, the conversion of (+)-**1** into (+)-**3** appears to be highly, if not completely, stereospecific, consistent with the assigned retention of configuration based upon the chemistry of the reaction, the known steric course of the sulfur addition reaction,[13] and the known[7,12,14] (corrected[8]) relationship among *R*-(+)-**1**, (*S*)-(−)-**5**, (*R*)-(−)-**6**, and *S*-(−)-**4**, as summarized in Scheme I.

While studied only with phosphinate systems in our laboratory, the reaction is presumably also applicable to phosphonate and secondary phosphine oxide species. Preliminary experiments indicate that phosphinothionates [R(RO)P(S)H] also react in an analogous manner, and these results will be reported at a future date. It is pertinent to report, however, that the treatment of ethyl methylphosphinate with methyl fluorosulfate ("Magic Methyl"), another powerful alkylating agent, reputedly comparable in strength to methyl triflate, did not produce any P^{III} species under the same conditions. In this case, a mixture of the highly toxic methyl and ethyl methylphosphonofluoridates [RO(Me)P(O)F] were obtained as the major products, together with other P^{IV} species. This result is of interest in view of the earlier report[15] that no examples were known in which methyl fluorosulfate reacted as a fluorinating agent.

Experimental Section

The synthesis and reactions of trivalent phosphorus species were all carried out in a dry, nitrogen atmosphere. Optical rotations were recorded on a Perkin-Elmer 141 autopolarimeter.

NMR Spectral Analyses. The ^{31}P nuclear magnetic resonance (NMR) spectra were recorded with a Varian FT-80A multinuclear Fourier-transform NMR spectrometer operating at 32.2 MHz in the external mode. Spectra were obtained at probe temperature (~31 °C), and phosphoric acid (85%) was used as the external reference. The chemical shift (δ) values reported are accurate to ±0.2 ppm and the coupling constants (J values) to ±1%; a positive chemical shift indicates the resonance is downfield with respect to the phosphoric acid reference. For each sample analyzed, 200–300 transients were accumulated, using a pulse width of 8 μs (~34 °), a sweep width of 8000 Hz, a filter bandwidth of 8000 Hz, an acquisition time of 0.5 s, and a pulse delay of 2.5 s. In addition, gated decoupling was used to eliminate any nuclear Overhauser effects (NOE). Quantitative data were obtained by digital integration of the peak areas; corrections were made on all peaks attenuated by the audiofilter.

The ^{1}H NMR studies were carried out at 60 MHz, using a Varian A-60D NMR spectrometer. Spectra were recorded at probe temperature (~31 °C), and quantitative data were obtained by electronic integration of the sample. Since all species present could be identified and observed by NMR, the mole fractions determined from the ^{1}H and ^{31}P spectra, together with the molecular weights of each species, the weight of the sample, and the weight of the starting material, could be used to calculate the total percent reaction and the weight percent yield of each component.

Raney Nickel. For the synthesis of (*R*)-(+)-**1**, as reported in Table I, the catalyst was prepared as described in the literature.[16] In subsequent runs, however, a fresh batch of catalyst was prepared in which isopropyl alcohol was used in place of ethanol both to wash and store the catalyst.

(*R*)-(+)-Isopropyl Methylphosphinate (1).[7] The Raney nickel catalyst, prepared and stored under ethanol, was washed with and stored under isopropyl alcohol, 24 h before it was used in the following experiment. To 26 g of an isopropyl alcohol slurry of Raney nickel in an additional 14 mL of dry isopropyl alcohol was added dropwise 3.01 g (0.0195 mol) of (*S*)-(−)-isopropyl methylphosphonothioic acid[17] (**5**, 49.8% ee). The mixture was then heated to reflux for 2 h, allowed to cool, and filtered through

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Celite on a coarse sintered-glass funnel. The filter cake was washed with about 12 mL of isopropyl alcohol. The filtrate and washings were combined and concentrated at 50 mm to give 3.53 g of a pale-yellow liquid. This liquid was dissolved in 10 mL of benzene, dried over $MgSO_4$, filtered, and concentrated at 102 mm on a rotary evaporator to give 2.13 g of a yellow liquid. This liquid was flash distilled and then redistilled at 53 °C (5 mm) to give 1.36 g (57%) of the desired product, 1 $[\alpha]^{27}_D$ +16.06° (*c* 4.31, ethanol), which corresponds to +32.25°, had optically pure **5** been used. Analysis of the product by ^{31}P NMR revealed a purity of 95 mol % (δ 30.9, *J* = 542 Hz). The major impurity (3.4 mol %), assumed to be ethyl methylphosphinate on the basis of its chemical shift (δ 33.6, *J* = 537 Hz), is apparently formed by transesterification of 1 with traces of ethanol still present on the Raney nickel. The results of the ^1H NMR analysis indicated 90.9 mol % of the isopropyl methylphosphinate (**1**), 4.1 mol % isopropyl alcohol, 0.3 mol % benzene, and 4.8 mol % impurities containing phosphorus. This product was then diluted with an equal weight of racemic 1[18] (98.3 mol % pure by ^1H and ^{31}P NMR) for use in the next step.

(*R*)-(+)-Isopropyl Methyl Methylphosphonite (3) in Benzene Solution. To 4.08 g (0.0249 mol) of methyl trifluoromethanesulfonate (Aldrich Chemical Co.) was added dropwise with stirring 2.51 g (0.0206 mol) of (*R*)-(+)-isopropyl methylphosphinate (**1**), $[\alpha]^{27}_D$ +8.01° (*c* 2.95, ethanol, 24.8% ee). The temperature was maintained below 40 °C by the rate of addition. (In another experiment, the reaction mixture was examined at this point by ^{31}P NMR. The major signal (75 mol %), due to the phosphonium salt (**2**), was observed at δ 73.4 (*J* = 656 Hz). Also present were 3.6 mol % of **7-H$^+$** and 3.3 mol % of **8-H$^+$** at δ 80.1 (*J* = 659 Hz) and δ 65.8 ($J \approx 655$ Hz), respectively.) After the addition, the resulting solution was added slowly to a stirred and cooled (−20 to −23 °C) solution of 6.00 g (0.0593 mol) of triethylamine in 8 mL of dry benzene. The reaction mixture was then allowed to warm to ambient temperature, whereby two layers had formed. These were separated, and the weight (9.75 g) and volume (12.0 mL) of the top layer and the weight (8.44 g) of the bottom layer were noted. Samples of both layers were submitted to ^1H and ^{31}P NMR analyses; in addition, samples of the top layer were removed for optical rotation studies. On the basis of the combined NMR data, the total product distribution was calculated, and the results are summarized in Table I. These data reveal that an overall total of 72% conversion of (+)-(1) to P^{III} species had been realized, even uncorrected for the starting material that was still present in the product. Of the P^{III} species, 96% had been converted to the desired isopropyl methyl methylphosphonite (**3**), which was readily obtained in almost its entirety (i.e., 87% of the total formed) in the top layer, in about 90% purity with respect to its organophosphorus content. The weight percent composition of the top layer was calculated to be as follows: benzene, 50.7%; triethylamine, 30.8%; isopropyl methyl methylphosphonite (**3**), 16.3%; dimethyl methylphosphonite (**7**), 0.2%; ethyl methyl methylphosphonite (**9**), 0.2%; diisopropyl methylphosphonite (**8**), 0.7%; isopropyl methylphosphinate (**1**), 0.7%; and alkyl dimethylphosphinate, 0.3%. From the above NMR data and an observed rotation of a benzene solution of the top layer (0.2 mL diluted to 1 mL with benzene, α_{obsd} +0.450°), a specific rotation $[\alpha]^{26}_D$ +16.8° (*c* 2.65, benzene with 6% TEA) was calculated for the (*R*)-(+)-isopropyl methyl methylphosphonite (**3**) present in this layer, corrected for the 1% contribution to the rotation from the (+)-1 starting material, still present. This result corresponds to $[\alpha]^{26}_D$ +67.7°, if optically pure starting material had been used. The rotation of this solution was followed during an additional 70 h standing in the polarimeter tube at ambient temperature. At this point, a rotation of 0.386° was observed (14% decrease).

Isolation of Neat (*R*)-(+)-Isopropyl Methyl Methylphosphinate (3). To 7.71 g (0.0470 mol) of methyl trifluoromethanesulfonate was added dropwise with stirring 4.79 g (0.0392 mol) of (*R*)-(+)-isopropyl methylphosphinate (**1**, 20% ee). The temperature was maintained at or below 43 °C by the rate of addition. The resulting solution was then added slowly to a stirred and cooled (−30 to −40 °C) solution consisting of 40 mL of sodium-dried ether and 7.51 g (0.127 mol) of trimethylamine, and a fine white precipitate immediately formed. The reaction mixture was stirred and allowed to warm to ambient temperature (26 °C), degassed over a 2.5-h period to remove the excess amine, and filtered through a coarse sintered glass funnel. The now sticky precipitate was washed 3 times with 1-mL portions of ether. The washings were combined with the filtrate and, after overnight storage in a freezer at −40 °C, concentrated on a rotary evaporator under reduced pressure (>160 mm) to give a colorless liquid. This liquid was degassed briefly and then distilled at 30 °C (3.25 mm) to give 2.64 g of a clear liquid, which was stored over the weekend in a freezer at −40 °C. After an analysis (^1H NMR) of the liquid revealed the presence of 22 mol % ether, it was redistilled under reduced pressure to give 1.47 g (27.5%) of product, bp 35–38 °C (34 mm). Analysis by ^{31}P NMR indicated the following mol % composition: **3**, δ 177.4, 88.0%; **7**, δ 183.8, 4.2%; **8**, δ 174.0, 5.3%; dimethyl methylphosphonate, δ 33.4, 0.3%; isopropyl methyl methylphosphonate, δ 32.6, 0.2%; diisopropyl methylphosphonate, δ 30.3, 1.5%; and **1**, δ 28.2, 0.5%. The ^1H NMR analysis of the product revealed only the additional impurity of 0.9 mol % ether. The observed rotation of the neat liquid when examined at 27° in a 1-dcm micropolarimeter tube, was +4.468°. Corrected for the wt % content of **3** in the product and for the optical purity of the *R*-(+)-**1** starting material, one calculates a value of +25.10° for the observed rotation of the (+)-**3** product, if optically pure *R*-(+)-**1** had been used for the reaction. The rotation of the neat product, after standing for an additional 80 min in the polarimeter tube at ambient temperature, was observed to be +3.490° (22% decrease).

(*S*)-(−)-Isopropyl Methylphosphonothionate (4). To the top product layer obtained as described above as (*R*)-(+)-**3** in benzene solution, calculated to contain 1.54 g (0.0113 mol) of the product, was added, piecemeal, 0.66 g (0.0206 mol) of sulfur. An exothermic reaction resulted, with the gradual dissolution of most of the sulfur. The reaction mixture was stirred for 1 h at ambient temperature, allowed to stand overnight, and then filtered to remove excess sulfur. The filtrate was washed 3 times with about 7-mL portions of water, then dried over $MgSO_4$, filtered, and concentrated to give 2.79 g of a brown liquid. This residue was degassed for 15 min at 30 °C (10 mm) and then distilled at 28 °C (0.60 mm) to give 1.74 g of a colorless product: (*S*)-(−)-**4**, δ 96.4, 92.4 wt % pure by ^1H and ^{31}P NMR, α^{26}_D −0.384° (neat), uncorrected for purity or possible contribution of any other species to this rotation. This result corresponds to a rotation of −1.55°, if the (*R*)-(+)-**3** starting material had been obtained from optically pure (*R*)-(+)-1.

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