Stereoselective Synthesis and Stereochemistry of Optically Active *tert*-Butylphenylphosphine Sulfide

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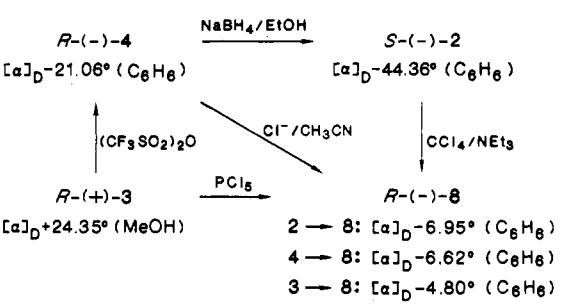
Stereoselective reduction of the mixed anhydride of *tert*-butylphenylphosphinothioic acid and trifluoromethanesulfonic acid by sodium borohydride provides optically active *tert*-butylphenylphosphine sulfide of high optical purity. A synthesis of optically active phosphinodithioates Bu^{t}PhP(S)SMe (**5**), phosphinothioic iodides (**6**), and thioselenophosphinic acid Bu^{t}PhP(Se)SH (**7**) of known configuration is described.

Compounds of the general formula RR′P(O)H (**1**) are among the most useful intermediates in organophosphorus chemistry. They contain a potentially ionizable hydrogen and exist in tautomeric forms RR′P(O)H ⇄ RR′POH. Several examples of **1** are known which have a chiral diastereoisomers.[1] Similar situations exist in the domain of sulfur analogues although until now only one optically active RR′P(S)H compound (**2**) has been described.[2] The *O*-menthyl phosphinothionates, R(R′O)P(S)H (R = Me, R′ = L-menthyl and R = Ph, R′ = L-menthyl), were prepared by DeBruin[3] as 1:1 diastereomeric mixtures. Recently P-epimers of the *O*-menthyl phosphinothionates R(R′O)P(S)H (R = Ph, R′ = L-menthyl) were prepared in this laboratory.[4]

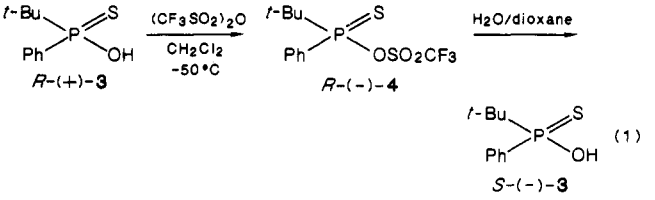
The synthesis of **2** described by Aaron et al.[2] was based on reduction of the optically active monothioacid RR′P(S)OH (**3**, R = $OCHMe_2$, R′ = Me) with the aid of Raney nickel into **1** (R = $OCHMe_2$, R′ = Me) and final conversion of **1** into **2** (R = $OCHMe_2$, R′ = Me) by P_4S_{10}. The product **2** (R = $OCHMe_2$, R′ = Me) was believed to be 68% optically pure and formed with predominant retention of configuration. In our studies on stereochemistry, we found that the above method is not suitable for the preparation of highly optically pure enantiomeric compounds **2** (R = Bu^t, R′ = Ph). In this paper we report a new strategy for preparation of optically active **2** based on mixed phosphorus–sulfonic anhydrides. Our experiments showed that when the optically active *R*-(+) or *S*-(−) enantiomers of the acid RR′P(S)OH (**3**, R = Bu^t, R′ = Ph)[5] were converted into the mixed anhydride **4**, preparation of highly optically pure **2** was easily achieved by selective reductive displacement with sodium borohydride. The sulfide **2** can serve as a source of new optically active organophosphorus compounds of known configuration, such as phosphinodithioates Bu^{t}PhP(S)SMe (**5**), phosphinothioic iodides (**6**), and thioselenophosphinic acid Bu^{t}PhP(Se)SH (**7**).

Scheme I



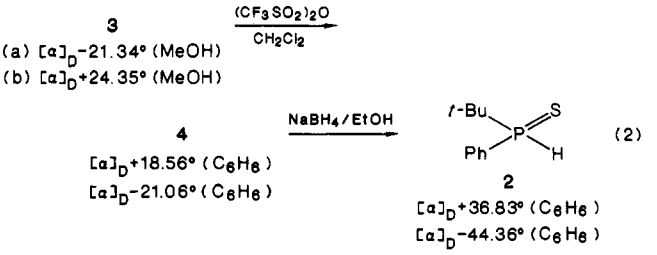
Results and Discussion

Synthesis of optically active mixed anhydrides **4** is best achieved by condensation of *R*-(+) or *S*-(−) acid **3** (R = Bu^t, R′ = Ph) with trifluoromethanesulfonic anhydride $(CF_3SO_2)_2O$. The chemical yield is relatively low, but its optical purity is almost the same as that of the starting acid **3**. This was established by hydrolysis of the optically active anhydride **4**, leading to the acid **3** of the same specific rotation value but of opposite configuration (eq 1). This



(1)

experiment provides a new example of the Walden cycle in organophosphorus chemistry analogous to that demonstrated earlier in this laboratory.[6] Formation of anhydride **4** proceeds without bond breaking or bond formation at the phosphorus center. This means that the hydrolysis step must proceed with full inversion of configuration at the phosphorus atom. The anhydride **4** was reduced by sodium borohydride in ethanol as reaction medium (eq 2). We have found that this method can only



(2)

(1) (a) Emmick, T. L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 3459. (b) Cervinka, O.; Belorsky, O.; Hepuerova, M.; *J. Chem. Soc., Chem. Commun.* **1970**, 562. (c) Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 5275. (d) Benshop, H, P.; Platenburg, D. H. J. M.; Meppelder, F. H.; Boter, H. L. *J. Chem. Soc., Chem. Commun.* **1970**, 33. (e) Benshop, H. P.; Van den Berg, G. R. *J. Chem. Soc., Chem. Commun.* **1970**, 1431. (f) Bonohue, J.; Mandal, N.; Farnham, W. B.; Murray, R. K.; Mislow, K.; Benshop, H. P.; *J. Am. Chem. Soc.* **1971**, *93*, 3792. (g) Van den Berg, G. R.; Platenburg, D. H. J. M.; Benshop, H. P.; *J. Chem. Soc., Chem. Commun.* **1971**, 606. (h) Benshop, H. P.; Platenburg, P. H. J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 1098. (i) Meppelder, F. H.; Benshop, H. P.; Kraay, G. N. *J. Chem. Soc., Chem. Commun.* **1970**, 431. (j) Farmham, W. B.; Murray, R. K.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 5809. (k) Farnham, W. B.; Murray, R. K.; Mislow, K. *J. Chem. Soc., Chem. Commun.* **1971**, 605; *Ibid.* **1971**, 146. (l) Michalski, J.; Skrzypczyński, Z. *J. Organomet. Chem.* **1975**, *97*, C31–C32. (m) Szafraniec, L. J.; Szafraniec, L. L.; Aaron, H. S. *J. Org. Chem.* **1982**, *47*, 1936.

(2) Szafraniec, L. J.; Reiff, L. P.; Aaron, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 6391.

(3) DeBruin, K. E.; Johnson, D. M. *Phosphorus Relat. Group V Elem.* **1974**, *4*, 12; *Ibid.* **1974**, *4*, 17.

(4) Łopusiński, A.; Łuczak, L.; Michalski, J., submitted for publication.

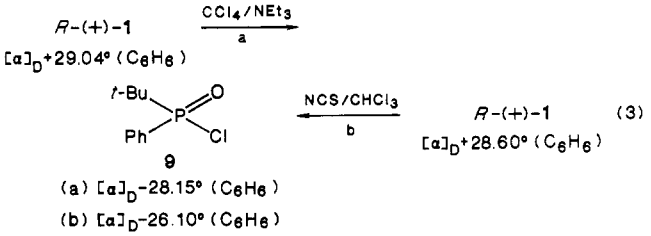
(5) The synthesis of an acid **3** (R = Bu^t, R′ = Ph) was described by Hoffmann and Schnellenbeck: Hoffmann, H.; Schnellenbeck, P. *Chem. Ber.* **1966**, *99*, 1134.

(6) Krawiecka, B.; Michalski, J.; Skrzypczyński, Z. *J. Chem. Soc. Chem. Commun.* **1974**, 1022.

0022-3263/88/1953-4549$01.50/0

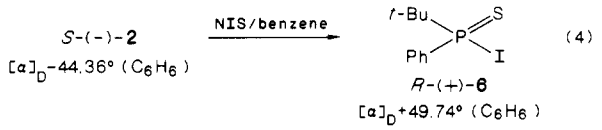
be applied to mixed anhydrides derived from trifluoromethanesulfonic acid. The high, most likely almost full, optical purity of the sulfide **2** was estimated by its conversion into the corresponding phosphinothioic chloride **8** (Scheme I), by Todd–Atherton chlorination[7] with carbon tetrachloride in the presence of triethylamine. This reaction most likely proceeds with retention of configuration at the phosphorus atom and gives a high optical yield.

Retention of configuration has been noted both in the reaction of optically active *tert*-butylphenylphosphine oxide (**1**) and carbon tetrachloride and in the reaction of optically active *tert*-butylphenylphosphine oxide (**1**) and *N*-chlorosuccinimide[1c] (eq 3).

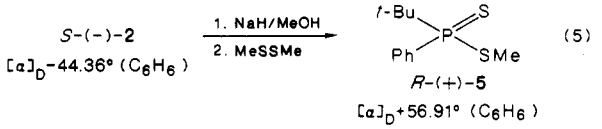


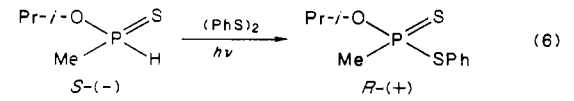
The optical purity of the chloride **8** formed from the sulfide **2** (Scheme I) was higher than in the reaction between acid **3** (R = Bu^t, R′ = Ph) and phosphorus pentachloride, which is known to proceed with inversion of configuration at the phosphorus atom.[8] The optical purity in the chlorination of the sulfide **2** was also higher than in the conversion of the anhydride **4** by direct nucleophilic displacement with chloride anion. Taking into account that reactions **3** → **8** and **4** → **8** proceed with inversion of configuration, the reduction of the anhydride **4** must also adopt the same stereochemical course.

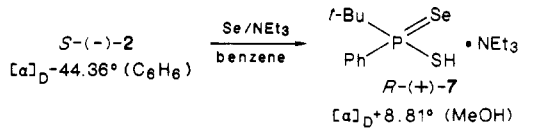
The optically active sulfide **2** can serve as a convenient starting material for preparation of a variety of optically active compounds of known configuration. *N*-Iodosuccinimide (NIS) reacts with sulfide **2** to give optically active **6** (eq 4).



Reaction with dimethyl disulfide under ionic conditions deserves special attention (eq 5). In our hands this reaction was performed by conversion of the sulfide **2** into its sodium derivate, followed by a subsequent reaction with dimethyl disulfide, to give dithioester **5** of high optical purity. This observation is contrary to that of Aaron et al.,[2] who found that optically active isopropyl methylphosphinothioate (**2**) (R = OCHMe$_2$, R′ = Me) was instantaneously racemized by 0.15 equiv of 0.06 M sodium methoxide in methanol solution. These authors[2] were, however, able to demonstrate that the reaction with diphenyl disulfide undergoes a free-radical process to give optically active *O*-isopropyl *S*-phenyl methylphosphonodithioate with retention of configuration (eq 6). The sulfide **2** was also converted into optically active thioselenoacid **7** presumably of high optical purity by addition of elemental selenium in the presence of triethylamine.







Optically active selenothioacid Et(EtO)P(Se)SH was first prepared in this laboratory[9] by optical resolution via its quininium salts. The preparation of optically active acids of the general formula R(RO)P(Se)SH was mentioned in the review article by Nuretdinov et al.[10] without any details concerning reaction conditions and the nature of R.

Experimental Section

All solvents and commercial reagents were dried and purified by conventional methods before use. NMR spectra were recorded on a Brucker MSL-300 instrument with 85% H_3PO_4 as external standard and internal deuterium lock. The instrument was operated at 121.468-MHz frequency with a quadrature detection system. Products were identified with an LKB Model 2091 gas chromatograph–mass spectrometer. Optical rotations were measured at 589 nm at 20 ± 2 °C on a Perkin-Elmer 141 polarimeter in benzene solution unless specified otherwise. Thin-layer chromatography (TLC) was performed on Merck silica gel 60F-254 sheets of 0.25-mm thickness. Column chromatography was performed on Merck silica gel 0.063–0.2 mesh. Elemental analyses were performed in the Microanalytical Laboratory of the Centre of Molecular and Macromolecular Studies, Łódź, Boczna 5. In each case the reaction products were characterized by comparison to authentic samples and found to be identical. Air- and moisture-sensitive reactions were performed under a blanket of dry nitrogen.

Starting Materials. *tert*-Butylphenylphosphinothioic acid (**3**) was synthesized by a known method.[3] Optically active *R*-(+)-*tert*-butylphenylphosphine oxide (**1**) was synthesized as described earlier.[11] Trifluoromethanesulfonic anhydride was purified on a vacuum line prior to use.

Resolution of Racemic Acid 3 (R = Bu^t, R′ = Ph). To a solution of 26.88 g (0.126 mol) of racemic acid **3** in 400 mL of anhydrous diethyl ether was added a solution of 15.224 g (0.126 mol) of (−)-α-phenylethylamine, $[\alpha]_D$ −37.8° (neat), in 200 mL of dry diethyl ether. After 12 h, the precipitated salt of *R*-(+)-**3** was filtered off and washed quickly with 50 mL of dry diethyl ether. Combined ethereal solutions were concentrated under reduced pressure. The resulting heavy syrup was dissolved in 200 mL of 0.7 M NaOH; liberated (−)-α-phenylethylamine was extracted with diethyl ether (8 × 15 mL). The alkaline water solution was acidified with an excess of hydrochloric acid and extracted with chloroform (15 × 15 mL). Combined chloroform fractions were dried over anhydrous $MgSO_4$ and after concentration gave 12.5 g of *S*-(−)-**3**, $[\alpha]_D$ −19.52° (*c* 2.5, MeOH). An analogous workup of the precipitated salt of *R*-(+)-**3** and (−)-α-phenylethylamine gave 13.5 g of *R*-(+)-**3**, $[\alpha]_D$ = +24.21° (*c* 1.6, MeOH).

Preparation of Optically Active *tert*-Butylphenylphosphinothioic Acid *O*-(Trifluoromethyl)sulfonyl Ester (4). To a solution of 4.83 g (0.0226 mol) of *R*-(+)-*tert*-butylphenylphosphinothioic acid (**3**), $[\alpha]_D$ = +24.35° (*c* 1.3, MeOH), in 50 mL of dry methylene chloride was added 6.365 g (0.0226 mol) of trifluoromethanesulfonic anhydride dropwise at −50 °C. After the addition was completed, the reaction mixture was

(7) Miller, B. In *Reactions of Trivalent Phosphorus Derivatives and Positive Halogen Sources*; Topics in Phosphorus Chemistry; Wiley-Interscience: New York, 1965; Vol. 2.
(8) Michalski, J.; Mikołajczyk, M.; Omelańczuk, J. *Tetrahedron Lett.* **1968**, 3565.
(9) Krawiecki, C.; Michalski, J.; Tulimowski, Z. *Chem. Ind. (London)* **1965**, 34.
(10) Nuretdinov, J. A.; Buina, N. A.; Bajandina, E. W.; Sibgatulina, F. G.; Sadkov, D. N.; Ginjatulina, M. A. *Chimia i Primienienie Fosforoorganiczieskich Soiedinieni*; Kiev, 1981; p 20.

warmed to room temperature and neutralized with an excess of calcium hydride. Precipitated salts were filtered off, and the filtrate was concentrated. Purification of the anhydride **4** was best accomplished by column chromatography (silica gel, 70–230 mesh; benzene). Pure optically active *R*-(−)-**4**, $[\alpha]_D$ −21.06° (*c* 2.2, C_6H_6), was obtained after concentration of the benzene fractions under reduced pressure: yield 0.73 g (9.2%); ^{31}P NMR ($CDCl_3$) 129.1 ppm.

Hydrolysis of *R*-(−)-4. A solution of 0.065 g (0.0003 mol) of *R*-(−)-**4**, $[\alpha]_D$ −22.15° (*c* 1.2, C_6H_6), prepared from *R*-(+)-**3**, $[\alpha]_D$ +25.62° (*c* 0.9, MeOH), in 0.3 mL of benzene was added to 10 mL of 1:1 v/v water/dioxane solution. The resulting solution was stirred for 2 h at room temperature, neutralized with diluted sodium hydroxide, and concentrated under reduced pressure to a total volume of 7 mL. The resulting solution was dissolved in 20 mL of distilled water, acidified with 1 mL of concentrated hydrochloric acid, and extracted with chloroform (10 × 15 mL). Combined extracts were dried over anhydrous $MgSO_4$ and gave, after concentration, 0.030 g of *S*-(−)-**3**, $[\alpha]_D$ −23.84° (*c* 1.1, MeOH), identical with an authentic sample: ^{31}P NMR ($CDCl_3$) +95.7 ppm.

Reduction of *R*-(−)-4 with Sodium Borohydride. A solution of 0.727 g (0.0021 mol) of *R*-(−)-**4**, $[\alpha]_D$ −21.06° (*c* 1.9, C_6H_6), in 1 mL of benzene was added with vigorous stirring to a solution of 0.79 g (0.021 mol) of $NaBH_4$ in 20 mL of anhydrous ethanol at −20 °C. After the vigorous evolution of hydrogen ceased, the reaction mixture was warmed to room temperature, diluted with 50 mL of benzene, and neutralized by addition of an ethanolic solution of acetic acid. Precipitated solids were filtered off, and the filtrate was concentrated under reduced pressure. Optically active *S*-(−)-**2**, $[\alpha]_D$ −44.36° (*c* 1.4, C_6H_6), was isolated by column chromatography (silica gel, 70–230 mesh, benzene): yield 0.32 g (77%); ^1H NMR (C_6D_6) δ 1.116 (9 H, d, $^3J_{PH}$ = 18.19 Hz), 6.789 (1 H, d, J_{PH} = 441.6 Hz), 7.3–7.6 (5 H, m); ^{31}P NMR (C_6D_6) 52.36 ppm; MS, *m/e* 198. Anal. Calcd for $C_{10}H_{15}PS$: C, 60.60; H, 7.57; P, 15.65; S, 16.16. Found: C, 60.46; H, 7.57; P, 15.59; S, 15.60.

Reaction of *S*-(−)-2 with Carbon Tetrachloride. A solution of 0.1 g (0.0005 mol) of *S*-(−)-**2**, $[\alpha]_D$ −44.36° (*c* 1.37, C_6H_6), in 0.3 mL of anhydrous benzene was added to a solution of 0.1 mL (0.0007 mol) of triethylamine in 2 mL of dry carbon tetrachloride. After 2 h, the reaction mixture was concentrated under reduced pressure. Chloride *R*-(−)-**8**, $[\alpha]_D$ −6.95° (*c* 1.72, C_6H_6), isolated by column chromatography (silica gel, 70–230 mesh, benzene) was identical with an authentic sample: ^{31}P NMR ($CDCl_3$) 114.68 ppm.

Reaction of *R*-(+)-1 (R = Bu^t, R′ = Ph) with Carbon Tetrachloride. A solution of 0.354 g (0.0019 mol) of *R*-(+)-**1**, $[\alpha]_D$ +29.94° (*c* 1.9, C_6H_6), in 2 mL of dry chloroform was added to a solution of 0.197 g (0.001 95 mol) of triethylamine in 5 mL of dry carbon tetrachloride. The reaction mixture was allowed to stand overnight at room temperature. After concentration under reduced pressure, chloride **9** was purified by column chromatography (silica gel, 70–230 mesh, benzene/acetone v/v, 7:1). Optically active *S*-(−)-**9**, $[\alpha]_D$ −28.15° (*c* 1.92, benzene), 0.335 g (83.5%), was identical with an authentic sample: ^{31}P NMR ($CDCl_3$) +69.4 ppm.

Reaction of *S*-(−)-2 with *N*-Iodosuccinimide (NIS). To a solution of 0.1 g (0.0005 mol) of *S*-(−)-**2**, $[\alpha]_D$ −44.36° (*c* 1.37, C_6H_6), in 0.3 mL of anhydrous benzene was added 0.15 g (0.0006 mol) of crystalline NIS. The reaction mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure. The iodide *R*-(+)-**6**, $[\alpha]_D$ +49.79° (*c* 1.9, C_6H_6), was purified by column chromatography (silica gel, 70–230 mesh, benzene): ^1H NMR ($CDCl_3$) δ 1.258 (9 H, d, $^3J_{PH}$ = 21.57 Hz), 7.4–8.1 (5 H, m); ^{31}P NMR ($CDCl_3$) 83.82 ppm; MS, *m/e* 324. Anal. Calcd for $C_{10}H_{14}PSI$: C, 37.03; H, 4.32; P, 9.56; S, 9.87. Found: C, 37.03; H, 4.44; P, 9.64; S, 9.84.

Reaction of *S*-(−)-2 with Dimethyl Disulfide. To a solution of 0.073 g (0.000 37 mol) of *S*-(−)-**2**, $[\alpha]_D$ −44.36° (*c* 1.37, C_6H_6), in 3 mL of anhydrous methanol was added 0.018 g of 50% sodium hydride dispersion in oil (Koch-Light Laboratories Ltd.) under an atmosphere of argon. When all the sodium hydride dissolved, 0.0345 g (0.000 37 mol) of dimethyl disulfide was added via a syringe into the reaction mixture. After 10 min, the reaction was brought to completion. After concentration under reduced pressure, the reaction product, the thiolo ester *R*-(+)-**5**, $[\alpha]$ +56.91° (*c* 1.8, C_6H_6), was isolated by column chromatography (silica gel, 70–230 mesh, benzene): ^1H NMR ($CDCl_3$) δ 1.533 (9 H, d, $^3J_{PH}$ = 18.322 Hz), 2.237 (3 H, d, $^3J_{PH}$ = 13.11 Hz), 7.3–8.1 (5 H, m); ^{31}P NMR (C_6H_6) 95.45 ppm; MS, *m/e* 244. Anal. Calcd for $C_{11}H_{17}PS_2$: C, 54.098; H, 6.96; P, 12.7; S, 26.22. Found: C, 54.51; H, 6.90; P, 13.30; S, 25.4.

Reaction of *S*-(−)-2 with Elemental Selenium. To the solution of 0.020 g (0.0001 mol) of *S*-(−)-**2**, $[\alpha]$ −44.36° (*c* 1.37, C_6H_6), in 1 mL of dry benzene were added 0.1 g (0.0018 mol) of elemental selenium (BDH Chemicals Ltd.) and 0.1 mL (0.0007 mol) of dry triethylamine. The reaction mixture was stirred overnight at room temperature, and then 3 mL of MeOH and 0.1 g of charcoal were added. The resulting mixture was stirred for 1 h, all solid material was filtered, and the solvents were removed under reduced pressure. The triethylammonium salt of *R*-(+)-**7**, $[\alpha]_D$ +8.81° (*c* 0.9, MeOH), was precipitated by the addition of 2 mL of anhydrous diethyl ether: ^{31}P NMR ($CDCl_3$) +74.80 ppm. Anal. Calcd for $C_{16}H_{30}PSSeN$: C, 50.79; H, 7.93; P, 8.20; S, 8.46. Found: C, 50.18; H, 7.88; P, 9.78; S, 10.29.

Registry No. (*R*)-(+)-**1**, 82945-11-7; (*R*)-(+)-**2**, 115591-22-5; (*S*)-(−)-**2**, 115591-16-7; **3**, 67314-76-5; (*R*)-(+)-**3**, 54100-47-9; (*S*)-(−)-**3**, 55705-77-6; (*R*)-(−)-**4**, 115591-15-6; (*S*)-(+)-**4**, 115591-21-4; (*R*)-(+)-**5**, 115603-43-5; (*R*)-(+)-**6**, 115591-18-9; (*R*)-(+)-**7**·NEt_3, 115591-20-3; (*R*)-(−)-**8**, 115591-17-8; (*S*)-(−)-**9**, 75213-02-4; $(CF_3SO_2)_2O$, 358-23-6.