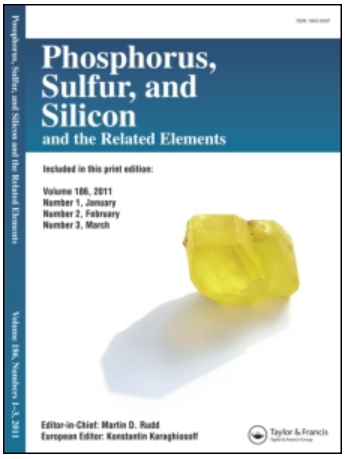

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C_2 SYMMETRY-ENANTIOPURE PHOSPHORO-THIOATES AND PHOSPHOROTHIOAMIDATES STARTING FROM 2,2',6,6'-BIPHENYLTETROL

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C_2 SYMMETRY-ENANTIOPURE PHOSPHOROTHIOATES AND PHOSPHOROTHIOAMIDATES STARTING FROM 2,2′,6,6′-BIPHENYLTETROL

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A straightforward procedure for the preparation of enantiopure phosphorothioates and diastereopure phosphorothioamidates of 2,2′,6,6′-biphenyltetrol is presented. Basic alcoholysis of compounds *trans*-**3** and *cis*-**3** proceeds in high diastereoselectivity to give only two of the six possible acyclic phosphorothioamidates **4a** and **4b** (or **5a** and **5b**). When diastereopure **4** and **5** are subjected to acid alcoholysis they lead to enantiopure cyclic phosphorothioates *trans*-**6** and *trans*-**7**, respectively. All compounds prepared are solid, air stable and possess a C_2 symmetry axis. Due to restricted rotation around the C1-C1′ bond, compounds **4a, 4b, 5a, 5b, 6** and **7** exist as stable atropisomers at rt. However for compounds *trans*-**3** and *cis*-**3**, the bridged biphenyl system intercorverts at rt with a half-life of 6 h. The structure of compounds *trans*-**2**, *trans*-**3**, and **5a** has been confirmed by X-ray analysis. Phosphorothioates and phosphorothioamidates can be tested as agrochemicals since these classes of compounds can inhibit acetylcholinesterase of many different insect species.

Keywords: Enantiopure phosphorothioates; diastereopure phosphorothioamidates; 2,2′,6,6′-biphenyltetrol; X-ray analysis

INTRODUCTION

Organothiophosphorus compounds find widespread use both as agrochemicals[1] and biochemicals,[1] and in chemistry,[2] as reagents. Since most biologically active organothiophosphorus compounds are chiral, there is a fundamental need to develop synthetic methods to prepare these compounds in a chiral form.[1,3]

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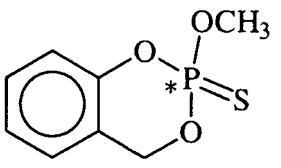
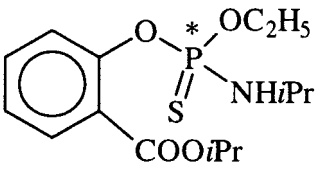


salithion



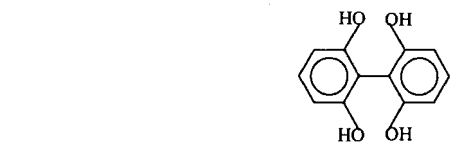
isofenphos

Moreover, little has been reported on the preparation of chiral non racemic O-aryl phosphorothioates and their analogues, although these compounds find application as insecticides.[4,5] Salithion[6] and isophenphos,[5] commercial chiral insecticides, are two examples of these compounds, whose individual enantiomers show different biochemical and toxicological proprieties. Since most pest and insects seem to have gained immunity towards several commercial agrochemicals, there is a common interest to investigate other structures. It is generally agreed that an aryl group in a phosphate moiety may enhance the pesticidal potency of the molecule.[7] A series of phosphorothioates and phosphorothioamidates derived from 1,1′-binaphthalene-2,2′-diol[7] have shown higher acetylcholinesterase inhibition than methyl parathion, a commercial pesticide.

RESULTS AND DISCUSSION

In continuation of our studies on the preparation and resolution of new atropisomeric 1,1′-biphenyl and 1,1′-binaphthyl organothiophosphorus derivatives,[8] we have focused our attention on biaryl molecules. They can be used as starting material for preparing new chiral biaryl phosphorothioates and phosphorothioamidates. Since the presence of a C_2 symmetry axis within the molecule usually provides a more stereochemical control compared to one lacking in such a symmetry element,[9] we have prepared the new compounds which contain C_2 symmetry. Furthermore, because of the importance of the phosphorus atom on biological activity,[10] a C_2 symmetry axis would allow us to prepare molecules having two equivalent phosphorus functionalities and thus, possibly to double the number of biologically active sites.

We have chosen 2,2′,6,6′-biphenyltetrol **1** as the starting material. The tetrol **1**, readily available by a known procedure,[11] is not chiral but becomes so by introducing proper substituents at the 2,2′,6,6′ positions.[12]



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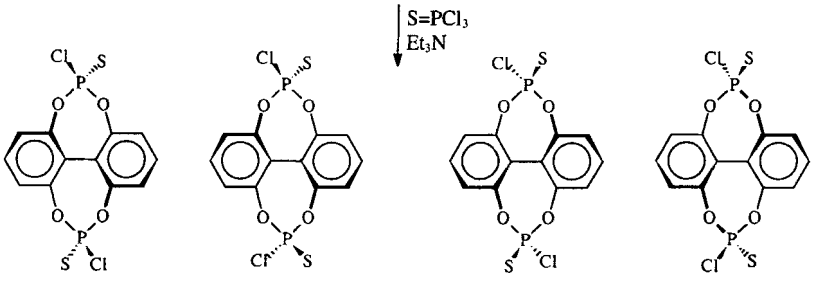
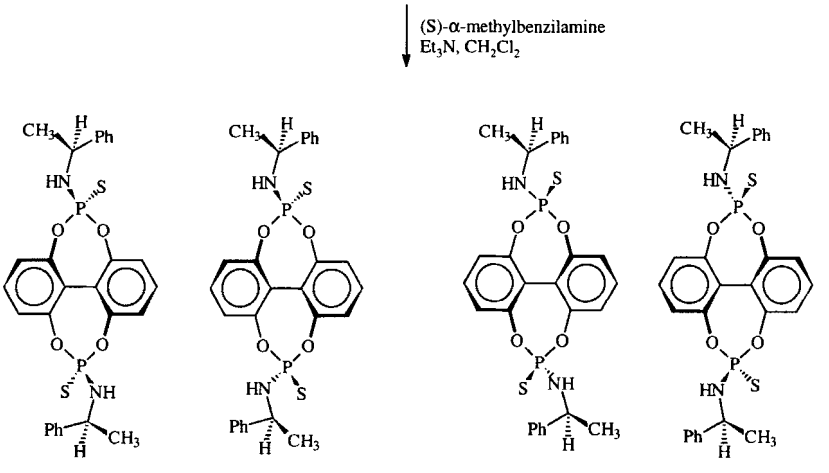
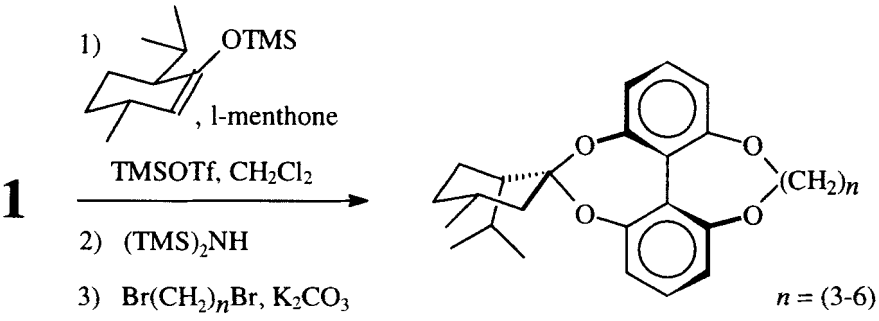


(M)-cis-**2** *(M)-trans*-**2** *(P)-cis*-**2** *(P)-trans*-**2**



(S,M,S)-cis-**3** *(S,M,S)-trans*-**3** *(S,P,S)-cis*-**3** *(S,P,S)-trans*-**3**

The substituents allow the control of the torsional angle ω and provide restriction of rotation around the 1,1′ bond. Among the many examples which appear in the literature on the preparation of chiral non-racemic 1,1′-biphenyl substituted at the 2,2′,6,6′-positions, to the best of our knowledge, only two use a bridge connecting the phenyl system.[13,14] In the first example[13] a *bis* crown ether was prepared starting from tetraethylene glycol ditosylate and tetrol **1** and then resolved by preparative HPLC. In the other one[14] the bridge structure was



obtained in three steps by monoacetalization of tetrol **1** with *l*-menthone and intermolecular monocyclization of **1** with 1,*n*-dibromoalkanes (eq 1).

We anticipate that the formation of a *bis* (1,3,2)-dioxaphosphepine derived from tetrol **1** would make the molecule chiral since the bridged biphenyl system is twisted and dissymetric.[15] (1,3,2)-Dioxaphosphepine **2** was readily prepared starting from tetrol **1** in the presence of thiophosphoryl chloride and using triethylamine as solvent. The two possible diastereomers *cis*-**2** and *trans*-**2** were produced in a 1:1 ratio. They are solid, relatively stable, and were easily separated and purified by flash-chromatography. Isomer *trans*-**2** was also isolated from a *cis-trans* mixture by two recrystallization from dichloromethane-petroleum ether and its structure was defined unequivocally by X-ray analysis (Figure 1). The acid chloride *trans*-**2**, which posseses a C_2 symmetry axis, assumes a rigid twisted structure (dihedral angle $C_{(1)}$-$C_{(4)}$-$C_{(5)}$-$C_{(8)}$ of - 45.3°) with the sulphur atoms directed towards opposite sides. In *trans*-**2**, the phosphorus atoms are not stereogenic centers since they lie along the C_2 symmetry axis. No attempts were made to resolve **2** into its enantiomers.

When phosphorothiochloride *trans*-**2** was treated with *S*-(-)-α-methylbenzylamine in the presence of triethylamine using dichloromethane as solvent, the two corresponding phosphorothioamidates *trans*-**3** were obtained in satisfactory yield and in a 1:1 ratio. The same compounds (*trans*-**3**) were also obtained starting from a 1:1 *cis trans* mixture of **2**; in fact the four corresponding phosphorothioamidates **3** were obtained in an equimolar ratio. Several attempts to separate each of the four diastereomers failed. We were able only to isolate the *trans* isomers by recrystallization of a *cis-trans* mixture from petroleum ether-dichloromethane. Fortunately, suitable crystals of both *trans* diastereomers were obtained. The lattice of such crystals contain both *trans* diastereomers. The perspective views of the two isomers of *trans*-**3** are shown in Figure (2).

Compounds *trans-(S,P,S)*-**3** and *trans-(S,M,S)*-**3** have a dihedral angle of 44° ($C_{(5)}$-$C_{(6)}$-$C_{(7)}$-$C_{(8)}$) and 45° ($C_{(33)}$-$C_{(34)}$-$C_{(35)}$-$C_{(36)}$), respectively. The value is comparable to that measured for compound *trans*-**2**.

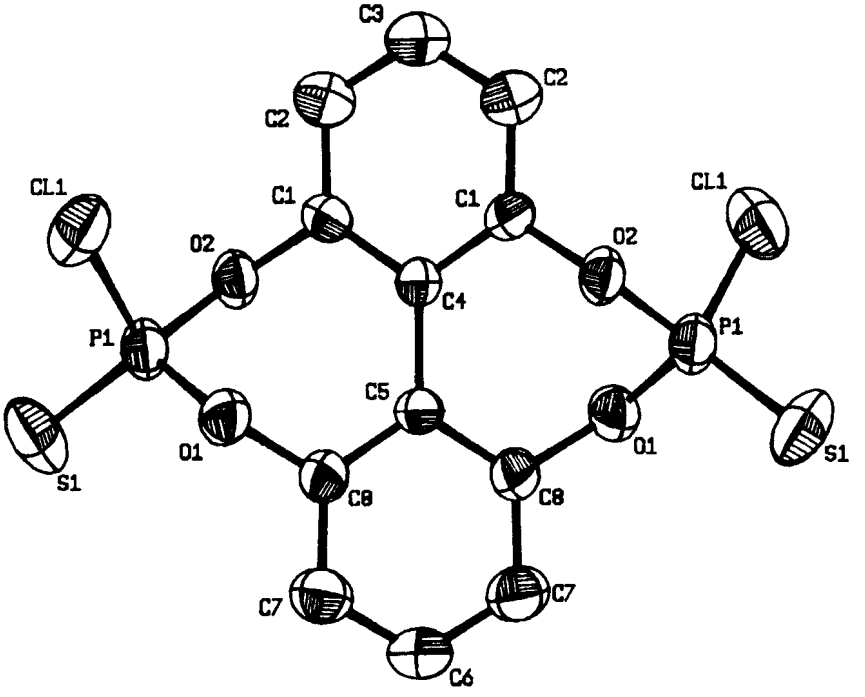


FIGURE 1 Perspective drawing of structure *trans*-**2** as determined by the X-ray diffractometric analysis. Hydrogen atoms are omitted.

Attention should be paid to the configuration of compounds **3**. They differ only in the chirality of the biaryl structure, whereas the phosphorus atoms are not stereogenic centers. Both isomers *trans*-**3** have quite a low atropisomerization barrier in solution in most solvents. Interconversion of the bridged biphenyl

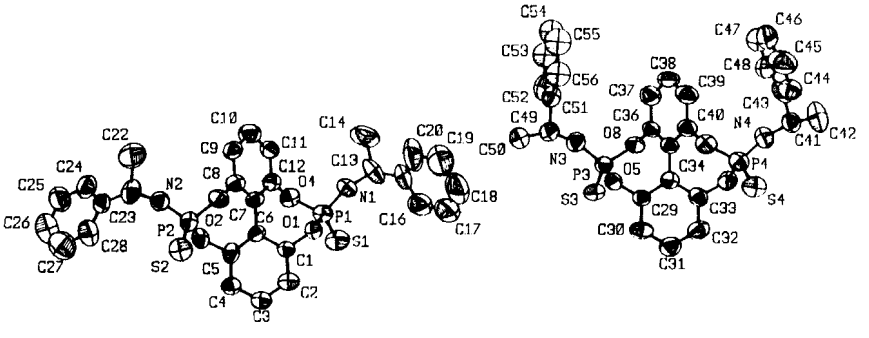


FIGURE 2 Perspective drawing of structures (*S,P,S*)-*trans*-**3** and (*S,M,S*)-*trans*-**3** as determined by the X-ray diffractometric analysis. Hydrogen atoms are omitted.

system was monitored by NMR spectroscopy. *Trans M* form converts to the *trans P* form (*cis M* form interconverts to the *cis P* form) within a half-life of 2 h at 60 °C and 6 hs at rt in deuterochloroform. Such fluxional behavior has also been seen in the cyclic derivative shown in eq (1).[14]

With the aim of preparing stable axially chiral phosphorothioates and phosphorothioamidates, we subjected compounds *trans*-**3** and *cis*-**3** to acid and basic alcoholysis. When phosphorothioamidates *trans*-**3** and *cis*-**3** were treated with a 4M solution of H_2SO_4 in methanol at rt, an undefined mixture of products were recovered. The same result was obtained by carrying out the reaction at a lower temperature.

In contrast to acid hydrolysis, basic alcoholysis of phosphorothioamidates *trans*-**3** and *cis*-**3** induced P-O cleavage and ring opening to afford the corresponding acyclic phosphorothioamidates **4** and **5**. The reaction was conducted in the presence of two equivalents of sodium methoxide or ethoxide in methanol or ethanol, respectively. Good yields and very high diastereoselectivity were produced. In fact, only two diastereomers **4a** and **4b** (or **5a** and **5b**) were recovered, starting from an equimolar *cis-trans* mixture of **3**. The high stereoselectivity may be related to the rigid aromatic structure, whereas it should not be affected by the nature of the nucleophilic reagent. NMR spectroscopic data of both phosphorothioamidates **4a** and **4b** (or **5a** and **5b**) show evidence of the presence of homochiral phosphorus atoms (aromatics area at proton resonance sufficiently simple and only one signal for ^{31}P for each diastereomer). Although we suppose that diastereomers **4a** and **4b** have opposite configuration at the biphenyl skeleton and at phosphorus atoms, we can not confirm this speculative hypothesis. In fact, we were only able to assign the absolute configuration to compounds **5a** (recrystallized from dichloromethane-petroleum ether). The perspective view (Figure 3) of the structure **5a** obtained by X-ray analysis shows considerably distorted benzene rings ($C_{(16)}$-$C_{(15)}$-$C_{(20)}$, 115.4°; $C_{(11)}$-$C_{(12)}$-$C_{(13)}$, 123.1°; $C_{(12)}$-$C_{(11)}$-$C_{(10)}$, 121.1°; $C_{(12)}$-$C_{(13)}$-$C_{(14)}$, 118.0°). *R* configuration for both phosphorus atoms and an a*S* configuration for biphenyl structure were determined unequivocally. The conformational stability of compounds **4a, 4b, 5a** and **5b** is confirmed by dihedral angle ($C_{(11)}$-$C_{(10)}$-$C_{(15)}$-$C_{(20)}$, 105°) of **5a** that shows a higher value than the cyclic derivatives **2** and **3**.

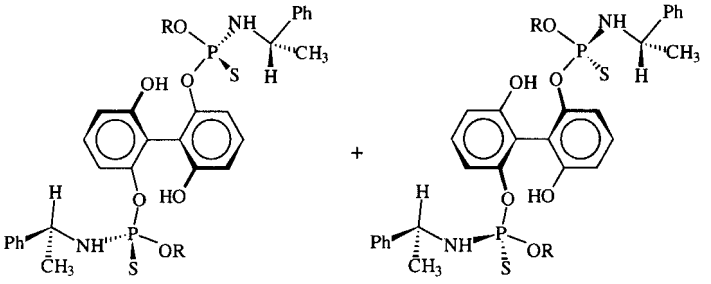
Acid alcoholysis of acyclic phosphorothioamidates **4** or **5** promotes cleavage of the P-N bond and affords the corresponding cyclic phosphorothioates. The reaction was carried out in the presence of a 4M solution of H_2SO_4 in methanol (or ethanol) at rt. Starting from diastereopure phophorothioamidate **4** and **5**, only *trans* phosphorothioates (*M*)-**6** and (*M*)-**7** were obtained in satisfactory yield, respectively. When a mixture of phosphorothioamidates **4** enriched in diastereomer **4b** (or **5b**), was subjected to the same acid alcoholysis, the opposite

indefinite mixture of products

↑ 4M H_2SO_4 in MeOH

(*S*,*M*,*S*)-*cis*-**3** (*S*,*M*,*S*)-*trans*-**3** (*S*,*P*,*S*)-*cis*-**3** (*S*,*P*,*S*)-*trans*-**3**

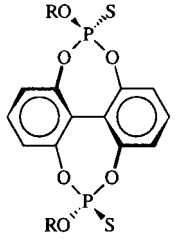
↓ NaOR in ROH



R = CH_3 (*S*,*R*,a*S*,*R*,*S*)-**4a** (a*R*)-**4b**

R = C_2H_5 (*S*,*R*,a*S*,*R*,*S*)-**5a** (a*R*)-**5b**

↓ 4M H_2SO_4 in ROH



R = CH_3 (*M*)-*trans*-**6** enantiopure

R = C_2H_5 (*M*)-*trans*-**7** enantiopure

enantiomer (*P*)-**6** (or (*P*)-**7**) was obtained as the main stereoisomer. The latter result agrees with our hypothesis about the opposite configuration of compound **4a** and **4b** (or **5a** and **5b**) of the biphenyl skeleton. Furthermore, although the configuration of the phosphorus atoms in compound **4a** was not supported by

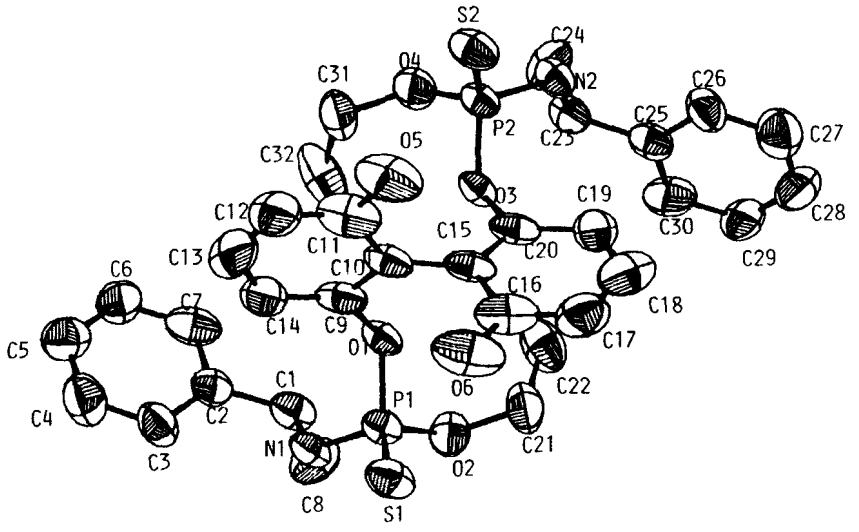


FIGURE 3 Perspective drawing of structure (*S,R*,a*S,R,S*)-**5a** as determined by the X-ray diffractometric analysis. Hydrogen atoms are omitted.

X-ray analysis, we assume compound **4a** to have the *R* configuration. (*S*)-α-Methylbenzylamine was recovered from the reaction mixture without loss of enantiomeric purity. No significant tiono-thiol transposition was found at any stage of the reactions.

Although we have not studied in detail the reaction mechanism, and we did not find evidence in the literature on the stereoselective P-N cleavage under acid alcoholysis,[16] experimental data show that the closure affords *trans* (1,3,2)dioxaphosphepines **6** and **7**.

In fact, compound **6** has identical ^{1}H-NMR and ^{31}P-NMR spectra to that of the phosphorothioate obtained by reaction of isomer *trans*-**2** with methanol and triethylamine using dichloromethane as solvent. A trigonal bipyramidal intermediate should be assumed to explain the different behavior in cyclization of compound **4** (or **5**) respect to cyclization of tetrol **1** by thiophosphoryl chloride that gives an equimolar mixture of *trans*-**2** and *cis*-**2** as previously shown in Scheme 1. In this latter case the cyclization goes through a O-aryl phophorodichloridate, loss of one of the two chlorides and subsequent closure of the ring to give [1,3,2]dioxaphosphepines *trans*-**2** and *cis*-**2**. It is customary to consider a trigonal bipyramidal intermediate[17] which is formed by attack of the nucleophile opposite to the leaving group, so that nucleophile and leaving group are placed in apical positions with departure of the leaving group before than any ligand reorganization has taken place. According to this hypothesis, exclusive

production of *trans*-**6** (or *trans*-**7**) starting from compound **4** (or **5**) can be explained by the fact that in the phosphorothioamidates **4** (or **5**) only one trigonal bipyramidal configuration can be formed.

Phosphorothioates **6** and **7** are optically stable in solution at room temperature in most solvents, but show racemization with a half-life of 1 h by warming at 70°C in chloroform.

In conclusion, we have developed an effective, economical method for the preparation of axially chiral biaryl organothiophosphorus compounds which possess a C_2 symmetry axis. The high symmetry makes the thiophosphorus functionalities equivalent with useful application in asymmetric synthesis and agrochemistry as well. This mild methodology should therefore be applicable to a wide variety of axially chiral biaryl derivatives available through the formation of a bridged biphenyl system. The procedure can also be scaled up easily. The new compounds can be tested as agrochemicals.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra were recorded with a Varian VXR 5000 spectrometer at 299.94 Mhz, 75.42 MHz and 121.42 MHz, respectively. ^{31}P-NMR chemical shifts are relative to H_3PO_4 (external standard) in $CDCl_3$. Elemental analyses were performed by Mr A. Canu in the Department of Chemistry at the University of Sassari. Optical rotations were measured with a Perkin-Elmer 241 spectropolarimeter. All reactions were conducted under a positive pressure of argon. Dichloromethane was freshly distilled from calcium chloride. Methanol and ethanol were dried on 4 Å molecular sieves. All other reagents were of commercial quality and used as purchased. Flash chromatography was carried out with silica gel 60 (230–400 mesh, Kiesgel, EM Reagents) eluting with appropriate solution in the stated v:v proportions. The purity of all new compounds was judged to be >98% by ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectral determination.

*[1,3,2]Benzodioxaphosphepino[6,5,4-d,e,f]*2-chloro-2-sulfide[1,3,2]benzodioxaphosphepine-2-chloro-2-sulfide 2

Thiophosphoryl chloride (1.08 g, 6.4 mmol) was slowly added to a solution of 2,2′,6,6′-biphenyltetrol **1** (0.5 g, 2.3 mmol) in 20 mL of dry dichloromethane. A solution of triethylamine (1.14 g, 11.3 mmol) in dry dichloromethane (10 mL) was added and the reaction mixture was stirred at room temperature for 7 h. The reaction was quenched by addition of 150 mL of water. A solution of 10%

HCl was added until pH neutral. The mixture was extracted with dichloromethane (5 × 20 mL), dried over Na_2SO_4 and rotoevaporated to give **2** as a 1:1 mixture of *trans* and *cis* isomers. The product, as colorless solid, was purified by flash chromatography (dichloromethane-petroleum ether, 1:1) to give **2** (0.55 g, 60%). The *trans* isomer was separated by two recrystallization with dichloromethane-petroleum ether and its structure was evaluated by X-ray crystallography; *trans*-**2**: mp 227°C (dichloromethane: petroleum); ^{1}H NMR ($CDCl_3$) δ 7.35 (dt, J = 8.4, 2.0 Hz, 2H), 7.39 (dt, J = 8.4, 2.0 Hz, 2H), 7.64 (t, J = 8.4 Hz, 2H), ^{13}C NMR δ 120.15 (m), 120.91 (m), 131.66 (m), 131.88 (m); ^{31}P NMR δ 73.50. Anal. Calcd for $C_{12}H_6O_4P_2S_2Cl_2$: C, 35.06; H, 1.47. Found: C, 35.20; H, 1.50. *cis*-**2**: ^{1}H NMR ($CDCl_3$) δ 7.33–7.41 (series of m, 4H), 7.64 (t, J = 8.1 Hz, 2H), ^{13}C-NMR, δ 120.24 (m), 120.81 (m), 131.74 (m), 131.76 (m); ^{31}P-NMR, δ 73.50.

[1,3,2]Benzodioxaphosphepino[6,5,4-d,e,f] (*S*)-(-)-2-*N*-α-methylbenzylamine -2-sulfide[1,3,2] benzodioxaphosphepine-(*S*)-(-)-2-*N*-α-methylbenzylamine-2-sulfide 3

A solution of triethylamine (1.34 g, 13.2 mmol), (*S*)-(-)-α-methylbenzylamine (1.41 g, 11.6 mmol) in 10 mL of dry dichloromethane was added slowly to a solution of equimolar *trans*-**2** + *cis*-**2** (2.18 g, 5.3 mmol) in 30 mL of dry dichloromethane. The reaction mixture was stirred at room temperature for 7 d and then quenched with 100 mL of water. A solution of 10% HCl was added until pH slightly acidic. The mixture was extracted with dichloromethane (5 × 20 mL) and the combined extract was dried over Na_2SO_4 and rotoevaporated to give an equimolar mixture of phosphorothioamidates *trans*-**3** and *cis*-**3**. The product was purified by flash chromatography (dichloromethane-petroleum ether, 3:1) to give 2.30 g of a colorless solid (75%). The two *trans* diastereomers were separated in a 8:2 ratio, by recrystallization from benzene-petroleum ether and their structures were evaluated by X-ray crystallography. *trans*-**3** (one diastereomer): ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 7.8 Hz, 3H), 3.68 (dd, J = 9.9, 10.2 Hz, 1H), 4.78 (m, 1H), 6.23 (dt, J = 8.1, 1.8 Hz, Ar, 2H), 7.02 (t, J = 8.1 Hz, Ar, 1H), 7.12–7.35 (series of m, Ar, 12 H), 7.44 (t, J = 8.1 Hz, Ar, 1H); ^{31}P NMR ($CDCl_3$) δ 80.29. *trans*-**3** (one diastereomer): ^{1}H NMR ($CDCl_3$) δ: 1.54 (d, J = 6.9 Hz, 3H), 3.81 (t, J = 11.1 Hz, 1H), 4.59 (m, 1H), 6.70 (dt, J = 8.1, 1.5 Hz, Ar, 2H), 6.97 (t, J = 8.1, Ar, 1H), 7.12–7.35 (series of m, Ar, 12 H), 7.49 (t, J = 8.1 Hz, Ar, 1H); ^{31}P NMR ($CDCl_3$) δ 78.63. *cis*-**3** (mixture of two diastereomers) ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 6H), 3.46–3.79 (series of m, 2H, 1 diast.), 4.53 (m, 1H, 1 diast.), 4.72 (m, 1H, 1diast.), 6.39 (ddd, J = 8.1, 3.0, 1.5 Hz, Ar, 2H, 1diast.), 6.86 (ddd, J = 8.1, 3.0, 1.5Hz,

Ar, 2H, 1diast.), 7.21–7.38 (series of m, Ar, 28H); ^{31}P NMR ($CDCl_3$), δ 80.12 (1 diast.), 78.59 (1 diast.).

Interconversion measurements of 3

A ^{1}H NMR sample in $CDCl_3$ was stirred at rt and was periodally monitored until complete inversion of the bridged biphenyl system. Half-life of 6 h was determined.

General procedure for the basic alcoholysis of phosphorothioamidates 3

To a solution of equimolar mixture of *trans*-**3** + *cis*-**3** (0.50g, 0.86 mmol) in methanol (20 mL) (or ethanol) a 1.2M solution of sodium methoxide (or ethoxide) (1.4 mL, 1.72 mmol) in methanol (or ethanol) was added slowly. After stirring at rt for 24 h, the reaction mixture was poured in 100 mL of water. A solution of 10% HCl was added until pH slightly acidic. The mixture was extracted with ether (5 × 20 mL), dried over Na_2SO_4 and the combined extract was rotoevaporated to give **4a** and **4b** (or **5a** and **5b**) as a 1:1 mixture of two diastereomers. Purification by flash chromatography (dichloromethane-petroleum ether, 3:1) give **4a** and **4b** (90%) (or **5a** and **5b**, 85%) as a colorless solid. The diastereopure product (*S,R,aS,R,S*)-**4a** was recrystallized from dichloromethane-petroleum ether to obtain colorless crystals (85%). The filtered solution was rotoevaporated to dryness to obtain a diastereomeric mixture of **4a** and **4b** (13:87) (or **5a** and **5b** as 30:70) as a viscous oil. (*S,R,*a*S,R,S*)-**4a** diastereopure: mp 155 °C (dichloromethane-petroleum ether); $[\alpha]^{20}_D$ + 54.5 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 6.9 Hz, 6H), 3.28 (d, J = 14.4 Hz, 6H), 3.45 (m, 2H), 4.30 (m, 2H), 5.45 (bs, 2H), 6.80 (d, J = 7.8 Hz, Ar, 2H), 6.90 (dd, J = 0.9, 8.1 Hz, Ar, 2H), 7.25–7.32 (series of m, Ar, 12H); ^{31}P NMR ($CDCl_3$) δ 64.90; Anal. Calcd for $C_{30}H_{34}O_6P_2S_2N_2$: C, 55.89; H, 5.32; N, 4.35. Found: C, 56.03; H, 5.10; N, 4.31. (a*R*)-**4b** (de 74%): ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 6.9 Hz, 6H), 3.16 (d, J = 14.1 Hz, 6H), 3.63 (m, 2H), 3.90 (m, 2H), 5.55 (bs, 2H), 6.96 (d, J = 8.1 Hz, Ar, 2H), 7.15 (d, J = 7.2 Hz, Ar, 2H), 7.20–7.40 (series of m, Ar, 12H); ^{31}P NMR ($CDCl_3$) δ 65.20. The diastereopure compound (*S,R,*a*S,R,S*)-**5a** (57%) was recrystallized from dichloromethane-petroleum to obtain colorless crystalls suitable for X-ray analysis (Figure 3): mp 115 °C (dichloromethane-petroleum); $[\alpha]^{20}_D$ + 55.0 (c 1, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.07 (t, J = 7.2 Hz, 6H), 1.40 (d, J = 6.9 Hz, 6H), 3.41–3.70 (series of m, 6H), 4.33 (m, 2H), 5.41 (bs, 2H), 6.78 (d, J = 8.4 Hz, Ar, 2H), 6.86 (d, J = 8.1 Hz, Ar, 2H), 7.25–7.32 (series of m, Ar, 12H); ^{31}P NMR ($CDCl_3$) δ:

66.95. Anal. Calcd for $C_{32}H_{38}O_6P_2S_2N_2$: C, 57.13; H, 5.69; N, 4.16. Found: C, 57.38; H, 5.40; N, 4.19. (a*R*)-**5b** (de 40%): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 6H), 1.34 (d, J = 6.9 Hz, 6H), 3.41–3.70 (series of m, 6H), 4.00 (m, 2H), 5.41 (bs, 2H), 6.94 (d, J = 7.8 Hz, Ar, 2H), 7.25–7.32 (series of m, Ar, 14H); ^{31}P NMR ($CDCl_3$) δ 65.95

General procedure of the acidic alcoholysis of phosphorothioamidates 4 and 5

A solution of concentred H_2SO_4 (7 mL) was slowly added to an ice cooled solution of diastereopure (*S,R*,a*S,R,S*)-**4a** (or **5a**) (1.0 mmol) in 20 mL of methanol (or ethanol). The reaction mixture was stirred at room temperature for 24 h and then poured in 100 mL of water. The mixture was extracted with ether (5 × 20 mL), dried over Na_2SO_4 and the combined organic extract was rotoevaporated to give (*M*)-**6** (or (*M*)-**7**) as colorless solid. The product was purified by flash chromatography (dichloromethane-petroleum ether, 1:1). (*M*)-**6** (90%) mp 190–2 °C (dichloromethane-petroleum ether); $[\alpha]^{20}_D$ + 110.9 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.02 (d, J = 14.1 Hz, 6H), 7.19 (dd, J = 1.2, 8.1 Hz, Ar, 2H), 7.28 (dd, J = 1.2, 8.1 Hz, Ar, 2H), 7.54 (t, J = 8.1 Hz, Ar, 2H), ^{31}P NMR ($CDCl_3$) δ 75.56; Anal. Calcd for $C_{14}H_{12}O_6P_2S_2$: C, 41.80; H, 3.01. Found: C, 42.05; H, 3.19. (*M*)-**7** (92%) mp 160–2 °C (dichloromethane: petroleum ether); $[\alpha]^{20}_D$ + 96.5 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.43 (t, J = 7.5 Hz, 6H), 4.42 (m, 4H), 7.18 (dd, J = 0.9, 8.1 Hz, Ar, 2H), 7.27 (dd, J = 0.9, 8.1 Hz, Ar, 2H), 7.52 (t, J = 8.1 Hz, Ar, 2H), ^{31}P NMR ($CDCl_3$) δ 73.81. Anal. Calcd for $C_{16}H_{16}O_6P_2S_2$: C, 44.65; H, 3.76. Found: C, 44.42; H, 3.72.

Following the same procedure a diastereomeric mixture of **4** (75% diastereomeric purity) gave (*P*)-**6** $[\alpha]^{20}_D$ − 80.5 (c 1, $CHCl_3$). Following the same procedure a diastereomeric mixture of **5** (40% diastereomeric purity) gave (*P*)-**7** $[\alpha]^{20}_D$ − 38.4 (c 0.6, $CHCl_3$).

Enantiomeric composition of (*M*)-**6** and (*P*)-**6** was nicely determined as diastereoisomeric solvates with enantiopure quinine by ^{1}H NMR spectroscopy[18].

Racemization measurements of (M)-6 and (M)-7

For each compound, appropriate chloroform solution was heated until the optically rotation decreased to zero. Half time of 1 h was detected at 70 °C.

Crystal structure determination

Atomic coordinates, bond distances, bond angles and structure factors tables have been deposited as supplementary material. Reflections were collected on a Philips PW 1100 four-circle diffractomer at rt. Crystal data for *trans*-**2**: $C_{12}H_6O_4P_2S_2Cl_2$: space group $C2_c$ N15, monoclinic, a = 15.6490, b = 12.2510, c = 9.7350, β = 122.50, Mo Kα monochromatized radiation (λ = 0.7107 Å), ϑ–2ϑ 2–28°. Crystal data for *trans*-**3**: $C_{28}H_{30}O_4P_2S_2N_2$, space group $P2_12_12_1$ N19, orthorhombic, a = 18.7690, b = 30.5230, c = 9.9540, Mo Kα monochromatized radiation (λ = 0.7107 Å), ϑ–2ϑ 3–60°. Crystal data for (*S,R*,a*S,R,S*)-**5a**: $C_{32}H_{38}O_6P_2S_2N_2$, space group $P2_12_12_1$ N4, monoclinic, a = 8.9480, b = 21.8430, c = 9.0920, β = 103.90, Cu Kα monochromatized radiation (λ = 0.15418 Å), ϑ–2ϑ 3–60°. The reflections were phased by SHELX 86 program and refined by blocked full matrix least squares using SHELX 76 program.

Supporting Information Available

Crystallographic data of compounds *trans*-**2**, *trans-(S,P,S)*-**3**, *trans-(S,M,S)*-**3** and (*S,R*,a*S,R,S*)-**5a**.

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