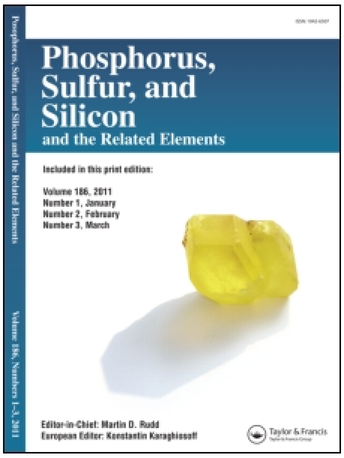

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ASYMMETRIC SYNTHESIS OF (*R_p*)- AND (*S_p*)-2-ETHYL-, (*R_p*)-2-PENTYLOXY-, (*S_p*)-2-PENTYLTHIO- AND (*S_p*)-2-PENTYLAMINO-4*H*-1,3,2-BENZODIOXAPHOSPHORIN 2-OXIDES

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ASYMMETRIC SYNTHESIS OF (R_p)- AND (S_p)-2-ETHYL-, (R_p)-2-PENTYLOXY-, (S_p)-2-PENTYLTHIO- AND (S_p)-2-PENTYLAMINO-4*H*-1,3,2-BENZODIOXAPHOSPHORIN 2-OXIDES

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2-Substituted-4*H*-1,3,2-benzodioxaphosphorin 2-oxides (2-substituted-BDPOs) are potent and stereoselective inhibitors of neuropathy target esterase (NTE) when the 2-substituent is *n*-alkyl, *n*-alkyloxy, *n*-alkylthio or *n*-alkylamino with maximum potency for the C_7 to C_9 analogs. Asymmetric syntheses were developed to assign the absolute configurations of each type of 2-substituted-BDPO. (S_p)-*O*-Methyl ethylphosphonothioic acid, the chiral starting material for (R_p)- and (S_p)-2-ethyl-BDPOs, was obtained by resolution of the racemate with quinine. It was ≥82% *e.e.* based on its stereospecific conversion to (R_p)-*O*-methyl ethylphosphonochloridothionate which was coupled with (S_c)-(-)-α-methylbenzylamine for analysis of the diastereomeric derivative by ^{1}H and ^{31}P NMR and HPLC. The final (R_p)- and (S_p)-2-ethyl compounds were 80 and 82% *e.e.*, respectively. The starting material for the chiral *O*-, *S*- and *N*-pentyl-BDPOs was (S_cR_p)-2-[1-(2-methoxycarbonylpyrrolidyl)]-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide which was recrystallized to 100% *d.e.* (R_p)-2-Pentyloxy-BDPO (94% *e.e.*) was obtained by two reaction sequences involving two or four steps. (S_p)-2-Pentylthio-BDPO (100% *e.e.*) and (S_p)-2-pentylamino-BDPO (58% *e.e.*) were prepared in three- and five-step reactions, respectively. Optical purities were determined by HPLC with a CHIRALCEL OC column. In each asymmetric synthesis, the stereochemical orientation assigned for the substituents on phosphorus was consistent with the chromatographic characteristics on the chiral column.

Key words: Asymmetric synthesis; 1,3,2-benzodioxaphosphorin 2-oxide; NTE inhibitors; stereochemistry.

INTRODUCTION

4*H*-1,3,2-Benzodioxaphosphorin 2-oxides (BDPOs) show two distinct types of biological activities depending on the 2-substituent. 2-Methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide (salithion) is a commercial insecticide which acts as an inhibitor of acetylcholinesterase after metabolic activation on oxidative desulfuration to 2-methoxy-BDPO.[1] In contrast, tri-*o*-cresyl phosphate, acting via the metabolite 2-(*o*-methylphenoxy)-BDPO, induces delayed neuropathy in birds and many mammals including humans.[1-3] The initial step in inducing the neurological lesions is proposed to be the inhibition of neuropathy target esterase (NTE).[3] The NTE-inhibitory potency *in vitro* of 2-(*o*-methylphenoxy)-BDPO is greatly increased on replacement of the *o*-methylphenoxy moiety with a C_7 to C_9 *n*-alkyl, *n*-alkyloxy, *n*-alkylthio or *n*-alkylamino substitutent.[4]

The BDPOs are stereoselective NTE inhibitors in studies comparing 22 pairs of individual enantiomers obtained from HPLC resolution with a CHIRALCEL OC

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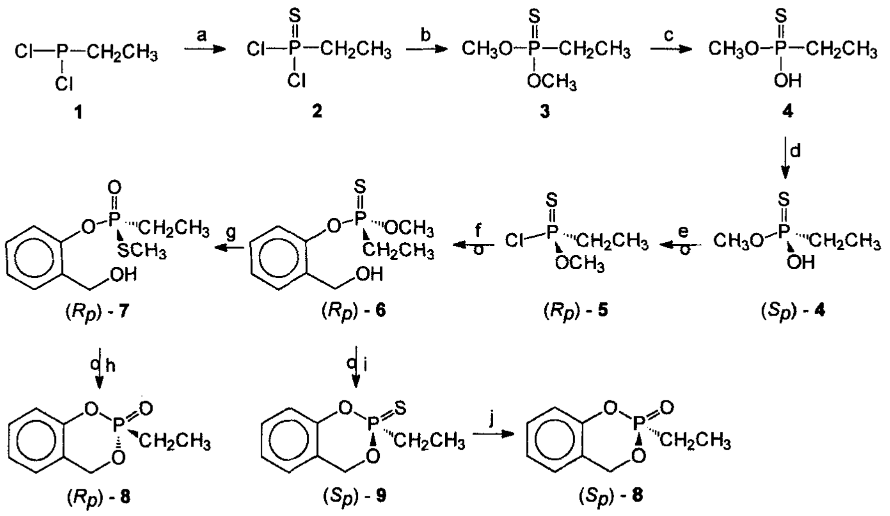
column.[5] In each pair of enantiomers, the one less retained on HPLC (designated Isomer-I) is less potent as an NTE inhibitor than the one more retained (Isomer-II).[5] The present investigation involves asymmetric syntheses to assign the absolute configurations for these HPLC-resolved enantiomers. (R_p)- and (S_p)-2-Ethyl-BDPOs were synthesized via (S_p)-*O*-methyl ethylphosphonothioic acid as the chiral starting material. (R_p)-2-Pentyloxy-, (S_p)-2-pentylthio- and (S_p)-2-pentylamino-BDPOs were prepared from (S_cR_p)-2-[1-(2-methoxycarbonylpyrrolidyl)]-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide. These optically-active products were analyzed by chiral HPLC as above.[5] This report describes the asymmetric syntheses along with the correlation between the stereochemical orientation of the substituents on phosphorus and the chiral HPLC resolving sequence of the enantiomeric BDPOs.

RESULTS AND DISCUSSION

Syntheses of (R_p)- *and* (S_p)-*2-ethyl-4H-1,3,2-benzodioxaphosphorin 2-oxides* [(R_p)-**8** *and* (S_p)-**8**] (*Figure 1*)

O-Methyl ethylphosphonothioic acid (**4**) as the racemate was synthesized by sulfuration of dichloroethylphosphine (**1**) under the catalysis of $AlCl_3$ to obtain ethylphosphonodichloridothionate (**2**) which was subjected to methanolysis and the *O*, *O*-dimethyl ethylphosphonothionate (**3**) produced was converted to **4** by treatment with KOH in methanol. Racemic **4** was resolved by formation of its diastereomeric quinine salts in acetone and recrystallization of the first crop of crystals three times



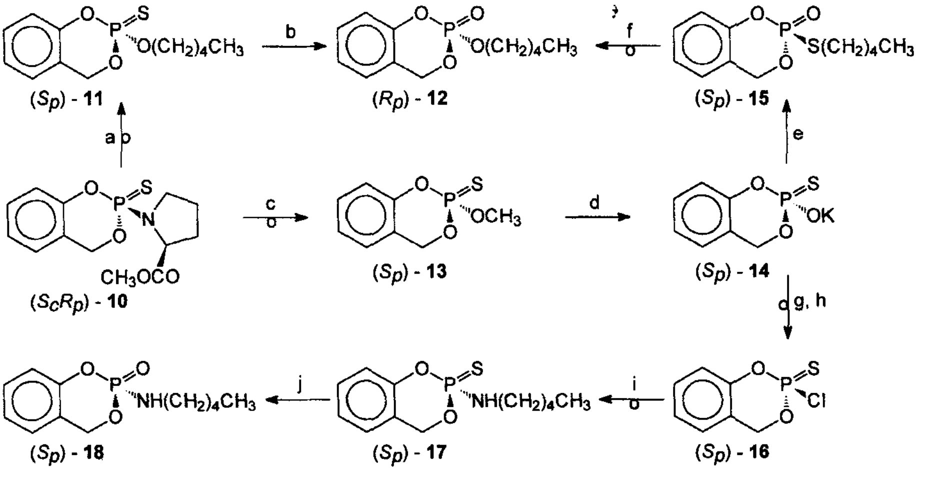
a : $S / AlCl_3$, b : CH_3OH, c : KOH / CH_3OH, d : quinine / $(CH_3)_2CO$, e : $PCl_5 / (C_2H_5)_2O$,
f : saligenin / $K_2CO_3 / (CH_3)_2CO$, g : $CH_3I / KCl / DMF$, h : $MCPBA / CDCl_3$, i : $K_2CO_3 / (CH_3)_2CO$,
j : $MCPBA / C_6H_6$.

FIGURE 1 Synthesis of (R_p)- and (S_p)-2-ethyl-4*H*-1,3,2-benzodioxaphosphorin 2-oxides [(R_p)- and (S_p)-**8**].

from acetone until a constant melting point was obtained [mp 174–176°C, the complex of (S_p)-**4** and quinine].[6–9] (S_p)-**4** was recovered by addition of aqueous NaOH to precipitate and separate the quinine, acidification of the aqueous solution with HCl, and extraction into ether. This enantiomer was converted to (R_p)-methyl ethylphosphonochloridothionate [(R_p)-**5**] by reacting with phosphorus pentachloride in ether in a replacement of hydroxy group by chloride that occurs with inversion.[10, 11] Reaction of (R_p)-**5** and 2-hydroxybenzyl alcohol (saligenin) formed (R_p)-*O*-ethyl *O*-(2-hydroxymethylphenyl) ethylphosphonothionate [(R_p)-**6**] with inversion.[12,13] Retention on Pistschimuka conversion[14,15] of (R_p)-**6** with iodomethane to (R_p)-*O*-(2-hydroxymethylphenyl) *S*-methyl ethylphosphonothiolate [(R_p)-**7**] was followed by inversion[16,17] on forming (R_p)-2-ethyl-4*H*-1,3,2-benzodioxaphosporin 2-oxide [(R_p)-**8**] by oxidizing the methylthio group with *m*-chloroperoxybenzoic acid (MCPBA). As an alternative, (R_p)-**6**, on heating with K_2CO_3 in acetone, cyclized to (S_p)-2-ethyl-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide [(S_p)-**9**] with inversion.[13,18] Oxidation with MCPBA converted (S_p)-**9** into (S_p)-2-ethyl-4*H*-1,3,2-benzodioxaphosphorin 2-oxide [(S_p)-**8**], with retention of the configuration.[19]

*Syntheses of (R_p)-2-pentyloxy-, (S_p)-2-pentylthio- and (S_p)-2-pentylamino-4H-1,3,2-benzodioxaphosphorin 2-oxides [(R_p)-**12**, (S_p)-**15** and (S_p)-**18**, respectively] (Figure 2)*

Preparation of (S_cR_p)-2-[(1-(2-methoxycarbonylpyrrolidyl)]-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide [(S_cR_p)-**10**] followed a described procedure[20] involving: 1) synthesis of the disastereomeric mixture of (S_cR_p)- and (S_cS_p)-**10** through the coupling reaction of racemic 2-chloro-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide with



a : $CH_3(CH_2)_4OH$ / H^+, b : MCPBA / C_6H_6, c : CH_3OH / H^+, d : $(CH_3)_2NC(S)SK$ / C_2H_5OH,
e : $CH_3(CH_2)_4I$ / $(CH_3)_2CO$, f : MCPBA / $CH_3(CH_2)_4OH$, g : H^+, h : PCl_5 / $(C_2H_5)_2O$,
i : $CH_3(CH_2)_4NH_2$ / CH_2Cl_2, j : MCPBA / C_6H_6.

FIGURE 2 Synthesis of (R_p)-2-pentyloxy-, (S_p)-2-pentylthio- and (S_p)-2-pentylamino-4*H*-1,3,2-benzodioxaphosphorin 2-oxides [(R_p)-**12**, (S_p)-**15** and (S_p)-**18**].

L-proline methyl ester; 2) recrystallization from hexane/ether to isolate the diastereomer (S_cR_p)-**10** with 100% *d.e.* based on ^{1}H and ^{31}P NMR and HPLC analysis. Acid-catalyzed alcoholysis of (S_cR_p)-**10** in *n*-pentanol or methanol occurs with inversion[20–23] and produced (S_p)-2-pentyloxy- or (S_p)-2-methoxy-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide [(S_p)-**11** or (S_p)-**13**], respectively. Oxidation of (S_p)-**11** with MCPBA yielded the 2-oxide (R_p)-**12** with retention.[19] Demethylation of (S_p)-**13** with potassium dimethyldithiocarbamate followed by pentylation of (S_p)-**14** with 1-iodopentane gave (S_p)-2-pentylthio-BDPO [(S_p)-**15**], in reactions not involving the chiral phosphorus center so the configuration was retained. Synthesis of (R_p)-**12** was also achieved with inversion[16,17] by oxidizing (S_p)-**15** with MCPBA in the presence of *n*-pentanol; as discussed later, the optical yields of (R_p)-**12** were dependent on the reaction conditions. Chlorination of (S_p)-**14** (after transformation to the acid) with phosphorus pentachloride afforded the chloridothionate (S_p)-**16**, which was converted to the amidate (S_p)-**17** by treating with *n*-pentylamine, both reactions occurring with inversion.[10,11,18] Similarly, (S_p)-**17** was oxidized to (S_p)-**18** by MCPBA with retention.[19]

Optical Purities

The optical purities of the synthesized (R_p)- and (S_p)-**8**, (R_p)-**12**, (S_p)-**15** and (S_p)-**18** were determined with a CHIRALCEL OC column under conditions similar to those for the preparative separations,[5] and their configurations are linked with the Isomer-I/Isomer-II designations used in previous studies[5] (Table I). The optical purity was 80% *e.e.* for (R_p)-**8**, 82% *e.e.* for (S_p)-**8**, and 94% *e.e.* for (R_p)-**12** synthesized from (S_p)-**11**, while that for (R_p)-**12** from (S_p)-**15** was dependent on the reaction conditions, *i.e.* 94% *e.e.* when the reaction was carried out in *n*-pentanol and starting at low temperature, but only 68% *e.e.* in *n*-pentanol/chloroform (1/9) at room temperature. The lower optical purity in the latter case might be due to transformation of the initially-formed (S_p)-**15** sulfoxide and/or sulfone to the phosphorus cation[24] resulting in racemization. In contrast with the 100% optical purity of (S_p)-**15**, (S_p)-**18** only showed 58% *e.e.* This probably resulted from partial racemization on conversion of (S_p)-**14** to (S_p)-**16**, which is an intermediate for (S_p)-**18** (Figure 2), since (S_p)-**14** should be optically pure [as demonstrated by forming 100% *e.e.* (S_p)-**15**], while (S_p)-**16** appeared to be low in *e.e.*, as discussed later.

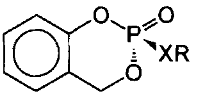
To study the optical purities and also confirm the absolute configurations of the intermediate chloridothionates (R_p)-**5** and (S_p)-**16**, these two compounds were converted to disastereomeric (S_cS_p)-**20** and (S_cS_p)-**10**, respectively, through reactions with commercial chiral amines (S_c)-(-)-α-methylbenzylamine [(S_c)-**19**] and *L*-proline methyl ester [(S_c)-**21**], respectively (Table II). (S_cS_p)-**20** and (S_cS_p)-**10** were analyzed by ^{1}H- and ^{31}P-NMR and HPLC with a LiChrospher Si-60 column. The combined results indicated that the preparation from (R_p)-**5** and (S_c)-**19** contained 91% of (S_cS_p)-**20** and 9% of (S_cR_p)-**20**; so the precursor (R_p)-**5** should be $\geq$82% *e.e.* by assuming that the two enantiomers of **5** reacted equally with (S_c)-**19**. It is clear that there is almost no difference in optical purity between (R_p)-**5** and (R_p)- and (S_p)-**8**, indicating the high stereospecificity of the reactions involved in the syntheses (Figure 1). Similarly, (S_cS_p)-**10** appeared to be 62% *d.e.*, therefore, (S_p)-

TABLE I

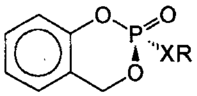
Chiral HPLC analyses of the synthesized (R_p)- and (S_p)-2-ethyl, (R_p)-2-pentyloxy, (S_p)-2-pentylthio- and (S_p)-2-pentylamino-4*H*-1,3,2-benzodioxaphosphorin 2-oxides

Products	2-Substituent	Isomer - I / Isomer - II			*e. e.*, %
		r. t., min	ratio, %	config.	
(Rp) - **8**	CH_2CH_3	33.3 / 37.5	90 / 10	*R / S*	80
(Sp) - **8**	CH_2CH_3	34.1 / 37.4	9 / 91	*R / S*	82
(Rp) - **12**[a]	$O(CH_2)_4CH_3$	14.3 / 16.2	3 / 97	*S / R*	94
(Rp) - **12**[b]	$O(CH_2)_4CH_3$	14.4 / 16.3	3 / 97	*S / R*	94
(Rp) - **12**[c]	$O(CH_2)_4CH_3$	14.4 / 16.5	16 / 84	*S / R*	68
(Sp) - **15**	$S(CH_2)_4CH_3$	18.5 / -[d]	100 / 0	*S / R*	100
(Sp) - **18**	$NH(CH_2)_4CH_3$	19.9 / 24.0	21 / 79	*R / S*	58

a : from (Sp) - **11**. b : from (Sp) - **15**, in $CH_3(CH_2)_4OH$, - 60 to 25°C. c : from (Sp) - **15**, in $CH_3(CH_2)_4OH$ / $CHCl_3$ (1 / 9), 25°C. d : 19.0 / 21.5 for racemate **15**.



Isomer - I



Isomer - II

X : CH_2, O, S, NH; R: alkyl

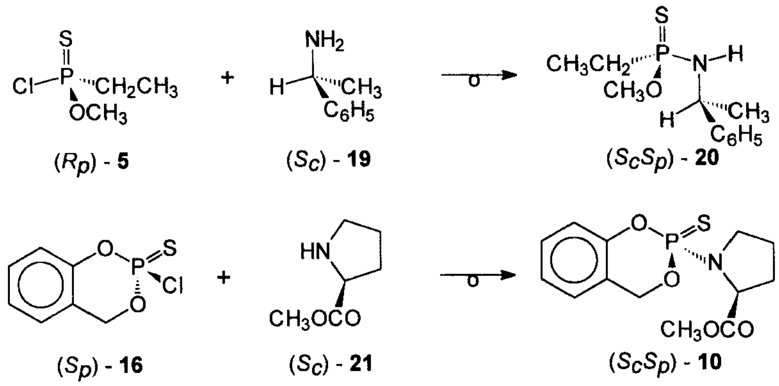
16 was estimated as ≥62% *e.e.* This might explain the low optical yield of (S_p)-**18** which was prepared from (S_p)-**16** (Figure 2). The ^{1}H-NMR results also supported the configuration assignment in the sense that the phenyl group of **20** showed a shielding effect on the adjacent P-OCH_3 in (S_cS_p)-**20** and P-C_2H_5 in (S_cR_p)-**20**,[18,25] and both ^{1}H and ^{31}P characteristic chemical shifts for (S_cS_p)- and (S_cR_p)-**10** were consistent with those reported before[20] (Table II). Because the conversion of (R_p)-**5** to (S_cS_p)-**20** and (S_p)-**16** to (S_cS_p)-**10** occurs with inversion,[18] the configurations of (R_p)-**5** and (S_p)-**16** were, therefore, confirmed from those of (S_cS_p)-**20** and (S_cS_p)-**10**, respectively.

Chiral HPLC Resolution

For each type of BDPO NTE inhibitor, the stereochemical orientation of the substituents on phosphorus is the key factor in determining their interaction with the chiral coating material in the HPLC column. Thus, as shown in Table I, each Isomer-I shares the same stereochemical orientation of the 2-substituent and benzodioxaphosphorin moiety and each Isomer-II the opposite orientation. This may indicate that for each Isomer-II the HPLC chiral selector preferentially chooses the benzodioxaphosphorin ring and 2-oxide rather than the 2-substituents to form diastereomeric complexes.

TABLE II

NMR and HPLC analyses of diastereomeric (S_cS_p)-**20** and (S_cS_p)-**10** prepared from the corresponding (R_p)-**5**, (S_p)-**16** and chiral amines



Products	S_cS_p / S_cR_p				d. e.
	^{1}H (ppm)	^{31}P (ppm)	HPLC (min)	ratio (%)	(%)
(S_cS_p) - **20**	1.19 / 0.95 (CH_2CH_3) 3.27 / 3.65 (OCH_3)	89.04 / 89.25	15.0 / 16.1	91 / 9	82
(S_cS_p) - **10**	4.52 / 4.59 (NC*H*) 5.35 / 5.38 (OCH_2)	60.07 / 60.11	12.7 / 13.7	81 / 19	62

EXPERIMENTAL

Spectroscopy. NMR spectra were recorded with a Bruker AM-300 Spectrometer at 300 MHz (^{1}H) or 121.5 MHz (^{31}P) for solutions in $CDCl_3$. Chemical shifts are referenced to internal tetramethylsilane for ^{1}H and external trimethyl phosphate in $CDCl_3$ for ^{31}P. They are reported in ppm on the δ scale with positive shifts downfield from the reference and coupling constants in Hz. Diastereomeric excess was determined by integration of the ^{1}H and ^{31}P resonances.

Chromatography. Thin-layer chromatography (TLC) was carried out on silica gel F_{254} chromatoplates (gel thickness: 0.25-, 0.5-, 1- and 2-mm). Column chromatography utilized silica gel 60 (0.040–0.063 mm). HPLC was performed at a flow rate of 1 mL/min with two columns: CHIRALCEL OC (Daicel, Tokyo, Japan; 4.6 mm i.d. × 25 cm) developed with 90/10 (v/v) hexane/isopropanol for enantiomeric analysis; LiChrospher Si-60 (Merck, Darmstadt, Germany; 4.0 mm i.d. × 12.5 cm, 5 μm) developed with selected hexane/ethyl acetate ratios [v/v 97/3 for (S_cS_p)-**20**; 90/10 for (S_cS_p)-**10**] for diastereomeric analysis. Quantitation was by integration of peak areas monitored at 254 nm.[5] Isomer-I refers to the BDPO enantiomer that is less retained in HPLC and Isomer-II to the more retained enantiomer.[5]

Ethylphosphonodichloridothionate (**2**). $AlCl_3$ (3 g, 0.02 mol) was added to dichloroethylphosphine (**1**, 50 g, 0.38 mol) followed by slow addition of sulfur (13 g, 0.4 mol). The mixture was stirred overnight before distillation at reduced pressure. Yield: 45 g, 74%, B.p. 69-71°C/24 mm Hg. ^{31}P: 92.37.

O, O-Dimethyl ethylphosphonothionate (**3**). Compound **2** (45 g, 0.28 mol) was refluxed in methanol (100 mL) for 1 h and the excess methanol evaporated under reduced pressure to give **3** quantitatively. ^{1}H: 1.18 (3H, 2t, J = 7.5, CH_2CH_3), 1.98 (2H, m, J = 7.6, CH_2CH_3), 3.73 [6H, d, J = 13.3, $(OCH_3)_2$]. ^{31}P: 103.34.

O-Methyl ethylphosphonothioic acid (**4**). Compound **3** (22 g, 0.14 mol) was mixed with KOH (7.8 g, 0.14 mol) and methanol (120 mL), then stirred at 50°C for 24 h. After evaporation of excess methanol, cold water (70 mL) was added to the residue and the aqueous solution was extracted with ether (20 mL × 2), then acidified with concentrated HCl and extracted again with ether (20 mL × 3). The combined ether extracts from the second extraction were dried over Drierite, filtered, concentrated, and crude **4** distilled in vacuum. Yield: 7.4 g, 38%. B.p. 83–85°C/0.2 mm Hg. ^{1}H: 1.23 (3H, 3d, *J* = 7.6, CH_2CH_3), 2.03 (2H, m, *J* = 7.7, CH_2CH_3), 3.77 (3H, d, *J* = 13.6, OCH_3). ^{31}P: 94.96.

(S_p)-O-Methyl ethylphosphonothioic acid [(S_p)-**4**]/*quinine salt*. Phosphonothioic acid **4** (7.4 g, 0.053 mol) and quinine (19 g, 90% chemical purity, 0.053 mol) were dissolved in hot acetone (250 mL). The volume of the solution was reduced by rotary evaporation until crystals appeared, then it was kept at −20°C for 2 h. The accumulated crystals were recrystallized 3 times from acetone at which time the melting point became constant. Yield: 2.6 g, 21%. M.p. 174–176°C.

(S_p)-O-Methyl ethylphosphonothioic acid [(S_p)-**4**]. The (S_p)-**4**/quinine salt (2.6 g, 5.6 mmol) was dissolved in warm methanol (10 mL), then mixed with NaOH (0.2 g) in water (1.5 mL). Quinine was precipitated by adding water (15 mL) and filtered from the solution. After washing with chloroform (5 mL × 2), the aqueous solution was acidified with concentrated HCl and extracted with ether (10 mL × 3). The ether phases were combined, dried over Drierite, filtered and the solvent evaporated to give (S_p)-**4**. Yield: 714 mg, 91%. ^{1}H- and ^{31}P-NMR data consistent with those of racemic **4**.

(R_p)-O-Methyl ethylphosphonochloridothionate [(R_p)-**5**]. (S_p)-**4** (714 mg, 5.1 mmol) in anhydrous ether (6 mL) was added to a stirred solution of phosphorus pentachloride (1.0 g, 5.1 mmol) in anhydrous ether (10 mL) at −10°C. The reaction was maintained at −10 to −5°C for 40 min, then the ether was evaporated and the residue chromatographed on a silica gel column with hexane. Yield: 590 mg, 73%. ^{31}P: 107.03.

(R_p)-O-(2-Hydroxymethylphenyl) O-methyl ethylphosphonothionate [(R_p)-**6**]. A solution of (R_p)-**5** (168 mg, 1 mmol), 2-hydroxybenzyl alcohol (124 mg, 1 mmol), and K_2CO_3 (138 mg, 1 mmol) in acetone (5 mL) was stirred overnight. After filtration and concentration, the desired product was isolated by TLC (dichloromethane/ether = 8/1). Yield: 108 mg, 44%. ^{1}H: 1.32 (3H, 2t, *J* = 7.6, CH_2CH_3), 2.22 (2H, m, *J* = 7.6, CH_2CH_3), 2.75 (1H, OH), 3.79 (3H, d, *J* = 13.9, OCH_3), 4.65 (2H, m, CH_2OH), 7.21 (4H, m, aromatic). ^{31}P: 100.83.

(R_p)-O-(2-Hydroxymethylphenyl) S-methyl ethylphosphonothiolate [(R_p)-**7**]. A mixture of (R_p)-**6** (60 mg, 0.24 mmol), iodomethane (0.5 mL), *N*,*N*-dimethylformamide (1.5 mL) and KCl (36 mg, 0.48 mmol) was stirred at 80°C overnight, then filtered and concentrated. TLC purification was performed with ether/ethyl acetate (4/1). Yield: 34 mg, 57%. ^{1}H: 1.38 (3H, 2t, *J* = 7.6, CH_2CH_3), 2.20 (3H, d, *J* = 12.9 SCH_3), 2.22 (2H, m, *J* = 7.5, CH_2CH_3), 4.44, 4.76 (2H, 2d, *J* = 12.3, 12.3, CH_2OH), 7.26 (4H, m, aromatic). ^{31}P: 59.41.

(R_p)-2-Ethyl-4H-1,3,2-benzodioxaphosphorin 2-oxide [(R_p)-**8**]. MCPBA (41 mg, 0.24 mmol) was added to a solution of (R_p)-**7** (20 mg, 0.08 mmol) in $CDCl_3$ (0.5 mL) with cooling by a dry-ice/acetone bath. The solution was removed from the cooling bath and the progress of the reaction followed by ^{31}P-NMR. After 1.5 h, the reaction mixture was filtered, concentrated, and the residue purified by TLC (ether/ethyl acetate = 6/1). Yield: 9 mg, 57%. ^{1}H: 1.20 (3H, m, CH_2CH_3), 1.98 (2H, m, CH_2CH_3), 5.08, 5.45 (2H, 2d, *J* = 18.6, 7.9, OCH_2), 7.2 (4H, m, aromatic). ^{31}P: 26.64.

(S_p)-2-Ethyl-4H-1,3,2-benzodioxaphosphorin 2-sulfide [(S_p)-**9**]. (R_p)-**6** (35 mg, 0.14 mmol) and K_2CO_3 (20 mg, 0.14 mmol) were mixed in acetone (3 mL) and kept at 50°C for 6 h. The (S_p)-**9** produced was purified by TLC (dichloromethane/ether = 8/1). Yield: 12 mg, 40%. ^{1}H: 1.28 (3H, 2t, *J* = 7.5, CH_2CH_3), 2.20 (2H, m, *J* = 7.6, CH_2CH_3), 5.08, 5.55 (2H, 2d, *J* = 20.6, 8.4, OCH_2), 7.1 (4H, m, aromatic). ^{31}P: 97.99.

(S_p)-2-Ethyl-4H-1,3,2-benzodioxaphosphorin 2-oxide [(S_p)-**8**]. MCPBA (30 mg, 0.163 mmol) was slowly added to (S_p)-**9** (12 mg, 0.056 mmol) in benzene (0.5 mL) and the reaciton was continued for 1 h before purification by TLC (ether). Yield: 4 mg, 36%. ^{1}H- and ^{31}P-NMR data consistent with those for (R_p)-**8**.

(S_cR_p)-2-[1-(2-Methoxycarbonylpyrrolidyl)]-4H-1,3,2-benzodioxaphosphorin 2-sulfide [(S_cR_p)-**10**]. A known procedure[20] was used to prepare (S_cR_p)-**10** by the reaction of 2-chloro-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide and *L*-proline methyl ester in the presence of triethylamine to form the diastereomeric mixture of (S_cR_p)- and (S_cS_p)-**10**, followed by resolution to 100% *d.e.* (S_cR_p)-**10** through recrystallization from hexane/ether. Yield: 30%. ^{1}H- and ^{31}P-NMR data consistent with the literature.[20]

(S_p)-2-Pentyloxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide [(S_p)-**11**]. A solution of (S_c,R_p)-**10** (150 mg, 0.479 mmol) in *n*-pentanol (10 mL) was treated with H_2SO_4 (0.5 g, 0.5 M) and the reaction allowed to continue at 60°C for 6 h and room temperature overnight. After partial evaporation, the residue was adjusted to pH 3 with saturated $NaHCO_3$ and extracted with dichloromethane (15 mL × 3). The combined dichloromethane phases were washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated. The crude (S_p)-**11** was purified on TLC (hexane/ether = 5/2). Yield: 35 mg, 27%. ^{1}H: 0.90 (3H, t, J = 7.0, CH_2CH_3), 1.2–1.4 [4H, m, $(CH_2)_2CH_3$], 1.71 [2H, m, $CH_2(CH_2)_2CH_3$], 4.22 (2H, m, OCH_2), 5.33 (2H, 2d, J = 11.6, 16.9, OCH_2Ar), 7.0–7.4 (4H, m, aromatic). ^{31}P: 56.16.

(R_p)-2-Pentyloxy-4H-1,3,2-benzodioxaphosphorin 2-oxide [(R_p)-**12**]. Oxidation of (S_p)-**11** with MCPBA was performed similarly to that of (S_p)-**9**. The product (R_p)-**12** was purified by TLC (ether). Yield: 49%; *e.e.*: 94%. ^{1}H- and ^{31}P-NMR data consistent with the literature for the racemate.[4]

(S_p)-2-Methoxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide [(S_p)-**13**]. Methanolysis of (S_c,R_p)-**10** and purification of (S_p)-**13** followed the published procedure.[20] Yield: 67%. ^{1}H- and ^{31}P-NMR data consistent with those of an authenic racemate.

(S_p)-2-Hydroxy-4H-1,3,2-benzodioxaphosphorin 2-sulfide, potassium salt [(S_p)-**14**]. Using the procedure for demethylating racemic **13**,[26] (S_p)-**13** was converted to (S_p)-**14** with potassium dimethyldithiocarbamate. Yield: 78%. M.p. 203–206°C (reported 204–209°C for the racemate).[26]

(S_p)-2-Pentylthio-4H-1,3,2-benzodioxaphosphorin 2-oxide [(S_p)-**15**]. (S_p)-**14** (150 mg, 0.625 mmol) and 1-iodopentane (124 mg, 0.625 mmol) were mixed in acetone (2 mL) and stirred overnight followed by TLC purification (ether) to obtain (S_p)-**15**. Yield: 150 mg, 88%; *e.e.*: 100%. ^{1}H- and ^{31}P-NMR data consistent with those of the racemate.[5]

*Oxidation of (S_p)-**15** with MCPBA in the presence of n-pentanol.* (S_p)-**15** (27 mg, 0.1 mmol) was dissolved in *n*-pentanol (1 mL) and the solution cooled to −60°C and treated with MCPBA (52 mg, 0.3 mmol). The reaction mixture was then stirred at room temperature for 5 h. The product (R_p)-**12** was purified by TLC (ether). Yield: 11 mg, 44%; *e.e.*: 94%. When the reactants were mixed at room temperature in *n*-pentanol/chloroform (1/9) for 3 h and worked up similarly, (R_p)-**12** was obtained in 29% yield and 68% *e.e.*

(S_p)-2-Chloro-4H-1,3,2-benzodioxaphosphorin 2-sulfide [(S_p)-**16**]. To change (S_p)-**14** to the free acid form, it was dissolved in dilute HCl, extracted into ether and dried over Na_2SO_4. After filtration and evaporation, the free acid was chlorinated to (S_p)-**16** with phosphorus pentachloride and the product purified by column chromatography under conditions similar to those described for chlorination of (S_p)-**4**. Yield: 53%. ^{1}H- and ^{31}P-NMR data consistent with those of racemic **16**.[20]

(S_p)-2-Pentylamino-4H-1,3,2-benzodioxaphosphorin 2-sulfide [(S_p)-**17**]. (S_p)-**16** (30 mg, 0.136 mmol) and *n*-pentylamine (24 mg, 0.272 mmol) were dissolved in dichloromethane (2 mL) and stirred for 2 h. The (S_p)-**17** formed was purified by TLC (hexane/ether = 1/1). Yield: 92%. ^{1}H: 0.89 (3H, t, J = 6.8, CH_3), 1.3 [4H, m, $(CH_2)_2CH_3$], 1.5 [2H, m, $CH_2(CH_2)_2CH_3$], 3.01 (2H, m, $NHCH_2$), 5.15, 5.62 (2H, 2d, J = 25.5, 6.0, OCH_2), 7.0–7.3 (4H, m, aromatic). ^{31}P: 62.13.

(S_p)-2-Pentylamino-4H-1,3,2-benzodioxaphosphorin 2-oxide [(S_p)-**18**]. Oxidative conversion of (S_p)-**17** to (S_p)-**18** was achieved under conditions similar to those for conversion of (S_p)-**9** to (S_p)-**8**. The product (S_p)-**18** was purified by TLC (ether/ethyl acetate = 4/1). Yield: 47%; *e.e.*: 58%. ^{1}H- and ^{31}P-NMR data consistent with those of racemic **18**.[5]

(S_c,S_p)-N-α-Methylbenzyl O-methyl ethylphosphonamidothionate [(S_c,S_p)-**20**. (R_p)-**5** (30 mg, 0.19 mmol) and (S_c)-(-)-α-methylbenzylamine [(S_c)-**19**, 46 mg, 0.38 mmol] were mixed in dichloromethane (5 mL). After 1.5 h reaction, the solvent was evaporated and the crude (S_c,S_p)-**20** purified by TLC (hexane/ether = 1/1). Yield: 33 mg, 71%; 91% (S_c,S_p)-**20** and 9% (S_c,R_p)-**20**. ^{1}H: 0.95 (minor isomer), 1.19 (major isomer) (3H, 2t, J = 7.5, CH_2CH_3), 1.48 (3H, d, J = 6.7, $CHCH_3$), 1.97 (2H, m, J = 7.6, CH_2CH_3), 3.27 (major isomer), 3.65 (minor isomer) (3H, d, J = 13.6, OCH_3), 4.32 (1H, m, $CHCH_3$), 7.3 (5H, m, aromatic). ^{31}P: 89.04 (major isomer), 89.25 (minor isomer).

(S_c,S_p)-2-[1-(2-Methoxycarbonylpyrrolidyl)]-4H-1,3,2-benzodioxaphosphorin 2-sulfide [(S_c,S_p)-**10**]. (S_p)-**16** and *L*-proline methyl ester [(S_c)-**21**] were reacted under the same conditions reported before.[20] The product (S_c,S_p)-**10** was purified by TLC (hexane/ether = 1/1). Yield: 94%; *d.e.*: 62%. ^{1}H- and ^{31}P-NMR data consistent with the literature.[20]

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