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Enantiopure *O*-Ethyl Phenylphosphonothioic Acid: A Solvating Agent for the Determination of Enantiomeric Excesses

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ABSTRACT An improved method, which is highly reproducible, was developed for the enantioseparation of racemic *O*-ethyl phenylphosphonothioic acid (**1a**) with brucine by introducing seeding to a supersaturated solution of the diastereomeric salt mixture. The present method gave both diastereomeric salts in high yields with a diastereomeric ratio of >99.5:0.5 upon choosing the crystallization solvent (MeOH for the (*R*)-**1a** salt and MeOH/H₂O for the (*S*)-**1a** salt). The enantiopure acid **1a** showed a good chirality-recognition ability for not only strong bases, such as amines and amino alcohols, but also weakly basic alcohols and was applicable as a solvating agent to the ¹H NMR determination of the enantiomeric excess of chiral amines, amino alcohols, and alcohols, including aliphatic substrates.

GRAPHICAL ABSTRACT

INTRODUCTION

The increasing demand for enantiopure compounds in pharmaceutical, agricultural, and material science/technology has stimulated the development of not only efficient strategies for asymmetric synthesis but also fast and accurate analytical methods for the determination of their enantiomeric excess (*ee*). Methods for the determination of *ee* are mainly classified into two categories, chromatographic and spectroscopic methods. Among them, NMR spectroscopy has emerged as one of convenient tools for the determination of *ee* as well as for the prediction of absolute configuration, in which target chiral compounds are covalently modified with an enantiopure derivatizing agent or are solvated with an enantiopure solvating agent; the resultant diastereomeric species are analyzed by NMR spectroscopy.¹⁻⁵ In general, enantiopure carboxylic, sulfonic, and phosphonic acids are used as acidic derivatizing/solvating agents. These acids have a stereogenic center nearby their acidic functional groups, conversely, the acidic functional groups of these acids are achiral. In contrast, the acidic functional group in phosphinothioic and phosphonothioic acids is surely chiral (Figure 1). The fundamental difference in chiral environment between the two classes made us to anticipate that enantiopure phosphinothioic and phosphonothioic acids would recognize the chirality of chiral compounds more efficiently than enantiopure carboxylic, sulfonic, and phosphonic acids. Indeed, several groups have intensively studied the application of enantiopure *t*-butylphenylphosphinothioic acid as a solvating agent.⁶⁻¹⁴

Fig 1. Chemical structures of carboxylic, sulfonic, phosphonic, phosphinothioic, and phosphonothioic acids.

Recently, we have found that enantiopure *O*-substituted aryl/alkylphosphonothioic acids were good to excellent resolving agents for racemic amines and amino alcohols.¹⁵⁻¹⁸ Among the *O*-substituted aryl/alkylphosphonothioic acids we examined, *O*-ethyl phenylphosphonothioic acid (**1a**) was found to be the most excellent. In the diastereomeric salt formation using enantiopure **1a**, one of the diastereomeric pair formed a 2₁ column-type crystal, as was

generally observed for the diastereomeric salts of enantiopure carboxylic acids with racemic amines/amino alcohols, while the other afforded a very rare cluster-type crystal; excellent chirality-recognition was always achieved, when the less-soluble diastereomeric salt was a cluster-type crystal.^{19,20} The formation of the characteristic cluster-type crystal and the distinguished chirality-recognition ability would arise from the unique structural feature of enantiopure **1a** that the phosphorus atom in **1a** is chiral. On the basis of the result, we considered that enantiopure *O*-substituted aryl/alkylphosphonothioic acids such as **1a** would possess an efficient chirality-recognition ability even in solutions to act as a sufficient solvating agent for chiral compounds.

Herein, we report the capability of the enantiopure *O*-ethyl phenylphosphonothioic acid (**1a**) as a solvating agent for the chiral compounds **2** and a reproducible method for the enantioseparation of racemic **1a**.

MATERIALS AND METHODS

General Information

All reagents were purchased from Tokyo Chemical Industry Co., Ltd. except for racemic 1-phenylethylamine, enantiopure 1-phenylethylamine, and enantiopure *erythro*-2-amino-1,2-diphenylethanol. Racemic 1-phenylethylamine was purchased from Nakalai Tesque Inc., and enantiopure 1-phenylethylamine and *erythro*-2-amino-1,2-diphenylethanol were gifted by Yamakawa Chemicals Co., Ltd. The reagents used as received. The ¹H and ³¹P NMR spectra were recorded on a Bruker Ascend 400 spectrometer operating at 400 MHz and 162 MHz, respectively. The chemical shifts are given in ppm relative to the singlet at 0.000 ppm of Me₄Si for ¹H NMR and 2.100 ppm of (MeO)₃PO for ³¹P NMR, respectively. The differences in chemical shift ($\Delta\delta$) between the diastereomers of enantiopure *O*-ethyl phenylphosphonothioic acid (**1a**) with the chiral compounds **2** are reported in ppm. The IR spectra were recorded on a JASCO model FT/IR-480plus.

Synthesis of racemic O-ethyl phenylphosphonothioic acid (racemic 1a)

A solution of NaOEt in EtOH (20 w%, 50 mL, 128 mmol) was added dropwise to a solution of phenylphosphonothioic dichloride (12.5 g, 62 mmol) in dry EtOH (30 mL) at 0 °C, and the mixture was stirred for 3 h at the temperature. After the solution was diluted with EtOH (30 mL), 5 M NaOH aq. (60 mL) was added dropwise at room temperature, and the mixture was heated under reflux for 9 h. The reaction mixture was concentrated to ca. 50 mL under reduced pressure and diluted with H₂O (100 mL), and then the resultant solution was extracted with CH₂Cl₂ (4 × 50 mL). 6 M HCl aq. (90 mL) was added dropwise to the aqueous layer at 0 °C,

and the mixture was extracted with CH_2Cl_2 (4×50 mL). The extracts were combined, washed with brine (150 mL), dried over Na_2SO_4 , filtrated, and concentrated to dryness under reduced pressure to give crude racemic **1a** (11.2 g, 55 mmol). A solution of dicyclohexylamine (11.8 g, 65 mmol) in Et_2O (50 mL) was added dropwise to a solution of the crude racemic **1a** (11.2 g, 55 mmol) in Et_2O (100 mL) with vigorous stirring at room temperature, and stirring was continued for 3 h. The precipitates deposited was collected by using a membrane filter and dried under reduced pressure to give the corresponding salt (17.7 g, 44 mmol, 80%). 5 M NaOH aq. (100 mL) was added dropwise to a solution of the salt (17.7 g, 44 mmol) in CHCl_3 (150 mL) at room temperature, and the mixture was stirred for 10 min. After the organic and aqueous layers were separated, the aqueous layer was extracted with CHCl_3 (3×80 mL), acidified with 6 M HCl aq. (100 mL), and extracted with CHCl_3 (3×120 mL). The combined extracts were washed with brine (150 mL), dried over Na_2SO_4 , filtrated, and concentrated to dryness under reduced pressure to give chemically pure racemic **1a** (8.90 g, 44 mmol, 71%).

IR (neat): ν 3000, 2380, 1440, 1120, 1020, 760, 730 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.33 (t, $J = 6.8$ Hz, 3H), 4.19 (q, $J = 6.8$ Hz, 2H), 7.42-7.55 (m, 3H), 7.88-7.92 (m, 2H) ppm. ^{31}P NMR (162 MHz, CDCl_3): δ 80.06 ppm.

Enantioseparation of racemic O-ethyl phenylphosphonothioic acid

At first, seeds for the present enantioseparation ((*R*)-**1a·3** and (*S*)-**1a·3** salts) were prepared from enantiopure (*R*)- and (*S*)-**1a**, obtained by the procedure in a literature²¹ with some modifications, and an equimolar amount of **3**, respectively.

A solution of brucine (**3**) (7.95 g, 20 mmol) in dry MeOH (40 mL) was added to a solution of racemic **1a** (4.00 g, 20 mmol) in dry MeOH (150 mL) at room temperature with vigorous stirring to give a suspension of white precipitates. The suspension was warmed up to 60 °C to afford a clear solution. Upon standing, the solution was cooled to 40 °C with maintaining the solution clear, seeded with a very small amount of finely powdered (*R*)-**1a·3** salt crystals, cooled to room temperature, and kept at the temperature overnight to give white precipitates. The precipitates were collected with a membrane filter and recrystallized from MeOH (140 mL) to give (*R*)-**1a·3** salt (5.36 g, 9.0 mmol, 90% yield based on a half amount of racemic **1a** used) with a diastereomeric ratio of >99.5:0.5. A solution of the (*R*)-**1a·3** salt (5.36 g, 9.0 mmol) in CHCl_3 (50 mL) was treated with 2 M NaOH aq. (75 mL), and the aqueous solution was extracted with CHCl_3 (5×50 mL). 6 M HCl aq. (50 mL) was added to the aqueous solution, and the aqueous mixture was extracted with CHCl_3 (3×60 mL). The extracts were combined, dried over Na_2SO_4 , filtrated, and concentrated to dryness under reduced pressure to give (*R*)-**1a** (1.59 g, 8.0 mmol, 80% yield based on a half amount of racemic **1a** used) with >99.5% ee.

$[\alpha]^{25}_{\text{D}} = +17.2^{\circ}$ (*c* 1.00, *i*-Pr₂O) [its dicyclohexylamine salt $[\alpha]^{25}_{\text{D}} = +8.1^{\circ}$ (*c* 1.00, MeOH)]. IR (neat): ν 3000, 2380, 1440, 1120, 1020, 760, 730 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.35 (t, *J* = 6.8 Hz, 3H), 4.20 (q, *J* = 6.8 Hz, 2H), 7.41-7.54 (m, 3H), 7.87-7.93 (m, 2H) ppm. ³¹P NMR (162 MHz, CDCl₃): δ 80.37 ppm.

The antipode, enantiopure (*S*)-**1a**, was obtained by a very simple operation. The filtrate, obtained in the above procedure for the enantioseparation, was concentrated under reduced pressure, and the resultant solid mass was solved in MeOH/H₂O (90:10, v/v; 45 mL) at 80 °C to afford a clear solution. Upon standing, the solution was cooled to 40 °C with maintaining the solution clear, seeded with a very small amount of finely powdered (*S*)-**1a**·**3** salt precipitates, cooled to room temperature, and kept at the temperature overnight to give white crystals of (*S*)-**1a**·**3** salt (4.45 g, 7.4 mmol, 74% yield based on a half amount of racemic **1a** used) with a diastereomeric ratio of >99.5:0.5. A similar treatment of the salt gave (*S*)-**1a** (1.38 g, 7.4 mmol, 70% yield based on a half amount of racemic **1a** used) with >99.5% ee. $[\alpha]^{25}_{\text{D}} = -17.2^{\circ}$ (*c* 1.00, *i*-Pr₂O) [its dicyclohexylamine salt $[\alpha]^{25}_{\text{D}} = -8.1^{\circ}$ (*c* 1.00, MeOH)]. The IR spectrum and ¹H and ³¹P NMR spectra were identical to those of (*R*)-**1a**.

Standard conditions for the determination of the ee of the chiral compounds 2 by ¹H NMR spectroscopy

To an NMR tube, the chiral compound **2** (50 mM in CDCl₃, 400 μ L) and enantiopure **1a** (100 mM in CDCl₃, 200 μ L) were successively added, and ¹H NMR spectrum was recorded at room temperature, in which the signals were accumulated for 128 times with a pulse interval of 4 sec. The *ee* of **2** was calculated on the basis of the integral ratio of two sets of signals of a pair of diastereomers in the CDCl₃ solution. The integral ratio was determined by using the integration of the signal at a lower magnetic field as a reference. When the integral ratio was difficult to calculate due to the overlap with other peak(s), we applied the ¹H homo-decoupling technique.

RESULTS AND DISCUSSION

Selection of a suitable phosphonothioic acid as a solvating agent

We at first examined the solvating ability of enantiopure *O*-ethyl, *O*-methyl, and *O*-phenyl phenylphosphonothioic acids (**1a-c**)¹⁵ for racemic 1-phenylethylamine (**2a**) in CDCl₃; other than enantiopure **1a**, we used enantiopure **1b,c** with expectations that the signal of the methyl group in enantiopure **1b** would be simpler than those of the ethyl group in enantiopure **1a** and that the phenyl group of enantiopure **1c** would show some shield/deshield effect to **2a**, which could not expect for the ethyl group in enantiopure **1a**. Contrary to our anticipation, however, enantiopure **1a** was found to be the most effective among the three *O*-substituted

phenylphosphonothioic acids from the viewpoint of the number of non-equivalent proton pairs (TABLE I).

TABLE I. Non-equivalence in proton signals between the diastereomers of the amine **2a with enantiopure **1a-c** and *ee* determined by ^1H NMR spectroscopy**

2a

Entry	Phosphonothioic Acid	in ppm ^a	<i>ee</i> ^b
1.1	1a	1: 0.025 2: 0.033	0 0 (0)
1.2	1b	1: sn 2: 0.025	0 (0)
1.3	1c	1: sn 2: 0.027	0 (0)

^asn, slightly non-equivalent. ^bValues in parentheses are the (*ee*)s determined with chiral HPLC.

Enantioseparation of racemic O-ethyl phenylphosphonothioic acid (racemic **1**)

Thus, enantiopure **1a** was found to have potential as a solvating agent for the determination of the *ee* of chiral compounds by ^1H NMR spectroscopy. Four groups have been reported the enantioseparation of racemic **1a** by using brucine (**3**) as a resolving agent through almost the same procedure.²²⁻²⁵ However, the reproducibility of the method was very poor, although we tried the enantioseparation of racemic **1a** with **3** with an all-out effort. Moreover, the groups have guaranteed the optical purities of the enantiomers of **1a** only on the basis of their specific rotations^{22,23} or those of the salts of **1a** with dicyclohexylamine,^{24,25} and opposite signs have been also reported for (*R*)-**1a**·dicyclohexylamine and (*S*)-**1a**·dicyclohexylamine. On the other hand, Lewis *et al.* have established a method for the enantioseparation of racemic **1a** with enantiopure 1-phenylethylamine.²¹ However, the method requires recrystallization for six times to lower the yield of enantiopure **1a**. Thus, in the application of enantiopure **1a** as a derivatizing/solvating/resolving agent, there is a serious drawback in the efficiency of the enantioseparation of racemic **1a**.

The situation prompted us to develop an efficient method for the enantioseparation of racemic **1a**. We applied several kinds of enantiopure amines, amino alcohols, and alkaloids as a resolving agent for racemic **1a**. Among them, **3** gave the most feasible result: The

diastereomeric ratio of the deposited salt **1a·3** could be improved by recrystallization, when the ratio was rather high. In contrast, the ratio could not be improved by recrystallization, when the ratio was moderate. Then, we thoroughly investigated the conditions for the crystallization of **1a·3** salt and finally found that the selection of the solvent was critical and that seeding was very effective, as shown Scheme 1. Thus, we could developed a reproducible method for the enantioseparation of racemic **1a** with **3**.

Scheme 1. Procedure for the enantioseparation of racemic **1a**.

Determination of the ee of the chiral compounds 2 by ¹H NMR spectroscopy

With enantiopure **1a** easily in hand, we tried to apply enantiopure **1a** as an enantiopure solvating agent for typical chiral compounds, the chiral amines **2a-f**. As can be seen from TABLE II showing the non-equivalence of proton signal(s) in the ¹H NMR spectra, enantiopure **1a** could recognize the chirality of the amines **2a-d**. Contrary to our expectation, however, the chirality of the amines **2e,f** having a stereogenic center at the β-position of the amino group could not be recognized, most likely due to the insufficient conformational fixation of the complexes of enantiopure **1a** with the amines **2e,f**.

TABLE II. Non-equivalence in proton signals between the diastereomers of the amines 2a-f with enantiopure 1a and *ee* determined by ¹H NMR spectroscopy

Entry	Substrate	in ppm ^a	<i>ee</i> ^b
2.1	2a	1: 0.025 2: 0.033	0 0 (0)
		1: 0.035 2: 0.026	47 47 (47)
2.2	2b	1: 0.070 2: 0.072	52 51 (52)
2.3	2c	1: 0.008 2: 0.012 3: nd 4: 0.030	0 0 (0) 0
2.4	2d	1: 0.010 2: 0.027 3: 0.016 4: eq	1 1 1 (0)
2.5	2e	1-3: eq	
2.6	2f	1-5: eq	

^and, could not determined due to complicated signal splitting arising from germinal non-equivalence so on; eq, equivalent,. ^bValues in parentheses are the (*ee*)s determined with chiral HPLC.

On the basis of these results, we next applied enantiopure **1a** as an enantiopure solvating agent for the amino alcohols **2g-n** with an expectation that enantiopure **1a** would also interact with the hydroxy group in **2g-n** to bring non-equivalence in proton signals larger than those of **2a-d** in their ¹H NMR spectra. As shown in TABLE III, enantiopure **1a** showed a good chirality-recognition ability for **2g-n**.

TABLE III. Non-equivalence in proton signals between the diastereomers of the amino alcohols 2g-n with enantiopure 1a and *ee* determined by ¹H NMR spectroscopy

Entry	Substrate	in ppm ^a	<i>ee</i> ^b
3.1	2g	1: ol 2: 0.070	0 (0)
3.2	2h	1: 0.042 2: 0.037	5 (5) 5
3.3	2i	1: nd 2: 0.070 3: ol	1 (0)
3.4	2j	1: ol 2: nd 3: 0.042	0 (0)
3.5	2k	1: ol 2: 0.060 3: eq 4: eq	0 (0)
3.6	2l	1: ol 2: 0.070 3: sn 4: 0.016	0 (0)
3.7	2m	1: nd 2: ol 3: 0.050	0 (0)
3.8	2n	1: ol 2: nd 3: ol 4: 0.050	0 (0)

^aol, overlapped with the protons of **1a**; nd, could not determined due to complicated signal splitting arising from germinal non-equivalence so on; eq, equivalent, sn, slightly non-equivalent. ^bValues in parentheses are the (*ee*)s determined with chiral HPLC.

The $\Delta\delta$ (0.070 ppm) for the proton at the stereogenic carbon of **2g** is obviously larger than that of **2a** (0.033 ppm), even though the difference in structure between **2g** and **2a** is an additional hydroxy group in **2g**. This means that the hydroxy group also sufficiently contributes to the complex formation of **2g** with **1a**, as we expected.

This result prompted us to apply **1a** for the determination of the *ee* of chiral alcohols. As anticipated, **1a** showed the chirality-recognition ability for the alcohols **2o-q**, although the ability was lower than that for the amines and amino alcohols to some extent (TABLE IV). The observed non-equivalence in proton signals for the alcohols **2o-q** strongly indicates that enantiopure **1a** can form diastereomeric complexes with the alcohols by hydrogen bond(s), owing to the very high hydrogen-donating ability of the phosphonothio group in **1a**.

TABLE IV. Non-equivalence in proton signals between the diastereomers of the alcohols 2o-q with enantiopure 1a and *ee* determined by ^1H NMR spectroscopy.

Entry	Substrate	in ppm ^a	<i>ee</i> ^b
4.1	2o	1: 0.004 2: eq	1 (0)
4.2	2p	1: 0.004 2: sn 3: sn 4: 0.003	2 (0) 1
4.3	2q	1: sn 2: 0.040	2 (0)

^ans, not shifted, ss, slightly shifted. ^bValues in parentheses are the (*ee*)s determined with chiral HPLC.

In the determination of the *ee* of the amines, amino alcohols, and amino alcohols **2a-q**, worth to note is that signal non-equivalences, applicable to the determination of the *ee*, were observed for protons not only at the stereogenic carbon but also at the α -position (entries 2.1, 2.2, 2.3, 2.4, 3.4, 3.7, 4.1, 4.2, and 4.3) and even at the β -position (entries 2.3, 3.6, 3.7, and 4.2) of the stereogenic carbon.

In contrast to the HPLC method, the present NMR method by using enantiopure **1a** as a solvating agent has a characteristic feature that the method is applicable to the direct determination of the *ee* of amines, amino alcohols, and alcohols having no UV absorbable group (entries 2.3, 2.4, 3.4, 3.5, 3.6, 3.7, 3.8, and 4.2); in the HPLC method, such substrates are usually converted to their derivatives with an achiral modifying agent having a UV absorbable group in order to detect the peaks of their enantiomers with a UV detector in a HPLC system.

CONCLUSION

A highly reproducible and efficient method was developed for the enantioseparation of racemic *O*-ethyl phenylphosphonothioic acid (**1a**) with brucine (**3**); (*R*)-**1a**·**3** and (*S*)-**1a**·**3** were easily obtained by seedings to a supersaturated solution of the diastereomeric salt mixture in MeOH and to a supersaturated solution of the residue, recovered from the filtrate, in MeOH/H₂O, respectively (diastereomeric ratios, >99.5:0.5). Enantiopure **1a** was successfully applied as a solvating agent to the determination of the enantiomeric excess (*ee*) of not only chiral amines and amino alcohols but also chiral alcohols by ¹H NMR spectroscopy. Diastereomeric signal non-equivalences were observed for the proton(s) at the α - and β -positions of a stereogenic carbon as well as that of the stereogenic carbon. The ¹H NMR spectroscopy using enantiopure **1a** was found to be applicable to the direct determination of the *ee* of chiral substrates having no UV absorbable group.

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LITERATURE CITED

1. Parker D. NMR determination of enantiomeric purity. *Chem Rev* 1991;91:1441-1457.
2. Eliel EL, Wilen SH, Mander LN. *Stereochemistry of Organic Compounds*. New York: John Wiley & Sons; 1994.
3. Seco JM, Quiñoá E, Riguera R. Assignment of the absolute configuration of polyfunctional compounds by NMR. *Chem Rev* 2004;104:17-117.
4. Wenzel TJ. *Discrimination of chiral compounds using NMR spectroscopy*. New York: John Wiley & Sons; 2007.
5. Seco JM, Quiñoá E, Riguera R. Assignment of the absolute configuration of polyfunctional compounds by NMR using chiral derivatizing agents. *Chem Rev* 2012;112:4603-4641.
6. Harger MJP. Proton magnetic resonance spectra of chiral phosphorus esters: Chemical

- shift non-equivalence of enantiomers induced by optically active phosphinothioic acids. *Tetrahedron Lett* 1978;32: 2927-2928.
7. Harger MJP. The proton magnetic resonance spectra of chiral phosphinate esters. Chemical shift nonequivalence of enantiomers induced by optically active phosphinothioic acids. *J Chem Soc, Perkin Trans. 2* 1980:1505-1511.
 8. Moriyama M, Bentrude WG. Optically active phosphines. Facile preparation of the optically active propylmethylbenzyl- and methylphenylbenzylphosphine oxides as precursors to the corresponding tertiary phosphines. *J Am Chem Soc* 1983;105:4727-4733.
 9. Bentrude WG, Moriyama M, Mueller M-D, Sopchik AE. The reactions of ethoxy radicals with optically active tertiary phosphines. Stereochemistry of the substitution process and the question of permutation modes for the possible phosphoranyl radical intermediates. *J Am Chem Soc* 1983; 105:6053-6061.
 10. Omelanczuk J, Sopchik AE, Lee SG, Akutagawa K, Cairns SM, Bentrude WG. Photo-Arbuzov rearrangements of benzyl phosphites. *J Am Chem Soc* 1988;110:6908-6909.
 11. Mikotajczyk M, Omelanczuk J, Perlikowska W, Markowski LV, Romanienko VK, Ruban AV, Drapailo AB. A new enantioselective asymmetric synthesis of tricoordinate phosphorus compounds from dicoordinate Λ^3 -aryl(alkyl)iminophosphines. *Phosphorus and Sulfur* 1988;36:267-270.
 12. Drabowicz J, Dudzinski B, Mikotajczyk M. Chiral t-butylphosphinothioic acid: A new NMR solvating agent for determination of enantiomeric excesses of sulfoxides. *Tetrahedron Asym* 1992;3:1231-1234.
 13. Omelanczuk J, Mikotajczyk M. Chiral t-buthylphosphinothioic acid: A useful chiral solvating agent for direct determination of enantiomeric purity of alcohols, thiols, amines, diols, aminoalcohols and related compounds. *Tetrahedron Asym* 1996;7:2687-2694.
 14. Drabowicz J, Dudzinski B, Mikotajczyk M, Colonna S, Gaggero N. Chiral t-butyphenylphosphinothioic acid in analysis of tertiary amine oxides with a stereogenic nitrogen atom. *Tetrahedron Asym* 1997;8:2267-2270.
 15. Kobayashi Y, Morisawa F, Saigo K. Enantiopure *O*-substituted phenylphosphonothioic acids: Chiral recognition ability during salt crystallization and chiral recognition mechanism. *J Org Chem* 2006;71:606–615.
 16. Kobayashi Y, Maeda J, Morisawa F, Saigo K. Synthesis and chiral recognition ability of *O*-phenyl ethylphosphonothioic acid with a conformationally flexible phenoxy group for CH/ π interaction, *Tetrahedron Asym* 2006;17:967-974.
 17. Kobayashi Y, Maeda J, Saigo K. Synthesis and chiral recognition ability of *O*-ethyl

- (2-naphthyl)phosphonothioic acid, *Tetrahedron Asym* 2006;17:1617-1621.
18. Ribeiro N, Kobayashi Y, Maeda J, Saigo K. Enantiopure cyclic *O*-substituted phenylphosphonothioic acid: Synthesis and chirality-recognition ability. *Chirality* 2011;23:438-448.
 19. Kobayashi Y, Handa H, Maeda J, Saigo K. Factors determining the pattern of a hydrogen-bonding network in the diastereomeric salts of 1-arylethylamines with enantiopure P-chiral acids. *Chirality* 2008;20:577-584.
 20. Kobayashi Y, Maeda J, Ando T, Saigo K. Halogen-bonding interaction stabilizing cluster-type diastereomeric salt crystals. *Crystal Growth & Design* 2010;10:685-690.
 21. Lewis V, Donarski JW, Wild RJ, Raushel MF. Mechanism and stereochemical course at phosphorus of the reaction catalyzed by a bacterial phosphotriesterase. *Biochem* 1988;27:1591-1597.
 22. Ohkawa H, Mikami N, Miyamoto J. Stereoselectivity in metabolism of the Optical Isomers of cyanofenphos (*O*-*p*-cyanophenyl *O*-ethyl phenylphosphonothioate) in Rats and liver microsomes. *Agric Biol Chem* 1977;41:369-376.
 23. Yoshikawa H, Shono T, Eto M. A facile synthesis and insecticidal activity of optically active phenylphosphonothioates. *J Pesticide Sci* 1984;9:455-462.
 24. DeBruin KE, Tang C-IW, Johnson DM, Wilde RL. Kinetic facile selectivity in nucleophilic displacements at tetracoordinated phosphorus: Kinetics and stereochemistry in the reaction of sodium ethoxide with *O,S*-dimethyl phenylphosphonothioate. *J Am Chem Soc* 1989;111:5871-5879.
 25. Kuo LY, Glazier SK. Stereochemical inversion of phosphonothioate methanolysis by La(III) and Zn(II): Mechanistic implications for degradation of organophosphate neurotoxins. *Inorg Chem* 2012;51:328-335.

SUPPORTING INFORMATION

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