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Article

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Title: Chemo- and Stereoselective Alcoholysis of Binaphthyl Phosphonothioates: Straightforward Access to both Stereoisomers of Biologically Relevant *P*-Stereogenic Phosphonothioates

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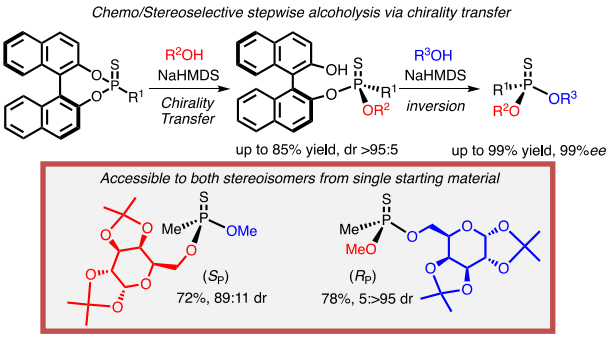


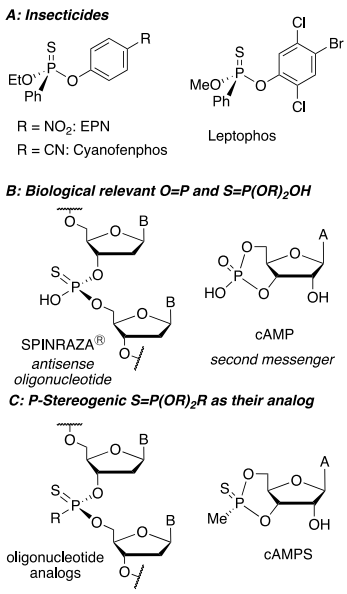
ABSTRACT:

P-Stereogenic phosphonothioates have attracted much attention due to their potent biological activities as analogs of phosphoric acids and phosphorothioates. We demonstrate here straightforward access to *P*-stereogenic phosphonothioates through the use of binaphthyl phosphonothioates as a chiral template. The 1st-step alcoholysis of binaphthyl phosphonothioates proceeded via a transfer of the axial chirality of a binaphthyl group to the central chirality of a phosphorus atom to give only mono-alcohol adducts with moderate to excellent diastereoselectivities. Further alcoholysis of the obtained products in the presence of a small excess of alcohol and base proceeded with complete elimination of a binaphthyl group to give the corresponding *P*-stereogenic phosphonothioates with high enantiomeric excess. A DFT study of the reaction mechanisms in 1st-step alcoholysis indicated that the coordination of a sulfur atom to a sodium cation is the key factor to control the diastereoselectivities. This method can be applied to prepare both stereoisomers of a G6P analog with high diastereomeric purity.

INTRODUCTION

P-Stereogenic phosphonothioates with tetrahedral S=P(OR)$_2$R are an important class of organophosphorus compounds, and have been widely applied in the fields of agrochemistry and medicinal chemistry.[1] Phosphonothioates shown in Scheme 1A act as acetylcholine esterase inhibitors and were used as insecticides until their use was regulated.[2-4] Furthermore, phosphonothioates have attracted much attention due to their potent biological activities as analogues of phosphoric acids and phosphorothioates (Scheme 1B and C).[5-9] Especially, much effort has been directed toward the stereoselective synthesis of *P*-stereogenic phosphonothioates because the stereochemistry at a phosphorus atom affects their biological activities.

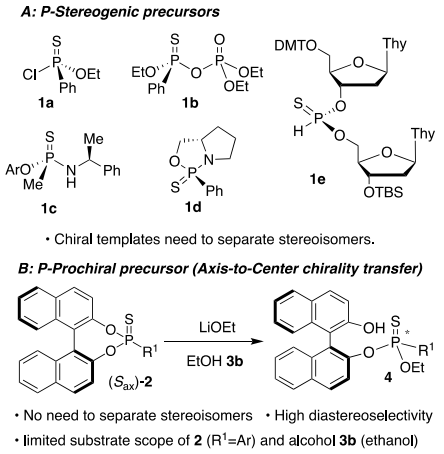
Scheme 1. Examples of Biologically Active Phosphonothioates



Generally, *P*-stereogenic phosphonothioates are synthesized from enantio- or diastereomerically pure *P*-stereogenic templates such as phosphonothioyl chloride **1a**, phosphonothioic acid anhydride **1b**, phosphoroamidethioate **1c**, oxazaphospholidine **1d**, and *H*-phosphonothioates **1e** (Scheme 2A).[2,10-13] The alcoholysis of **1a-d**[2,10-12] or the cross-coupling reaction of **1e** by transition metal catalysts[13] proceeds with high stereoselectivity to give the corresponding phosphonothioates without any decrease in the stereochemical purity of the starting materials. However, the preparation of these *P*-stereogenic templates generally requires the separation of their diastereomers by recrystallization or silica gel column chromatography.[1b] In this regard, we have demonstrated that an axis-to-center chirality transfer of phosphonates and phosphonothioates having a binaphthyl group with carbon nucleophiles and metal

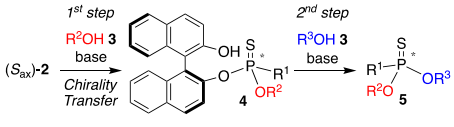
hydroxides leads to the formation of *P*-stereogenic organophosphorus compounds.[14] For example, the reaction of phosphonothioates **2**, which are easily prepared from phosphorus trichloride, elemental sulfur, Grignard reagents and optically active 1,1'-bi-2-naphthol (BINOL), with alkoxides gives *P*-stereogenic compounds via an axis-to-center chirality transfer (Scheme 2B).[14c] The reaction of aromatic carbon substituents at the phosphorus atom of phosphonothioates **2** and ethanol (**3b**) as a solvent gave the corresponding ethanol adduct **4** with high diastereoselectivities (Scheme 2B). However, in the case of aliphatic carbon substituents at the phosphorus atom of phosphonothioates **2**, some improvements are necessary to achieve alcoholysis with high diastereoselectivity.

Scheme 2. Selected Examples of Chiral templates for the Synthesis of *P*-Stereogenic Phosphonothioate



Herein, we report stepwise chemo- and stereoselective alcoholysis of **2** which allows access to a range of *P*-stereogenic phosphothioates **5** (Scheme 3). The 1st-step alcoholysis of **2** with a range of alcohols under basic conditions affords *P*-stereogenic product **4** with high diastereoselectivity via the transfer of the axial chirality of the binaphthyl group to the central chirality of the phosphorus atom. Subsequent alcoholysis of the obtained diastereomerically pure **4** can also proceed with high stereoselectivity to give the desired *P*-stereogenic phosphonothioates **5**. To accomplish this reaction sequence, we have to consider the chemoselectivity in each alcoholysis step. In the 1st-step, selective mono-alcoholysis of **2** is required without further alcoholysis of **4** which would detach the binaphthol moiety completely from the phosphorus atom. In the 2nd-step, the binaphthol moiety must be selectively removed from **4** over an alkoxy group (–OR^2) introduced at the 1st-step

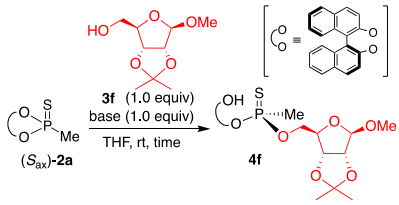
Scheme 3. Stepwise Alcoholysis of Phosphonothioates 2 via Chirality Transfer



RESULTS AND DISUCUSSIONS

Binaphthyl methylphosphonothioate **2a** and ribose derivative (**3f**) were selected as model substrates for the optimization of 1st-step alcoholysis (Table 1). The alcoholysis was facilitated by using sodium hexamethyldisilazide (NaHMDS) as a base in THF solvent to give the desired product **4f** in 67% isolated yield with >95:5 dr (entry 1). The addition of 1.0 equivalent of 18-crown-6 increased the product yield with lower diastereoselectivity (entry 2). The use of LiHMDS or Cs_2CO_3 instead of NaHMDS decreased the yield and diastereoselectivity (entries 3 and 4). 1,8-Diazabicyclo[5.4.0]undec-7ene (DBU) also promoted the alcoholysis of **2a** to give **4f** in comparable yield as the reaction with NaHMDS, but the diastereoselectivity was reduced (entry 5). 1,4-Diazabicyclo[2.2.2]octane (DABCO), and *tert*-butylmagnesium chloride which is used as a phosphorylating reagent for nucleosides in some cases,[15] did not give **4f**, and only the starting material **2a** was recovered (entries 6 and 7).

Table 1. Optimization of the Reaction Condition



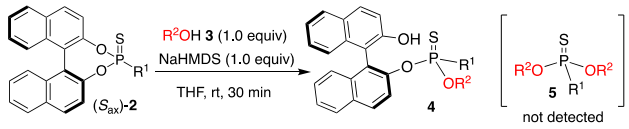
entry	base	additive	time (h)	yield (%)[a]	dr[b]
1	NaHMDS	-	1	89 (67)	>95:5
2	NaHMDS	18-crown-6	1	100	82:18
3	LiHMDS	-	1	41	79:21
4	Cs_2CO_3	-	1	47	82:18
5	DBU	-	1.5	86 (62)	75:25
6	DABCO	-	1	n.r.	-
7	^{t}BuMgCl	-	1.5	n.r.	-

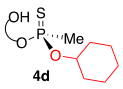
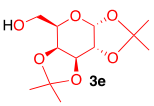
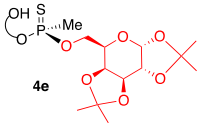
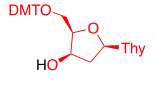
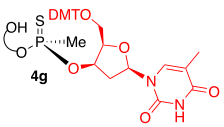
[a] The yields were calculated by ^{31}P NMR analysis of the crude reaction mixtures. Isolated yields are shown in the parentheses. [b] Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

The substrate scope of this alcoholysis was examined with the reaction conditions for entry 1 in Table 1 as the optimal conditions (Table 2). In all cases, further alcoholysis of product **4** did not occur under the optimized conditions. The reaction of **2a** with simple aliphatic alcohols such as methanol (**3a**), ethanol (**3b**), benzyl alcohol (**3c**) or cyclohexanol (**3d**) proceeded smoothly to give the corresponding products **4a-4d** in moderate to high yields with high diastereoselectivities (entries 1-4). Galactopyranose derivative (**3e**) gave the adducts **4e** in high yield with excellent diastereoselectivity (entry 5). To our delight, nucleoside **3g** was tolerated in the presence of a strong base to give the desired product **4g** in 56% yield with >95:5 dr (entry 6). On the other hand, phenol (**3h**) did not give the adduct **4h**, and only the starting material **2a** was recovered (entry 7). The carbon substituents in phosphonothioate **2** affected the diastereoselectivities of the

products **4**. Lower diastereoselectivity was observed in the ethanolysis of phosphonothioate **2b** having a phenyl group attached to the phosphorus atom, while phosphonothioate **2c** having a mesityl group was converted to **4j** as a single diastereomer (entries 8 and 9). The relationship between the carbon substituents and diastereoselectivities is in sharp contrast to our previous report (Scheme 4).[14c] Higher diastereoselectivities were observed in the ethanolysis of phosphonothioates **2** having an aromatic group attached to the phosphorus atom with the use of ethanol as a solvent instead of THF. Furthermore, the absolute configuration at the phosphorus atom of the obtained products was different depending on the solvent.

Table 2. Substrate Scope of Phosphonothioate 2 and Alcohol 3



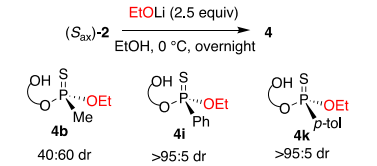
entry	S.M. 2	alcohol 3	product 4	yield (%)[a]	dr[b]
1	 **2a**	MeOH **3a**	 **4a**	63	>95:5
2	 **2a**	EtOH **3b**	 **4b**	85	>95:5
3	 **2a**	BnOH **3c**	 **4c**	64	>95:5
4	 **2a**	 **3d**	 **4d**	66	>95:5
5	 **2a**	 **3e**	 **4e**	84	>95:5
6[c]	 **2a**	 **3g**	 **4g**	56	>95:5
7	 **2a**	PhOH **3h**	 **4h**	n.r.	-
8[d]	 **2b**	EtOH **3b**	 **4i**	76	24:76
9[d]	 **2c**	EtOH **3b**	 **4j**	70	>95:5

[a] Isolated yields are shown. [b] Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures. [c] The reaction was carried out with 1.5 equiv of alcohol **3g** and 3.0 equiv of NaHMDS. [d] The reaction was carried out with 1.2 equiv of alcohol **3b** and 1.2 equiv of NaHMDS.

The absolute configuration of the major isomer of **4d** was determined by a single-crystal X-ray diffraction analysis (Supporting Information, Figure S1). The phosphorus atom in **4d** exhibited an S_P configuration. The signal of S_P isomer of **4d** in ^{31}P NMR spectra was

observed at a higher field than the signal of R_P isomer. In the case of **4k** having a *p*-tolyl group, we previously revealed that the signals of the S_P isomer appeared at a lower field in the ^{31}P NMR spectra.[14c] The absolute configurations of products **4** except **4j** were estimated based on a comparison of the chemical shifts of **4d** and **4k** (Supporting Information, Table S1).

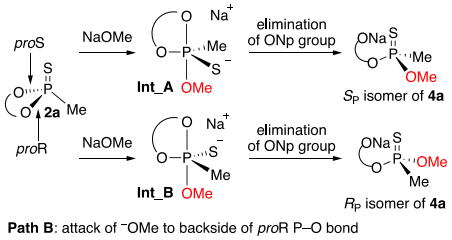
Scheme 4. Ethanolysis of Phosphonothioates 2 by the Use of Ethanol as a Solvent



Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

The plausible pathway for the methanolysis of phosphonothioate **2a** is shown in Scheme 5.[16,17] The sodium methoxide attacks the backside of the P–O bond to generate the trigonal bipyramidal (TBP) intermediates **Int_A** or **B**. Subsequently, the P–O bond in apical positions is cleaved to give the products **4a**. The diastereoselectivity can be determined by whether the sodium methoxide attacks the backside of the *pro*S P–O bond (**Path A**) or that of the *pro*R P–O bond (**Path B**) to give the identical product (S_P)-**4a** or (R_P)-**4a**, respectively.

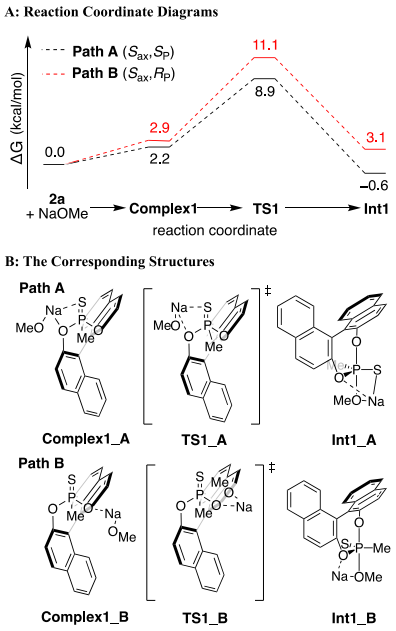
Scheme 5. Plausible Reaction Pathway of Methanolysis of Phosphonothioate 2a



To compare the activation energies of these pathways, theoretical investigations of the detailed transition state (TS) models were conducted using density functional theory (DFT) calculations with the B3LYP functional and the 6-31G(d,p) basis set. The energies are shown in Scheme 6 and Figure 1 including the effects of THF to calculate the single point energy using a PCM model. The reaction coordinate diagrams for the reaction of phosphonothioate **2a** with sodium methoxide were shown in Scheme 6. The structures corresponding to **TS1_A** and **TS1_B** are shown in Figure 1, which are highest-energy position in the energy diagrams (Supporting Information, Scheme S2). The Gibbs free energy of **TS1_A** is 2.2 kcal/mol lower than that of **TS1_B**. In the geometry of **TS1_A**, the sulfur atom and two oxygen atoms coordinate to the sodium cation. In contrast, in the geometry of **TS1_B**, the sodium cation only coordinates to two oxygen atoms (Figure 1,

side view). These results indicate that the diastereoselectivity of the chirality transfer reaction could be controlled by the direction of the nucleophilic attack of an alkoxide to the phosphorus atom due to the energy differences based on coordination between a sulfur atom and a sodium cation, although we cannot exclude the possibility of isomerization of the TBP intermediates **Int1** through Berry's *pseudorotation* process at the present stage.[17,18] The TBP intermediates **Int1** gave the corresponding isomers **4a** by the cleavage of the P–O bond in apical positions through the lower energy transition state (**TS2**) than **TS1** (Supporting Information, Scheme S2). These results are consistent with the experimental result that the methanolysis of **2a** at room temperature gave (S_P)-**4a** as a major isomer. The control experiment clearly shows the importance of a chiral binaphthyl group for achieving high stereoselectivity in this chirality transfer reaction (Scheme 7). The achiral substrates **2a'** having a biphenyl group showed only moderate diastereoselectivity in alcoholysis with the chiral alcohol **3e**.

Scheme 6. DFT Calculations for the Reaction of the Phosphonothioate 2a with sodium methoxide



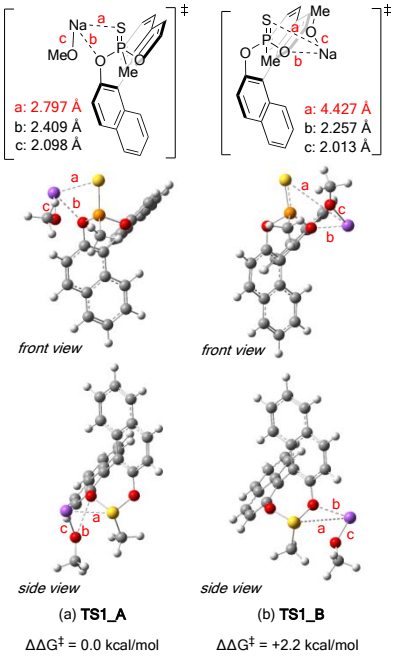
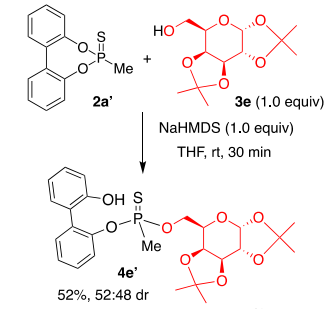


Figure 1. Length of S–Na and O–Na bonds, front and side views of 3D structures, and the relative Gibbs free energies of (a) **TS1_A** and (b) **TS1_B**.

Scheme 7. A Control Experiment by the Use of Biphenyl Derivative 2a'

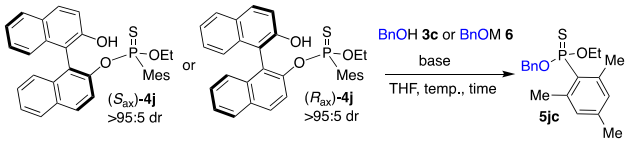


Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

In the next stage, further alcoholysis of the obtained product **4j** with benzyl alcohol (**3c**) was examined (Table 3). We chose **4j**, synthesized with high stereoselectivity in the 1st-step, as a model substrate to avoid potential side reaction such as α-deprotonation of a phosphonate group. The phosphonothioate **4j** reacted with sodium benzyloxide (**6a**) in THF at reflux temperature for 30 min to give the desired product **5jc** in 72% yield with −88%*ee* (entry 1). The enantioselectivity dropped in the reaction with lithium benzyloxide (**6b**) instead of **6a** (entry 2). The enantioselectivities were improved by pre-deprotonation of a binaphthyloxy group of **4j** with NaHMDS or *n*-BuLi followed by the reaction with benzyloxide **6a** or **6b** (entries 3 and 4). DBU did not work well in this 2nd alcoholysis (entry 5). Finally, phosphonothioate **5jc** was obtained in 92% yield with 98%*ee* by simply reacting **4j** with benzyl alcohol (**3c**) and NaHMDS in THF at room

temperature (entry 6). The reaction conditions in entry 6 in Table 3 were selected as optimal conditions for 2nd-step alcoholysis.

Table 3. Optimization of the Reaction Condition of 2nd Alcoholysis

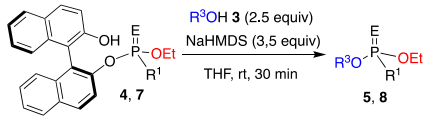


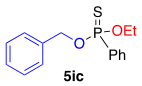
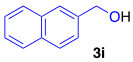
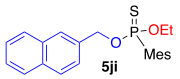
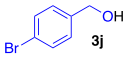
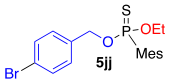
entry	reactant	base	4j	temp. (°C)	time (h)	yield (%)	*ee* (%)[a]
1	BnONa **6a** (3.5 equiv)	-	(R_{ax})	65	0.5	72	–88
2	BnOLi **6b** (3.5 equiv)	-	(R_{ax})	65	4	86	–58
3	BnONa **6a** (2.5 equiv)	NaHMDS (1.0 equiv)	(S_{ax})	65	0.5	70	98
4	BnOLi **6b** (2.5 equiv)	*n*-BuLi[b] (1.0 equiv)	(R_{ax})	65	4	84	–99
5	BnOH **3c** (2.5 equiv)	DBU (3.5 equiv)	(S_{ax})	rt	24	15	66
6	BnOH **3c** (2.5 equiv)	NaHMDS (3.5 equiv)	(S_{ax})	rt	0.5	92	98

Isolated yields are shown. [a]The enantiometric excess was determined by HPLC analysis using Daicel Chiralpak AD-H column. [b]*n*-BuLi was added at −78 °C.

With the optimal conditions in hand, the substrate scope of 2nd-step alcoholysis was elucidated (Table 4). The reaction of phosphonothioate (S_{ax}, R_P)-**4i**, synthesized with previous conditions[14c], having a less sterically hindered phenyl ring with benzyl alcohol (**3c**) proceeded in a stereoselective manner to give the corresponding product **5ic** in high yield with a high enantiomeric excess (entry 1). The reactions with 2-naphthalenemethanol (**3i**) and 4-bromobenzyl alcohol (**3j**) gave the corresponding products **5ji** and **5jj** with excellent enantiomeric excesses (entries 2 and 3). The reaction of phosphonothioate **4j** with cyclohexyl alcohol (**3d**) afforded **5jd** in 83% yield with 94%*ee*, but required a longer reaction time (entry 4). This alcoholysis could be applied to the reaction of the selenium analog **7j** to give phosphonoselenoate **8jd** with a high enantiomeric excess (entry 5).

Table 4. Substrate Scope of Phosphonothioate 4 and Alcohol 3

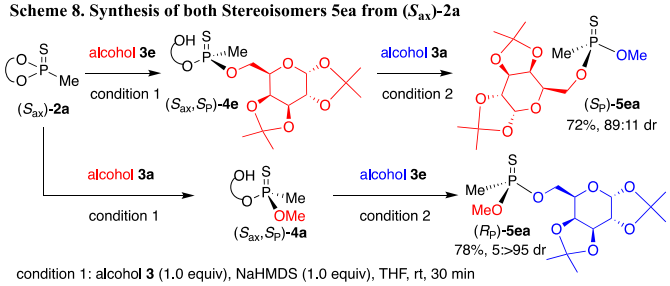


entry	S.M. 4,7	dr	alcohol 3	product 5,8	time (h)	yield (%)	ee[a]
1	 (S_{ax},R_P)-4i	>95:5	 3c	 5ic	0.5	99	82
2[b]	 (S_{ax})-4j	>95:5	 3i	 5ji	0.5	77	>99
3	 (S_{ax})-4j	>95:5	 3j	 5jj	0.5	70	89
4	 (S_{ax})-4j	>95:5	 3d	 5jd	18	83	94
5	 (S_{ax})-7j	>95:5	 3d	 8jd	11	62	91

[a] The enantiometric excess was determined by HPLC analysis using Daicel Chiralpak AD-H, IA and IB column.
[b] The reaction was carried out with *n*-BuLi instead of NaHMDS at 65 ºC.

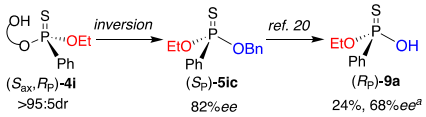
This sequential alcoholysis provided access to both stereoisomers of phosphonothioates **5** from the single starting material **2** by simply changing the order of alcohol addition (Scheme 8). Phosphonothioate **5ea** was obtained with 89:11 dr by the sequential alcoholysis of phosphonothioate **2a** with galactopyranose (**3e)** and then with methanol (**3a**). On the other hand, the diastereomer of **5ea** was obtained with 5:>95 dr by a 1st-step alcoholysis with methanol (**3a**) and a 2nd-step alcoholysis of the resulting (S_{ax}, S_P)-**4a** with galactopyranose (**3e)**. The X-ray crystal structure analysis of **5ea** revealed that the phosphorus atom adopts an *R* configuration (Supporting Information, Figure S2). We can estimate that the stereocenter at the phosphorus atom of **5ic** is *R* by comparing the optical rotation of the obtained **9a** (68%*ee*, $[\alpha]_D^{20}$ +6.1, c = 2.2 in MeOH) to the literature value for (R_P)-**9a** (99%*ee*, $[\alpha]_D^{20}$ −15, c = 3.0 in MeOH)[19] after converting **5ic** to the corresponding phosphonothioic acid **9a** (Scheme 9).[20] These results clearly suggest that the 2nd-step alcoholysis proceeds with inversion of the configuration at the phosphorus atom.

Scheme 8. Synthesis of both Stereoisomers 5ea from (S_{ax})-2a



condition 1: alcohol **3** (1.0 equiv), NaHMDS (1.0 equiv), THF, rt, 30 min
condition 2: alcohol **3** (2.5 equiv), NaHMDS (3.5 equiv), THF, rt, 30 min

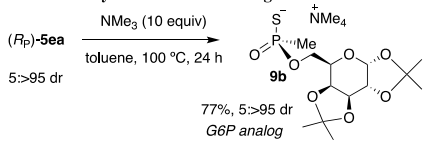
Scheme 9. Debenzylation of Phosphonothioate 5ic to Phosphonothioic Acid 9a



[a] Enantiomeric excess was determined by ^{1}H NMR analysis of diastereomeric salt with **9a** and 1.0 equivalent of (*R*)-1-phenylethylamine.

To demonstrate the applicability of the series of alcoholysis via chirality transfer, the obtained phosphonothioate **5** was converted to a biologically relevant phosphonothionyl scaffold (Scheme 10). Demethylation of (R_P)-**5ea** with an excess amount of trimethylamine afforded the glucose-6-phosphate (G6P) analog **9b** without a decrease of the diastereomeric ratio.[21]

Scheme 10. Synthesis of G6P analog



Ratio of diastereomers was determined by ^{31}P NMR analysis of the crude reaction mixtures.

CONCLUSIONS

In summary, we have demonstrated a sequential alcoholysis of phosphonothioates **2** having a binaphthyl group to *P*-stereogenic phosphonothioates **5**. The 1st-step alcoholysis proceeded via the axial chirality transfer of the binaphthyl group to the central chirality of the phosphorus atom to give *P*-stereogenic products **4** having a binaphthyloxy group with moderate to excellent diastereoselectivities. A range of alcohols including a nucleoside participated in the 1st-step alcoholysis. The DFT computational analysis suggested two TS models, leading to major and minor isomers. The differences in the coordination of a sulfur atom to a sodium cation on the phosphorus atom in the TS geometries could be caused by a binaphthyl group, and may determine the direction of nucleophilic attack of alkoxides to the phosphorus atom. The 2nd-step alcoholysis of **4** was promoted by the addition of an excess amount of the alcohols and NaHMDS affording *P*-stereogenic phosphonothioates **5** with high enantioselectivities. Pre-deprotonation of the binaphthyl moiety is crucial in improving the product enantioselectivity. Based on X-ray crystal structure analysis of **4** and optical rotation of phosphonothioic acid derivatized from **5**, we determined that the 2nd-step alcoholysis proceeded by inversion of configuration at the phosphorus atom. The obtained phosphonothioates **5** could be converted to diastereo-enriched biologically relevant phosphonothionylated scaffold.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise noted, materials were purchased from commercial supplies and used as received. Ethanol (Japan Alcohol Corporation) was distilled from magnesium. Toluene (Kanto Chemical Co., Ltd.) was distilled from sodium metal. Phosphonothioate **2a** and **2c**, phosphonothioate **4b**, **4d**, and **4j**, phosphonoselenoates **7j** were prepared with reported procedures.[14b,c] Silica gel 60 N (spherical neutral) 40-50 μm (Kanto Chemical Co., Ltd.) was used for flash column chromatography. All manipulations were carried out under argon atmosphere.

All NMR samples were prepared using $CDCl_3$ or $(CD_3)_2SO$. The ^1H NMR spectra were recorded on JEOL ECX-400P (400 MHz). Chemical shifts of protons were recorded in δ values referred to chloroform and dimethyl sulfoxide as an internal standard in $CDCl_3$ and $(CD_3)_2SO$, respectively, and the following abbreviations are used: s: singlet, d: doublet, t: triplet, m: multiplet, br: broad. The $^{13}C\{^1H\}$ NMR spectra were measured on a JEOL ECX-400P (100 MHz). The $^{31}P\{^1H\}$ NMR spectra were measured on a JEOL ECX-400P (160 MHz) and with 85% H_3PO_4 as an external standard. The ^{77}Se NMR spectra were measured on a JEOL ECX-400P (76 MHz) and with Me_2Se as an external standard. Attenuated total reflectance infrared (IR) spectra were obtained as a KBr pellet in the solid state or neat liquid, as indicated. All mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained by ionizing samples via electron ionization (EI) in positive mode using a magnetic sector analyzer. Enantiomeric excesses (*ee*) were determined by normal-phase. Preparative recycling gel permeation chromatography (GPC) was carried out using $CHCl_3$ as the eluent. HPLC analysis with a commercially available chiral stationary phase, using a mixture of hexane−2-propanol as eluent and with UV detector set as 254 nm.

6-Methyldibenzo[d, f][1,3,2]dioxaphosphepine-6-sulfide (**2a'**). To a 200 mL two-necked flask were added 6-chlorodibenzo[*d, f*][1,3,2]dioxaphosphepine[22] (1.0 M toluene solution, 10 mL, 10 mmol) under Ar atmosphere. The solution was heated to 40 °C. Methylmagnesium bromide (1.0 M in Et_2O solution, 10 mL, 10 mmol) was added dropwise for 10 min to the heated solution, and the resulting solution was stirred for 30 min. Sulfur (0.38 g, 11 mmol) was then added to the solution, and the reaction was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with ethyl ether (Et_2O) three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:10, Rf = 0.53) gave **2a'** (1.23 g, 47%) as a colorless solid. mp: 152-154 °C; IR (KBr): 2988, 1498, 1433, 1246, 1196, 1093, 935, 805, 638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.10 (d, J = 14.8 Hz, 3H), 7.26 (d, J = 7.6

Hz, 2H), 7.38 (dd, J = 7.6 Hz, 7.2 Hz, 2H), 7.45 (dd, J = 7.6 Hz, 7.2 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 19.3 (d, $^1J_{C\text{-}P}$ = 103.4 Hz), 122.0, 126.6, 129.8, 130.0, 130.3, 148.4, 148.5; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 111.3 (s) ; MS (EI) m/z 262 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{13}H_{11}O_2PS$: 262.0217, Found: 262.0200.

(S_{ax})-4-Phenylbinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine-4-sulfide (**2b**). This compound was synthesized according to literature procedure[23] with (S_{ax})-BINOL (1.44 g, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), dichlorophenylphosphine sulfide (0.8 mL, 5.0 mmol) and CH_2Cl_2 (25 mL) to give (S_{ax})-**2b** (1.69 g, 80%) as a colorless solid. mp: 246-248 °C; IR (KBr): 1588, 1234, 1119, 950, 862, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, J = 8.7 Hz, 1H), 7.29-7.40 (m, 5H), 7.47-7.57 (m, 4H), 7.66 (d, J = 8.7 Hz, 1H), 7.70-7.76 (m, 2H), 7.79 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.99 (d J = 8.2 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 121.2, 122.1, 122.4, 122.8, 125.9, 126.8, 127.2, 127.4, 128.3, 128.4, 128.6, 128.7, 130.0 (d, $^1J_{C\text{-}P}$ = 141.9 Hz), 130.6, 131.0, 131.7, 132.0, 132.1, 132.2, 132.6, 132.7, 133.4, 146.0, 146.1, 148.5, 148.6; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 101.2 (s); MS (EI) m/z 424 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{26}H_{17}O_2PS$: 424.0687, Found: 424.0663.

General procedure 1 for the preparation of phosphonothioate 4 (GP1)

To a 20 mL Schlenk tube were added phosphonothioate **2** (1.0 equiv), alcohol **3** (1.0-1.5 equiv), and THF (1.0 mL). NaHMDS (1.0 M THF solution, 1.0-1.5 equiv) was added to the reaction mixture After stirring for 30 min at room temperature, the mixture was quenched with sat. NH_4Cl aq. (2.0 mL). The aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude mixture by column chromatography on silica gel provided **4**.

(S_{ax},S_P)-O-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) O-methyl methylphosphonothioate (**4a**). This compound was synthesized via GP1, with (S_{ax})-**2a** (189 mg, 0.5 mmol), **3a** (20 μL, 0.5 mmol) and NaHMDS (0.5 mL, 0.5 mmol). Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:20, Rf = 0.15) gave **4a** (124 mg, 63%, >95:5 dr) as a colorless solid. mp: 78-80 °C; IR (KBr): 3406, 3057, 2946, 1506, 1211, 1045, 985, 897, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.66 (d, J = 15.7 Hz, 3H), 3.18 (d, J = 14.4 Hz, 3H), 5.24-5.39 (br, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.26-7.38 (m, 5H), 7.44-7.52 (m, 2H), 7.85-7.87 (m, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 9.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 22.5 (d, $^1J_{C\text{-}P}$ = 115.6 Hz), 52.0 (d, $^2J_{C\text{-}P}$ = 7.5 Hz), 114.9, 118.5, 121.8, 122.7, 123.8, 125.0, 125.9, 126.2, 127.0, 128.1, 128.4, 129.1, 130.5, 130.8, 131.8, 133.7, 133.8, 148.1, 148.2, 151.7;

$^{31}P\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ 97.8 (s, major), 98.5 (s, minor); MS (EI) m/z 394 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{22}H_{19}O_3PS$: 394.0793, Found: 394.0804.

*(S_{ax},S_P)-O-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) O-benzyl methylphosphonothioate (**4c**).* This compound was synthesized via GP1, with (S_{ax})-**2a** (107 mg, 0.3 mmol), **3c** (31 μL, 0.3 mmol) and NaHMDS (0.3 mL, 0.3 mmol). Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:10, Rf = 0.15) gave **4c** (90 mg, 64%, >95:5 dr) as a colorless solid. mp: 63-65 °C; IR (KBr): 3420, 2922, 1620, 1216, 983, 814, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (d, J = 15.3 Hz, 3H), 3.89 (dd, J = 11.7 Hz, 8.1 Hz, 1H), 4.78 (dd, J = 11.7 Hz, 8.1 Hz, 1H), 5.39 (br, 1H), 6.94-6.96 (m, 2H), 7.15 (d, J = 8.5 Hz, 1H), 7.20-7.39 (m, 8H), 7.43 (d, J = 9.0 Hz, 1H), 7.48-7.52 (m, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.87 ,(d, J = 9.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 9.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 23.2 (d, $^{1}J_{C\text{-}P}$ = 114.6 Hz), 66.9 (d, $^{2}J_{C\text{-}P}$ = 6.6 Hz), 115.0, 118.6, 121.6, 122.8, 123.9, 125.0, 125.9, 126.2, 127.0, 127.7, 128.1, 128.2, 128.37, 128.42, 128.5, 129.2, 130.6, 130.9, 131.8, 133.7, 133.8, 135.7, 135.8, 148.2, 148.3, 151.7; $^{31}P\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ 96.3 (s, major), 97.1 (s, minor); MS (EI) m/z 470 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{28}H_{23}O_3PS$: 470.1106, Found: 470.1108.

(S_{ax},S_P)-O-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) O-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) methylphosphonothioate (**4e**).

This compound was synthesized via GP1 with (S_{ax})-**2a** (0.90 g, 2.5 mmol), **3e** (0.66 g, 2.5 mmol) and NaHMDS (2.5 mL, 2.5 mmol). Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:5, Rf = 0.25) gave **4e** (1.31 g, 84%, >95:5 dr; 5.5 mmol scale, 2.87 g, 83%, >95:5 dr) as a colorless solid. mp: 165-167 °C; IR (KBr): 3421, 2987, 1382, 1213, 1071, 989, 903, 815 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.40 (s, 3H), 1.49 (d, J = 15.3 Hz, 3H), 3.60-3.67 (m, 1H), 3.75-3.79 (m, 1H), 4.04 (dd, J = 8.1 Hz, 2.5 Hz, 1H), 4.10-4.17 (m, 1H), 4.26 (dd, J = 5.2 Hz, 2.2 Hz, 1H), 4.53 (dd, J = 7.9 Hz, 2.2 Hz, 1H), 5.46 (d, J =4.9 Hz, 1H), 5.54 (br, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.22-7.35 (m, 5H), 7.46-7.50 (m, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.89 (d, J =9.0 Hz, 1H), 7.95 (d, J =8.1 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 22.7 (d, $^{1}J_{C\text{-}P}$ =114.6 Hz), 24.6, 25.0, 25.9, 26.0, 65.0, 66.5, 70. 5, 70.7, 96.3, 108.9, 109.7, 114.5, 118.3, 121.7, 122.5, 123.7, 125.1, 126.0, 126.1, 126.9, 127.5, 128.0, 128.4, 129.0, 130.5, 130.6, 131.7, 133.7, 148.3, 148.4, 151.8; $^{31}P\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ 96.9 (s, major), 97.8 (s, minor); MS

(EI) m/z 622 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{33}H_{35}O_8PS$: 622.1790, Found: 622.1790.

(S_{ax},S_P)-O-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)O-(((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl) methylphosphonothioate (**4f**).

This compound was synthesized via GP1 with (S_{ax})-**2a** (109 mg, 0.30 mmol), **3f** (64 mg, 0.30 mmol) and NaHMDS (0.30 mL, 0.30 mmol). Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:5, Rf = 0.25) gave **4f** (114 mg, 67%, >95:5 dr) as a colorless solid. mp: 90-92 °C; IR (KBr): 3433, 2924, 1619, 1213, 984, 814, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.38 (s, 3H), 1.59 (d, *J* = 15.3 Hz, 3H), 3.25 (s, 3H), 3.27-3.34 (m, 1H), 3.80-3.84 (m, 1H), 4.01-4.05 (m, 1H), 4.19 (d, *J* = 5.5 Hz, 1H), 4.42 (d, *J* = 5.5 Hz, 1H), 4.86 (m, 1H), 5.42-5.62 (br, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 7.24-7.36 (m, 5H), 7.47-7.50 (m, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 23.0 (d, $^1J_{C\text{-}P}$ = 115.6 Hz), 25.0, 26.5, 55.2, 66.0 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 81.5, 84.7, 85.0, 109.1, 112.6, 114.6, 118.5, 121.6, 122.8, 123.7, 125.0, 125.9, 126.1, 126.9, 127.7, 128.2, 128.5, 129.0, 130.6, 130.7, 131.8, 133.7, 148.0, 148.1, 151.7; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 96.1 (s, major), 97.5 (s, minor); MS (EI) m/z 566 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{30}H_{31}O_7PS$: 566.1528, Found: 566.1530.

(S_{ax},S_P)-O-((3S)-2-((Bis(4-methoxyphenyl)(phenylmethoxy)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl) O-2'-hydroxy-[1,1'-binaphthalen]-2-yl) methylphosphonothioate (**4g**).

This compound was synthesized via GP1 with (S_{ax})-**2a** (112 mg, 0.31 mmol), **3g** (252 mg, 0.46 mmol) and NaHMDS (0.90 mL, 0.90 mmol). Purification of the crude mixture by column chromatography on silica gel (CH_2Cl_2:MeOH = 50:1 with 0.5% of Et_3N, Rf = 0.25) gave **4g** (156 mg, 56%, >95:5 dr) as a colorless solid. mp: 156-158 °C; IR (KBr): 3395, 2925, 1508, 1252, 985, 907 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.22 (d, *J* = 15.6 Hz, 3H), 1.48 (s, 3H), 2.00-2.05 (m, 1H), 2.21-2.28 (m, 1H), 3.15 (dd, *J* = 10.5 Hz, 3.2 Hz, 1H), 3.23 (dd, *J* = 10.5 Hz, 4.1 Hz, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 4.00 (dd, *J* = 6.2 Hz, 3.2 Hz, 1H), 5.24-5.31 (m, 1H), 6.05 (dd, *J* = 8.2 Hz, 6.4 Hz, 1H), 6.86-6.89 (m, 4H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.17-7.39 (m, 13 H), 7.45-7.50 (m, 2H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 8.03-8.07 (m, 2H), 9.59 (br, 1H), 11.4 (br, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 11.7, 21.6 (d, $^1J_{C\text{-}P}$ =112.8 Hz), 37.2, 45.8, 55.0, 55.1, 63.1, 75.9, 83.6, 86.2, 109.9, 113.25, 113.30, 113.6, 118.4, 121.6, 122.6, 124.4, 124.6, 125.3, 125.7, 126.3, 126.7, 126.9, 127.66, 127.74, 127.9, 128.0, 128.1, 128.3, 129.6, 129.7, 130.9, 133.3, 133.7, 135.1,

135.3, 135.5, 144.5, 146.8, 150.3, 153.2, 158.2, 163.6; $^{31}P\{^{1}H\}$ NMR (160 MHz, DMSO-d6): δ 95.2 (s, major), 95.9 (s, minor). Anal. calcd for $(C_{52}H_{47}N_2O_9PS)_{0.8}(CH_2Cl_2)_{0.2}$ (%): C 67.61; H 5.16; N 3.02, found C 67.52; H 5.19; N 3.07.

(S_{ax},S_P)-O-Ethyl O-(2'-hydroxy-[1,1'-binaphthalen]-2-yl) phenylphosphonothioate (**4i**). This compound was synthesized via GP1 with (S_{ax})-**2b** (102 mg, 0.25 mmol), **3b** (18 μL, 0.30 mmol) and NaHMDS (0.30 mL, 0.30 mmol). Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:10, Rf = 0.25) gave **4i** (87 mg, 76%, 24:76 dr) as a colorless solid. mp: 110-112 °C; IR (KBr): 3433, 2924, 1619, 1213, 984, 814, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.2 Hz, 2.4 H), 1.14 (t, J = 7.2 Hz, 0.6H), 3.28-3.36 (m, 0.8H), 3.73-3.87 (m, 1H), 3.91-3.99 (m, 0.2H), 5.14 (br, 0.2H), 5.43 (br, 0.8H), 7.08-7.15 (m, 1.6H), 7.20 (d, J = 9.0 Hz, 0.8H), 7.22-7.42 (m, 7.6H), 7.45-7.53 (m, 1.8H), 7.58 (d, J = 9.0 Hz, 0.2H), 7.69 (d, J =9.0 Hz, 0.2H), 7.73-7.79 (m, 1.6H), 7.85 (d, J = 8.1 Hz, 0.8H), 7.88-7.93 (m, 2H), 7.95 (d, J = 8.1 Hz, 0.2H), 8.03 (d, J = 9.0 Hz, 0.2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.7 (d, $^{3}J_{C\text{-}P}$ = 7.5 Hz), 16.0 (d, $^{3}J_{C\text{-}P}$ = 8.5 Hz), 62.8 (d, $^{2}J_{C\text{-}P}$ = 6.6 Hz), 63.1 (d, $^{2}J_{C\text{-}P}$ = 6.6 Hz), 114.8, 115.1, 118.4, 118.6, 121.4, 122.0, 122.5, 122.7, 123.5, 123.7, 125.0, 125.8, 125.9, 126.0, 126.1, 126.7, 126.8, 127.6, 127.9, 128.1, 128.3, 128.4, 128.5, 129.1, 129.2, 130.3, 130.35, 130.39, 130.6, 130.7, 131.2, 131.3, 131.6, 131.7, 132.0, 132.6, 132.7, 133.5, 133.7, 133.9, 134.1, 148.46, 148.54, 148.6, 151.7; $^{31}P\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ 85.9 (s, minor), 86.5 (s, major); MS (EI) m/z 470 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{28}H_{23}O_3PS$: 470.1106, Found: 470.1088.

(S_{ax},R_P)-O-Ethyl O-(2'-hydroxy-[1,1'-binaphthalen]-2-yl) phenylphosphonothioate (**4i**).

To a 20 mL Schlenk tube were added phosphonothioate **2b** (0.84 g, 2.0 mmol) and ethanol (**3b**) (2.0 mL). The reaction mixture was cooled to 0 °C. Then, lithium ethoxide (1.0 M ethanol solution, 5.0 mL, 5.0 mmol) was added to the cooled solution. After that, the mixture was added to 1N HCl (3.0 mL), and the aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated unuder reduced pressure. Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:10, Rf = 0.20) provided **4i** (0.84 g, 90%, >95:5 dr) as a colorless solid. mp: 141-143 °C; IR (KBr): 3343, 2980, 1589, 1214, 1023, 983, 818, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7.2 Hz, 3H), 3.81-3.87 (m, 1H), 3.91-3.99 (m, 1H), 5.20 (br, 1H), 7.10-7.16 (m, 4H), 7.22-7.39 (m, 7H), 7.46-7.50 (m, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.70 (d, J =9.0 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$):

δ 16.0 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 63.1 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 114.8, 118.4, 122.1, 122.5, 123.5, 125.0, 125.9, 126.1, 126.7, 127.6, 127.9, 128.1, 128.4, 129.1, 130.3, 130.4, 130.6, 131.7, 132.1, 132.7 (d, $^1J_{C\text{-}P}$ = 123.9 Hz), 133.5, 133.7, 148.5, 148.6, 151.7; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 85.9 (s, major), 86.5 (s, minor); MS (EI) m/z 470 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{28}H_{23}O_3PS$: 470.1106, Found: 470.1084.

O-(2'-Hydroxy-[1,1'-biphenyl]-2-yl) O-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) methylphosphonothioate(**4e'**).

This compound was synthesized via GP1 with **2a'** (550 mg, 2.1 mmol), 1,2:3,4-di-*O*-α-D-galactopyranose (**3e**) (581 mg, 2.2 mmol) and NaHMDS (2.2 mL, 2.2 mmol). Purification of the crude mixture by column chromatography on silica gel (EtOAc:hexane = 1:5, Rf = 0.25) gave **4e'** (584 mg, 52%, 52:48 dr) as a colorless solid. mp: 50-51 °C; IR (KBr): 3420, 2934, 1384, 1211, 1070, 917, 764 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 1.32-1.33 (m, 6H), 1.44 (s, 1.5H), 1.45 (s, 1.5H), 1.50 (s, 1.5H), 1.53 (s, 1.5H), 1.59-1.63 (m, 3H), 3.98-4.10 (m, 2.6H), 4.15-4.25 (m, 1.4H), 4.31-4.33 (m, 1H), 4.58 (dd, *J* = 7.9 Hz, 2.5 Hz, 0.5H), 4.62 (dd, *J* = 7.9 Hz, 2.5 Hz, 0.5H), 5.28-5.34 (br, 1H), 5.52-5.53 (m, 1H), 6.96-7.02 (m, 2H), 7.14-7.22 (m, 1H), 7.28-7.42 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.9 (d, $^1J_{C\text{-}P}$ = 114.6 Hz), 21.9 (d, $^1J_{C\text{-}P}$ = 115.6 Hz), 24.6, 24.7, 25.1, 26.1, 26.2, 65.1, 65.4, 66.8, 67.1, 70.5, 70.6, 70.7. 70.8, 96.4, 109.0, 109.7, 116.8, 120.7, 122.9, 123.0, 124.8, 126.0, 129.5, 129.8, 130.4, 130.5, 131.5, 132.2, 148.8, 148.9, 153.26, 153.31; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 97.1 (s), 97.6 (s); MS (EI) m/z 522 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{25}H_{31}O_8PS$: 522.1477, Found: 522.1470.

General procedure 2 for the preparation of phosphonothioate 5 (GP2)

To a 20 mL Schlenk tube were added phosphonothioate **4** (1.0 equiv and THF (1.0 mL). The solution was cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 1.0 equiv) was then added to the cooled solution. After stirring for 30 min the solvent was removed under reduced pressure at room temperature. THF (0.5 mL), and lithium alkoxide (1.0 M in THF, 2.5 equiv) were added to the dried reaction mixture, and the resulting reaction mixture was stirred at 65 °C for 4 h. The reaction was quenched with sat. NH_4Cl aq. (2.0 mL), and the aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude mixture by column chromatography on silica gel gave **5**.

O-Benzyl O-ethyl mesitylphosphonothioate (**5jc**). This compound was synthesized via GP2 with (S_{ax})-**4j** (255 mg, 0.50 mmol, >95:5 dr), *n*-BuLi (1.6 M in hexane, 0.31 mL, 0.50 mmol), lithium benzyl-oxide (**6b**) (1.0 M in THF, 1.3 mL, 1.3 mmol) at 65 °C for 4

h. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:20, Rf = 0.38) gave **5jc** (154 mg, 92%, 98%*ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak AD-H column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, t_R = 25.8 min (major), t_R = 28.1 min (minor). $[\alpha]_D^{20}$ −1.5° (*c* = 1.0, THF); IR (neat): 2976, 2360, 1605, 1455, 1030, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.26 (s, 3H), 2.54 (s, 6H), 3.87-3.98 (m, 1H), 4.06-4.17 (m, 1H), 5.09-5.24 (m, 2H), 6.87 (s, 1H), 6.88 (s, 1H), 7.31-7.34 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $^3J_{C\text{-}P}$ = 7.2 Hz), 21.1, 23.6, 62.1 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 67.4 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 128.3 (d, $^1J_{C\text{-}P}$ = 154.8 Hz), 128.4, 128.7, 130.9, 131.0, 136.37, 136.43, 141.3, 141.4; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 85.9 (s); MS (EI) m/z 334 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{23}O_2PS$: 334.1156, Found: 334.1154.

O-Ethyl O-(naphthalene-2-ylmethyl) mesitylphosphonothioate (**5ji**). This compound was synthesized via GP2 with (S_{ax})-**4j** (255 mg, 0.50 mmol, >95:5 dr), *n*-BuLi (1.6 M in hexane, 0.31 mL, 0.50 mmol), lithium 2-naphthalenemethyl-oxide (1.0 M in THF, 1.3 mL, 1.3 mmol) at 65 °C for 4 h. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:20, Rf = 0.48) gave **5ji** (148 mg, 77%, >99%*ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak AD-H column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, t_R = 28.5 min (minor), t_R = 33.2 min (major). $[\alpha]_D^{20}$ −3.2° (*c* = 1.0, THF); mp: 61-62 °C; IR (KBr): 2976, 1605, 1450, 1030, 812, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 2.57 (s, 6H), 3.91-4.00 (m, 1H), 4.09-4.19 (m, 1H), 5.27-5.41 (m, 2H), 6.88 (s, 1H), 6.89 (s, 1H), 7.48-7.55 (m, 3H), 7.83-7.88 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 21.1, 23.6, 23.7, 62.2 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 67.6 (d, $^2J_{C\text{-}P}$ = 6.6 Hz), 126.0, 126.5, 127.3, 127.9, 128.2, 128.3 (d, $^1J_{C\text{-}P}$ = 155.6 Hz), 128.5, 130.9, 131.1, 133.26, 133.31, 133.8, 133.9, 141.3, 141.4; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 86.1 (s); MS (EI) m/z 384 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{22}H_{25}O_2PS$: 384.1313, Found: 384.1310.

General procedure 3 for the preparation of phosphonothioate 5 (GP3)

To a 20 mL Schlenk tube were added phosphonothioate **4** (1.0 equiv), alcohol **3** and THF. NaHMDS (1.0 M in THF solution, 2.5 equiv) was added to the reaction mixture. After stirring for 0.5-18 h at room temperature, the mixture was quenched with sat. NH_4Cl aq. (2.0 mL) and the aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude mixture by column chromatography on silica

gel gave phosphonothioate **5**.

(S_P)-O-Benzyl O-ethyl phenylphosphonothioate (**5ic**). This compound was synthesized via GP3 with (S_{ax}, R_P)-**4i** (703 mg, 1.5 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 5.3 mL, 5.3 mmol), benzyl alcohol (**3c**) (0.39 mL, 3.8 mmol) and THF (1.5 mL) at room temperature for 30 min. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:10, Rf = 0.50) gave **5ic** (434 mg, 99%, 82%*ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IA column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, t_R = 19.2 min (major), t_R = 21.9 min (minor). $[\alpha]_D^{20}$ 12.3° (*c* = 1.0, THF); IR (neat): 2980, 1439, 1122, 1010, 958, 736, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 4.05-4.14 (m, 2H), 5.00-5.17 (m, 2H), 7.23-7.38 (m, 7H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (d, $^3J_{C\text{-}P}$ = 7.5 Hz), 21.7, 63.0 (d, $^2J_{C\text{-}P}$ = 5.6 Hz), 68.0 (d, $^2J_{C\text{-}P}$ = 4.7 Hz), 128.1, 128.3, 128.6, 129.1, 129.2, 131.1, 131.3; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 88.3 (s);); MS (EI) m/z 306 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{19}O_2PS$: 306.0843, Found: 306.0834.

O-(4-Bromobenzyl) O-ethyl mesitylphosphonothioate (**5jj**). This compound was synthesized via GP3 with (S_{ax})-**4j** (103 mg, 0.20 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 0.7 mL, 0.70 mmol), 4-bromobenzyl alcohol (**3j**) (96 mg, 0.50 mmol) and THF (0.7 mL) at room temperature for 30 min. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:20, Rf = 0.28) gave **5jj** (142 mg, 70%, 89%*ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IB column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, t_R = 22.0 min (minor), t_R = 24.8 min (major). $[\alpha]_D^{20}$ −4.9° (*c* = 1.0, THF); mp: 67-68 °C; IR (KBr): 2923, 1605, 1487, 1451, 1038, 999, 784, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 2.53 (s, 6H), 3.91-4.00 (m, 1H), 4.07-4.17 (m, 1H), 5.04-5.19 (m, 2H), 6.87 (s, 1H), 6.88 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2 (d, $^3J_{C\text{-}P}$ = 7.7 Hz), 21.2, 23.7, 62.3 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 66.7 (d, $^2J_{C\text{-}P}$ = 6.7 Hz), 122.5, 128.1 (d, $^1J_{C\text{-}P}$ = 151.4 Hz), 130.0, 130.9, 131.1, 131.9, 135.5, 141.3, 141.4, 141.6; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 86.3 (s); MS (EI) m/z 412 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{22}BrO_2PS$: 412.0261, Found: 412.0252.

O-Cyclohexyl O-ethyl mesitylphosphonothioate (**5jd**). This compound was synthesized via GP3 with (S_{ax})-**4j** (154 mg, 0.30 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol), cyclohexanol (**3d**) (70 μL, 0.8 mmol) and THF (0.3 mL) at room temperature for 18 h. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:20, Rf = 0.28) gave **5jd** (83 mg, 83%, 94%*ee*) as a colorless liquid.

The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IA column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, t_R = 13.9 min (major), t_R = 15.3 min (minor). $[\alpha]_D^{20}$ +3.0° (*c* = 1.0, THF); IR (neat): 2935, 2857, 1606, 1450, 1382, 1045, 985, 793, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19-1.30 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.37-1.43 (m, 2H), 1.49-1.65 (m, 2H), 1.74-1.78 (m, 2H), 1.96-1.99 (m, 1H), 2.09-2.12 (m, 1H), 2.25 (s, 3H), 2.59 (s, 6H), 4.07-4.20 (m, 2H), 4.67-4.76 (m, 1H), 6.87 (s, 1H), 6.88 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 16.2 (d, $^3J_{C\text{-}P}$ = 8.4 Hz), 21.1, 23.8, 23.9, 24.2, 25.4, 33.6 (d, $^3J_{C\text{-}P}$ = 6.0 Hz), 34.1 (d, $^3J_{C\text{-}P}$ = 2.4 Hz), 62.6 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 76.1 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 128.7 (d, $^1J_{C\text{-}P}$ = 154.8 Hz), 130.9, 131.0, 141.1, 141.2, 141.3 ; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 83.5 (s); MS (EI) m/z 326 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{27}O_2PS$: 326.1469, Found: 326.1462.

O-Cyclohexyl O-ethyl mesitylphosphonoselenoate (**8jd**). This compound was synthesized via GP3 with (S_{ax})-**7j** (279 mg, 0.50 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 1.8 mL, 1.8 mmol), cyclohexanol (**3d**) (0.13 mL, 1.3 mmol) and THF (0.5 mL) at room temperature for 11 h. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:5, Rf = 0.75) gave **8jd** (118 mg, 62%,91 %*ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IA column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, t_R = 18.1 min (major), t_R = 19.0 min (minor). $[\alpha]_D^{20}$ +1.8° (*c* = 1.0, THF); IR (neat); 2936, 2857, 1605, 1449, 1041, 984, 653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21-1.29 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.40-1.46 (m, 2H), 1.50-1.67 (m, 3H), 1.73-1.81 (m, 2H), 1.96-2.00 (m, 1H), 2.12-2.16 (m, 1H), 2.26 (s, 3H), 2.57 (s, 6H), 4.12-4.26 (m, 2H), 4.73-4.80 (m, 1H), 6.85 (s, 1H), 6.87 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.0 (d, $^3J_{C\text{-}P}$ = 8.5 Hz), 21.1, 23.7, 24.2, 25.3, 33.4, 34.0, 63.8 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 77.3 (d, $^2J_{C\text{-}P}$ = 8.5 Hz), 129.6 (d, $^1J_{C\text{-}P}$ = 140.9 Hz), 131.0, 131.2, 140.8, 140.9, 141.2; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 85.4 (d, $^1J_{P\text{-}Se}$ = 830.8 Hz); ^{77}Se NMR (76 MHz, $CDCl_3$): δ −215.9 Hz (d, $^1J_{P\text{-}Se}$ = 832.3 Hz); MS (EI) m/z 374 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{27}O_2PSe$: 374.0914, Foud: 374.0917.

(R_P)-O-Methyl O-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) methylphosphonothioate (**5ea**).

This compound was synthesized via GP3 with (S_{ax}, S_P)-**4a** (194 mg, 0.50 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 1.8 mL, 1.8 mmol), 1,2:3,4-di-*O*-α-D-galactopyranose (**3e**) (1.0 M in THF, 1.3 mL, 1.3 mmol) and THF (0.5 mL) at room temperature for 30 min. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:5, Rf = 0.33) gave (R_P)-**5ea** (143 mg, 78%, 5:>95 dr) as a colorless solid. mp: 76-78 °C; IR (KBr): 2925, 1383, 1215, 1077, 1030, 1004, 905, 762 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 6H), 1.44 (s, 3H), 1.53 (s, 3H), 1.84 (d, J = 15.6 Hz, 3H), 3.71 (d, J = 13.7 Hz, 3H), 4.02-4.05 (m, 1H), 4.15-4.23 (m, 2H), 4.24 (dd, J = 5.0 Hz, 2.3 Hz, 1H), 4.32 (dd, J = 5.0 Hz, 2.3 Hz, 1H), 4.61 (dd, J = 7.8 Hz, 2.8 Hz, 1H), 5.53 (d, J = 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.2 (d, $^1J_{C\text{-}P}$ = 114.6 Hz), 24.6, 25.1, 26.1, 52.6, 65.7, 67.3, 70.6, 70.8, 70.9, 96.4, 108.9, 109.8; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 99.1 (s, minor), 100.0 (s, major); MS (EI) m/z 355 $(M-CH_3)^+$; HRMS (EI) m/z: $[M - CH_3]^+$ Calcd for $C_{13}H_{22}O_7PS$: 353.0824, Found: 353.0822.

(S_P)-O-Methyl O-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) methylphosphonothioate (**5ea**).

This compound was synthesized via GP3 with (S_{ax}, S_P)-**4e** (62 mg, 0.10 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 0.35 mL, 0.35 mmol), methanol (**3a**) (10 μL, 0.25 mmol) and THF (0.2 mL) at room temperature for 30 min. Purification of the crude mixture by column chromatography on silica gel (EtOAc:Hexane = 1:5, Rf = 0.38) gave (S_P)-**5ea** (27 mg, 72%, 89:11 dr; 4.2 mmol scale, 1.17 g, 76%, 90:10 dr) as a colorless oil. IR (neat): 2937, 1382, 1303, 1256, 1212, 1072, 1031, 908, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 6H), 1.44 (s, 3H), 1.55 (s, 3H), 1.85 (d, J = 15.7 Hz, 3H), 3.70 (d, J = 13.9 Hz, 3H), 4.04-4.17 (m, 2H), 4.24 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 4.32-4.35 (m, 2H), 4.61 (dd, J = 7.7 Hz, 2.4 Hz, 1H), 5.54 (d, J = 4.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.3 (d, $^1J_{C\text{-}P}$ = 116.0 Hz), 24.6, 25.1, 26.1, 52.7, 65.5, 67.3, 70.5, 70.8, 70.9, 96.5, 108.9, 109.8; $^{31}P\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ 99.1 (s, major), 100.0 (s, minor); MS (EI) m/z 353 $(M-CH_3)^+$; HRMS (EI) m/z: $[M - CH_3]^+$ Calcd for $C_{13}H_{22}O_7PS$: 353.0824, Found: 353.0836.

*(R_P)-O-Ethyl phenylphosphonothioic acid (**9a**)*[20]

To a vial with screw cap were added phosphonothioate (S_{ax},R_P)-**5ic** (274 mg, 0.9 mmol) and CH_2Cl_2 (1.0 mL). The solution was cooled to −78 °C. Boron trichloride (1.0 M in CH_2Cl_2, 1.0 mL, 1.0 mmol) was added to the cooled solution. The reaction mixture was warmed to 0 °C over 30 min, and it was further stirred at 0 °C for 1 h. The reaction was quenched with sat. $NaHCO_3$ aq. (2.0 mL), and the aqueous layer was washed with CH_2Cl_2 (5 mL × 3). The aqueous layer was added 1N HCl until the pH reached to 1, and it was extracted with Et_2O (8 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude mixture by GPC gave **9a** (45 mg, 24% as a colorless oil. The enantiomeric excess was determined by ^1H NMR spectra to lead diastereomeric salt with (*R*)-1-phenylethyl amine. IR (neat): 3433, 2928, 1034, 952, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, J = 7.0 Hz, 3H), 4.16-4.24 (m, 2H), 6.12 (br, 1H), 7.43-7.55 (m, 3H), 7.88-7.95 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2, 62.8, 128.4, 128.5, 130.7, 130.8, 132.3, 133.9

(d, $^{1}J_{C\text{-}P}$ = 153.2 Hz); $^{31}P\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ 80.7 (s); MS (EI) m/z 202 (M^+); HRMS (EI) m/z: $[M]^+$ Calcd for $C_8H_{11}O_2PS$: 202.0217, Found: 202.0221.

(R_P)-Tetramethylammonium O-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro -5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) methylphosphonothioate (**9b**)

To a vial were added phosphonothioate (R_P)-**5ea** (26.3 mg, 0.07 mmol) and trimethylamine (1.0 M in toluene solution, 0.7 mL, 0.7 mmol), and the vial was sealed with a Teflon cap. The reaction solution was heated to 100 °C, and stirred for 24 h. After cooling the reaction mixture at room temperature, it was concentrated under reduced pressure. The residue was washed with cold Et_2O (5 mL), and filtered to give **9b** (23.7 mg, 77%, 5:>95 dr) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 6H), 1.41 (s, 3H), 1.51 (s, 3H), 1.67 (d, J = 13.9 Hz, 3H), 3.45 (s, 12H), 3.94-3.99 (m, 1H), 4.09-4.16 (m, 2H), 4.27-4.30 (m, 2H), 4.56 (dd, J =7.9 Hz, 2.2 Hz, 1H), 5.51 (d, J = 5.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 24.2 (d, $^{1}J_{C\text{-}P}$ = 99.6 Hz), 24.3, 25.1, 26.1, 26.3, 56.0, 63.9, 68.0, 70.5, 70.6, 71.1, 94.5, 108.6, 109.1; $^{31}P\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ 71.8 (s, minor), 72.5 (s, major); MS (EI) m/z 353 $(M-NMe_4^+)^+$; HRMS (EI) m/z: $[M - NMe_4^+]^+$ Calcd for $C_{13}H_{22}O_7PS$: 353.0824, Found: 353.0808.

Supporting Information

NMR spectra data (^{1}H and ^{13}C) and chiral HPLC chromatograms for all synthesized compounds, the listed ^{31}P NMR chemical shifts of synthesized **4**, and calculated energy profiles for the 1st-step alcoholysis of **2a**

X-ray crystallographic data for **4d** (CCDC no. 1980826)

X-ray crystallographic data for **5ea** (CCDC no. 1980825)

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