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Synthesis of chiral, nonracemic α-sulfanylphosphonates and derivatives

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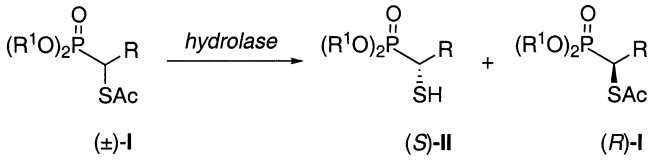
Abstract—Optically active α-sulfanylphosphonates and the corresponding methyl sulfides were prepared in three steps starting from chiral, nonracemic (ee 93–97%) α-hydroxyphosphonates obtained by enzymatic resolution. Reaction conditions for the reduction of racemisation-prone substrates were found to preserve the enantiomeric excesses.

1. Introduction

Certain sulfanylcarboxylic acid derivatives are strong inhibitors of zinc containing metalloenzymes such as angiotensin-converting enzyme[1] (ACE), neutral endopeptidase[1] (NEP) and matrix metalloproteinases.[2] Increasing efforts have lately been directed towards the synthesis of chiral, nonracemic sulfanyl substituted carboxylic acids including α-lipoic acid and their derivatives by stereospecific syntheses[3] and lipase-catalysed[3b,4] resolutions. Therefore, phosphonic acid analogues of α-sulfanyl carboxylic acids are interesting candidates as metalloenzyme inhibitors. Several chiral α-hydroxy- and α-aminophosphonic acids (analogues of natural hydroxy- and aminocarboxylic acids) are important for their biological activity,[5] but to the best of our knowledge the corresponding thiols have not been the subject of biological tests. Recently, some of us reported the first asymmetric synthesis of α-sulfanylphosphonates by a diastereoselective asymmetric [2,3]-sigmatropic rearrangement of dimenthyl (allylsulfanyl)methylphosphonate.[6]

The preparation of chiral thiols by enzymatic hydrolysis of acetylthio derivatives (thioesters) has not often been described. Lipase-catalysed resolution gave α-sulfanylcarboxylic acid derivatives in moderate to poor enantiomeric excesses at good conversions.[3b,4] Almost enantiopure α-hydroxyphosphonates were obtained by kinetic resolution of α-acetoxy- and α-chloroacetoxyphosphonates using hydrolases.[7] Therefore, in preliminary investigations, we tested the hydrolysis of racemic diethyl 1-(acetylthio)benzylphosphonate (±)-**I** ($R^1 = Et$, $R = Ph$) using, amongst others, enzymes known to give good results for the corresponding dimethyl and diisopropyl 1-(acetoxy)benzylphosphonates under similar reaction conditions[8] (Scheme 1).

However, a rapid, complete and non-enantioselective hydrolysis was observed with lipases AP 6, Prozyme 6 and protease Chirazyme P-2 yielding racemic diethyl (1-sulfanyl)benzylphosphonate. Furthermore, lipases from *Candida rugosa* and *C. cylindracea* and lipase FAP-15 did not hydrolyse racemic diethyl 1-(acetylthio)benzylphosphonate and the starting material was recovered unchanged. These failures show that the enzymatic resolution, successful for the preparation of



(±)-**I** (*S*)-**II** (*R*)-**I**

Scheme 1.

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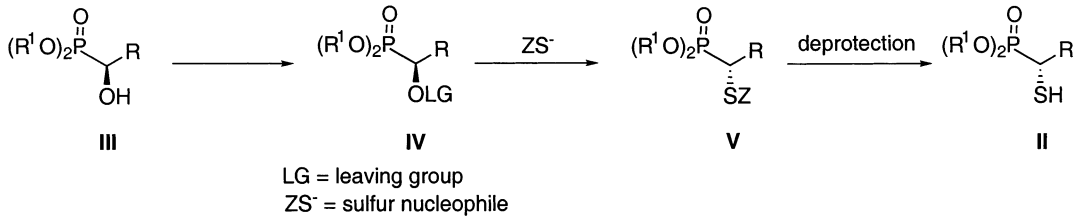
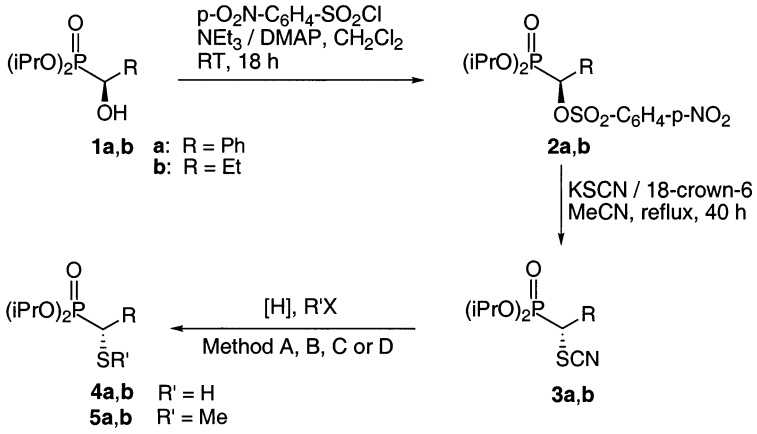


Scheme 2.



Scheme 3.

chiral, nonracemic α-hydroxyphosphonates, cannot be readily extended to the sulfur analogues. Therefore, we did not investigate further the hydrolase-catalysed enantioselective hydrolysis of 1-acetylthiophosphonates or the enantioselective esterification of α-sulfanylphosphonates, but decided to explore chemical procedures (Scheme 2). The stereospecific conversion of easily accessible α-hydroxyphosphonates **III** of high ee into their α-sulfanyl analogues **II** was very attractive. The results of the synthesis of chiral, nonracemic α-sulfanylphosphonates and the corresponding methyl sulfides are described herein.

2. Results and discussion

The stereospecific substitution of the hydroxyl (OH) for the sulfanyl (SH) group on a carbon α to a carbanion-stabilizing group is not trivial. We tested mesylates, tosylates and *p*-nitrobenzenesulfonates of α-hydroxyphosphonates as substrates with a variety of sulfur nucleophiles such as potassium thioacetate, potassium ethyl xanthate, sodium hydrogen sulfide or potassium thiocyanate.[3a,9] We also examined the Mitsunobu procedure using thiolacetic acid[3a] as nucleophile, but the yield was low and could not be improved by modification of the ratio of reagents. The various experiments performed in the racemic and optically active series allowed us finally to select the *p*-nitrobenzenesulfonyloxy group as nucleofuge and thiocyanate as nucleophile. Good yields and high stereoselectivities were observed under these conditions (Scheme 3, only transformation for (*S*)-**1** is given). Starting from racemic α-hydroxyphosphonates (±)-**1a**,**b** with R being a phenyl or an ethyl group, the *p*-nitrobenzenesulfonates (±)-**2a**,**b** were obtained in excellent yields. In the optically active series, the alcohols (*S*)-**1a**,[8]**b**[10] obtained with high enantiomeric excesses by enzymatic resolution gave *p*-nitrobenzenesulfonates (*S*)-**2a**,**b** without racemisation (Table 1). The nucleophilic substitution of the *p*-nitrobenzenesulfonyloxy group with thiocyanate afforded α-thiocyanatophosphonates **3a**,**b** in good yields and with inversion of configuration (Table 2).

Table 1. Transformation of α-hydroxyphosphonates **1** to *p*-nitrobenzenesulfonates **2**

Entry	R	Starting alcohol **1** (ee %)	Product **2** (ee %)	Yield (%)
1	Ph	(±)-**1a**	(±)-**2a**	92
2	Et	(±)-**1b**	(±)-**2b**	80
3	Ph	(*S*)-**1a** (98)	(*S*)-**2a** (98)	92
4	Et	(*S*)-**1b** (96)	(*S*)-**2b** (96)	78

Table 2. Transformation of *p*-nitrobenzenesulfonates **2** to α-thiocyanatophosphonates **3**

Entry	R	Starting product **2** (ee %)	Product **3** (ee %)	Yield (%)
1	Ph	(±)-**2a**	(±)-**3a**	90
2	Et	(±)-**2b**	(±)-**3b**	92
3	Ph	(*S*)-**2a** (98)	(*S*)-**3a** (97)	91
4	Et	(*S*)-**2b** (96)	(*S*)-**3b** (93)	92

To be useful for the preparation of chiral, nonracemic α-sulfanylphosphonates, the third step of the sequence, the conversion of the thiocyanates to the thiols, had to occur without racemisation. Different reductive conditions[11] were first tested in the racemic series (Zn/AcOH, $NaBH_4$/EtOH, $LiBH_4$/THF, $LiAlH_4$/THF, EtMgBr/THF). The best results were obtained using an excess of $NaBH_4$ in EtOH (95%) at rt. By trapping the intermediate thiolate **6** with HCl/H_2O (Method A) or MeI (Method B) the expected racemic thiols **4a**,**b** or racemic sulfides **5a**,**b** were obtained (Table 3, entries 1–4).

The reduction of (±)-**3a** was monitored by ^{31}P NMR spectroscopy. After 5 min, the thiocyanate was converted completely into an equimolar mixture of disulfide **8a** (as a 1:1 mixture of two diastereomers: $\delta = 20.7$ and 21.4 ppm) and thiolate **7a** ($\delta = 29.6$ ppm). After an additional 90 min, only **7a** could be detected in the reaction mixture. These observations suggest a mechanism proceeding by an initial attack of the hydride anion at the cyanide carbon to give intermediate **6** which undergoes fragmentation to the thiolate anion and hydrogen cyanide (Scheme 4, only transformation for (*R*)-**3** is given). Then, thiolate **7** attacks starting material **3** at the sulfur atom, leading to disulfide **8** and cyanide anion. This step has been confirmed by an independent experiment[12] and a similar mechanism was reported for the base-catalysed methanolysis of a thiocyanate.[13] Disulfide **8** is then slowly reduced to the thiolate **7**.

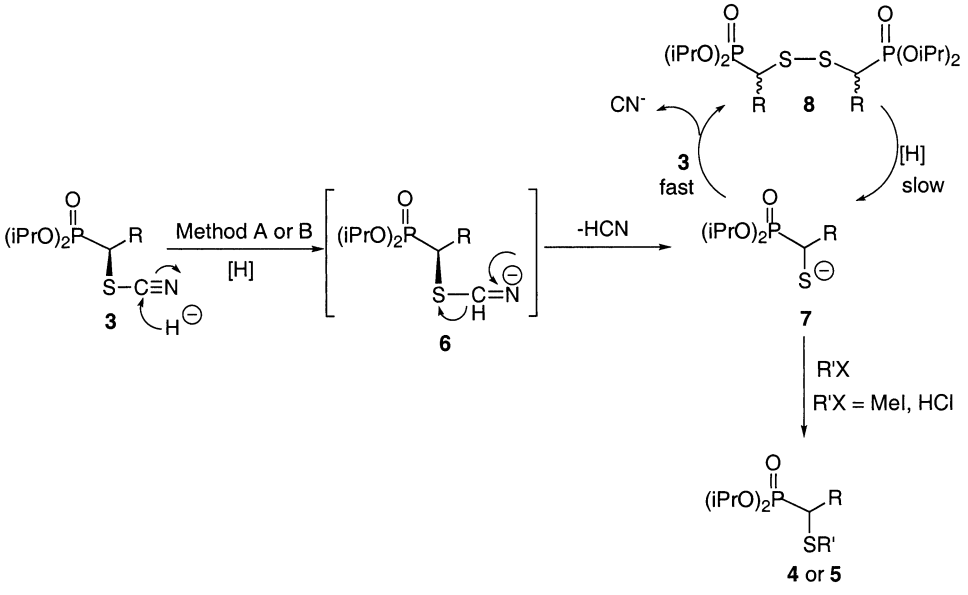
We then applied the same conditions (Methods A or B) to thiocyantophosphonates (*S*)-**3a**,**b** of ee 93–97%. Unexpectedly, the resulting thiols (*S*)-**4a**,**b** and methyl sulfides (*S*)-**5a**,**b** (Table 3, entries 5–8) had only enantiomeric excesses of 14–50%.

The racemisation of the stereogenic center could occur via a prototropic equilibrium between anion **6** or thiolate **7** and their respective α-carbanions. Indeed, partial racemisation was more significant for (*S*)-**3a** (R = Ph)

Table 3. Conversion of α-thiocyanatophosphonates **3** to sulfanyl- and methylsulfanylphosphonates **4** and **5**, respectively

Entry	R	R′	Starting product **3** (ee %)	Conditions	Product **4** or **5** (ee %)	Yield (%)
1	Ph	H	(±)-**3a**	A	(±)-**4a**	96
2	Ph	Me	(±)-**3a**	B	(±)-**5a**	82
3	Et	H	(±)-**3b**	A	(±)-**4b**	51
4	Et	Me	(±)-**3b**	B	(±)-**5b**	74
5	Ph	H	(*S*)-**3a** (97)	A	(*S*)-**4a** (27)	94
6	Ph	Me	(*S*)-**3a** (97)	B	(*S*)-**5a** (14)	80
7	Et	H	(*S*)-**3b** (93)	A	(*S*)-**4b** (60)	50
8	Et	Me	(*S*)-**3b** (93)	B	(*S*)-**5b** (50)	71
9	Ph	H	(*S*)-**3a** (97)	C	(*S*)-**4a** (97)	76
10	Ph	Me	(*S*)-**3a** (97)	D	(*S*)-**5a** (97)	77
11	Et	H	(*S*)-**3b** (93)	C	(*S*)-**4b** (92)	61
12	Et	Me	(*S*)-**3b** (93)	D	(*S*)-**5b** (88)	70

Method A: (1) $NaBH_4$/EtOH/2 h/rt; (2) 2N HCl. B: (1) $NaBH_4$/EtOH/2 h/rt; (2) MeI. C: (1) Me_3SiCl; (2) $LiBH_4$/THF/5 min/rt. D: (1) MeI; (2) $LiBH_4$/THF/5 min/rt.



Scheme 4.

than (*S*)-**3b** (R = Et), which parallels the carbanion stabilizing effect of these groups in α-position to the phosphonyl group. Neither low temperature nor the use of $LiBH_4$ in THF as aprotic solvent could stop racemisation. However, under the latter conditions, the reduction of the thiocyanates was found to be much faster (after 10 min, only thiolate **7** was observed by ^{31}P NMR spectroscopy in the reaction mixture) and the yield remained good.

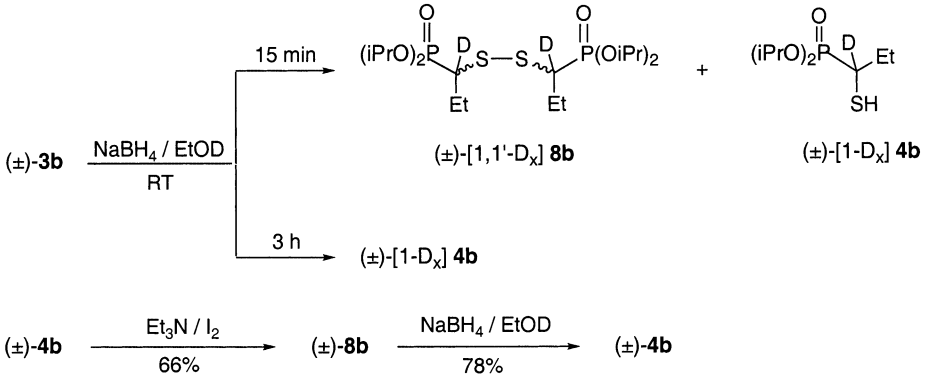
Some additional experiments were performed to corroborate the proposed reaction mechanism. When thiocyanate (±)-**3b** was reduced with $NaBH_4$-deuteriated ethanol (EtOD) at rt for 15 min and then worked up, the crude product was a mixture of starting material (3%), a 1:1 mixture of diastereomeric disulfides (±)-[1,1′-D_x]**8b** (82%) and α-sulfanylphosphonate (±)-[1-D_x]**4b** (14%) as determined by ^1H and ^{31}P NMR spectroscopy (Scheme 5). The incorporation of deuterium for both products was at most 10% (^1H NMR).

When the reduction was performed under the same conditions, except for a reaction time of 3 h instead of 15 min, only α-sulfanylphosphonate (±)-[1-D_x]**4b** was detected and isolated in 65% yield. This time the labelling was significantly higher (25% D at α-position). Additionally, disulfide (±)-**8b** obtained by iodine/Et_3N catalysed oxidation of (α-sulfanyl)propylphosphonate (±)-**4b**, was reduced with $NaBH_4$ in EtOH to starting (±)-**4b** cleanly. Finally, (±)-**3a** was reduced similary. When the reaction was worked up after 3 h, only (α-sulfanyl)benzylphosphonate was detected which was highly labelled (98% D). Alternatively, the reaction was quenched by adding MeI after 10 min. Again no disulfide could be detected. The (α-methylsulfanyl)benzylphosphonate (±)-**5a** was isolated in 73% yield. This time the labelling was only 51%. The differences in exchange of H for D reflect the higher acidity of the α-hydrogen in **3a** (R = Ph) compared to **3b** (R = Et).

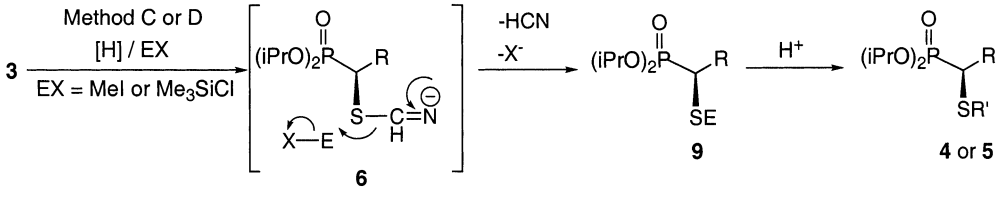
We therefore presumed that racemisation could be avoided by the addition of an appropriate electrophile able to react at the sulfur atom of the anionic species **6** or **7** (see Scheme 4), as soon as they are formed to give neutral product **9** (Scheme 6). We chose Me_3SiCl and MeI as electrophiles, which could afford the desired thiols **4** or methyl sulfides **5** after acidic work-up. The mixture of the electrophile and thiocyanate **3** in THF was added to a solution of $LiBH_4$ in THF (conditions required by the use of Me_3SiCl[14]). This time, intermediates thiolate **7** and disulfide **8** could not be observed by ^{31}P NMR spectroscopy. Only the silylated or methylated product was detected. Thus, starting from thiocyanates (*S*)-**3a**,**b** and using Me_3SiCl or MeI as electrophiles, the enantiomeric excesses for the resulting thiols **4a**,**b** and sulfides **5a**,**b** were excellent (almost complete preservation of the configuration) and yields were good (Table 3, entries 9–12).

3. Conclusion

In conclusion, as an alternative to unsuccessful attempts of kinetic enzymatic resolution of α-acetylthiophosphonates, we succeeded in the stereoselective transformation of chiral α-hydroxyphosphonates easily obtained with high enantiomeric excess by hydrolase-catalysed resolutions into α-sulfanyl- and α-methylthiophosphonates. An efficient and general procedure was developed to reduce chiral, nonracemic α-thiocyanatophosphonates to the corresponding α-sulfanylphosphonates without racemisation.



Scheme 5.



Scheme 6.

4. Experimental

4.1. General

Most of the reactions were monitored by TLC and some by ^{31}P NMR spectroscopy. TLC was carried out on 0.25 mm thick Merck plates, silica gel 60 F_{254}. Spots were visualized by dipping the plate into a solution of 24 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 1 g of $Ce(SO_4)_2\cdot 4H_2O$ in 500 ml of 10% H_2SO_4 in water, followed by heating with a heat gun. Products were purified by flash column chromatography on Merck silica gel 60 (230–400 mesh). Solvents were dried by distillation prior to use. The NMR spectra were recorded in $CDCl_3$ or C_6D_6 with a Brucker DP spectrometer at 250 MHz or 400 MHz. The chemical shifts (δ) are expressed in ppm relative to TMS for ^1H, ^{13}C (in part J modulated) nuclei and to H_3PO_4 for ^{31}P nucleus (broad band decoupling); the coupling constants (J) are given in Hz; conventional abbreviations are used. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Melting points are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 16 PC FT-IR spectrometer from films on a Si disc[15] or between NaCl discs. Enantiomeric excesses of chiral compounds **2**, **3**, **4** and **5** were determined using (*R*)-(+)-*t*-butyl(phenyl)-phosphinothioic acid as chiral shift reagent (40 μmol of shift reagent for 20 μmol of α-substituted phosphonate in 0.6 mL of C_6D_6) and by ^{31}P NMR or by ^1H NMR spectroscopy.[16,17]

4.2. Preparation of *p*-nitrobenzenesulfonates 2 (general procedure A)

p-Nitrobenzenesulfonylchloride (5.1 mmol, 1.2 equiv.), NEt_3 (1.5 mL) and 4-(*N*,*N*-dimethylamino)pyridine (50 mg) were added to a solution of hydroxyphosphonate **1** (4.3 mmol) in dry CH_2Cl_2 (20 mL) under argon at 0°C. The reaction mixture was stirred at rt for 18 h. After the addition of a mixture of water (10 mL) and 12N HCl (15 mL), the organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2 (10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (yields and ee are given in Table 1).

4.2.1. (±)- and (*S*)-Diisopropyl 1-(*p*-nitrobenzenesulfonyloxy)benzylphosphonate (±)- and (*S*)-2a. (±)-**2a** was prepared from α-hydroxyphosphonate (±)-**1a** according to the general procedure A. The crude product was purified by flash chromatography (PE/AcOEt = 2/1, $R_f = 0.2$) to give a white solid, mp 105–107°C (hexane/few drops of $CHCl_3$). (*S*)-**2a** was prepared similarly from (*S*)-**1a**,[8] ee 98%; mp 120–122°C; $[\alpha]_D^{20}$ −36.8 (*c* 1.0, acetone).

(±)-**2a**: IR (Si) ν_{max} cm^{-1}: 997, 1189, 1351, 1377, 1535, 2983, 3108. ^1H NMR ($CDCl_3$, 400.13 MHz): 0.97 (d, $J = 6.2$, 3H, CH_3); 1.26 (d, $J = 6.2$, 3H, CH_3); 1.33 (d, $J = 6.2$, 3H, CH_3); 1.34 (d, $J = 6.2$, 3H, CH_3); 4.51 (m, 1H, CHOP); 4.77 (m, 1H, CHOP); 5.67 (d, $J^{HP} = 15.6$, 1H, PCH); 7.10–7.32 (m, 5H, C_6H_5); 7.94 (AA′BB′ system, $J = 8.9$, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 23.20 (d, $J = 5.4$, CH_3); 23.70 (d, $J = 5.4$, CH_3); 24.11 (d, $J = 3.1$, CH_3); 24.14 (d, $J = 3.1$, CH_3); 72.84 (d, $J = 6.9$, CHOP); 73.13 (d, $J = 6.9$, CHOP); 79.32 (d, $J = 174.4$, PCH); 123.74 (2×CH_{arom}); 128.31 (d, $J = 2.1$, 2×CH_{arom}); 128.84 (d, $J = 6.1$, 2×CH_{arom}); 129.13 (2×CH_{arom}); 129.54 (d, $J = 3.1$, 2×CH_{arom}); 130.98 (d, $J = 2.3$, C_{arom}); 142.79 (d, $J = 1.5$, C_{arom}); 150.26 (C_{arom}). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 13.80. Anal. calcd for $C_{19}H_{24}NO_8PS$: C, 49.88; H, 5.29; N, 3.06. Found: C, 49.76; H, 5.23; N, 2.96.

4.2.2. (±)- and (*S*)-Diisopropyl 1-(*p*-nitrobenzenesulfonyloxy)propylphosphonate (±)- and (*S*)-2b. (±)-**2b** was prepared from α-hydroxyphosphonate (±)-**1b** according to the general procedure A. The crude product was purified by flash chromatography (PE/AcOEt = 2/1, $R_f = 0.3$) to give a crystalline solid, mp 50–52°C (hexane/few drops of CH_2Cl_2). (*S*)-**2b** was prepared similarly from (*S*)-**1b**,[10], ee 96%; $[\alpha]_D^{20}$ +10 (*c* 0.8, acetone).

(±)-**2b**: IR (Si) ν_{max} cm^{-1}: 991, 1188, 1257, 1351, 1376, 1535, 2982. ^1H NMR ($CDCl_3$, 400.13 MHz): 1.05 (t, $J = 7.4$, 3H, CH_3CH_2); 1.25 (d, $J = 6.1$, 3H, CH_3); 1.27 (d, $J = 6.1$, 3H, CH_3); 1.31 (d, $J = 6.1$, 6H, 2×CH_3); 1.86–1.98 (m, 2H, CH_3CH_2); 4.63–4.74 (m, 2H, 2×CHOP); 4.83 (dt, $J = 4.7$, $J = 8.8$, 1H, PCH); 8.30 (AA′BB′ system, $J = 8.3$, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 10.20 (d, $J = 10.5$, CH_3); 23.68 (d, $J = 5.0$, CH_3); 23.88 (d, $J = 4.6$, CH_3); 23.94 (CH_2); 23.95 (d, $J = 3.9$, CH_3); 24.01 (d, $J = 3.7$, CH_3); 72.08 (d, $J = 8.2$, CHOP); 72.20 (d, $J = 7.0$, CHOP); 79.72 (d, $J = 170.8$, PCH); 124.11 (2×CH_{arom}); 129.30 (2×CH_{arom}); 142.79 (C_{arom}); 150.62 (C_{arom}). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 17.24. Anal. calcd for $C_{15}H_{24}NO_8PS$: C, 44.01; H, 5.91; N, 3.42; S, 7.83. Found: C, 43.93; H, 5.93; N, 3.48; S, 7.69.

4.3. Preparation of thiocyanates 3 (general procedure B)

A mixture of *p*-nitrobenzenesulfonate **2** (2 mmol), KSCN (8 mmol) and 18-crown-6 (210 mg) in dry acetonitrile (20 mL) was heated at reflux for 40 h under argon. After addition of water (10 mL), the mixture was extracted three times with AcOEt (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (yields are given in Table 2).

4.3.1. (±)- and (*S*)-Diisopropyl 1-thiocyanatobenzylphosphonate (±)- and (*S*)-3a. (±)-**3a** was prepared from *p*-nitrobenzenesulfonate (±)-**2a** according to the general procedure B. The crude product was purified by flash chromatography (PE/AcOEt = 2/1, $R_f = 0.32$) to give a yellow solid, mp 48–50°C (hexane/few drops of $CHCl_3$). (*S*)-**3a** was prepared similarly from (*S*)-**2a** (ee 98%); mp 36–38°C; ee 97%; $[\alpha]_D^{20}$ +111.6 (*c* 0.9, acetone).

(±)-**3a**: IR (Si) ν_{max} cm^{-1}: 994, 1103, 1256, 1376, 1387, 1454, 2156, 2935, 2982. ^1H NMR ($CDCl_3$, 400.13

MHz): 0.91 (d, $J=6.2$, 3H, CH_3); 1.27 (d, $J=4.0$, 3H, CH_3); 1.36 (d, $J=6.0$, 3H, CH_3); 1.37 (d, $J=6.0$, 3H, CH_3); 4.48 (d, $J^{HP}=18.3$, 1H, PCH); 4.59 (m, 1H, CHOP); 4.79 (m, 1H, CHOP); 7.30–7.68 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 22.96 (d, $J=5.4$, CH_3); 23.79 (d, $J=5.5$, CH_3); 23.99 (d, $J=3.6$, CH_3); 24.18 (d, $J=3.0$, CH_3); 48.34 (d, $J=149.1$, PCH); 72.80 (d, $J=7.3$, CHOP); 73.57 (d, $J=7.2$, CHOP); 110.78 (d, $J=11.2$, SCN), 129.06 ($2\times CH_{arom}$); 129.30 (d, $J=6.1$, $2\times CH_{arom}$);129.35 (d, $J=2.0$, CH_{arom}), 132.51 (d, $J=4.0$, C_{ipso}). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 16.63. Anal. calcd for $C_{14}H_{20}NO_3PS$: C, 53.66; H, 6.43; N, 4.47; S, 10.23. Found: C, 53.55; H, 6.39; N, 4.52; S, 10.03.

4.3.2. (±)- and (*S*)-Diisopropyl 1-thiocyanatopropylphosphonate (±)- and (*S*)-3b. (±)-**3b** was prepared from *p*-nitrobenzenesulfonate (±)-**2b** according to the general procedure B. The crude product was purified by flash chromatography (PE/AcOEt = 1/1, $R_f=0.32$) to give a yellow viscous oil. (*S*)-**3b** was prepared similarly from (*S*)-**2b** (ee 96%); ee 93%; $[\alpha]_D^{20}$ +9 (*c* 1.1, acetone).

(±)-**3b**: IR (Si) ν_{max} cm^{-1}: 992, 1252, 1386, 1456, 2156, 2935, 2980. ^1H NMR ($CDCl_3$, 400.13 MHz): 1.20 (t, $J=7.3$, 3H, CH_3CH_2); 1.38 (d, $J=6.2$, 12H, $2\times(CH_3)_2CH$); 1.88 (m, 1H, CH_3CHH); 2.26 (m, 1H, CH_3CHH); 2.97 (ddd, $J^{HH}=4.2$, $J^{HH}=9.9$, $J^{HP}=15.5$, 1H, PCH); 4.61–4.80 (m, 2H, 2×CHOP). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 11.86 (d, $J=11.3$, CH_3CH_2); 23.29 (CH_2); 23.85 (d, $J=3.6$, CH_3); 23.90 (d, $J=3.5$, CH_3); 24.01 (d, $J=4.0$, CH_3); 24.06 (d, $J=3.8$, CH_3); 45.30 (d, $J=150.4$, PCH); 72.39 (d, $J=7.1$, CHOP); 72.56 (d, $J=7.2$, CHOP); 110.42 (d, $J=5.0$, SCN). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 19.83. Anal. calcd for $C_{10}H_{20}NO_3PS$: C, 45.27; H, 7.60; N, 5.28. Found: C, 45.53; H, 7.45; N, 5.23.

4.4. Preparation of 1-sulfanylphosphonates (±)-4 (general procedure C, Method A)

A solution of thiocyanate (±)-**3** (0.5 mmol) in EtOH 95% (5 mL) was added dropwise to a stirred solution of $NaBH_4$ (5 equiv., 2.5 mmol) in of EtOH 95% (5 mL) at rt. The mixture was stirred for 2 h (the reaction was monitored by TLC), then poured into a cooled solution of 2N HCl (10 mL) at 0°C and extracted with AcOEt (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography. Compounds **4** were stored under argon in the freezer to avoid their oxidation to disulfides.

When EtOH was replaced by EtOD, partially labeled products were obtained.

4.4.1. (±)-Diisopropyl 1-sulfanylbenzylphosphonate (±)-4a. (±)-**4a** was prepared from thiocyanate (±)-**3a** according to the general procedure C. The crude product was purified by flash chromatography (PE/AcOEt = 1/1, $R_f=0.5$) to give (±)-**4a** as a pale yellow oil.

(±)-**4a**: IR (Si) ν_{max} cm^{-1}: 987, 1105, 1178, 1251, 1385, 1453, 2932, 2979. ^1H NMR ($CDCl_3$, 400.13 MHz): 0.87 (d, $J=6.4$, 3H, CH_3); 1.17 (d, $J=4.0$, 3H, CH_3); 1.24 (d, $J=6.0$, 3H, CH_3); 1.27 (d, $J=6.0$, 3H, CH_3); 2.57 (dd, $J^{HH}=8.4$, $J^{HP}=10.9$, 1H, SH); 3.94 (dd, $J^{HH}=8.4$, $J^{HP}=19.2$, 1H, PCH); 4.38 (m, 1H, CHOP); 4.68 (m, 1H, CHOP); 7.15–7.88 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 23.08 (d, $J=6.1$, CH_3); 23.77 (d, $J=5.3$, CH_3); 23.95 (d, $J=3.1$, CH_3); 24.18 (d, $J=3.1$, CH_3); 39.01 (d, $J=149.9$, PCH); 72.00 (d, $J=7.7$, CHOP); 72.39 (d, $J=6.9$, CHOP); 127.81 (d, $J=3.0$, CH_{arom}); 128.48 (d, $J=1.5$, $2\times CH_{arom}$); 128.88 (d, $J=7.0$, $2\times CH_{arom}$); 136.86 (d, $J=3.8$, C_{ipso}). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 22.28. Anal. calcd for $C_{13}H_{21}O_3PS$: C, 54.15; H, 7.34. Found: C, 53.84; H, 7.32.

4.4.2. (±)-Diisopropyl 1-sulfanylpropylphosphonate (±)-4b. (±)-**4b** was prepared from thiocyanate (±)-**3b** according to the general procedure C. The crude product was purified by flash chromatography (PE/AcOEt = 1/1, $R_f=0.3$) to give (±)-**4b** as a pale yellow oil.

(±)-**4b**: IR (Si) ν_{max} cm^{-1}: 986, 1107, 1248, 1375, 1386, 2935, 2979. ^1H NMR ($CDCl_3$, 400.13 MHz): 1.03 (t, $J=6.8$, 3H, CH_3CH_2); 1.27 (d, $J=6.3$, 12H, $2\times(CH_3)_2CH$); 1.49 (m, 1H, CH_3CHH); 1.77 (t, $J^{HH}=J^{HP}=8.6$, 1H, SH); 2.05 (m, 1H, CH_3CHH); 2.60 (dddd, $J=3.8$, 8.6, 8.9, 15.6, 1H, PCH); 4.61–4.76 (m, 2H, 2×CHOP). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 12.38 (d, $J=13.0$, CH_3CH_2); 24.25 (d, $J=3.0$, CH_3); 24.30 (d, $J=3.1$, CH_3); 24.51 (d, $J=3.1$, CH_3); 24.59 (d, $J=3.0$, CH_3); 26.04 (d, $J=1.6$, CH_3CH_2); 37.04 (d, $J=150.2$, PCH); 71.66 (d, $J=6.8$, CHOP); 71.88 (d, $J=6.9$, CHOP). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 25.48. Anal. calcd for $C_9H_{21}O_3PS$: C, 44.98; H, 8.81. Found: C, 44.76; H, 8.63.

4.5. Oxidation of 1-sulfanylphosphonate (±)-4a to disulfide (±)-8b and reduction of (±)-8b to (±)-4b

Triethylamine (0.02 mL, 0.14 mmol) was added to a solution of α-sulfanylphosphonate (±)-**4b** (29 mg, 0.12 mmol) in dry THF (0.6 mL). After cooling to 0°C a solution of iodine (18 mg, 0.072 mmol) in dry THF (0.3 mL) was added dropwise. The mixture was stirred at rt for 2 h and then concentrated. The residue was taken up in dichloromethane. After washing with water and an aqueous solution of $Na_2S_2O_3$, the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (PE/AcOEt = 1/1; $R_f=0.29$, AcOEt) to give disulfide (±)-**8b** as an oil, 1:1 mixture of two diastereomers (^1H and ^{13}C NMR).

IR (Si) ν_{max} cm^{-1}: 983, 1107, 1248, 1386, 2933, 2978. ^1H NMR ($CDCl_3$, 400.13 MHz): 1.075 (t, $J=7.3$, 3H, CH_3CH_2); 1.072 (t, $J=7.3$, 3H, CH_3CH_2);1.27 (overlapping d, $J=6.1$, 24H, $4\times(CH_3)_2CH$); 1.74 (m, 2H, $2\times CH_3CHH$); 1.99 (m, 2H, $2\times CH_3CHH$); 2.95 (ddd, $J=4.8$, 8.8, 16.4, 2H, 2×PCH); 3.00 (ddd, $J=4.8$, 8.6, 16.7, 2H, 2×PCH); 4.68 (m, 4H, 4×CHOP). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 11.78 (d, $J=9.9$, CH_3CH_2);

11.82 (d, $J=10.0$, CH_3CH_2); 22.61 (CH_2); 23.95 (d, $J=5.4$, CH_3); 23.98 (d, $J=5.4$, 3×CH_3); 24.15 (d, $J=3.8$, 4×CH_3); 51.01 (d, $J=144.6$, PCH); 51.03 (d, $J=144.6$, PCH); 51.15 (d, $J=144.6$, PCH); 51.17 (d, $J=144.6$, PCH); 71.08 (d, $J=6.9$, CHOP); 71.12 (d, $J=6.9$, CHOP); 71.14 (d, $J=6.9$, CHOP); 71.17 (d, $J=7.7$, CHOP). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 24.6.

Disulfide (±)-**8b** (19 mg, 0.041 mmol) was reduced with $NaBH_4$ (2.5 equiv.) to (±)-**4b** in 78% yield in 6 h by general procedure C.

4.6. Preparation of racemic 1-(methylsulfanyl)benzylphosphonates (±)-5 (general procedure D, Method B)

A solution of thiocyanate (±)-**3** (0.5 mmol) in EtOH 95% (5 mL) was added dropwise to a stirred solution of $NaBH_4$ (5 equiv., 2.5 mmol) in of EtOH 95% (5 mL) at rt. The mixture was stirred for 2 h, then pure CH_3I (2 equiv., 1 mmol) was added and stirring continued for 1 h. The reaction mixture was hydrolysed with a solution of 2N HCl (10 mL) and extracted with AcOEt (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography.

4.6.1. (±)-Diisopropyl 1-(methylsulfanyl)benzylphosphonate (±)-5a. (±)-**5a** was prepared from thiocyanate (±)-**3a** according to the general procedure D. The crude product was purified by flash chromatography (PE/AcOEt = 1/1, $R_f=0.53$) to give (±)-**5a** as a pale yellow oil.

(±)-**5a**: IR (Si) ν_{max} cm^{-1}: 986, 1106, 1250, 1374, 1385, 2922, 2979. ^{1}H NMR ($CDCl_3$, 400.13 MHz): 0.94 (d, $J=6.3$, 3H, CH_3); 1.18 (d, $J=6.0$, 3H, CH_3); 1.22 (d, $J=6.1$, 3H, CH_3); 1.25 (d, $J=6.3$, 3H, CH_3); 2.02 (d, $J=1.0$, 3H, SCH_3); 3.79 (d, $J=20.2$, 1H, PCH); 4.48 (m, 1H, CHOP); 4.67 (m, 1H, CHOP); 7.18–7.41 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 15.74 (d, $J=6.8$, S CH_3); 23.20 (d, $J=6.1$, CH_3); 23.83 (d, $J=5.4$, CH_3); 24.08 (d, $J=3.1$, CH_3); 24.23 (d, $J=3.1$, CH_3); 47.95 (d, $J=148.4$, PCH); 71.52 (d, $J=7.7$, CHOP); 71.85 (d, $J=6.9$, CHOP); 127.58 (d, $J=3.1$, C_{arom}); 128.33 (d, $J=1.5$, 2×C_{arom}); 129.43 (d, $J=6.9$, 2×C_{arom}); 135.44 (d, $J=4.0$, C_{ipso}). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 21.35. Anal. calcd for $C_{14}H_{23}O_3PS$: C, 55.61; H, 7.67. Found: C, 55.40; H, 7.42.

4.6.2. (±)-Diisopropyl 1-(methylsulfanyl)propylphosphonate (±)-5b. (±)-**5b** was prepared from thiocyanate (±)-**3b** according to the general procedure D. The crude product was purified by flash chromatography (PE/AcOEt = 1/1, $R_f=0.3$) to give (±)-**5b** as a pale yellow oil.

(±)-**5a**: IR (Si) ν_{max} cm^{-1}: 986, 1108, 1247, 1385, 2933, 2977. ^{1}H NMR ($CDCl_3$, 400.13 MHz): 1.11 (t, $J=6.3$, 3H, CH_3CH_2); 1.34 (d, $J=6.2$, 12H, 2×$(CH_3)_2CH$); 1.55 (m, 1H, CH_3CHH); 1.99 (m, 1H, CH_3CHH); 2.24 (d, $J=0.9$, 3H, SCH_3); 2.41 (m, 1H, PCH); 4.61–4.82 (m, 2H, 2×CHOP). ^{13}C NMR ($CDCl_3$, 100.61 MHz): 11.97 (d, $J=13.0$, CH_3CH_2); 14.91 (SCH_3); 21.81 (CH_3CH_2); 23.84 (d, $J=2.3$, CH_3); 23.89 (d, $J=2.3$, CH_3); 24.15 (d, $J=2.3$, CH_3); 24.18 (d, $J=3.0$, CH_3); 43.55 (d, $J=150.7$, PCH); 70.96 (d, $J=7.6$, 2×CHOP). ^{31}P NMR ($CDCl_3$, 161.98 MHz): 25.61. Anal. calcd for $C_{10}H_{23}O_3PS$: C, 47.23; H, 9.12. Found: C, 46.99; H, 8.84.

4.7. Preparation of chiral, nonracemic 1-sulfanylphosphonates 4 (general procedure E, Method C)

At rt, a solution of chiral thiocyanate (*S*)-**3** (0.25 mmol) and Me_3SiCl (5 equiv., 1.25 mmol) in THF (3 mL) was added dropwise into a stirred solution of $LiBH_4$ (5 equiv., 1.25 mmol) in THF (3 mL) under argon. The mixture was stirred for 5 min, then poured into a solution of 2N HCl (10 mL) cooled to 0°C and extracted with AcOEt (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography. The spectroscopic data of (*S*)-**4a** {$[\alpha]_D^{20}$ −19.6 (*c* 0.56, acetone)} and (*S*)-**4b** {$[\alpha]_D^{20}$ −19.6 (*c* 0.56, acetone)} are identical with those of the racemic compounds. The enantiomeric excess of (*S*)-**4a** and (*S*)-**4b** were determined by use of (*R*)-(+)-*t*-butyl(phenyl)phosphinothioic acid as chiral shift reagent and by ^{1}H NMR spectroscopy (C_6D_6, 250.13 MHz). The resonances of the SH groups of the diastereomeric complexes were well separated and allowed the accurate determination of the ee.

(±)-**4a**: 3.11 (dd, $J^{HH}=8.4$, $J^{HP}=10.9$, SH); 3.21 (dd, $J^{HH}=8.4$, $J^{HP}=10.9$, SH). (*S*)-**4a**: 3.11 (dd, $J^{HH}=8.4$, $J^{HP}=10.9$, SH); ee 97%. (±)-**4b**: 2.29 (t, $J^{HH}=J^{HP}=8.6$, SH); 2.40 (t, $J^{HH}=J^{HP}=8.6$, SH). (*S*)-**4b**: 2.29 (t, $J^{HH}=J^{HP}=8.6$, SH); ee 92%.

4.8. Preparation of chiral, nonracemic 1-(methylsulfanyl)phosphonates 5 (general procedure F, Method D)

At rt, a solution of chiral thiocyanate (*S*)-**3** (0.25 mmol) and CH_3I (5 equiv., 1.25 mmol) in THF (3 mL) was added dropwise into a stirred solution of $LiBH_4$ (5 equiv., 1.25 mmol) in THF (3 mL) under argon. The mixture was stirred for 5 min, then poured into a solution of 2N HCl (10 mL) and extracted with AcOEt (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography. The spectroscopic data of (*S*)-**5a** {$[\alpha]_D^{20}$ +58.6 (*c* 0.58, acetone)} and (*S*)-**5b** {$[\alpha]_D^{20}$ −23.0 (*c* 0.65, acetone)} are identical with those of the racemic compounds. The enantiomeric excesses of (*S*)-**5a** and (*S*)-**5b** were determined by use of (*R*)-(+)-*t*-butyl(phenyl)phosphinothioic acid as chiral shift reagent and by ^{1}H NMR spectroscopy (C_6D_6, 250.13 MHz). The resonances of the SMe groups of the diastereomeric complexes were well separated and allowed the accurate determination of the ee.

^{1}H NMR (C_6D_6, 250.13 MHz): (±)-**5a**: 1.88 (d, $J=1.0$, SCH_3); 1.99 (d, $J=1.0$, SCH_3). (*S*)-**5a**: 1.88 (d, $J=1.0$, SCH_3); ee 97%. ^{1}H NMR (C_6D_6, 400.13 MHz): (±)-**5b**:

1.72 (d, $J=0.9$, SCH_3); 1.80 (d, $J=0.9$, SCH_3). (*S*)-**5b**: 1.72 (d, $J=0.9$, SCH_3); ee 88%.

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