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PAPER

Rearrangement of lithiated *S*-alkyl *O*,*O*-dialkyl thiophosphates: Scope and stereochemistry of the thiophosphate–mercaptophosphonate rearrangement†

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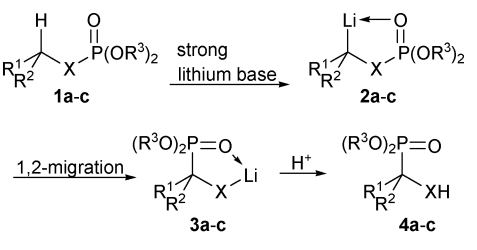
S-Alkyl *O*,*O*-dialkyl thiophosphates are prepared by alkylation of the triethylammonium salt of *O*,*O*-diisopropyl thiophosphoric acid. *S*-Benzyl thiophosphate was metallated at temperatures of ≥–45 °C by trityllithium and LiTMP (lithium 2,2,6,6-tetramethylpiperidide) and *S*-alkyl thiophosphates only by LiTMP to give dipole-stabilised carbanions which rearrange to α-mercaptophosphonates in yields of up to 45%. Metallation occurs with a high primary kinetic isotope effect (k_H/k_D up to ≈50). When the lithium (*R*)-*N*-isopropyl-1-phenylethylamide was used to induce the isomerisation of *S*-pentyl thiophosphate an α-mercaptophosphonate with an ee of 22% was isolated. (*R*)-*S*-[1-D_1]hexyl *O*,*O*-diisopropyl thiophosphate was rearranged to a dextrorotary α-mercapto-[1-D_1]hexylphosphonate, whose (*R*)-configuration was determined by chemical correlation. The thiophosphate–mercaptophosphonate rearrangement proceeds with retention of configuration.

Introduction

Some zinc-containing metallo-enzymes are strongly inhibited by derivatives of mercaptocarboxylic acids, whereby the sulfur atom is an extra ligand for the metal cofactor. Renin,[1] angiotensin-converting enzyme[2] (ACE), neutral endopeptidase[2] and matrix metalloproteinases[3] are typical representatives of this enzyme class. We reasoned that α-mercaptophosphonic acids as structural analogues of α-mercaptocarboxylic acids could produce even stronger inhibitors. α-Mercaptophosphonic acid derivatives can be transformed into α-phosphonosulfonic acids acting as squalene synthase inhibitors.[4] Generally applicable methods for the preparation of racemic and especially chiral, nonracemic α-mercaptophosphonates and derivatives thereof are missing despite various approaches to them.[5] Recently, we have shown that chiral, nonracemic α-hydroxyphosphonates can be manipulated to afford α-mercaptophosphonates of the same ee as the starting material.[6]

Results and discussion

In the course of our ongoing program[7] directed at the use of the phosphate–phosphonate and phosphonate–phosphate rearrangements, we decided to test it also for the synthesis of α-mercaptophosphonates. Briefly, this 1,2-migration of the phosphinyl group follows metallation of phosphates **1a** and phosphoramidates[8] **1b** with strong bases at low temperatures (Scheme 1). The intermediate α-hetero-atom substituted lithium complexed carbanions **2a,b** are configurationally stable and rearrange with retention of configuration to phosphonates **3a,b** giving **4a,b** on workup. The intermediates **2a,b** represent a unique class of dipole-stabilised and very likely short-lived carbanions. The reverse processes are also known. To be more precise, the 1,2-migration of the dialkoxyphosphinyl group from the hetero-atom to the carbon atom should be termed phosphate–α-hydroxyphosphonate rearrangement for X = O and phosphoramidate–α-aminophosphonate rearrangement for X = NR. It was tempting to extend this rearrangement to *S*-alkyl thiophosphates **1c**. Surprisingly, only rare examples related to this rearrangement have been reported in the literature. Kawashima *et al.* reported that *S*-methyl phosphinothioates **5** furnished methylthiomethylphosphinoxides **6**, along with other products, on metallation with lithium dialkylamides and alkylation with methyl iodide.[10] Masson *et al.* found that the phosphorylated mercaptophosphonate **7**, which can be deprotonated easily by *n*BuLi, gives mercaptodiphosphonate **8** (Scheme 2).[11] The third example of Scheme 2 refers to the α-mercaptophosphonate–thiophosphate rearrangement.[12]



Scheme 1 1,2-Migration of dialkoxyphosphinyl groups.

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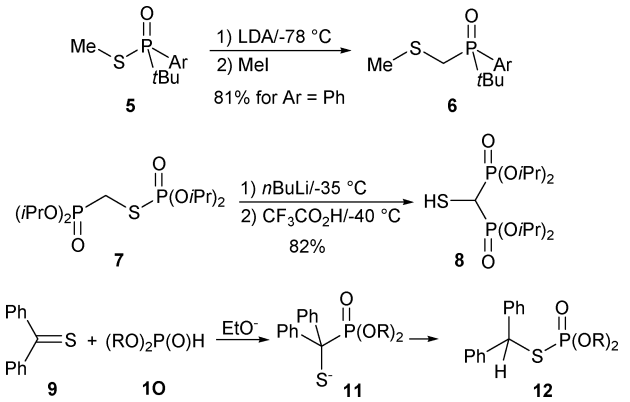
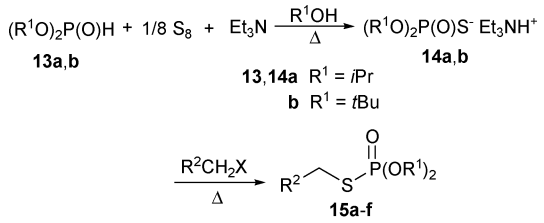
† Electronic supplementary information (ESI) available: Full characterisation data for **18d** and ^{1}H, ^{13}C and ^{31}P NMR spectra of **18f**. See DOI: 10.1039/c1ob05246b



Scheme 2 Examples for the thiophosphate–α-mercaptophosphonate rearrangement and the reverse process.

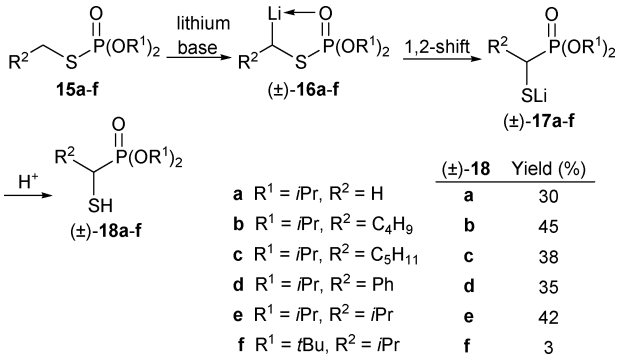
To study the metallation of thiophophates, we first prepared the *S*-alkyl thiophosphates **15** by a modified literature procedure (Scheme 3).[13] Reaction of phosphites **13** with sulfur and triethylamine at 50 °C for 2 h or at reflux for 30 min furnished triethylammonium salts **14**, which were alkylated by primary alkyl halides or *p*-tosylates to give *S*-alkyl phosphates **15** as distillable oils. The isopropyl group was the preferred protecting group as it is quite stable under basic conditions and shields the phosphorus atom against nucleophilic attack. When *S*-pentyl thiophosphate **15b** was treated in analogy to the rearrangement of phosphates with 2 equiv. of *s*BuLi/TMEDA in dry diethyl ether or THF at –78 °C for 2 h, the starting material was consumed, but surprisingly no α-mercaptophosphonate could be detected by ^{1}H NMR spectroscopy in the crude product after workup (Scheme 4).



15: R^1/R^2; X of R_2CH_2X	Yield of **15** (%)
a: *i*Pr/H; I	72
b: *i*Pr/C_4H_9; Br	77
c: *i*Pr/C_5H_{11}; OTs	73
d: *i*Pr/Ph; Br	84
e: *i*Pr/*i*Pr; Br	85
f: *t*Bu/*i*Pr; Br	44

Scheme 3 Preparation of *S*-alkyl thiophosphates.

Probably, *s*Bu$^-$ did not metallate the *S*-alkyl thiophosphate, but attacked it at the phosphorus atom to substitute $C_5H_{11}S^-$. Similarly, thiophosphate **15f** with an even more shielded phosphorus atom than **15b** did not give the desired α-mercaptophosphonate. Therefore, a sterically hindered, non nucleophilic base was mandatory and we decided to test LiTMP (lithium 2,2,6,6-tetramethylpiperidide, pK_a 37.3).[14] When one equiv. was used to induce the rearrangement of a thiophosphate, virtually no α-mercaptophosphonate was formed. However, when a mixture of thiophosphate **15b** and 2 equiv. of LiTMP prepared from the



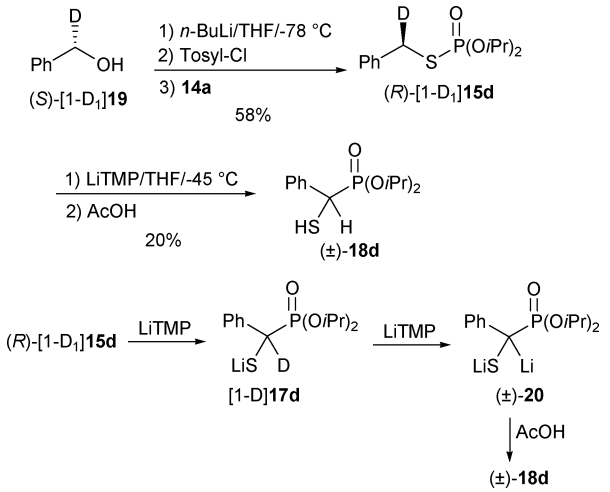
	(±)-**18**	Yield (%)
a R^1 = *i*Pr, R^2 = H	**a**	30
b R^1 = *i*Pr, R^2 = C_4H_9	**b**	45
c R^1 = *i*Pr, R^2 = C_5H_{11}	**c**	38
d R^1 = *i*Pr, R^2 = Ph	**d**	35
e R^1 = *i*Pr, R^2 = *i*Pr	**e**	42
f R^1 = *t*Bu, R^2 = *i*Pr	**f**	3

Scheme 4 Rearrangement of *S*-alkyl thiophosphates.

amine and *n*BuLi in dry diethyl ether or THF at 0 °C was stirred at –78 °C for 25 h and at –50 °C for 2 h, quenched with AcOH and worked up, the α-mercaptophosphonate (±)-**18b** was obtained in 31% and 36% yield, respectively. Some starting material (25%) was recovered as well. The experiment was repeated similarly, except that the reaction was performed at –45 °C for 7 h. The starting thiophosphate was virtually consumed (TLC) and the α-mercaptophosphonate was obtained in 45% yield. As the yields in THF were higher than in diethyl ether, THF was also used as solvent for the rearrangement of thiophosphates **15a,c–e**. The yield for α-mercaptophosphonate (±)-**18f** was merely 3%. The very low yield was attributed to an E2-elimination of isobutene from a *t*butyl group, which is more favorable than the elimination of propene from an isopropyl group, as an alternative to metallation. Although the yields were low and need improvement, these experiments demonstrate the feasibility of this rearrangement for the preparation of α-mercaptophosphonates. Normally, the crude products contained a few percentages (^{1}H NMR) of dialkyl phosphite which was probably formed by a base-catalysed decomposition of α-mercaptophosphonates. This retro-Abramov reaction yielded an unstable thioaldehyde.[15] One exploratory experiment was performed with the lithium amide derived from (*R*)-*N*-isopropyl-1-phenylethylamine[16] and thiophosphate **15b** under standard conditions (THF, –45 °C, 4 h). The corresponding chiral, nonracemic α-mercaptophosphonate (+)-**18b** {$[\alpha]_D^{20}$ +3.82 (*c* 2.2 in acetone)} was obtained in 35% yield. Its enantiomeric excess of 22% was determined by ^{31}P NMR spectroscopy using (*R*)-(+)-*t*-butylphenylmonothiophosphinic acid (2 equiv.) as chiral solvating agent in C_6D_6.[17] Two signals were observed at 26.08 and 26.01 ppm, the former being the more intense. Although the absolute configuration of the major enantiomer cannot be given, the method can be extended to the preparation of chiral, nonracemic α-mercaptophosphonates.

To determine the configurational stability of the dialkyloxyphosphinylthio-substituted carbanion **16d** and the stereochemistry of the rearrangement, deuterated (*R*)-*S*-benzyl thiophosphate (*R*)-[1-D_1]**15d** was prepared (Scheme 5).

Benzyl alcohol (*S*)-[1-D_1]**19** was prepared by horse-liver alcohol dehydrogenase catalysed reduction[18] of [formyl-D_1]benzaldehyde[19] obtained by Swern oxidation of dideuterated benzyl alcohol. The homochiral alcohol was transformed into the alcoholate and *p*-tosylated. The crude product was treated with the thiophosphate **14a**. Rearrangement of (*R*)-[1-D_1]**15d** under the standard conditions (LiTMP, –45 °C, THF, 6 h, quenching with AcOH) furnished α-mercaptophosphonate **18d**, which was both nondeuterated (by

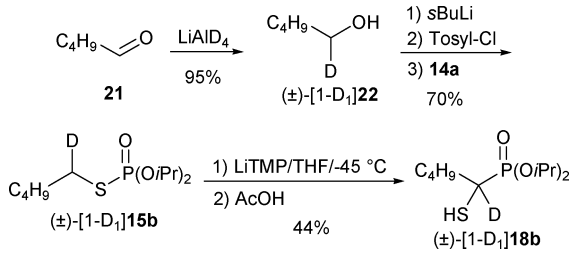


Scheme 5 Preparation and rearrangement of deuterated *S*-benzyl thiophosphate (*R*)-[1-D$_1$]**15d**.

^{1}H NMR spectroscopy, 400 MHz) and racemic proven by ^{31}P NMR spectroscopy with the chiral solvating agent given above. The signal of the two diastereomeric complexes at 22.06 and 22.11 ppm were of equal intensity. We propose the following mechanism for that result. Metallation of (*R*)-[1-D$_1$]**15d** with preferential removal of the proton over the deuteron induced a rearrangement producing mainly mercaptide [1-D]**17d** of unknown configuration, which is dedeuterated by LiTMP. The dianion **20** is configurationally labile and is protonated by AcOH when quenched. It is likely that metallation of [1-D]**17d** is as easy as that of (*R*)-[1-D$_1$]**15d**. Nevertheless, we tested also tritylllithium[20] with a pK_a of 32.9[21] as base (Et$_2$O, 2 equiv. of base, –78 °C, 16 h, or THF, –45 °C, 2 h; AcOH for quenching), which is weaker than LiTMP. Only nondeuterated, α-mercaptophosphonates (±)-**18d** (20%, 25%) were isolated along with some starting material (14%) when diethyl ether was used as solvent. The complementary experiment using nondeuterated thiophosphate **15d**, but AcOD for quenching, furnished deuterated (D > 95% by ^{1}H NMR) α-mercaptophosphonate (±)-[1-D]**18d** in 25% yield. Surprising results were obtained when only 1.1 equiv. of tritylllithium were used as base for the rearrangement of (±)-[1-D$_1$]**15d** in diethyl ether at –78 °C and –45 °C for 16 h and 8 h, respectively. The yields of the α-mercaptophosphonates (±)-[1-D]**18d** were 19% (77% D) and 10% (34% D) and of the starting materials 30% and 24%, respectively. The rearrangement of (±)-[1-D$_1$]**15d** with 2 equiv. of tritylllithium in diethyl ether at –45 °C for 1 h gave only nondeuterated (±)-**18d** (24%) along with a small amount of starting material (3%).

To see whether the second metallation is limited to the benzylic position, deuterated pentyl thiophosphate (±)-[1-D$_1$]**15b** was prepared as well and isomerised (Scheme 6).

When tritylllithium was used as base (2 equiv./Et$_2$O/–78 °C/19 h, AcOH for quenching), the starting material was consumed, but no α-mercaptophosphonate was formed. With LiTMP (2 equiv./THF/–45 °C/6 h/AcOH) as base for the rearrangement the desired, deuterated α-mercaptophosphonate was isolated (44%). The extent of deuteration (98%) is significant and indicates a high primary kinetic isotope effect ($k_H/k_D \approx 50$). The isotope effects for the metallation of phosphates[9] and phosphoramidates[8]

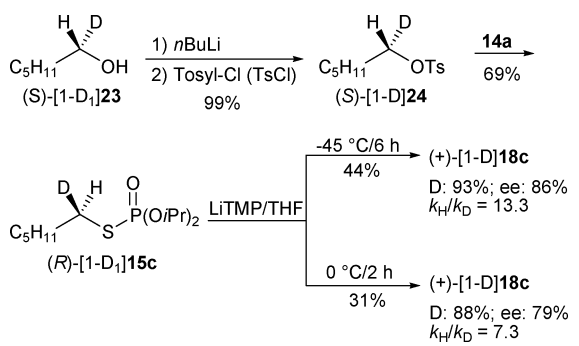


Scheme 6 Preparation and rearrangement of *S*-pentyl thiophosphate (±)-[1-D$_1$]**15b**.

are also high (up to 100 at –78 °C). With this information in hand, we could address the configurational stability of the intermediate α-thioalkyl carbanions of the thiophosphate–mercaptophosphonate rearrangement using a chirally deuterated substrate.

Rearrangement of (*R*)-*S*-[1-D$_1$]hexyl thiophosphate and determination of the configuration of (+)-α-mercaptohexylphosphonate formed

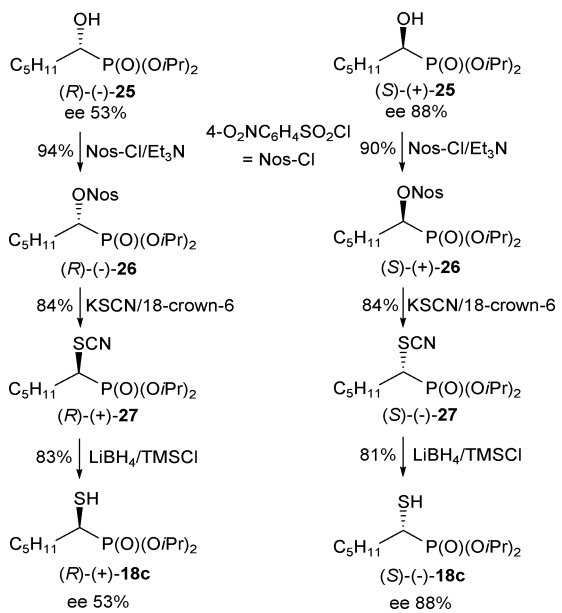
Homochiral (*S*)-[1-D$_1$]hexanol (D ≥ 99%, ee ≥ 98%),[9] accessed again by horse-liver alcohol dehydrogenase catalysed reduction[18] of [1-D$_1$]hexanal, was converted *via* tosylate to the levorotary (*R*)-[1-D$_1$]hexyl thiophosphate (*R*)-[1-D$_1$]**15c** (Scheme 7). The rearrangement was performed at –45 and 0 °C yielding dextrorotary α-mercapto-[1-D]hexylphosphonates in yields of 44 and 31%, respectively. The deuterium content decreased from 93% for the experiment performed at –45 °C to 88% for the one at 0 °C, corresponding to significant primary kinetic isotope effects k_H/k_D of 13.3 and 7.3, respectively. The enantiomeric excesses could be determined by using the above given CSA and NMR (^{1}H and ^{31}P, C$_6$D$_6$) spectroscopy and were inversely proportional to the deuterium contents. Assuming that the intermediate α-thiohexyllithiums are configurationally stable for their short lifetime and the rearrangement is stereospecific, the labelled and unlabelled species will give α-mercaptophosphonates of opposite configuration. Consequently, the product from the experiment performed at –45 °C will be a mixture with an enantiomeric ratio of 93 : 7, giving an ee of 86%, in perfect agreement with experiment (86%). The enantiomeric ratio for the experiment performed at 0 °C was 88 : 12, corresponding to a calculated ee of 76%, still in agreement within experimental error with the one found (79%). Therefore, the supposedly (very) short-lived



Scheme 7 Preparation and rearrangement of (*R*)-*S*-[1-D$_1$]hexyl thiophosphate.

α-thioalkyllithiums are microscopically configurationally stable up to 0 °C from generation by deprotonation to the rearrangement. If the intermediate α-thiohexyllithiums were configurationally labile, the enantiomeric ratio could reach a value of 50 : 50 at worst for completely labile species. To unravel the stereochemistry of this stereospecific 1,2-migration of the phosphinyl group, whether it follows a retentive or an invertive course, the configuration of the dextrorotary α-mercaptohexylphosphonate (1-D]**18c** has to be determined.

The starting materials for the chemical correlation were the known chiral, nonracemic α-hydroxyphosphonates (*R*)-(−)- and (*S*)-(+)-**25** (Scheme 8). They were obtained by acetylating[22] (±)-**25**[23] and performing a lipase AP 6 catalysed kinetic resolution[24] (conversion 45%) of the ester in a biphasic phosphate buffer system. The isolated α-hydroxyphosphonate (*S*)-(+)-**25** had an ee of 88% and the recovered ester furnished upon transesterification (*R*)-(−)-**25** of 53% ee. The further transformations of the latter into the desired mercaptophosphonate (*R*)-(+)-**18c** were straight forward in analogy to a literature procedure.[6] First, the alcohol was esterified with *p*-nitrobenzenesulfonyl chloride to furnish *p*-nitrobenzenesulfonate (nosylate) (*R*)-(−)-**26** in 94%, which was converted to the thiocyanate (*R*)-(+)-**27** with inversion of configuration (as sulfur has a higher atomic weight than phosphorus, the descriptor does not change) in 84% yield. Reduction delivered α-mercaptophosphonate (*R*)-(+)-**18c** in 83% yield with an ee of 53% (CSA, NMR), the same as that of the starting α-hydroxyphosphonate. Similarly, the enantiomeric α-hydroxyphosphonate (*S*)-(+)-**25** of 88% ee was converted to the α-mercaptophosphonate (*S*)-(−)-**18c** with an ee of again 88%. These two complementary reaction sequences show that the dextrorotary [1-D]**18c** formed from (*R*)-[1-D_1]**15c** (Scheme 7) must also have (*R*)-configuration. Therefore, the thiophosphate–mercaptophosphonate rearrangement follows a retentive course.



Scheme 8 Conversion of enantiomeric α-hydroxyhexylphosphonates **25** to the corresponding mercaptophosphonates **18c**.

Finally, the rearrangement of **15e** with LiTMP in THF was studied qualitatively by ^{31}P NMR spectroscopy starting at –60 °C. The temperature was increased every 10 min by 10 °C and a spectrum was recorded. At –40 °C the reaction rate was very slow, but increased from –30 °C on to +10 °C rapidly. The resonances of the thiophosphate and lithiated α-mercaptophosphonate were 36.79 and 27.84 ppm, respectively. After 10 min at +10 °C the signal for the starting material had disappeared and only the signal of the rearranged product was visible. It was a clean transformation, although the yield of isolated α-mercaptophosphonate (±)-**18e** was 35% on a preparative scale.

Conclusions

In summary, we have achieved the metallation of easily accessible *S*-alkyl *O*,*O*-dialkyl thiophosphates and their rearrangement to α-mercaptophosphonates. Furthermore, we have unraveled some mechanistic details of this transformation and found that the isomerisation proceeds with retention of configuration. Although the intermediate secondary α-(dialkoxyphosphinylthio)alkyllithiums are very likely short-lived, they are microscopically configurationally stable. This finding enlarges the small number of configurationally stable (microscopically or macroscopically) α-thioalkyllithiums.[25]

Experimental

General experimental

^{1}H, ^{13}C (*J* modulated) and ^{31}P NMR spectra were recorded in $CDCl_3$ (unless otherwise given) at 300 K on a Bruker AM 400 WB (400.13, 100.61 and 161.98 MHz) and a Bruker DPX 250 (250.1 and 62.9 MHz). Chemical shifts were referenced to residual $CHCl_3$ (δ_H 7.24) and $CDCl_3$ (δ_C 77.00) and external H_3PO_4 (85%). Chemical shifts are given in δ in ppm and *J* values in Hz. IR spectra were run on a Perkin–Elmer 1600 FT-IR spectrometer; samples were measured as films (normally obtained by applying part of the NMR sample and evaporation of $CDCl_3$) on a silicon disc.[26] Optical rotations were measured at 20 °C on a Perkin–Elmer 351 polarimeter in a 1 dm cell. TLC was carried out on Merck plates, silica gel 60 F_{254} (0.25 mm thick) on glass. Flash (column) chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualised by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (23.0 g) and of $Ce(SO_4)_2{\cdot}4H_2O$ (1.0 g) in 10% aqueous H_2SO_4 (500 mL), followed by heating with a heat gun. CH_3CN and pyridine were dried by refluxing over P_2O_5 and powdered CaH_2, respectively, then distillation and storage over molecular sieves (4 Å). CH_2Cl_2 was dried by passing through aluminum oxide 90 active, neutral (0.063–0.200 mm, activity I) and stored over molecular sieves (3 Å). Hexane was dried by storage over molecular sieves (4 Å). Et_2O was refluxed over $LiAlH_4$, THF over potassium and distilled prior to use. Melting points were determined on a Reichert Thermovar instrument and were uncorrected.

Preparation[13] of *S*-alkyl *O*,*O*-diisopropyl thiophosphates (general procedure A). A mixture of (*i*PrO)$_2$P(O)H (1.66 g, 10 mol), sulfur (0.32 g, 10 mmol) and Et_3N (1.21 g, 1.67 mL, 12 mmol) in *i*PrOH (25 mL) was stirred for 2 h at 50 °C or 30 min at reflux. The mixture was cooled, the halogenoalkane (12 mmol) or alkyl *p*-tosylate (12 mmol) was added and stirring and heating at 50 °C were continued for 3 h (refluxing for 1 h for tosylates and 6 h for **15e**).

The cold solution was concentrated *in vacuo*. Water (10 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with H_2O (2×10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography, followed by bulb to bulb distillation if appropriate.

Thiophosphate–mercaptophosphonate rearrangement using lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as base (general procedure B). A solution of *n*BuLi (1.9 mL, 3 mmol, 1.6 M in hexane) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.42 g, 0.5 mL, 3 mmol) in dry THF (4 mL) at 0 °C under argon. After 30 min, the solution was cooled to –45 °C and the *S*-alkyl thiophosphate (1.5 mmol) dissolved in dry THF (2 mL) was added. Stirring was continued for some h (see individual compounds) at that temperature kept constant within ±2.5 °C. The reaction was quenched with a solution of AcOH (0.5 mL) in dry THF (1 mL). The cooling bath was removed and the reaction mixture was concentrated when it had warmed up to room temperature. The residue was taken up in CH_2Cl_2 (25 mL) and washed with HCl (10 mL, 2 N) and a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography.

Thiophosphate–mercaptophosphonate rearrangement using triphenylmethyllithium as base (general procedure C). A solution of *n*BuLi (1.95 mL, 3.1 mmol, 1.6 M) was added dropwise to a stirred solution of Ph_3CH (0.73 g, 3 mmol) in dry THF (4 mL) at ambient temperature under argon. After 30 min, the solution was cooled to –45 °C and the *S*-alkyl thiophosphate (1.5 mmol) dissolved in dry THF (2 mL) was added. The further procedure is as given in general procedure B.

***O*,*O*-Diisopropyl *S*-methyl thiophosphate (15a).** It was prepared according to general procedure A using MeI (2 h at 25 °C, 1 h at 50 °C). Flash chromatography (hexane-EtOAc 3 : 1, R_f 0.48) of the crude product and bulb to bulb distillation (83–90 °C/6 mm) furnished thiophosphate **15a** (1.52 g, 72%) as a colourless liquid; δ_H (250.1 MHz) 1.37 (d, *J* 6.2, 6H), 1.39 (d, *J* 6.2, 6H), 2.29 (d, *J* 14.9, 3H), 4.77 (dsept, *J* 6.2, 9.1, 2H); δ_C (62.9 MHz) 12.6 (d, *J* 4.6), 23.5 (d, *J* 5.5, 2C), 23.8 (d, *J* 4.1, 2C), 72.5 (d, *J* 6.0, 2C); δ_P (162 MHz) 27.1; IR (Si): ν_{max} 2980, 2935, 1387, 1376, 1254, 982 cm^{-1}; $C_7H_{17}O_3PS$ (212.25): calcd. C 39.61, H 8.07; found: C 39.53, H 8.13.

***O*,*O*-Diisopropyl *S*-pentyl thiophosphate (15b).** It was prepared from $(iPrO)_2P(O)H$ (20 mmol) and 1-bromopentane (3.62 g, 24 mmol) according to general procedure A. Flash chromatography (hexane-EtOAc 3 : 1, R_f 0.42) of the crude product and bulb to bulb distillation (80 °C/0.2 mm) furnished thiophosphate **15b** (4.10 g, 77%) as a colourless liquid; δ_H (400.1 MHz) 0.90 (t, *J* 7.0, 3H), 1.35 (d, *J* 6.5, 6H), 1.36 (m, 4H), 1.37 (d, *J* 6.5, 6H), 1.70 (quint, *J* 7.5, 2H), 2.83 (dt, *J* 7.5, 13.6, 2H), 4.74 (dsept, *J* 6.5, 9.0, 2H); δ_C (100.6 MHz) 13.8, 22.1, 23.6 (d, *J* 5.4, 2C), 23.9 (d, *J* 3.8, 2C), 30.4 (d, *J* 6.1), 30.7, 31.0 (d, *J* 3.8), 72.4 (d, *J* 6.1, 2C); δ_P (162 MHz) 27.1; IR (Si): ν_{max} 2979, 2933, 2874, 1468, 1386, 1375, 1256, 978 cm^{-1}; $C_{11}H_{25}O_3PS$ (268.32): calcd. C 49.23, H 9.39; found: C 49.20, H 9.46.

Preparation of (±)-*O*,*O*-diisopropyl *S*-[1-D_1]pentyl thiophosphate {(±)-[1-D_1]15b}

(±)-[1-D_1]Pentanol {(±)-[1-D_1]22}. A solution of pentanal (1.62 g, 18.8 mmol) in dry Et_2O (15 mL) was added dropwise to a stirred suspension of $LiAlD_4$ (0.395 g, 9.4 mmol, 98% atom% D) in dry Et_2O (25 mL). The mixture was refluxed for 30 min, cooled and cautiously quenched with water. Hydrochloric acid (4 M) was added until precipitate had dissolved. The organic layer was separated and the aqueous phase was extracted with Et_2O (2×15 mL). The combined organic layers were washed with H_2O and a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and cautiously concentrated *in vacuo*. Bulb to bulb distillation (80–90 °C/80 mm) of the residue furnished deuterated pentanol (±)-[1-D_1]**22** (1.59 g, 95%) as a colourless liquid; δ_H (400.1 MHz, $CDCl_3$) 0.87 (t, *J* 6.8, 3H), 1.29 (m, 4H), 1.52 (br.q, *J* 6.7, 2H), 1.76 (br.s, 1H); δ_C (100.6 MHz, $CDCl_3$) 14.0, 22.4, 27.9, 32.3, 62.5 (t, *J* 21.8).

(±)-*O*,*O*-Diisopropyl *S*-[1-D_1]pentyl thiophosphate {(±)-[1-D_1]15b}. To a solution of (±)-[1-D_1]pentanol (0.89 g, 10 mmol) in dry THF (20 mL), stirred at –78 °C under argon, *n*BuLi (7.5 mL, 12 mmol, 1.6 M solution in hexane) was added, followed by a solution of *p*-tosyl chloride (2.28 g, 12 mmol) in dry THF (8 mL) after 5 min. The reaction mixture was allowed to warm up in the cooling bath to –10 °C within 5 h. Water and CH_2Cl_2 were added. The organic phase was separated and aqueous one was extracted with CH_2Cl_2. The combined organic layers were washed twice with H_2O, dried (Na_2SO_4) and concentrated *in vacuo*. The crude tosylate was dissolved in *i*PrOH (10 mL) and used for the alkylation of the triethylammonium salt of *O*,*O*-diisopropyl thiophosphoric acid prepared from 10 mmol of $(iPrO)_2P(O)H$ according to general procedure A. Flash chromatography (hexane-EtOAc 4 : 1) of the crude thiophosphate and bulb to bulb distillation (90–95 °C/0.7 mm) furnished thiophosphate (±)-[1-D_1]**15b** (1.98 g, 70%) as a colourless liquid; the spectroscopic data were identical to those of **15b** except for δ_H (400.1 MHz) 1.68 (quint, *J* 6.6, 2H), 2.81 (dtt, *J* 1.6, 6.6, 12.1, 1H, SCHD) and δ_C (100.6 MHz) 30.3 (d, *J* 6.1), 30.7 (dt, *J* 3.8, 22.2, SCHD).

***S*-Hexyl *O*,*O*-diisopropyl thiophosphate (15c).** Hexanol (1.02 g, 10 mmol) was transformed according to the procedure used for the preparation of (±)-[1-D_1]**15b** into thiophosphate **15c**. Flash chromatography (hexane-EtOAc 4 : 1, R_f 0.33) of the crude product and bulb to bulb distillation (95 °C/0.3 mm) furnished thiophosphate **15c** (2.07 g, 73%) as a colourless liquid; δ_H (400.1 MHz) 0.86 (t, *J* 7.0, 3H), 1.31 (m, 6H), 1.32 (d, *J* 6.3, 6H), 1.34 (d, *J* 6.3, 6H), 1.66 (quint, $J \approx 7.3$, 2H), 2.80 (dt, *J* 7.3, 13.4, 2H), 4.71 (dsept, *J* 6.3, 9.1, 2H); δ_C (100.6 MHz) 14.0, 22.5, 23.6 (d, *J* 6.1, 2C), 23.9 (d, *J* 4.0, 2C), 28.3, 30.7 (d, *J* 6.1), 31.1 (d, *J* 4.6), 31.2, 72.4 (d, *J* 6.9, 2C); δ_P (162 MHz) 27.0; IR (Si): ν_{max} 2979, 2931, 2859, 1386, 1375, 1256, 978 cm^{-1}; $C_{12}H_{27}O_3PS$ (282.38): calcd. C 51.04, H 9.64; found: C 51.07, H 9.40.

(*R*)-(–)-[1-D_1]-*S*-Hexyl *O*,*O*-diisopropyl thiophosphate {(*R*)-[1-D_1]15c}. (*S*)-(+)-[1-D_1]Hexanol {0.106 g, 1.03 mmol; $[\alpha]_D^{20}$ +0.34 (*c* 20.05, acetone), D ≥ 99% , ee ≥ 98} was converted to (*R*)-[1-D_1]**15c** {0.20 g, 69%; $[\alpha]_D^{20}$ –0.22 (*c* 10.72, CH_2Cl_2)} according to the procedure used for the preparation of the unlabelled thiophosphate **15c**, except that the tosylate was reacted with the salt of the *O*,*O*-diisopropyl thiophosphoric acid for 2.5 h at 80 °C

and that the thiophosphate was not bulb to bulb distilled. The spectroscopic data were identical to those of **15c** except for δ_H (400.1 MHz) 1.65 (q, *J* 7.3, 2H), 2.79 (m, 1H) and δ_C (100.6 MHz) 30.5 (d, *J* 6.1), 30.8 (dt, *J* 3.8, 22.2, SCHD).

***S*-Benzyl *O*,*O*-diisopropyl thiophosphate (15d).** It was prepared according to general procedure A using benzyl bromide (2.05 g, 12 mmol) as alkylating agent. Flash chromatography (hexane-EtOAc 4 : 1, R_f 0.48 for 3 : 1) of the crude product and bulb to bulb distillation (100 °C/0.15 mm) furnished thiophosphate **15d** (2.41 g, 84%) as a colourless liquid; δ_H (250.1 MHz) 1.31 (d, *J* 6.2, 6H), 1.35 (d, *J* 6.2, 6H), 4.08 (d, *J* 13.0, 2H), 4.71 (dsept, *J* 6.2, 8.9, 2H), 7.34 (m, 5H); δ_C (62.9 MHz) 23.5 (d, *J* 6.0, 2C), 23.8 (d, *J* 4.1, 2C), 35.2 (d, *J* 3.7), 72.6 (d, *J* 6.4, 2C), 127.5, 128.6 (2C), 128.9 (2C), 137.5 (*J* 6.0); δ_P NMR (162 MHz) 25.3; IR (Si): ν_{max} 2980, 2935, 1455, 1386, 1375, 1257, 979 cm^{-1}; $C_{13}H_{21}O_3PS$ (288.35):calcd. C 54.15, H 7.34; found: C 54.17, H 7.45.

(*R*)-(−)- and (±)-*S*-[1-D_1]benzyl *O*,*O*-diisopropyl thiophosphate {(*R*)-(−)- and (±)-[1-D_1]15d}. (*S*)-(+)-[1-D_1]Benzyl alcohol [0.763 g, 7 mmol, $[\alpha]_D^{20}$ +1.59 (neat)] was transformed by the procedure used for the preparation of (±)-[1-D_1]**15b** into the thiophosphate. Flash chromatography of the crude product and bulb to bulb distillation (100–107 °C/0.2 mm) furnished thiophosphate (*R*)-[1-D_1]**15d** (1.178 g, 58%) as a colourless liquid; $[\alpha]_D^{20}$ −0.61 (*c* 23.45, acetone), $[\alpha]_{365}^{20}$ −2.53 (*c* 23.45, acetone); the spectroscopic data were identical to those of **15d** except for δ_H (400.1 MHz) 4.06 (dt, *J* 1.4, 12.9, 1H) and δ_C (100.6 MHz) 34.8 (dt, *J* 3.8, 22.2) and 137.4 (d, *J* 6.1). (±)-[1-D_1]**15d** was prepared similarly from racemic [1-D_1]benzyl alcohol in 63% yield.

***O*,*O*-Diisopropyl *S*-2-methylpropyl thiophosphate (15e).** It was prepared according to general procedure A using isobutyl bromide (1.64 g, 12 mmol) as alkylating agent (refluxing for 6 h). Flash chromatography (hexane-EtOAc 4 : 1, R_f 0.63 for 3 : 1) of the crude product and bulb to bulb distillation (68 °C/0.2 mm) furnished thiophosphate **15e** (2.17 g, 85%) as a colourless liquid; δ_H (250.1 MHz, $CDCl_3$) 1.03 (d, *J* 6.6, 6H), 1.37 (d, *J* 6.2, 6H), 1.39 (d, *J* 6.2, 6H), 1.94 (non, *J* 6.6, 1H), 2.76 (dd, *J* 6.6, 12.6, 2H), 4.76 (dsept, *J* 6.2, 9.1, 2H); δ_C (62.9 MHz, $CDCl_3$) 21.7 (2C), 23.6 (d, *J* 5.5, 2C), 23.9 (d, *J* 4.1, 2C), 29.5 (d, *J* 6.4), 39.5 (d, *J* 3.7), 72.4 (d, *J* 6.4, 2C); δ_P NMR (162 MHz, $CDCl_3$) 27.2; IR (Si): ν_{max} 2979, 2933, 1386, 1375, 979 cm^{-1}; $C_{10}H_{23}O_3PS$ (254.33): calcd. C 47.23, H 9.12; found: C 47.35, H 8.91.

***O*,*O*-Di-*t*-butyl *S*-2-methylpropyl thiophosphate (15f).** A mixture of $(t\text{BuO})_2P(O)H$ (1.94 g, 10 mmol), sulfur (0.32 g, 10 mmol) and Et_3N (1.11 g, 1.53 mL, 11 mmol) in *t*-BuOH (25 mL) was stirred for 19 h at 80 °C. The mixture was cooled, isobutyl bromide (1.64 g, 12 mmol) was added and stirring and refluxing were continued for 7 h. The cold solution was concentrated *in vacuo*. Water (10 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with H_2O (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane-EtOAc 5 : 1, R_f 0.57 for 3 : 1) to furnish thiophosphate **15f** (1.25 g, 44%) as a colourless liquid. δ_H (250.1 MHz) 1.02 (d, *J* 6.7, 6H), 1.55 (s, 9H), 1.56 (s, 9H), 1.95 (sept, *J* 6.7, 1H), 2.74 (dd, *J* 6.7 13.5, 2H); δ_C (100.6 MHz) 21.7 (2C), 29.2 (d, *J* 6.1), 30.2 (d, *J* 4.6, 6C), 39.9 (d, *J* 4.6), 84.1 (d, *J* 9.2, 2C); δ_P (162 MHz) 19.2; IR (Si): ν_{max} 2979, 2931, 1370, 1263, 1170, 1038, 976 cm^{-1}; $C_{12}H_{27}O_3PS$ (282.38): calcd. C 51.04, H 9.64; found: C 51.04, H 9.40.

Diisopropyl mercaptomethylphosphonate (18a). Thiophosphate **15a** (0.32 g, 1.5 mmol) was rearranged according to general procedure B (reaction time: 6 h). Flash chromatography (hexane-EtOAc 2 : 1, R_f 0.23 for 1 : 1) of the crude product furnished mercaptophosphonate **18a** (0.10 g, 30%) as a colourless liquid and starting material (0.08 g, 25%); δ_H (250.1 MHz) 1.36 (d, *J* 6.2, 6H), 1.37 (d, *J* 6.2, 6H), 1.83 (dt, *J* 8.2, 9.4, 1H), 2.65 (dd, *J* 8.2, 13.3, 2H), 4.77 (dsept, *J* 6.2, 7.5, 2H); δ_C (100.6 MHz) 18.6 (d, *J* 152.2), 23.9 (d, *J* 5.4, 2C), 24.0 (d, *J* 3.2, 2C), 71.4 (d, *J* 6.9, 2C); δ_P (162 MHz) 21.5; IR (Si): ν_{max} 2979, 1386, 1252, 1107, 986 cm^{-1}; $C_7H_{17}O_3PS$ (212.25): calcd. C 39.61, H 8.07; found: C 39.49, H 8.11.

(±)-Diisopropyl 1-mercaptopentylphosphonate {(±)-18b}, (+)-18b and (±)-[1-D_1]18b}. Thiophosphate **15b** (0.40 g, 1.5 mmol) was rearranged according to general procedure B (reaction time: 7 h). Flash chromatography (hexane-EtOAc 4 : 1, R_f 0.19) of the crude product furnished thiol (±)-**18b** (0.18 g, 45%) as a colourless liquid and starting material (0.10 g, 25%). Similarly, thiophosphate (±)-[1-D_1]**15b** was rearranged (6 h) to (±)-[1-D_1]**18b** (0.18 g, 44%). The rearrangement of thiophosphate **15b** according to general procedure B (reaction time: 6 h) replacing TMPH by (*R*)-$PhCH(CH_3)NHiPr$ $[\alpha]_D^{20}$ +61.8 (neat) furnished (+)-**18b** {(0.14 g, 35%, $[\alpha]_D^{20}$ +3.82 (*c* 2.2, CH_2Cl_2), ee 22%} and starting material (0.16 g, 39%). δ_H (400.1 MHz) 0.85 (t, *J* 7.0, 3H), 1.27 (d, *J* 6.5, 9H), 1.28 (d, *J* 6.5, 3H), 1.28 (m, 3H), 1.45 (m, 1H), 1.58 (m, 1H), 1.79 (t, *J* 8.5, 1H), 1.95 (m, 1H), 2.67 (dddd, *J* 3.5, 8.5, 10.0, 15.1, 1H), 4.70 (m, 2H); δ_C (100.6 MHz) 13.8, 22.1, 23.87 (d, *J* 5.4), 23.89 (d, *J* 5.4), 24.1 (d, *J* 6.9), 24.3 (d, *J* 6.9), 29.3 (d, *J* 12.2), 31.7 (d, *J* 1.5), 34.8 (d, *J* 150.7), 71.2 (d, *J* 7.6), 71.4 (d, *J* 6.9); δ_P (162 MHz) 25.9; IR (Si): ν_{max} 2978, 2934, 2873, 1467, 1385, 1375, 1247, 1107, 1010, 986 cm^{-1}; $C_{11}H_{25}O_3PS$ (268.35): calcd. C 49.23, H 9.39; found: C 49.48, H 9.36.

(±)-Diisopropyl 1-mercaptohexylphosphonate [(±)-18c]. Thiophosphate **15c** (0.42 g, 1.5 mmol) was rearranged according to general procedure B (reaction time: 2 h). Flash chromatography (hexane-EtOAc 5 : 1, R_f 0.12 for 4 : 1) of the crude product furnished (±)-**18c** (0.16 g, 38%) as a colourless liquid; δ_H (400.1 MHz) 0.83 (t, *J* 6.8, 3H), 1.27 (d, *J* 6.1, 9H), 1.28 (d, *J* 6.1, 3H), 1.29 (m, 3H), 1.46 (m, 2H), 1.60 (m, 2H), 1.80 (t, *J* 8.6, 1H), 1.94 (m, 1H), 2.67 (dddd, *J* 3.5, 8.3, 10.2, 18.7, 1H), 4.70 (m, 2H); δ_C (100.6 MHz) 14.0, 22.4, 23.8 (d, *J* 2.3), 23.9 (d, *J* 2.3), 24.1 (d, *J* 3.1), 24.2 (d, *J* 3.1), 26.8 (d, *J* 12.2) 31.1, 32.0 (d, *J* 1.5) 34.8 (d, *J* 150.7), 71.2 (d, *J* 7.7), 71.4 (d, *J* 6.9); δ_P (162 MHz) 25.9; IR (Si): ν_{max} 2978, 2958, 2932, 1385, 1375, 1241, 1010, 988 cm^{-1}; $C_{12}H_{27}O_3PS$ (282.38): calcd. C 51.04, H 9.64; found: C 51.25, H 9.46.

(+)-Diisopropyl 1-mercapto-[1-D_1]hexylphosphonate {(+)-[1-D_1]18c}. Deuterated *S*-hexyl thiophosphate (*R*)-[1-D_1]**15c** (0.81 mmol, 0.23 g) was isomerised by general procedure B (LiTMP, −45 °C/6 h). Flash chromatography (hexane-EtOAc 5 : 1, R_f 0.41 for 3 : 1) gave recovered thiophosphate (0.008 g, 4%) and (+)-[1-D_1]**18c** (0.10 g, 44%) as a colourless oil; $[\alpha]_D^{20}$ +21.32 (*c* 1.60, CH_2Cl_2), ee 86% (determined by using 2 equiv. of (*S*)-(+)-*t*-butylphenylmonothiophosphinic acid as CSA, C_6D_6, ^1H and ^{31}P NMR); D 93%, k_H/k_D 13.3.

Similarly, an experiment performed at 0 °C for 2 h yielded (+)-[1-D_1]**18c** (0.042 g, 31%); $[\alpha]_D^{20}$ +16.04 (*c* 2.08, CH_2Cl_2); ee 79%; D 88%; k_H/k_D 7.3.

The spectroscopic data of (+)-[1-D_1]**18c** were identical to those of (±)-**18c** except for δ_H (400.1 MHz) 1.82 (d, *J* 8.8, 1H) and 2.57 (missing signal) and δ_C (100.6 MHz) 31.9 (d, *J* 2.3) and 34.3 (dt, *J* 22.2, 150.7, CDP).

(±)-Diisopropyl 1-mercapto-1-phenylmethylphosphonate [(±)-18d]. Thiophosphate **15d** (0.43 g, 1.5 mmol) was rearranged according to general procedure B (reaction time: 7.5 h). Flash chromatography (hexane-EtOAc 4 : 1, R_f 0.26 for 3 : 1) of the crude product furnished (±)-**18d**[6] (0.15 g, 35%) as a colourless liquid and starting material (0.075 g, 17%).

15d (0.43 g, 1.5 mmol) was also rearranged according to general procedure C (reaction time: 16 h/−78 °C). Flash chromatography (hexane-EtOAc 5 : 1) of the crude product furnished (±)-**18d** (0.14 g, 32%) and starting material (0.020 g, 5%). The analytical data of (±)-**18d** (see ESI†) agreed with those of the literature.[6]

(±)-Diisopropyl 1-mercapto-2-methylpropylphosphonate [(±)-18e]. Thiophosphate **15e** (0.38 g, 1.5 mmol) was rearranged according to general procedure B (reaction time: 7 h). Flash chromatography (hexane-EtOAc 6 : 1, R_f 0.15 for 4 : 1) of the crude product furnished (±)-**18e** (0.16 g, 42%) as a colourless liquid and starting material (0.05 g, 13%); δ_H (400.1 MHz) 0.94 (d, *J* 6.5, 3H), 0.98 (dd, *J* 1.5, 6.5, 3H), 1.27 (d, *J* 6.3, 9H), 1.28 (d, *J* 6.0, 3H), 1.63 (t, *J* 10.6, 1H), 2.32 (ddsept, *J* 3.0, 6.5, 8.3, 1H), 2.66 (ddd, *J* 3.0, 10.6, 19.5, 1H), 4.70 (m, 2H); δ_C (100.6 MHz) 17.4 (d, *J* 2.3), 21.5 (d, *J* 15.3), 23.8 (d, *J* 5.4), 23.9 (d, *J* 5.4), 24.1 (d, *J* 3.1), 24.3 (d, *J* 3.1), 28.6, 42.0 (d, *J* 147.6), 71.0 (d, *J* 7.6), 71.5 (d, *J* 7.6); δ_P (162 MHz) 25.2; IR (Si): ν_{max} 2978, 2933, 1386, 1374, 1247, 988 cm^{-1}; $C_{10}H_{23}O_3PS$ (254.33): calcd. C 47.23, H 9.12; found: C 47.34, H 8.44.

(±)-Di-*t*-butyl 1-mercapto-2-methylpropylphosphonate [(±)-18f]. Thiophosphate **15f** (0.42 g, 1.5 mmol) was rearranged according to general procedure B (reaction time: 8 h). Flash chromatography (hexane-EtOAc 6 : 1, R_f 0.13 for 4 : 1) of the crude product furnished (±)-**18f** (0.010 g, 3%) as a colourless oil; δ_H (250.1 MHz) 1.03 (d, *J* 6.6, 3H), 1.08 (dd, *J* 1.5, 6.6, 3H), 1.54 (s, 9H), 1.55 (s, 9H), 1.69 (dd, *J* 9.4, 11.9, 1H), 2.41 (m, 1H), 2.67 (ddd, *J* 3.4, 9.4, 18.0, 1H); δ_C (100.6 MHz) 17.6 (d, *J* 3.1), 22.2 (d, *J* 14.5), 29.0, 29.7 (2C), 30.4 (d, *J* 3.8, 3C), 30.5 (d, *J* 3.8, 3C), 44.3 (d, *J* 149.9); δ_P (162 MHz) 18.4; IR (Si): ν_{max} 2962, 2928, 1369, 1261, 1038, 1009, 983 cm^{-1}.

(*R*)-(−)- and (*S*)-(+)-diisopropyl 1-hydroxyhexylphosphonate {(*R*)-(−)- and (*S*)-(+)-25}. Racemic phosphonate (±)-**25**[23] (3.2 g, 12 mmol) was acetylated[22] and purified by flash chromatography (CH_2Cl_2-EtOAc 2 : 1, R_f 0.67) and bulb to bulb distillation (90–130 °C/0.8 mbar) to give the acetate[24] (3.58 g, 97%). The spectroscopic data were identical to those of the literature.[24] Racemic α-acetoxyphosphonate (3.42 g, 11.1 mmol) were kinetically resolved at room temperature (50 mL of 50 mM phosphate buffer, 17 mL of hexane, 6 ml of *t*-BuOMe, 0.6 g of AP 6, pH kept constant with an autotitrator using 0.5 M NaOH, conversion: 45%). Flash chromatography (hexane-EtOAc 1 : 1, R_f 0.61 and 0.40 for α-acetoxyphosphonate and α-hydroxyphosphonate, respectively, for 1 : 2) of the crude mixture gave recovered α-acetoxyphosphonate {1.82 g (53%), $[\alpha]_D^{20}$ −16.01 (*c* 3.04, acetone)} and α-hydroxyphosphonate (*S*)-(+)-**25** {0.62 g (21%), $[\alpha]_D^{20}$ +12.50 (*c* 1.48, acetone), ee 88% by ^{31}P NMR[24] of (*R*)-Mosher ester}. The α-acetoxyphosphonate (1.58 g, 5.44 mmol) was transesterified (mixture of 54.4 mL of MeOH, 2.72 mL of H_2O and 10.88 mL of Et_3N, ambient). Concentration of the reaction mixture after 48 h *in vacuo* and flash chromatography (hexane-EtOAc 1 : 1, R_f 0.40 for 1 : 2) gave (*R*)-(−)-**25** {1.28 g, 88%, $[\alpha]_D^{20}$ −6.89 (*c* 1.93, acetone), ee 53% by ^{31}P NMR of (*R*)-Mosher ester}.

(*R*)-(−)- and (*S*)-(+)-*O*,*O*-diisopropyl 1-(*p*-nitrobenzene-sulfonyloxy)hexylphosphonate [(*R*)-(−)- and (*S*)-(+)-26]. Freshly distilled Et_3N (0.75 mL) and 0.06 g DMAP dissolved in dry CH_2Cl_2 (1 mL) were added to a solution of α-hydroxyphosphonate (*R*)-(−)-**25** (0.53 g, 2 mmol) in dry CH_2Cl_2 (7 mL) under argon.[6] Then *p*-nitrobenzenesulfonyl chloride (0.53 g, 2.4 mmol, 1.2 equiv., dissolved in 2 mL of dry CH_2Cl_2) was added at 0 °C. After stirring for 22 h at room temperature, H_2O (5 mL) and concentrated HCl (0.8 mL) were added. The organic phase was separated and the aqueous one extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane-EtOAc 3 : 1, R_f 0.50 for 2 : 1) to give nosylate (*R*)-(−)-**26** (0.85 g, 94%) as a colourless oil; $[\alpha]_D^{20}$ −4.29 (*c* 1.17, acetone).

Similarly, (*S*)-(+)-**25** (0.53 g, 2 mmol) was converted to (*S*)-(+)-**26** (0.81 g, 90%); $[\alpha]_D^{20}$ +10.76 (*c* 1.05, acetone).

δ_H (400.1 MHz) 0.80 (t, *J* 6.8, 3H), 1.18 (d, *J* 6.6, 3H), 1.20 (d, *J* 6.6, 3H), 1.21 (m, 4H), 1.24 (d, *J* 6.6, 6H), 1.39 (m, 2H), 1.80 (m, 2H), 4.57 (dsept, *J* 6.6, 7.1, 1 H), 4.64 (dsept, *J* 6.6, 7.1, 1H), 4.82 (dt, *J* 4.6, 9.0, 1H), 8.21 (AA′BB′-system, *J* 8.9, 4H); δ_C (100.6 MHz) 13.9, 22.3, 23.7 (d, *J* 5.4), 23.9 (d, *J* 5.4), 24.00 (d, *J* 4.6), 24.04 (d, *J* 3.8), 25.1 (d, *J* 9.9), 30.4, 31.1, 72.1 (d, *J* 7.7), 72.2 (d, *J* 6.9), 78.6 (d, *J* 170.6), 124.1 (2C), 129.3 (2C), 142.9, 150.7; δ_P (162 MHz) 16.3; IR (Si): ν_{max} 2981, 2958, 2934, 1535, 1376, 1351, 1313, 1187, 993 cm^{-1}; $C_{18}H_{30}NO_8PS$ (451.47): calcd. C 47.89, H 6.70, N 3.10; found: C 47.68, H 6.50, N 3.07.

(*R*)-(+)- and (*S*)-(−)-diisopropyl 1-thiocyanatohexylphosphonate [(*R*)-(+)- and (*S*)-(−)-27]. A mixture of *p*-nitrobenzenesulfonate (*R*)-(−)-**26** (0.73 g, 1.62 mmol), KSCN (0.63 g, 6.48 mmol, 4 equiv.), 18-crown-6 (0.17 g) and dry CH_3CN (15 mL) was refluxed for 23 h under argon.[6] After cooling and addition of water (10 mL), the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was flash chromatographed (hexane/EtOAc 2 : 1, R_f 0.65 for 1 : 1) to yield thiocyanate (*R*)-(+)-**27** (0.42 g (84%) as an oil; $[\alpha]_D^{20}$ +5.80 (*c* 2.47, acetone).

Similarly, (*S*)-(+)-**26** (0.73 g, 1.62 mmol) was converted to thiocyanate (*S*)-(−)-**27** (0.42 g, 84%); $[\alpha]_D^{20}$ −10.55 (*c* 2.82, acetone).

δ_H (400.1 MHz) 0.85 (t, *J* 6.8, 3H), 1.25 (m, 4H), 1.31 (d, *J* 6.3, 12H), 1.44 (m, 1H), 1.63 (m, 1H), 1,76 (m, 1H), 2.09 (m, 1H), 2.94 (ddd, *J* 4.2, 10.3, 15.4, 1H), 4.72 (m, 2H); δ_C (100.6 MHz) 13.9, 22.3, 23.8 (d, *J* 4.6), 23.9 (d, *J* 4.6), 24.0 (d, *J* 3.8), 24.0 (d, *J* 3.8), 26.6 (d, *J* 10.7), 29.5, 30.9, 43.4 (d, *J* 150.7), 72.4 (d, *J* 6.9), 72.5 (d, *J* 7.7), 110.3 (d, *J* 4.6); δ_P (162 MHz) 20.1; IR (Si): ν_{max} 2980, 2959, 2933, 2873, 2155, 1467, 1387, 1376, 1256, 1105, 990 cm^{-1}; $C_{13}H_{26}NO_3PS$ (307.39): calcd. C 50.80, H 8.53, N 4.56; found: C 50.74, H 8.43, N 4.50.

(*R*)-(+)- and (*S*)-(−)-diisopropyl 1-mercaptohexylphosphonate [(*R*)-(+)- and (*S*)-(−)-18c]. A solution of thiocyanate (*R*)-(+)-**27** (0.098 g, 0.32 mmol) and TMSCl (0.17 g, 1.59 mmol. 0.20 mL, 5 equiv.) in dry THF (4 mL) was added dropwise to a stirred solution of $LiBH_4$ (0.020 g, 1.59 mmol, 5 equiv.) in dry THF (4 mL) under argon at room temperature.[6] After stirring for 3 h, the mixture was poured into HCl (10 mL, 2 M, 0 °C) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash chromatography (hexane-EtOAc 3 : 1, R_f 0.75 for 1 : 1) to yield α-mercaptophosphonate (*R*)-(+)-**18c** (0.075 g, 83%) as an oil; $[\alpha]_D^{20}$ +16.23 (*c* 1.06, CH_2Cl_2), ee 54% (2 equiv. of CSA, C_6D_6, ^1H and ^{31}P NMR).

Similarly, thiocyanate (*S*)-(−)-**27** (0.098 g, 0.32 mmol) was converted to α-mercaptophosphonate (*S*)-(−)-**18c** (0.073 g, 81%); $[\alpha]_D^{20}$ −32.51 (*c* 2.11, CH_2Cl_2), ee 88%.

The spectroscopic data of the two enantiomers were identical to those of the racemate.

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