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A convenient route to the phosphorus and sulfur stereoisomers of ethyl menthyl (methylsulfinyl)methylphosphonate

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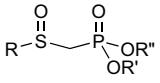
Abstract—The four phosphorus and sulfur stereoisomers of ethyl menthyl (methylsulfinyl)methylphosphonate were obtained by preparing the corresponding sulfides from commercially available diethyl (methylthio)methylphosphonate and subjecting them to a highly diastereoselective hydroperoxide oxidation in the presence of catalytic amounts of a titanium (*R*)- or (*S*)-BINOL complex. The configuration at the sulfur stereogenic centre was assigned by a chemical correlation based upon a displacement reaction with Grignard reagents, whereas the configuration at the phosphorus stereogenic centre was assigned by taking advantage of a reaction sequence based upon the use of menthyl (R_P)-methylphosphonothioic acid as a starting material.

1. Introduction

Chiral nonracemic sulfoxides are widely used intermediates in asymmetric synthesis[1–3] while some of them also have interesting pharmacological activities.[4,5] In connection with our continuing efforts on chiral sulfoxides,[6–12] we reported the synthesis and applications of chiral nonracemic dialkyl (arylsulfinyl)- or (alkylsulfinyl)methylphosphonates (Fig. 1).[6–8]

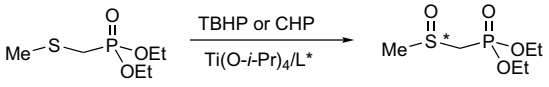


R= aryl, alkyl R', R" = alkyl

Figure 1.

These compounds can be considered structurally related to bisphosphonates.[13] The latter phosphorus compounds represent a family of molecules, which have antiresorbing activities and are currently used against osteoporosis as well as being employed in antitumour therapy.[14] More recently, some bisphosphonates have been reported to display activity against parasitic protozoa of the genera *Trypanosoma*, *Leishmania*, *Toxoplasma* and *Plasmodium*.[15,16]

Dimethyl (*S*)- or (*R*)-(*p*-tolylsulfinyl)methylphosphonate was prepared according to the Andersen procedure or by resolution.[17] Additionally, we have reported[7,8] that diethyl (arylsulfinyl)- or (alkylsulfinyl)methylphosphonates can be produced by an enantioselective oxidation of the corresponding sulfides with hydroperoxides in the presence of a chiral titanium complex. In particular, diethyl (methylsulfinyl)methylphosphonate was obtained with up to 80% ee by using a complex between titanium and diethyl (*R*,*R*)-tartrate (DET)[7] and in >98% ee by performing the oxidation in the presence of a catalytic amount of a complex between titanium and (*S*)- or (*R*)-1,1′-bi-2-naphthol (BINOL)[8] (Scheme 1).



L*= DET or BINOL

Scheme 1.

At variance with other reports,[18,19] the titanium/BINOL catalysed oxidation of sulfides occurred in high yields with the formation of only negligible amounts of sulfone.

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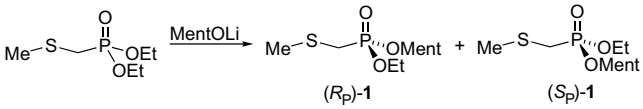
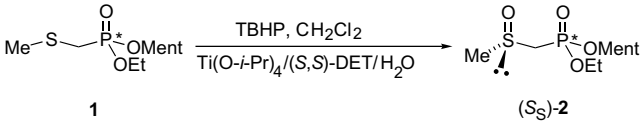
The oxidation process was also performed on ethyl menthyl (methylthio)methylphosphonate, which had a stereogenic phosphorus centre.[7] Indeed, ethyl menthyl (methylthio)methylphosphonate was prepared as a mixture of diastereomers, which were epimeric at the phosphorus centre (Scheme 2). The diastereomers were separated by column chromatography.



Scheme 2.

The prevailing phosphorus stereoisomer was oxidised with cumene hydroperoxide in the presence of a complex between titanium and diethyl (*R*,*R*)- or (*S*,*S*)-tartrate, to yield the corresponding (methylsulfinyl)methylphosphonates **2** (76–82% de).[7] Using diethyl (*S*,*S*)-tartrate as ligand, sulfoxide **2** was obtained in a diastereomerically pure form[7] (>98% de, upon recrystallisation) and was shown to have an (S_S)-configuration (Scheme 3).



Scheme 3.

Furthermore, in view of the results obtained with a sample of a mixture of the four stereoisomers of **2** in some preliminary tests as anticancer agents,[20] we decided to set up a procedure for the synthesis of all these isomers in enantiomerically pure form and with an established configuration at both the heteroatom stereogenic centres, for a better evaluation of their biological properties.

2. Results and discussion

Our strategy directed towards the synthesis of the stereoisomers of compound **2** was developed along the following lines:

1. Synthesis of ethyl menthyl (methylthio)methylphosphonate **1**.
2. Diastereoselective oxidation of ethyl menthyl (methylthio)methylphosphonate **1**.
3. Configuration assignments.

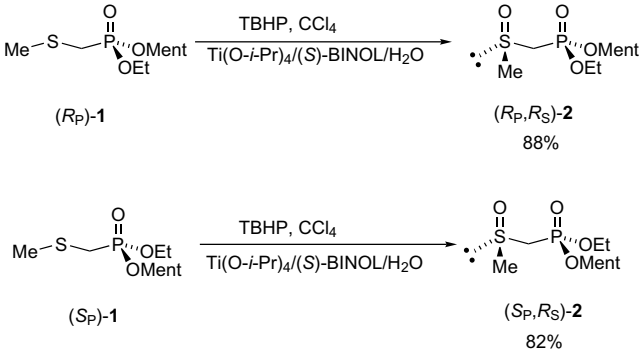
2.1. Synthesis of ethyl menthyl (methylthio)methylphosphonate 1

The diastereomers of the ethyl menthyl (methylthio)methylphosphonate were prepared in a 4:1 ratio by treating a solution of (1*R*,2*S*,5*R*)-(−)-menthol in THF with *n*-butyllithium in *n*-hexane, and then adding a solution of commercially available diethyl (methylthio)methylphosphonate in THF (Scheme 2).[7] Herein we found that, in order to increase the amount of the less abundant isomer, which was necessary for the oxidation process, it is sufficient to reduce the THF/hexane ratio used in the reaction. Indeed, as detailed in the Experimental section, with a suitable ratio of the solvents couple, an almost 1:1 mixture of the sulfides was obtained. The diastereomers can be separated by column chromatography on silica gel. On the basis of the spectral properties (see below, configuration assignments), the (R_P)-configuration can be attributed to the prevailing stereoisomer obtained in the previous work.[7]

2.2. Diastereoselective oxidation of ethyl menthyl (methylthio)methylphosphonate

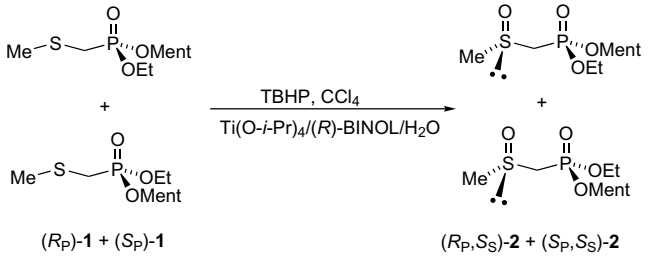
Both stereoisomers of ethyl menthyl (methylthio)methylphosphonate, (R_P)-**1** and (S_P)-**1**, were oxidised with *tert*-butyl hydroperoxide in the presence of a complex between titanium and (*R*)- or (*S*)-BINOL according to our previously reported procedure.[8] Ethyl menthyl (methylsulfinyl)methylphosphonate **2** was obtained in high yield (82–90%) and in high diastereomeric purity (>95% de, >98% de after purification) at the sulfur stereogenic centre. As occurred in the reaction previously reported,[8] in this new highly stereoselective titanium/BINOL catalysed oxidation the amount of sulfone produced was very low (<5%).

We were able to oxidise both (R_P)-**1** and (S_P)-**1** by using (*S*)-BINOL as a chiral ligand, with the formation of (R_P,R_S)-**2** and (S_P,R_S)-**2**, respectively (Scheme 4). The configuration at the sulfur stereogenic centre was attributed by a correlation based upon a stereocontrolled reaction with Grignard reagents (see below).



Scheme 4.

Similar results were obtained in the oxidation performed in the presence of (*R*)-BINOL as a chiral ligand (90% isolated yield, >95% de). However, in this case, rather than separating the sulfides before effecting the oxidation, it was found experimentally more convenient to oxidise the mixture of the sulfides (R_P)-**1** and (S_P)-**1**, and to subject the mixture of the resulting sulfoxides (R_P,S_S)-**2** and (S_P,S_S)-**2** to an easier chromatographic separation (Scheme 5).



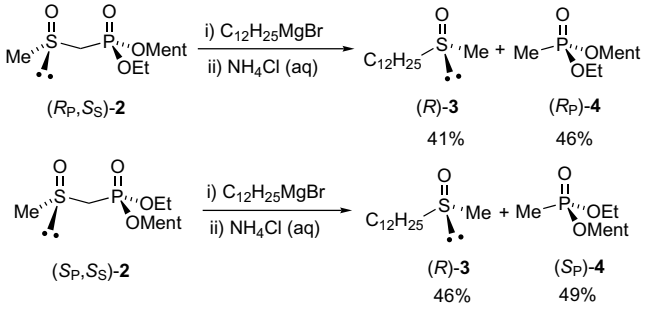
Scheme 5.

Also in this case, the configuration of the sulfur stereogenic centre was attributed by reacting these products with Grignard reagents (see below). Furthermore, (R_P,S_S)-**2** had identical spectral properties with the compound, which had been obtained in a previous work by subjecting the (R_P)-stereoisomer of ethyl menthyl (methylthio)methylphosphonate **1** to a diastereoselective oxidation with cumene hydroperoxide in the presence of a complex between titanium and diethyl (*S*,*S*)-tartrate.[7]

2.3. Configuration assignments

2.3.1. Configuration at the sulfur centre. In our previous work,[8] the diethyl (methylsulfinyl)methylphosphonate obtained from the oxidation in the presence of (*R*)-BINOL was reacted with Grignard reagents. Since the obtained aryl or alkyl methyl sulfoxide had an (*R*)-configuration and these reactions occur with inversion of configuration, an (*S*)-configuration was attributed to the starting material. For example, (*R*)-(−)-*n*-dodecyl methyl sulfoxide **3** can be obtained from diethyl (*S*)-(methylsulfinyl)methylphosphonate. On the other hand, the (*R*)-configuration was attributed to the sulfinylmethylphosphonate obtained in the oxidation, which employed (*S*)-BINOL.

Herein, the sulfinylmethylphosphonates **2** obtained from the oxidation of the sulfides (R_P)-**1** and (S_P)-**1** by using (*R*)-BINOL as a ligand of titanium were reacted with *n*-dodecylmagnesium bromide. (*R*)-(−)-*n*-Dodecyl methyl sulfoxide **3** was produced together with ethyl menthyl (R_P)- or (S_P)-methylphosphonate **4** (Scheme 6).



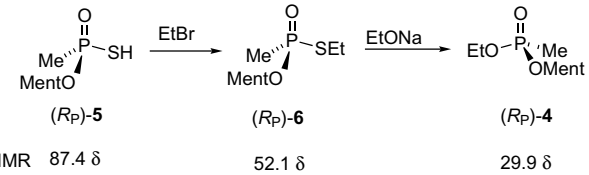
Scheme 6.

Since these reactions occur with inversion of configuration,[7,8] the formation of (*R*)-**3** lead us to the conclusion that the (S_S)-configuration can be attributed to the sulfinylmethylphosphonates **2** used in these reactions. Hence, the *tert*-butyl hydroperoxide oxidation of (methylthio)methylphosphonate in the presence of a complex between titanium and (*R*)-BINOL produced sulfoxides with the (S_S)-configuration, as it had been reported also for the oxidation of the diethyl ester of (methylthio)methylphosphonate.[8] On the other hand, the (R_S)-configuration could be assigned to the (methylsulfinyl)phosphonates, which were obtained in the reaction involving (*S*)-BINOL as a ligand.

2.3.2. Configuration at the phosphorus centre. The configuration at the phosphorus stereogenic centre was attributed by analysing the pair of epimeric ethyl menthyl methylphosphonates **4**. These diastereoisomers had different ^{31}P NMR chemical shift ($\delta = 30.3$ and 29.9). Thus, we decided to prepare (R_P)- or (S_P)-**4** by a different method, in order to compare the spectral properties with the phosphonates, which were produced from the reactions depicted in Scheme 6.

Menthyl methyl (R_P)-methylphosphonate was prepared starting from the resolved menthyl (R_P)-methylphosphonothioic acid **5**.[21] We repeated the same reactions sequence to obtain ethyl menthyl methylphosphonate **4** on a satisfactory scale for NMR analysis. For this purpose, menthyl methylphosphonothioic acid **5** was prepared by treating commercially available methylphosphonothioic dichloride with 1 equiv menthol, according to a procedure used in similar cases.[22] Following a literature protocol,[21,23] compound **5** was partially resolved with (*R*)-phenylethylamine, with formation of a mixture of menthyl (R_P)- and (S_P)-methylphosphonothioic acid in 86% de. We observed that (R_P)-**5**, which is known to be the predominant isomer,[21] had a ^{31}P NMR chemical shift $\delta_P = 87.4$, whereas the signal of the residual (S_P)-isomer was $\delta = 88.7$.

The mixture having (R_P)-**5** as the predominant isomer was alkylated with ethyl bromide resulting in *S*-ethyl *O*-menthyl methylphosphonothioate **6** being produced (Scheme 7). The predominant (R_P)-**6** had a ^{31}P NMR chemical shift $\delta = 52.1$, whereas the signal of the residual (S_P)-isomer was $\delta = 52.8$.



Scheme 7.

S-Ethyl *O*-menthyl methylphosphonothioate **6** was treated with sodium ethoxide according to the literature[21] to give ethyl menthyl methylphosphonate **4** in an almost quantitative yield (97%). This type of reaction

has been reported to occur with full inversion of configuration[21] and, consequently, the predominant (R_P)-**6** should lead to (R_P)-**4** (Scheme 7). Ethyl menthyl (R_P)-methylphosphonate **4**, which was the predominant product of this reaction, had a ^{31}P NMR chemical shift $\delta_P = 29.9$. The signal of the residual (S_P)-isomer was $\delta = 30.3$.

Having clearly established the ^{31}P NMR chemical shift of compounds (R_P)-**4** and (S_P)-**4** (Scheme 7), it was possible to assign the configurations to compounds **4**, which were obtained in the reactions depicted in Scheme 6. Furthermore, the identical phosphorus configuration could then be attributed to the sulfinylmethylphosphonates **2**, which had produced (R_P)-**4** and (S_P)-**4** (Scheme 6) and to the corresponding sulfides (Schemes 4 and 5).

3. Conclusion

According to the protocol reported herein, the four sulfur and phosphorus stereoisomers of ethyl menthyl (methylsulfinyl)methylphosphonate have been prepared by taking advantage of a highly diastereoselective oxidation of the corresponding sulfides conducted in the presence of catalytic amounts of a titanium/BINOL complex. The configuration of both sulfur and phosphorus stereogenic centres were unambiguously established through a correlation involving compounds and reactions of known stereochemistry. In view of the results of the preliminary tests performed on the mixture of stereoisomers **2**,[20] the same compounds obtained in a pure stereochemical form appear now of undoubted interest from a pharmacological point of view.

4. Experimental

The purified reaction products were characterised by ^{1}H, ^{13}C and ^{31}P NMR spectra, recorded in $CDCl_3$ at 500, 125 and 202 MHz, respectively. Their mass spectra were determined by GC/MS analysis (SE30, 30 m, capillary columns and Mass Selective Detector, 70 eV). The composition of the diastereoisomeric mixtures of **1** was determined by GC analysis (capillary column, SE30).

4.1. Synthesis of ethyl menthyl (methylthio)methylphosphonate 1

A ca. 1:1 diastereomers mixture was prepared according to the following protocol. A solution (25.3 mL) of *n*-BuLi (1.6 M in hexane) was added at 0 °C to a solution of 6.3 g (40.4 mmol) of (1*R*,2*S*,5*R*)-(−)-menthol in 70 mL of anhydrous THF. After 10 min stirring, a solution of 4 g of commercially available diethyl (methylthio)methylphosphonate (20.2 mmol) in 20 mL of anhydrous THF was added. The mixture was stirred at rt for 24 h, and then quenched with a saturated NH_4Cl solution. The mixture was extracted with methylene chloride and the extracts dried and evaporated. The excess menthol was distilled off by a Kugelrohr distillation ($T = 60$–65 °C, $p = 3 \times 10^{-4}$ mbar). The two diastereomeric sulfides were obtained in a ca. 1:1 mixture (77% overall yield) and were separated by column chromatography (silica gel, eluent petroleum ether/ethyl acetate 7:3).

4.1.1. Ethyl menthyl (S_P)-(methylthio)methylphosphonate 1 (first eluted stereoisomer). Colourless liquid. $[\alpha]_D^{25} = -78.5$ (*c* 1, $CHCl_3$). MS 70 eV *m*/*e* (relative intensity) 308 (M^+, 5), 171 (46), 170 (56), 143 (25), 124 (100), 97 (29). ^{1}H NMR ($CDCl_3$, 500 MHz) 4.24 (ddt, $J = 4.5$, $J = 7.1$, $J = 10.8$ Hz, 1H), 4.15 (ddq, $J = 7.7$, $J = 10.0$, $J = 7.1$ Hz, 1H), 4.11 (ddq, $J = 7.3$, $J = 10.0$, $J = 7.1$ Hz, 1H), 2.70–2.59 (m, 2H), 2.25 (d, $J = 1.2$ Hz, 3H), 2.19–2.14 (m, 1H), 2.13–2.07 (m, 1H), 1.65–1.59 (m, 2H), 1.48–1.38 (m, 2H), 1.31 (td, $J = 7.1$, $J = 0.5$ Hz, 3H), 1.13 (q-like, $J = 12.6$ Hz, 1H), 1.02–0.92 (m, 1H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 7.2$ Hz, 3H), 0.85–0.80 (m, 1H), 0.78 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 78.04 (d, $J = 7.9$ Hz), 62.40 (d, $J = 6.2$ Hz), 48.47 (d, $J = 7.3$ Hz), 43.41, 34.01, 31.50, 27.85, (d, $J = 151.9$ Hz), 25.59, 22.80, 21.98, 20.98, 17.43, 16.44 (d, $J = 6.4$ Hz), 15.74. ^{31}P NMR ($CDCl_3$, 202 MHz) 24.2. Anal. Calcd for $C_{14}H_{29}O_3PS$: C, 54.52; H, 9.48. Found: C, 54.38; H, 9.22.

4.1.2. Ethyl menthyl (R_P)-(methylthio)methylphosphonate 1 (second eluted stereoisomer). ^{31}P NMR ($CDCl_3$, 202 MHz) 24.0. Other spectroscopic and physical data were identical to those reported.[7]

4.2. Diastereoselective oxidation of ethyl menthyl (methylthio)methylphosphonate with *tert*-butyl hydroperoxide in the presence of a titanium/BINOL complex. Representative procedure

A solution of Ti(O-*i*-Pr)$_4$ (35 mg, 0.12 mmol) in 20 mL of CCl_4 was added to a solution of (*R*)- or (*S*)-1,1′-bi-2-naphthol (70 mg, 0.24 mmol) in 10 mL of CCl_4. Water (44 μL) was then added and the mixture stirred for 1 h at rt. After addition of 1.5 g of sulfide **1** (4.86 mmol) in 20 mL of CCl_4, the mixture was stirred for 30 min. A commercial 80% solution (0.7 mL) of *tert*-butyl hydroperoxide (in di-*tert*-butylperoxide/water 3:2) were then added. After stirring the mixture at rt for 5 h, the solvent was removed in vacuo. The crude reaction mixture was separated by column chromatography (silica gel, eluent ethyl acetate/petroleum ether 9:1) and the obtained products crystallised.

4.2.1. Ethyl menthyl (R_P,R_S)-(methylsulfinyl)methylphosphonate 2. White solid. mp 103–105 °C (hexane) $[\alpha]_D^{25} = +4.1$ (*c* 1, $CHCl_3$). MS 70 eV *m*/*e* (relative intensity) 187 (100), 170 (8), 124 (54), 97 (65), 61 (90). ^{1}H NMR ($CDCl_3$, 500 MHz) 4.28 (ddt, $J = 4.4$, $J = 7.4$, $J = 10.8$ Hz, 1H), 4.19 (ddq, $J = 8.1$, $J = 10.1$, $J = 7.0$ Hz, 1H), 4.14 (ddq, $J = 7.8$, $J = 10.1$, $J = 7.0$ Hz, 1H), 3.36 (ddd, $J = 18.2$, $J = 14.1$, $J = 0.7$ Hz, 1H), 3.21 (t-like, $J = 14.1$ Hz, 1H), 2.84

(d, $J = 0.7$ Hz, 3H), 2.20–2.14 (m, 1H), 2.09–2.00 (m, 1H), 1.69–1.62 (m, 3H), 1.49–1.40 (m, 1H), 1.34 (dt, $J = 0.5$ Hz, $J = 7.0$, 3H), 1.19 (q-like, $J = 12.1$ Hz, 1H), 1.03–0.93 (m, 1H), 0.91 (d, $J = 6.6$ Hz, 6H), 0.88–0.81 (m, 1H), 0.79 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 79.25 (d, $J = 8.0$ Hz), 62.93 (d, $J = 7.2$ Hz), 53.09 (d, $J = 134.5$ Hz), 48.29 (d, $J = 6.3$ Hz), 43.09, 41.32 (broad), 33.84, 31.56, 25.62, 22.79, 21.84, 20.83, 16.33 (d, $J = 6.3$ Hz), 15.57 ppm. ^{31}P NMR ($CDCl_3$, 202 MHz) 15.0. Anal. Calcd for $C_{14}H_{29}O_4PS$: C, 51.83; H, 9.01. Found: C, 52.16; H, 9.11.

4.2.2. Ethyl menthyl (S_P,R_S)-(methylsulfinyl)methylphosphonate 2. White solid. mp 63–65 °C (pentane) $[\alpha]_D^{25} = -6.3$ (c 1, $CHCl_3$). MS 70 eV m/e (relative intensity) 187 (100), 170 (11), 124 (60), 97 (66), 61 (99). ^{1}H NMR ($CDCl_3$, 500 MHz) 4.29 (ddt, $J = 4.5$, $J = 7.2$, $J = 10.8$ Hz, 1H), 4.15 (ddq, $J = 8.0$, $J = 10.1$, $J = 7.1$ Hz, 1H), 4.12 (ddq, $J = 8.0$, $J = 10.1$, $J = 7.1$ Hz, 1H), 3.34 (ddd, $J = 17.9$, $J = 14.2$, $J = 0.8$ Hz, 1H), 3.24 (t-like, $J = 13.9$ Hz, 1H), 2.84 (d, $J = 0.8$ Hz, 3H), 2.16–2.11 (m, 1H), 2.08–2.02 (m, 1H), 1.69–1.62 (m, 3H), 1.49–1.39 (m, 1H), 1.34 (dt, $J = 0.5$ Hz, $J = 7.1$, 3H), 1.17 (q-like, $J = 11.9$ Hz, 1H), 1.04–0.93 (m, 1H), 0.90 (d, $J = 7.0$ Hz, 6H), 0.88–0.81 (m, 1H), 0.79 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 79.14 (d, $J = 7.7$ Hz), 62.79 (d, $J = 6.4$ Hz), 51.93 (d, $J = 136.5$ Hz), 48.33 (d, $J = 7.2$ Hz), 43.27, 41.25 (broad), 33.87, 31.54, 25.71, 22.72, 21.92, 20.92, 16.30 (d, $J = 6.4$ Hz), 15.53. ^{31}P NMR ($CDCl_3$, 202 MHz) 15.4. Anal. Calcd for $C_{14}H_{29}O_4PS$: C, 51.83; H, 9.01. Found: C, 51.45; H, 9.18.

4.2.3. Ethyl menthyl (S_P,S_S)-(methylsulfinyl)methylphosphonate 2 (first eluted stereoisomer). White solid. mp 101–103 °C (hexane) $[\alpha]_D^{25} = -119.7$ (c 1, $CHCl_3$). MS 70 eV m/e (relative intensity) 187 (100), 170 (11), 124 (43), 97 (46), 61 (31). ^{1}H NMR ($CDCl_3$, 500 MHz) 4.27 (ddt, $J = 4.5$, $J = 7.5$, $J = 10.8$ Hz, 1H), 4.18 (ddq, $J = 8.2$, $J = 10.1$, $J = 7.1$ Hz, 1H), 4.11 (ddq, $J = 7.8$, $J = 10.1$, $J = 7.1$ Hz, 1H), 3.36 (ddd, $J = 18.5$, $J = 14.2$, $J = 0.8$ Hz, 1H), 3.23 (t-like, $J = 14.0$ Hz, 1H), 2.84 (d, $J = 0.9$ Hz, 3H), 2.15–2.10 (m, 1H), 2.05–1.97 (m, 1H), 1.69–1.62 (m, 3H), 1.50–1.39 (m, 1H), 1.34 (dt, $J = 0.5$ Hz, $J = 7.1$, 3H), 1.17 (q-like, $J = 12.0$ Hz, 1H), 1.05–0.94 (m, 1H), 0.91 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.88–0.81 (m, 1H), 0.80 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 79.29 (d, $J = 7.8$ Hz), 62.65 (d, $J = 6.5$ Hz), 52.33 (d, $J = 135.7$ Hz), 48.25 (d, $J = 7.2$ Hz), 43.39, 41.43 (d, $J = 2.3$ Hz), 33.87, 31.57, 25.82, 22.77, 21.91, 20.89, 16.30 (d, $J = 6.4$ Hz), 15.60. ^{31}P NMR ($CDCl_3$, 202 MHz) 15.3. Anal. Calcd for $C_{14}H_{29}O_4PS$: C, 51.83; H, 9.01. Found: C, 52.13; H, 8.76.

4.2.4. Ethyl menthyl (R_P,S_S)-(methylsulfinyl)methylphosphonate 2 (second eluted stereoisomer). ^{31}P NMR ($CDCl_3$, 202 MHz) 15.1. Other spectral and physical data were identical to those reported.[7]

4.3. Reaction of ethyl menthyl (methylsulfinyl)methylphosphonates with *n*-dodecylmagnesium bromide

A solution of *n*-dodecylmagnesium bromide in THF was reacted with a solution of the sulfoxide **2** in benzene at 0 °C, according to our previously reported procedure.[6–8] The crude reaction mixture was subjected to a chromatographic separation (silica gel, eluent ethyl acetate/petroleum ether 9:1). Yields of isolated products are reported in Scheme 6.

4.3.1. (*R*)-*n*-Dodecyl methyl sulfoxide 3. White solid. mp 60–62 °C (hexane) (lit.[24] mp 53 °C). $[\alpha]_D^{25} = -62.5$ (c 1, acetone).

4.3.2. Ethyl menthyl (S_P)-methylphosphonate 4. Colourless liquid. $[\alpha]_D^{25} = -58.3$ (c 0.5, $CHCl_3$). MS 70 eV m/e (relative intensity) 125 (100), 123 (7), 97 (65). ^{1}H NMR ($CDCl_3$, 500 MHz) 4.21 (ddt, $J = 4.6$, $J = 7.7$, $J = 10.7$ Hz, 1H), 4.08 (ddq, $J = 7.6$, $J = 10.0$, $J = 7.1$ Hz, 1H), 4.01 (ddq, $J = 7.5$, $J = 10.0$, $J = 7.1$ Hz, 1H), 2.19–2.13 (m, 1H), 2.04–1.99 (m, 1H), 1.67–1.61 (m, 3H), 1.44 (d, $J = 17.4$ Hz, 3H), 1.35–1.25 (m, 4H), 1.11 (q-like, $J = 12.0$ Hz, 1H), 1.03–0.93 (m, 1H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.87–0.82 (m, 1H), 0.80 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 77.14 (d, $J = 7.3$ Hz), 61.03 (d, $J = 6.4$ Hz), 48.43 (d, $J = 7.4$ Hz), 43.45, 34.07, 31.45, 25.63, 22.84, 21.98, 20.95, 16.33 (d, $J = 6.5$ Hz), 15.69, 11.67 (d, $J = 145.4$ Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) 30.3. Anal. Calcd for $C_{13}H_{27}O_3P$: C, 59.52; H, 10.37. Found: C, 59.82; H, 10.01.

4.3.3. Ethyl menthyl (R_P)-methylphosphonate 4. Colourless liquid. $[\alpha]_D^{25} = -59.8$ (c 0.5, $CHCl_3$). MS 70 eV m/e (relative intensity) 125 (100), 123 (7), 97 (75). ^{1}H NMR ($CDCl_3$, 500 MHz) 4.18 (ddt, $J = 4.4$, $J = 7.8$, $J = 10.7$ Hz, 1H), 4.10 (ddq, $J = 7.5$, $J = 10.1$, $J = 7.0$ Hz, 1H), 4.03 (ddq, $J = 7.8$, $J = 10.1$, $J = 7.0$ Hz, 1H), 2.22–2.19 (m, 1H), 2.14–2.07 (m, 1H), 1.65–1.58 (m, 3H), 1.45 (d, $J = 17.4$ Hz, 3H), 1.32–1.25 (m, 4H), 1.12 (q-like, $J = 11.7$ Hz, 1H), 1.03–0.93 (m, 1H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.87–0.81 (m, 1H), 0.79 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 77.20 (d, $J = 7.2$ Hz), 61.29 (d, $J = 5.6$ Hz), 48.47 (d, $J = 6.6$ Hz), 43.09, 34.04, 31.45, 25.48, 22.79, 21.93, 20.95, 16.40 (d, $J = 6.3$ Hz), 15.64, 12.73 (d, $J = 145.3$ Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) 29.9. Anal. Calcd for $C_{13}H_{27}O_3P$: C, 59.52; H, 10.37. Found: C, 59.39; H, 10.51.

4.4. Synthesis of menthyl methylphosphonothioic acid 5

A solution of menthol (3 g, 19.2 mmol) and triethylamine (2.9 mL) in 30 mL of toluene was added dropwise to a solution of 2 mL of methylphosphonothioic dichloride (19.1 mmol) in 20 mL of toluene. After 18 h at rt, the solvent was removed and the crude reaction mixture treated with 30 mL of an aqueous solution of

NaOH 2 M and with 30 mL of dioxane. The mixture was heated to reflux for 3 h and, after standing for 12 h at rt, was diluted with water and washed with $CHCl_3$. The organic phase was discarded and the aqueous phase acidified by adding dropwise HCl 12 M. The solution was extracted with CH_2Cl_2 and the organic phase dried and evaporated to give 1.6 g of **5** (33%). Compound **5** was subjected to resolution with (*R*)-(+)-phenylethylamine, according to the literature protocol.[21,23]

4.4.1. Menthyl (R_P)-methylphosphonothioic acid 5. White solid. mp 78–80 °C (lit.[21] 82 °C), $[\alpha]_D^{25} = -83.1$ (*c* 1, C_6H_6) for a 86% de {lit.[21] $[\alpha]_D^{25} = -87.3$ (C_6H_6)}.

4.5. Synthesis of *S*-ethyl *O*-menthyl (R_P)-methylphosphonothioate 6

A solution of 0.14 g (0.56 mmol) of acid **5** [(R_P)-**5** predominant] in 4 mL of DMSO was treated with 2.5 mL of a solution of NaOH 0.25 M and then with 0.13 mL of ethyl bromide. After 3 h, the mixture was evaporated and the residue diluted with brine and extracted with CH_2Cl_2. The organic extracts were dried and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 1:1) and then by crystallisation. Yield 39%.

4.5.1. *S*-Ethyl *O*-menthyl (R_P)-methylphosphonothioate 6. White solid. mp 51–53 (pentane), $[\alpha]_D^{25} = -57.8$ (*c* 1, $CHCl_3$) for a 83% de. ^{1}H NMR ($CDCl_3$, 500 MHz) 4.32 (dq, $J = 4.4$, $J = 10.4$ Hz, 1H), 2.90 (ddq, $J = 12.6$, $J = 11.9$, $J = 7.4$ Hz, 1H), 2.84 (tq, $J = 12.6$, J = 7.5 Hz, 1H), 2.28–2.22 (m, 1H), 2.10–2.03 (m, 1H), 1.75 (d, $J = 15.6$ Hz, 3H), 1.69–1.60 (m, 3H), 1.36 (t, $J = 7.5$ Hz, 3H), 1.34–1.26 (m, 1H), 1.11 (q-like, $J = 12.0$ Hz, 1H), 1.06–0.95 (m, 1H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.87–0.82 (m, 1H), 0.81 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) 77.39 (d, $J = 8.8$ Hz), 48.63 (d, $J = 5.6$ Hz), 42.98, 34.06, 31.54, 25.76, 25.08 (d, $J = 2.4$ Hz), 22.94, 22.03, 21.02, 20.77 (d, $J = 110.2$ Hz), 16.54, 15.69 (d, $J = 2.4$ Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) 52.1. Anal. Calcd for $C_{13}H_{27}O_2PS$: C, 56.09; H, 9.78. Found: C, 55.90; H, 9.91.

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