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Synthesis, characterization and resolution of racemic (2-methylsulfinyl)phenylphosphonic acid methyl ester via its cinchoninium salts

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Abstract—The synthesis of new (2-methylsulfinyl)phenylphosphonic acid methyl and dimethyl esters in both racemic and non-racemic forms is reported. Resolution of the racemic phosphonic acid mono-ester **1** was accomplished via diastereomeric salt formation with cinchonine. The absolute stereochemistry of the phosphonic ester products was deduced from asymmetric sulfoxidation experiments and confirmed by chemical correlation with (*S*)-(−)-2-methylsulfinylaniline. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Since Goldberg's pioneering work,[1] optically active sulfoxides have attracted considerable interest as auxiliaries in asymmetric synthesis[2] and as promising ligands in reactions involving transition metal complexes.[3] Complexes with chelating sulfoxides are expected to play a major role in catalytic processes.[4–6] Over the last few years, special attention has been paid to the search for new platinum complexes related to cisplatin and carboplatin that would offer more favorable anti-tumor activity.[7–9] In this particular area, methylsulfinyl-carboxylates as leaving bidentate ligands have been described by Pasini et al.[10] and cationic diamine–platinum(II) complexes linked to amino phosphonic acids were developed by Klenner and his group.[11] In connection with our studies on mixed phosphorus–sulfur compounds[12–14] and given the isosteric nature of the carboxylic and phosphonic acid groups, we anticipated that (2-methylsulfinyl)phenylphosphonic acid methyl ester **1**, together with its dimethyl analog **2**, could display similar coordination chemistry (Fig. 1).

As phosphorus-based members of thiosalicylic acid derivatives, structures **1** and **2** have a chiral sulfinyl center. Therefore, it is believed that their biological properties would depend on their stereochemistry. Moreover, in order to make use of *o*-phosphonophenyl sulfoxides as chiral ligands in asymmetric synthesis, these compounds must be easily available in enantiomerically pure form. Herein we report the synthesis of the enantiopure form of the phosphonic acid di-ester **2** by resolution of the racemic phosphonic acid mono-ester **1** through its cinchoninium salts followed by methylation.


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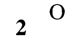
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Figure 1.

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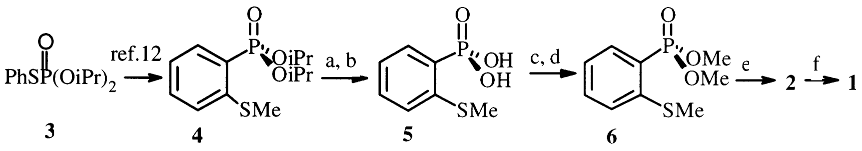
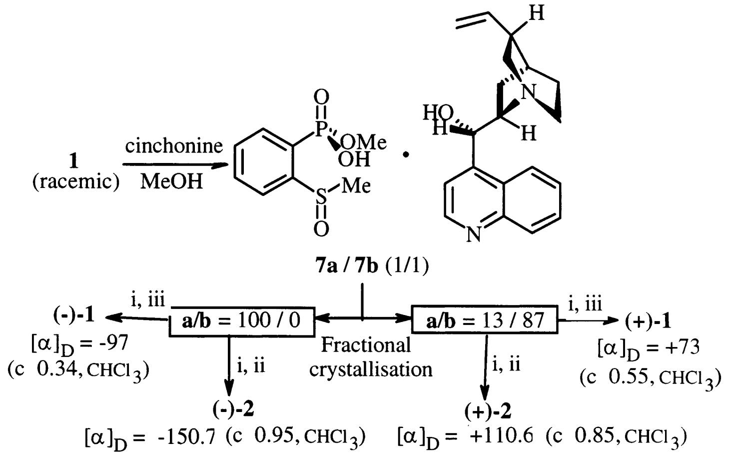


Scheme 1. *Reagents and conditions*: (a) $Me_3SiBr–CH_2Cl_2$; (b) $MeOH–CH_2Cl_2$, rt; (c) $Me_4NOH–H_2O$; (d) MeI–MeCN, Δ; (e) $NaIO_4–Me_2CO–H_2O$; (f) $NaOH–H_2O$–dioxan and HCl.



Scheme 2. *Reagents and conditions*: (i) aq. $NaHCO_3$; (ii) MeI–MeCN; (iii) dilute H_2SO_4.

2. Results and discussion

2.1. Synthesis of racemic methyl phenyl sulfoxides 1 and 2

The general synthetic route is summarized in Scheme 1. The starting material, diisopropyl (2-methyl-sulfanyl)phenylphosphonate **4** was readily accessible from thiophosphate **3** by LDA-mediated phenylthiophosphate–mercaptophenylphosphonate rearrangement,[13] followed by quenching with methyl iodide. Di-ester **4** was then converted into its less hindered dimethyl analog **6** in high yield by means of the elegant *trans*-silylation method developed by McKenna[15,16] and subsequent dimethylation of the tetramethylammonium salt of the phosphonic acid intermediate **5**.

The synthesis of the racemic target **1** was finally achieved via selective oxidation of sulfide **6** with $NaIO_4$ in a mixture of acetone–water and half-hydrolysis under alkaline conditions[17] of the dimethyl phenylphosphonate **2**. Based on **3**, the overall yield of **1** was 55%.

2.2. Resolution of (±)-methyl (2-methylsulfinyl)phenylphosphonic acid 1

As shown in Scheme 2, racemic phenylphosphonic acid mono-ester **1** readily formed diastereomeric salts **7a** and **7b** with cinchonine. Diastereomer **7a**, which was less soluble in acetone than **7b**, was purified by successive recrystallizations until its specific rotation remained constant. Compound **7a** was finally isolated in 25% yield (^{31}P NMR 13.6 ppm). The diastereomerically enriched salt **7b**, recovered from the first mother liquor and recrystallized once, displayed in its ^{31}P NMR spectrum two distinct P-resonances at 13.6 and 14 ppm (**7a**/**7b** = 13/87).

2.3. Optically pure (−)-(2-methylsulfinyl)phenylphosphonic methyl and dimethyl esters 1 and 2

The purified diastereomer **7a**[†] was subsequently mixed with aqueous sodium bicarbonate solution so as to remove cinchonine and the resulting sodium salt was acidified with dilute sulfuric acid yielding the sulfinyl mono-ester (−)-**1** in optically pure form. In contrast, hydrolysis of **7a** with 1N HCl was found, in screening experiments, to occur with a partial racemization of the chiral sulfinyl center affording optically active sulfoxide **1**. This result was not surprising since halide ions are known to catalyze the racemization of sulfoxides.[18,19] More interestingly, the ^1H NMR spectrum (500 MHz) of a $CDCl_3$ solution of this partially resolved sulfoxide **1**, in which the ratio of enantiomers was 88:12, revealed enantiomer self discrimination as judged by the doubling of the multiplicity of S(O)Me and POMe signals. The magnetic non-equivalence value for the S(O)Me protons was observed to be much bigger (ca. 7.7 Hz) than for the P-OMe protons (3.3 Hz). Such behavior can be accounted for by hydrogen-bonded associations in non-polar solvents. This is in agreement with the literature reports dealing with this phenomenon;[20–22] in this case we propose that the observed effect is caused

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[†] The absolute configuration of the chiral sulfur atom was established as (*S*) by X-ray crystallographic analysis of **7a**. However, the calculated R_r value (0.1074) might be deemed too large to draw an unequivocal conclusion.

by the formation of the diastereomeric cyclic dimers **I** and **II** in which the sulfinyl oxygen and phosphonic acid moieties participate in the intermolecular hydrogen bond formation (Fig. 2).

In Table 1 the ^{1}H NMR chemical shifts δ(SOMe) and the magnitude of magnetic non-equivalence, $\Delta\delta$, for different mixtures of (−)- and (+)-enantiomers of *o*-sulfinylated phenylphosphonic acid mono-ester **1** are collected. As a general trend, the minor enantiomer was found to display the SOMe singlet at higher field regardless of its configuration and the chemical shift difference, $\Delta\delta$, decreased as the enantiomers were approaching equimolarity.

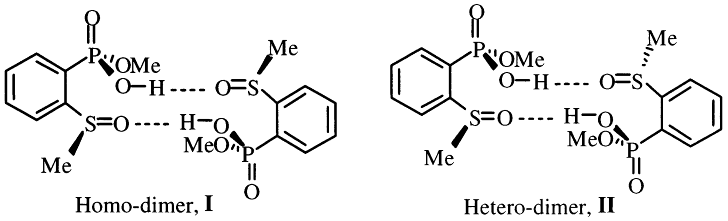
The synthesis of enantiopure sulfinylated phosphonic di-ester **2** was easily achieved by simple reflux of an acetonitrile solution of the sodium salt obtained by basic treatment of **7a** with an excess of methyl iodide. Since the complete inversion of sulfur during the protonation or alkylation process at the phosphonic site is unlikely, it could be deduced that the resulting levorotatory compounds **1** and **2** have the same absolute configuration at sulfur as the diastereomerically pure cinchoninium salt **7a**.

2.4. Non-racemic methyl and dimethyl (+)-(2-methylsulfinyl)phenylphosphonic esters 1 and 2

As also depicted in Scheme 2, the diastereomerically enriched cinchoninium salt **7b** has been similarly converted to optically active sulfoxides **1** and **2**. Both compounds were isolated in high yields with 74% e.e. In sharp contrast to phosphonic mono-ester **1**, phosphonic dimethyl ester **2** did not show any enantiomer self discrimination. The enantiomeric purity of **2** was determined by ^{1}H NMR with (*S*)-(+)-α-methoxyphenylacetic acid (MPAA)[22] as a chiral solvating reagent. When it was added to racemic phosphonate **2**, this reagent caused splitting of the methylsulfinyl and one P-OMe group into two singlets and a double doublet, respectively. Thus, the ^{1}H NMR spectrum of a $CDCl_3$ solution containing (±)-**2** and 3 equiv. of (*S*)-MPAA displayed two sharp singlets of approximately equal intensity at δ 2.81 and 2.82 for the S(O)Me group and three doublets at δ 3.78, 3.79 and 3.82 for the two P-OMe groups (only the upfield doublet was split). Enantiomeric analysis under these standard conditions with a sample of enriched phosphonate (+)-**2** allowed the determination of the e.e. of the latter by integration of the S(O)Me pair signals. The minor (−)-enantiomer gave rise to the low-field methylsulfinyl resonance. This is in contrast to the conclusion reached by Buist[23] with various sulfoxides. In attempting to deduce the absolute configuration of the predominant (+)-**2** enantiomer through the use of (*S*)-MPAA, we suggest that the phosphonate group *ortho* to the phenylsulfinyl group is involved in the formation of hydrogen-bonded complexes. Structures like **III** and **IV** may rationalize the observed effect (Fig. 3, the dashed lines indicate H-bonds). Accordingly, (+)-**2** would be of (*R*) configuration.

2.5. Asymmetric oxidation of dimethyl (2-methylsulfanyl)phenylphosphonate 6

To establish a relationship between the chirality at sulfur and a sign of optical rotation within *o*-(*O*-dimethylphosphonyl)phenyl methyl sulfoxide **2** (and hence of the acid **1**), we briefly studied the asymmetric oxidation of its sulfide precursor **6**. Three methods, known to give sulfoxides with predictable stereoselectivities, were screened. Oxidation of **6** was performed, firstly, by the Sharpless-modified reagent (method A), following a procedure described by Kagan et al.[24] with either 2 equiv. of cumene or *tert*-butyl hydroperoxide (CHP and TBHP, respectively) in the presence of a stoichiometric amount of water-modified titanium complex and (*R*,*R*)-(+)-diethyl tartrate: [Ti(*O*-*i*Pr)$_4$–(+)-DET–H_2O = 1:2:1] in CH_2Cl_2 at −20°C; secondly, with



Homo-dimer, **I**

Hetero-dimer, **II**

Figure 2.

Table 1. ^{1}H NMR chemical shifts for SOMe signals of mixtures of enantiomers of **1**[a]

$[\alpha]_D$	Opt. purity	δ (+)-SOMe	δ (−)-SOMe	$\Delta\delta$ (ppm/Hz)	E.e. (%)
−97.0	100	–	2.822	0	100
−59.7	61.5	2.795	2.808	0.013/6.5	62
−41.2	42.4	2.797	2.804	0.007/3.5	42
0	0	2.801	2.801	0	0
+21.9	22.6	2.802	2.799	0.003/1.5	22
+72.0	74.2	2.811	2.796	0.015/7.5	74

[a] Approximately 0.14 M $CDCl_3$ solution, $CHCl_3$ signal adjusted to 7.260 ppm, measured at 500 MHz.

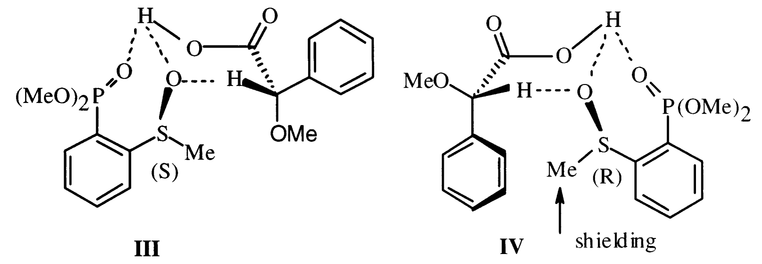
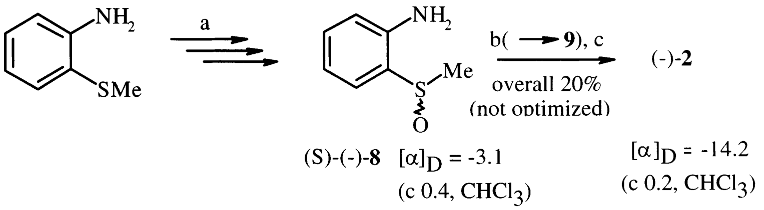


Figure 3.

Table 2. Enantioselective oxidation of sulfide **6** into sulfoxide **2**: comparative data[a]

Method	Time (h)	Yield (%)	E.e. (%)	$[\alpha]_D$	Config.
A (CHP)	48	76	15	+23.1	*R*
A (TBHP)	72	80	32	+48.4	*R*
B (CH_2Cl_2)	15	72	57	−85.9	*S*
B (CCl_4)	25	82	73	−110.5	*S*
C	16	77	30	−44.9	*S*

[a] Configurations were deduced from the predictable sense of induction based on the chirality of the oxidizing system.



Scheme 3. *Reagents and conditions*: (a) see Ref. 27 (BzOOH was replaced by mCPBA); (b) $NaNO_2$ in AcOH–H_2O, 0°C, 30 min then aq. KI; (c) $NaP(O)(OMe)_2$, THF–MeCN, 20°C, hν.

a chiral Davis' oxaziridine[25] (method B), using (+)-(2*R*,8a*S*)-8,8-dichloro-(camphorylsulfonyl)-oxaziridine in either CH_2Cl_2 or CCl_4 at room temperature; and thirdly, with a chiral metal/Schiff base[26] (method C), using 0.25 mol% of the catalyst formed in situ from $[VO(acac)_2]$ (acac = acetylacetonate) and a chiral ligand derived from (*S*)-*tert*-leucinol and 3,5-di-*tert*-butyl salicylic aldehyde. This reaction took place at room temperature in dichloromethane with hydrogen peroxide as the oxygen source. The results of these experiments are summarized in Table 2.

If the absolute configuration at sulfur is controlled by the chirality of the oxidizing systems used in methods A–C, meaning that these results are consistent with those reported for many aryl methyl sulfoxides including methyl 2-methylsulfinylbenzoate, we may conclude that (−)-**2** as well as its resolved acid precursor (−)-**1** have (*S*) configuration The e.e. values were measured by ^1H NMR using (*S*)-MPAA and by specific rotation of purified samples. Chiral methyl phenyl sulfoxide **2** appended with a spatially proximate phosphonate diester group was formed in satisfactory yield by the three methods. Method B, using a chiral oxaziridine, gave the highest (but still moderate) enantiomeric excess (e.e.s of 57–73% were obtained). In methods A and B, the rates of oxidation as well as the level of chiral induction were influenced by the nature of the oxidant and solvent, respectively. The asymmetric oxidation carried out with Kagan's modified Sharpless reagent, method A, proceeded more slowly.

2.6. Absolute configuration of dimethyl (2-methylsulfinyl)phenylphosphonate (−)-2

In order to obtain additional experimental support for the assignment of the absolute configuration of enantiomers of **2**, it was synthesized in two steps starting from the known optically active (*S*)-(−)-2-methylsulfinylaniline **8**. This compound was prepared according to a slightly modified procedure described by Folli et al.,[27] who used perbenzoic acid as an oxidant (see Scheme 3). aUnfortunately, we were unable to improve the diastereomeric purity of (2-methylsulfinyl)anilinium (+)-camphorsulfonate salts by recrystallization, so the mixture was hydrolyzed with aqueous sodium hydroxide solution to yield (*S*)-(−)-**8**. Next, this non-racemic material was diazotized and, upon further treatment with aqueous KI, the resulting 2-iodophenyl methyl sulfoxide **9** was isolated in 55% yield and directly subjected to photophosphonylation with a four-fold excess of sodium dimethylphosphite in a THF/CH_3CN 1:4 mixture at room temperature. Subsequent purification of the mixture by column chromatography provided the desired sulfoxide **2** in 36% yield.

Taking into account the fact that the diazotization as well as the photostimulated nucleophilic substitution

($S_{RN}1$) reactions do not disturb configuration at the sulfinyl center, one can conclude that the levorotatory compound **2** (hence its resolved precursor **1**) has the (*S*) absolute configuration and the dextrorotatory enantiomer the (*R*) configuration. Moreover, this chemical correlation clearly indicates that the stereochemistry of the major component of **2** obtained by asymmetric sulfoxidation of **6** is also controlled by the chirality of the oxidizing agents used (see Table 2).

3. Conclusion

We have shown that the classical resolution via crystallization of diastereomeric salts can be a convenient route for preparing chiral methyl phenyl sulfoxides bearing either the methyl phosphonic acid or dimethyl phosphonate group in the *ortho* position of the aromatic ring. Our present studies have demonstrated that enantiomers of **1** as well as **2** can be distinguished by ^{1}H NMR as a consequence of their strong hydrogen-bonding properties. ^{1}H NMR can also give reliable information regarding the absolute configuration of this class of compound.

Encouraged by these results, we are currently investigating the syntheses of structurally related chiral sulfoxides and their applications as ligands in stoichiometric and catalytic reactions.

4. Experimental

4.1. General

Reactions were carried out under a nitrogen atmosphere and monitored by TLC using silica gel plates. Flash column chromatography was performed on Merck 70–230 mesh silica gel. Organic solvents were dried and distilled prior to use. Commercially available chemicals were not purified. Melting points are uncorrected. The synthesis of compound **4** has been described previously.[12]

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz/^{1}H, 62.9 MHz/^{13}C, in $CDCl_3$ unless otherwise stated, using TMS as internal standard and ^{31}P NMR/101.2 MHz with H_3PO_4 as external standard). Mass spectra were determined with a Nermag R 10 10 H spectrometer (EI = 70 eV); *m*/*z* and relative abundance are given. Optical rotation values were measured on a Perkin–Elmer 241 polarimeter for the sodium D line ($\lambda = 589$ nm) at 20°C. (*S*)-Methoxyphenylacetic acid was used as a shift reagent for enantiomeric excess determination. Satisfactory analytical data were obtained for C, H, O, and P at the Service de Microanalyse ICSN, Gif sur Yvette, or the 'Service Central d'Analyse CNRS', Vernaison, France, and for S at the LCMT, Caen, following Debal and Levy's method (*Bull. Chem. Soc. Fr.* **1968**, 426). HRMS were obtained with a JEOL JMS-AX 500 mass spectrometer.

4.2. (2-Methylsulfanyl)phenylphosphonic acid 5

To a stirred solution of phosphonate **4** (2.88 g, 10 mmol) in CH_2Cl_2 (20 mL) was added dropwise bromotrimethylsilane (5 mL, 39.6 mmol) at room temperature. The reaction was monitored by TLC (petroleum ether–ethyl acetate 1:1). After complete conversion, the solvent was evaporated. A mixture of CH_2Cl_2–MeOH 3:1 was then added to the resulting silylated product. Solvents were removed under reduced pressure affording a white solid (1.96 g, 96%). A sample of the crude phosphonic acid **5** was recrystallized from CH_2Cl_2. Mp 174°C. δ_H (CD_3OD): 2.51 (3H, s, SCH_3), 7.17–7.26 (m, 1H, *Ar*), 7.41–7.54 (2H, m, *Ar*), 7.86 (1H, ddd, $^4J_{HH}$ 1.3, $^3J_{HH}$ 7.4, $^3J_{HP}$ 14.5, *Ar*). δ_P (CD_3OD): 15.2. δ_C (CD_3OD): 16.8 (s, SCH_3), 125.3 (d, $^3J_{CP}$ 13.8, *Ar*), 128.0 (d, $^3J_{CP}$ 12.4, *Ar*), 130.2 (d, $^1J_{CP}$ 188.8, *Ar*), 133.5 (s, *Ar*), 134.0 (d, $^2J_{CP}$ 8.6, *Ar*); 143.8 (d, $^2J_{CP}$ 8.5, *Ar*). Anal. calcd for $C_7H_9O_3PS$: C, 41.18; H, 4.44; P, 15.17. Found: C, 41.19; H, 4.46; P, 15.07%.

4.3. Dimethyl (2-methylsulfanyl)phenylphosphonate 6

The acid **5** (1.02 g, 5 mmol) was dissolved in methanol (10 mL) and neutralized with a 25% aqueous solution of tetramethylammonium hydroxide. After evaporation in vacuo, the remaining salt (δ_P +8.1) was dissolved in CH_3CN (50 mL) and heated overnight at 50°C with an excess of CH_3I (20 mmol). The solvent was removed and the residue extensively washed with CH_2Cl_2. The dichloromethane solution was filtered through Celite. After evaporation, the residue was purified on a silica gel column with EtOAc as eluent to provide pure phosphonate **6** as a pale yellow oil (1.13 g, 98%). δ_H 2.48 (3H, s, SCH_3), 3.77 (6H, d, $^3J_{HP}$ 11.2, $CH_3O\times2$), 7.18 (1H, ddt, $^4J_{HH}$ 1.1, $^4J_{HP}$ 3.4, $^3J_{HH}$ 7.5, *Ar*), 7.24–7.31 and 7.42–7.51 (2H, m, *Ar*), 7.88 (1H, ddd, $^4J_{HH}$ 1.6, $^3J_{HH}$ 7.6, $^3J_{HP}$ 14.5, *Ar*). δ_P 21.7. δ_C 14.9 (s, SCH_3), 51.5 (d, $^2J_{CP}$ 5.4, $CH_3O\times2$), 123.0 (d, $^3J_{CP}$ 14.0, *Ar*), 123.7 (d, $^1J_{CP}$ 188.7, *Ar*), 124.8 (d, $^3J_{CP}$ 13.2, *Ar*), 131.9 (s, *Ar*), 133.7 (d, $^2J_{CP}$ 8.8, *Ar*), 142.4 (d, $^2J_{CP}$ 8.7, *Ar*). Anal. calcd for $C_9H_{13}O_3PS$: C, 46.55; H, 5.64; P, 13.34. Found: C, 46.25; H, 5.57; P, 13.43%.

4.4. Racemic dimethyl (2-methylsulfinyl)phenylphosphonate 2

To a solution of sulfide **6** (1.67 g, 7.2 mmol) in acetone (15 mL) and water (5 mL) was added aqueous $NaIO_4$ (1.7 g, 7.9 mmol) at −5°C over 10 min. The reaction mixture was stirred at 0°C for 1 h and allowed to stand at 5°C overnight. The precipitated salts were filtered off, washed with acetone and discarded. After removal of acetone, the remaining aqueous solution was extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude extract was purified by flash chromatography on silica gel with EtOAc–CH_3OH 19:1 as eluent. Pure sulfoxide **2** was obtained as a pale yellow oil (1.72 g, 96%).

4.5. Racemic methyl (2-methylsulfinyl)phenylphosphonic acid 1

To a solution of sulfoxide **2** (2.5 g, 10 mmol) dissolved in 1,4-dioxane (25 mL) was added dropwise 3 M aqueous sodium hydroxide (12.5 mL). The resulting solution was stirred for 2–3 h at room temperature and then evaporated in vacuo. Water (5 mL) was added and the mixture extracted with CH_2Cl_2 (3×20 mL). The aqueous layer was acidified with dilute HCl and partially concentrated before extracting with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to provide mono-acid **1** as a viscous colorless oil (2.3 g, 98%).

4.6. Resolution of racemic 1 with cinchonine

The acid **1** (3.1 g; 13.5 mmol) and cinchonine (3.8 g, 12.9 mmol) were stirred in methanol (180 mL) for 2 h. The solution was concentrated under reduced pressure. The cinchoninium salts **7a/b** were obtained as a white powder (6.94 g), δ_P 13.6 and 14 ppm (1:1). These salts were recrystallized four times from a mixture of methanol–acetone 1:4 to give diastereomerically pure salt **7a** (1.78 g, 25%) according to ^{31}P NMR: δ_P 13.6 (100%). $[\alpha]_D$ +68 (*c* 5.3, $CHCl_3$).

The first mother liquor was evaporated and the resulting yellow solid was recrystallized once as above to afford 1.75 g of salt **7b**, δ_P 13.6 (13%) and 14 (87%).

4.7. Optically pure (−)- or enriched (+)-methyl (2-methylsulfinyl)phenylphosphonic acid 1

Pure salt **7a** (49 mg) or diastereomerically enriched **7b** (50 mg) was dissolved in distilled water and neutralized with an aqueous solution of sodium bicarbonate. After extraction three times with $CHCl_3$ (3×5 ml) in order to remove cinchonine, the aqueous phase was acidified with dilute sulfuric acid (partial racemization was observed with 1N HCl) and concentrated under vacuum. The resulting salts were washed with $CHCl_3$. On evaporation, the acid (−)-**1**; 20 mg, yield 92%; $[\alpha]_D = -97$ (*c* 0.45, $CHCl_3$) or the acid (+)-**1**; 18 mg, yield 90%; $[\alpha]_D = +73$ (*c* 0.55, $CHCl_3$) was isolated as a colorless oil. δ_H 2.82 [3H, s, S(O)C*H*$_3$], 3.74 (3H, d, $^3J_{HP}$ 11.5, C*H*$_3$O), 7.56 (1H, ddt, $^4J_{HH}$ 1.1, $^4J_{HP}$ 3.2, $^3J_{HH}$ 7.5, *Ar*), 7.78 (1H, tt, $^4J_{HH}$ 1.4, $^5J_{HP}$ 1.4, $^3J_{HH}$ 7.7, *Ar*), 7.88 (1H, ddd, $^4J_{HH}$ 1.3, $^3J_{HH}$ 7.5, $^3J_{HP}$ 13.8, *Ar*), 8.22 (1H, ddd, $^4J_{HH}$ 1.1, $^4J_{HP}$ 5.1, $^3J_{HH}$ 7.9, *Ar*). δ_P 16.9. δ_C 43.8 [s, S(O)*C*H$_3$], 52.5 (d, $^2J_{CP}$ 6.0, *C*H$_3$O), 123.7 (d, $^3J_{CP}$ 12.1, *Ar*), 126.1 (d, $^1J_{CP}$ 190.5, *Ar*), 130.5 (d, $^3J_{CP}$ 12.8, *Ar*), 133.0 (d, $^2J_{CP}$ 8.2, *Ar*), 133.4 (s, *Ar*), 148.9 (d, $^3J_{CP}$ 10.1, *Ar*). HRMS *m*/*z* 234.01155 (M$^+$); calcd: 234.01236 for $C_8H_{11}O_4PS$.

4.8. Optically pure (−)- or enriched (+)-dimethyl (2-methylsulfinyl)phenylphosphonate 2

Cinchonine was removed as above from **7a** (150 mg) or **7b** (114 mg). The aqueous phase was concentrated under reduced pressure. The resulting sodium salts were dissolved in acetonitrile (25 mL) and heated overnight at 50°C with excess methyl iodide. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The solution was concentrated in vacuo after filtration on CH_2Cl_2-impregnated Celite. The resulting oil was purified by column chromatography on silica gel with EtOAc as eluent to yield almost quantitatively pure sulfoxide (−)-**2**; 70 mg; $[\alpha]_D = -151$ (*c* 0.95, $CHCl_3$) or enriched (+)-**2**; 41 mg; $[\alpha]_D = +110.6$ (*c* 0.85, $CHCl_3$). δ_H 2.82 [3H, s, S(O)C*H*$_3$], 3.78 and 3.82 (6H, 2d, $^3J_{HP}$ 11.4 and $^3J_{HP}$ 11.1, C*H*$_3$O×2), 7.57 (1H, ddt, $^4J_{HH}$ 1, $^4J_{HP}$ 3.5, $^3J_{HH}$ 7.5, *Ar*), 7.79–7.87 (2H, m, *2Ar*), 8.30–8.35 (1H, dd, $^4J_{HP}$ 5.1, $^3J_{HH}$ 7.6, *Ar*). δ_P 18.7. δ_C 43.8 [s, S(O)*C*H$_3$], 52.2 (d, $^2J_{CP}$ 6.2, *C*H$_3$O), 123.0 (d, $^3J_{CP}$ 12.3, *Ar*), 123.2 (d, $^1J_{CP}$ 190.0, *Ar*), 129.7 (d, $^3J_{CP}$ 13.3, *Ar*), 132.1 (d, $^2J_{CP}$ 8.5, *Ar*), 133.1 (s, *Ar*), 150.5 (d, $^2J_{CP}$ 11.9, *Ar*). Anal. calcd for $C_9H_{13}O_4PS$: C, 43.55; H, 5.28; P, 12.48; S, 12.92. Found: C, 43.22; H, 5.01; P, 12.48; S, 12.63%.

4.9. Asymmetric oxidation of sulfide 6 (see Table 2)

4.9.1. Method A: Oxidation with the Sharpless modified reagent.[24] Into a flask containing (*R*,*R*)-(+)-diethyl tartrate (0.17 mL, 1 mmol) in dry CH_2Cl_2 (3 mL) was introduced via syringe titanium (IV) isopropoxide (1.5 mL, 0.5 mmol). After a few minutes of stirring, distilled water (9 µL, 0.5 mmol) was added dropwise at 16°C. When the yellow solution became homogeneous a solution of sulfide (116 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was cooled to −20°C, stirred for 5 min and either TBHP (2 M in CH_2Cl_2, 0.5 mL, 1 mmol) or CHP (1 mL, 1 mmol) was introduced. The reaction was monitored by TLC (EtOAc–MeOH 19:1 as eluent). Hydrolysis was achieved by adding water (2 mL) and stirring for 1 h at room temperature. The solution was filtered on CH_2Cl_2-impregnated Celite and directly concentrated in vacuo (treatment with NaOH must be avoided since partial hydrolysis of the phosphonate group occurs). The sulfoxide was purified by flash chromatography using EtOAc–MeOH 19:1 as eluent.

4.9.2. Method B: Oxidation using a chiral Davis oxaziridine.[25] To a stirred solution of (+)-(2*R*,8a*S*)-8,8-dichloro-(camphorylsulfonyl)oxaziridine (0.8 g, 0.4 mmol) in CH_2Cl_2 or CCl_4 (1 mL) at room temperature was added sulfide **6** (100 mg, 0.43 mmol). At the end of the reaction (TLC monitoring with petroleum ether–EtOAc 1:1) triethylamine (0.5 mL) was introduced. After evaporation of the solvents the sulfoxide was isolated as in method A.

4.9.3. Method C: Oxidation using a chiral vanadium–Schiff base catalyst.[26] A mixture of $[VO(acac)_2]$ (1.12 mg, 0.0043 mmol) and (*S*)-2-*N*(*N*-3,5-di-*tert*-butylsalicylidene)amino-3,3-dimethylbutan-1-ol (1.43 mg, 0.0045 mmol) was stirred in $CHCl_3$ (1 ml) at room temperature until the mixture turned blue–green. The sulfide (400 mg, 1.7 mmol) was introduced followed by the dropwise addition of 30% H_2O_2 (180 µl, 1.8 mmol). After the reaction was completed, hydrolysis was carried out by saturated aqueous ammonium chloride. The aqueous layer was extracted with $CHCl_3$, the combined extracts were concentrated in vacuo and the crude product purified as in method A.

4.9.4. Determination of the enantiomeric excess of 2. In an NMR tube were placed 3 equiv. of (*S*)-MPAA (α-methoxyphenylacetic acid). A solution of partially resolved sample of sulfoxide (10 mg, ca. 0.04 mmol) in $CDCl_3$ was added. The mixture was stirred vigorously and the ^1H NMR spectrum was recorded (see Table 2).

4.10. Conversion of enriched (*S*)-(−)-2-methylsulfinylaniline 8 into (−)-2

The required optically active (*S*)-2-aminophenyl methyl sulfoxide **8** was obtained by oxidation of (2-methylsulfanyl)anilinium (+)-camphorsulfonate salt with MCPBA according to a modification of the procedure reported by Folli et al.,[27] who used a perbenzoic acid oxidant. The resulting diastereomeric salts, recrystallized once from MeOH–EtOAc, were dissolved in $CHCl_3$ and basified with NaOH aqueous solution. The aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried and evaporated to afford (*S*)-(−)-**8**, $[\alpha]_D=-3.1$ (*c* 0.4, $CHCl_3$). To a cooled solution (0°C) of **8** (1.55 g, 10 mmol) in a mixture of AcOH (4 mL) and water (4 ml) was added dropwise sodium nitrite (1.4 g, 20 mmol) in H_2O (5 mL). Upon stirring, the diazonium salt solution turned orange. An excess of KI (5 g, 30 mmol) in water (8 mL) was then added cautiously over 20 min. After stirring overnight the reaction mixture was extracted with ether (3×20 mL). The extracts were washed successively with aqueous NaOH and sodium thiosulfate, dried and concentrated. The remaining oily 2-iodophenyl methyl sulfoxide **9** (1.45 g, 5.5 mmol) was next photophosphonylated without purification, according to Collignon's procedure.[28]

Sodium hydride, previously washed in light petroleum ether (0.18 g, 4.5 mmol), and THF (3 mL) were stirred vigorously in a HERAUS (type UV TQ 150, mercury lamp) photochemical reactor under nitrogen. Dimethylphosphite (0.42 mL, 4.5 mmol) was dropped into the stirred NaH suspension. When hydrogen evolution ceased sulfoxide **9** (0.3 g, 1.13 mmol) was introduced followed by the addition of CH_3CN (12 mL). After 1 h of irradiation (reaction progress was monitored by TLC using EtOAc–MeOH 19:1 as eluent), the mixture was quenched with saturated aqueous NH_4Cl and extracted with ether (3×15 mL). The ethereal extract was dried and evaporated. The residue which was contaminated with several unidentified organophosphorus compounds was purified by column chromatography over silica to afford the sulfoxide (−)-**2** in 35% yield. $[\alpha]_D=-14.2$ (*c* 0.2, $CHCl_3$) and e.e. 9%.

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