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Synthesis of Optically Active Hydroxyphosphonates

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ABSTRACT: *The reduction of dimenthyl ketophosphonates with sodium borohydride involves asymmetric induction at the α-carbon atom, resulting in a small excess of the (R)-enantiomer of the α-hydroxyphosphonate formed. A higher ee purity was achieved if the reduction of chiral dimenthyl ketophosphonates was carried out by the chiral complex of $NaBH_4$-L-proline, owing to the double asymmetric induction at the α-carbon atom. The hydroxyphosphonates obtained were isolated in a diastereomerically pure state and were transformed to the optically active, free hydroxyalkylphosphonic acids. The (R)-configuration of one of them was proved by X-ray crystal structure analysis.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:133–139, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20391

INTRODUCTION

α-Hydroxyphosphonates and α-phosphonic acids possess important biological activity through the inhibition of a number of enzymes, and the absolute configuration at the α-position of substituted phosphonic acids has been shown to influence their biological properties significantly [1–3]. While enantioselective syntheses of α-aminophosphonic acids have been studied extensively [4], the synthesis of enantiomerically pure α-hydroxyphosphonates has not yet developed sufficiently [5–8]. The previously employed methods provide access to many α-hydroxyphosphonates, but the use of chiral auxiliaries and/or catalysts is required to improve the stereoselectivity of these methods [9]. A possible method for the stereoselective introduction of the hydroxyl group is a stereoselective reduction of prochiral keto compounds. Reductions with chirally modified metal hydrides, catalytic hydrogenation in the presence of chiral metal complexes, asymmetric hydrosilylation, hydroboration, etc. are widely used for their preparation.

In this article, we describe the synthesis of optically active α-hydroxyphosphonic acids by reduction of dimenthyl α-ketophosphonates **1**. The resulting α-hydroxyphosphonates can easily be purified by crystallization, and can, after removal of the menthyl groups, be transformed to the corresponding optically active α-hydroxyphosphonic acids.

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RESULTS AND DISCUSSION

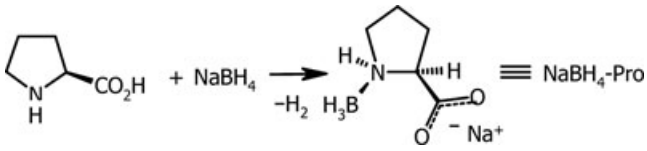
The initial α-ketophosphonates **1** were prepared by two procedures: one-step reaction of tris(1*R*,2*S*,5*R*)-menthylphosphite with aroyl chlorides (*Method a*) and by a two-step procedure (*Method b*) that comprises preparation of α-hydroxyphosphonates by the reaction of di-(1*R*,2*S*,5*R*)-menthylphosphite with aldehydes followed by their conversion without isolation and purification to ketophosphonates **1** in high yields (90%–100%) by treatment with the pyridinium dichromate/trimethylchlorosilane oxidizing system [10].

The ketophosphonates prepared by the first method (Method a) were purified by column chromatography and were isolated in satisfactory yields (60%–80%), Thus, the reaction of 4-fluorobenzoyl chloride with trimenthylphosphite proceeded smoothly at room temperature in toluene, affording α-ketophosphonate **1b** in 80% yield (Scheme 1).

The chemical purity and yields of ketophosphonates **1** prepared by Method b were considerably higher than by Method a, achieving 90% yield or more. Therefore, the ketophosphonates prepared by this procedure were used in transformations without further purification.

The structure of compounds **1** has been confirmed by ^{1}H and ^{31}P NMR spectroscopy. ^{31}P NMR spectra reveal a singlet in the region $\delta_P = -3.1$ to -3.3 ppm. ^{1}H NMR spectra display signals for the protons of the menthyl group as well as the aromatic protons of the expected multiplicity and intensity.

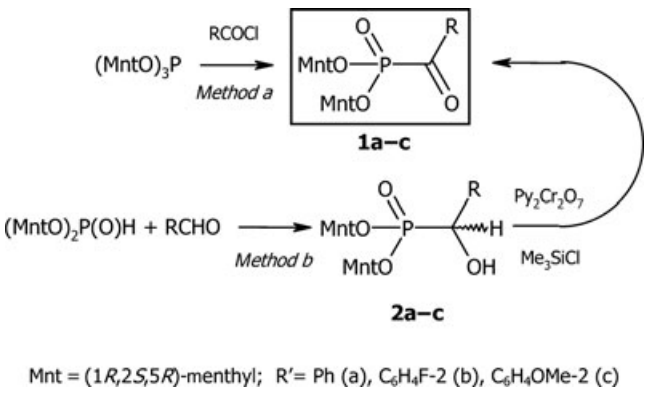
The treatment of α-ketophosphonates **1** with sodium borohydride in ethanol proceeded with moderate stereoselectivity to afford a mixture of (*R*)- and (*S*)-diastereomers, with higher contents of the corresponding (*R*)-hydroxybenzylphosphonates. The crystallization of (*R*)-α-hydroxyphosphonates from acetonitrile provided stereochemically pure (*R*)-distereomers (Scheme 2). The stereoselectivity was reversed when the reduction was performed in THF, leading to the preferential formation of the (*S*)-diastereomer.



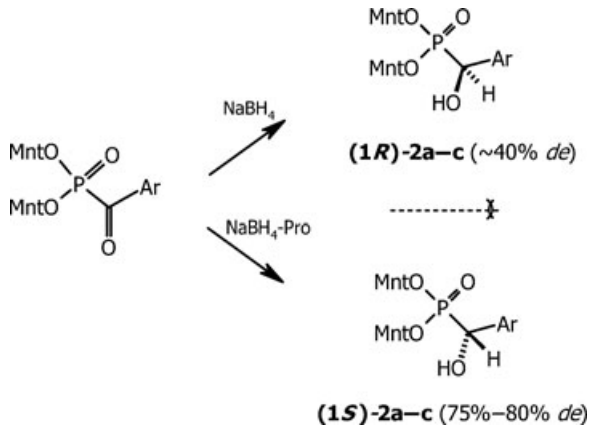
SCHEME 2

We succeeded in improving the stereoselectivity of ketophosphonate reduction by using the chiral complex of sodium borohydride with natural L-proline ($NaBH_4$-Pro). For the preparation of this reducing reagent, an equimolar amount of L-proline was added to sodium borohydride suspended in THF, and the mixture was stirred at room temperature for several hours [11]. The ketophosphonate was then added to $NaBH_4$-Pro, resulting in the formation of (*S*)-hydroxyphosphonate with a stereoselectivity in the range from 75% to 80% *de* purity. Compounds (*S*)-**2a–c** were crystallized from hexane and isolated in approximately 100% optical purity (Scheme 3)

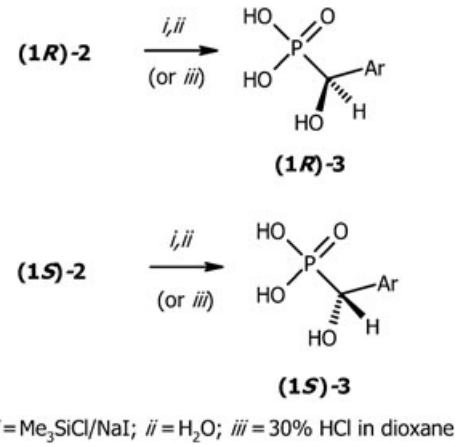
The chiral menthyl groups of **2a–c** were cleaved off under mild conditions by a modified procedure of Morita et al. [12]. The reaction of the dimenthyl α-hydroxyphosphonates **2a–c** with trimethylsilyl chloride and NaI in acetonitrile led to bis(trimethysilyl)-α-hydroxyphosphonates, which were finally hydrolyzed in a mixture of water/ethanol to afford the optically active α-hydroxyphosphonic acids **3a–c** (Scheme 4). The treatment of α-hydroxyphosphonates **2a–c** with hydrochloric acid in water/dioxane solution also gave the



SCHEME 1



SCHEME 3

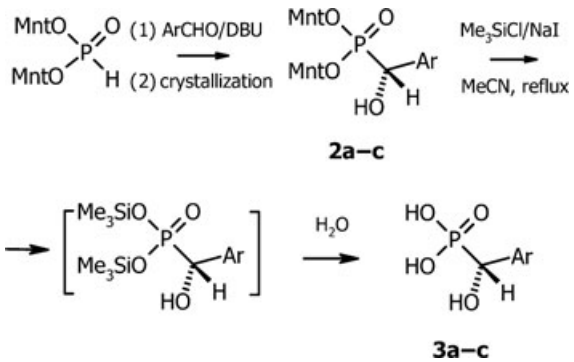


SCHEME 4

corresponding free optically active phosphonic acids **3a–c** in good yields. Owing to the steric hindrance of the esters **2a–c**, it was necessary to use longer reaction times and higher temperatures.

Similarly, α-hydroxyphosphonates **2a–c** were prepared by phospha-aldol addition of aromatic aldehydes to dimenthylphosphite as shown in Scheme 5 [9,13]. The reaction was performed at room temperature in the absence of solvent, with 1,8-diazabicyclo[5.4.0]undecene (DBU) as the catalyst, and according to a method described by us earlier [9] to give a mixture of (*R*)- and (*S*)-diastereomers of α-hydroxyphosphonates **2a–c**, which were purified by crystallization from hexane to give (*R*)-diastereomers of 100% *de* purity. Compounds **2a–c** were identical to (*R*)-hydroxyphosphonates prepared by the reduction of ketophosphonates with sodium borohydride (Scheme 5).

Compounds **2** and **3** were identified by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and liquid chromatography. Dimenthyl α-hydroxyphosphonates are easily crystallizable compounds, which are obtained in a stereochemically pure state.



SCHEME 5

^{31}P NMR spectra of compounds **2a–c** show signals for the two diastereomers, with δ_P values in the region 21.0–21.5 ppm, The downfield signal belongs to the (*R*)-diastereomer and the upfield signal to the (*S*)-diastereomer of α-hydroxyphosphonates **2**.

^{1}H NMR spectra of compounds **2a–c** revealed that the signals belong to the protons of the menthyl group, aromatic protons of appropriate multiplicity and intensity, a broad signal due to the OH group at $\delta_H = 3.7$ ppm, and a CH doublet at $\delta_H = 4.9$ ppm. ^{1}H and ^{13}C NMR spectra of compounds **2a–c** indicate that the molecules are asymmetric, because the signals of the two menthyl groups bonded to phosphorus are magnetically nonequivalent.

The configuration of (*R*)-(+)-α-hydroxybenzylphosphonic acid (**2a**) was confirmed by comparing its optical rotation with literature data [8]. The configuration of the newly formed stereogenic center in the major diastereomer of compound **2b** was established as *R* by single crystal X-ray structure analysis. The structure of **2b** is shown in Fig. 1. The coordination at phosphorus is distorted tetrahedral, with angles between 102.88(5)° (O4—P—C1) and 113.82(6)° (O1—P—C1); the largest angles, as usual, involve the phosphoryl oxygen atom. The P—O bond lengths are: P=O1: 147.16(10) pm; P—O3: 158.01(8) pm, and P—O4: 156.91(9) pm.

Very short (H···O: 194(2) pm) and linear (O—H···O: 169.6(18)°) intermolecular hydrogen bonds between the hydroxyl hydrogen and the phosphoryl oxygen link the molecules to form chains parallel to the *y* axis.

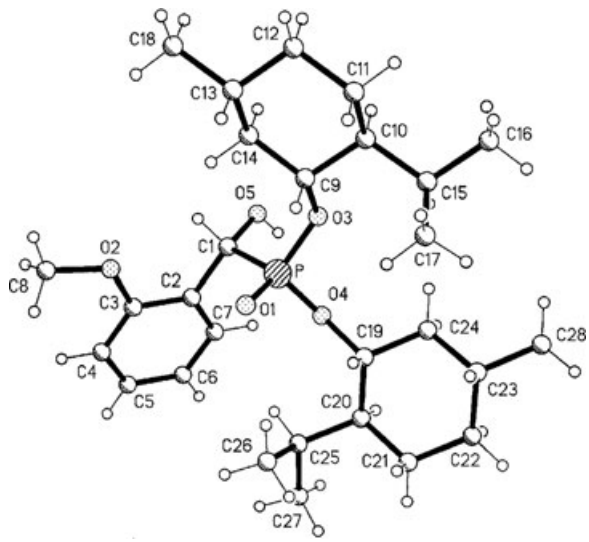


FIGURE 1 Molecular structure of di-(1*R*,2*S*,5*R*)-menthyl-(*R*)-1-hydroxy-1-(*o*-methoxyphenyl) methylphosphonate **2b** in the crystal.

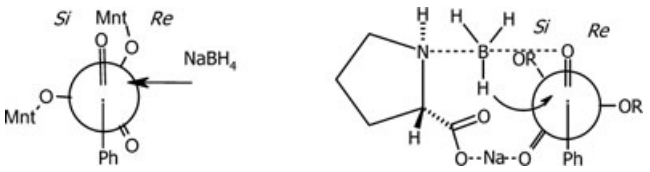


FIGURE 2 Facial attack on the α-phenylketophosphonate carbonyl group by $NaBH_4$ (left) and $NaBH_4$-Pro (right).

The preferential formation of (*R*)-diastereomers observed in the reduction of α-ketophosphonates **1** with $NaBH_4$ in ethanol can be anticipated to some extent by examining their molecular models. The molecular structures of α-ketophosphonate **1a** and α-hydroxyphosphonate **2b** indicate the high asymmetry of the molecules owing to a propeller-like arrangement of the menthyl groups around the phosphorus atom. Thus, one can make the reasonable assumption that the attack of the reducing agent on the carbonyl group will take place preferentially from the side leading to the (*R*)-configuration rather than from the opposite side, which is shielded by the menthyl group (Fig. 2, left). This corresponds to an approach to the more exposed face of the α-ketophosphonate.

The selectivity of the reduction with $NaBH_4$-Pro depends upon the geometry of the complex formed by coordination of the carbonyl oxygen to the boron atom and of the carboxylic sodium to the oxygen of the P=O group. The reaction cycle inside the favored intermediate complex is shown in Fig. 2, right. It is evident that in this case the attack of the chiral reducing agent on the carbonyl group will take place preferentially from the side leading to the (*S*)-configuration rather than the opposite *Re* side.

In summary, the described asymmetric reduction of dimenthyl α-ketophosphonates provides an easy route to both stereoisomers of optically active α-hydroxyphosphonic acids in good yield and in enantiomeric excess. The reduction of dimenthyl ketophosphonates with $NaBH_4$ led preferably to the formation of (*R*)-α-hydroxyphosphonates, whereas the reduction with $NaBH_4$-Pro furnishes (*S*)-hydroxyphosphonates.

EXPERIMENTAL

All the experiments were carried out with exclusion of air and moisture. Solvents were purified and dried according to the usual methods. NMR spectra were recorded on a BRUKER AC-200 spectrometer with working frequencies of 200 MHz (^{1}H) and 81 MHz (^{31}P), respectively. All ^{1}H chemical shifts are reported in δ (ppm) relative to Me_4Si as an internal standard. ^{31}P NMR spectra were recorded, relative to 85% H_3PO_4 as an external standard. All manipulations were carried out under argon, solvents were distilled in an inert atmosphere from the drying agents listed in parentheses: diethyl ether, hexane, heptane, benzene, tetrachloromethane (P_2O_5), methanol, triethylamine (sodium), and ethyl acetate (calcium chloride). Pyridinium dichromate was obtained from ACROS. Dimenthylphosphite was prepared according to the method of Kolodiazhnyi et al. [14].

HPLC separations were carried out on the "Milichrom-1A" instrument (Russia). Silasorb DEA, column 120 mm × 2 mm (hexane/isopropanol mixture in a 95:5 ratio as eluent); Silasorb C-18, column 120 mm × 2 mm (50% aqueous acetonitrile as eluent); UV detector, λ = 260 nm. Column chromatography was performed using Silicagel L 100/160.

Optical rotations were measured on a Perkin-Elmer Model 241 spectropolarimeter. Melting points are uncorrected.

*Di-(1*R*,2*S*,5*R*)-menthyl-benzoylphosphonate (**1a**)*

Method a. A solution of benzoyl chloride (1.41 g, 10 mmol) in 5 mL of toluene was added to a solution of tris(1*R*,2*S*,5*R*)-menthylphosphite (4.96 g, 10 mmol) in 10 mL of toluene with cooling (−20°C), and the reaction mixture was left to stand overnight. The solvent was evaporated, and the menthyl chloride formed was removed in vacuo (0.02 mmHg). The product obtained was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1 as eluent), TLC: $R_f = 0.3$ (hexane/ethyl acetate = 4.5:1).

Yield: 2.8 g (60%). $[\alpha]_D^{20}$ −62 (c 1.5, $CHCl_3$). Calcd. for $C_{27}H_{43}O_4P$: P, 6.70%. Found: P, 6.61%. ^{1}H NMR ($CDCl_3$): δ = 0.7–1.0 (m, CH_3); 1.1–2.2 (m, CH_2 + CH); 4.15 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 7.35 (m, C_6H_5); 7.45 (m, C_6H_5). ^{31}P NMR ($CDCl_3$): $\delta_P = -3.5$.

Method b. Trimethylchlorosilane (0.6 g, 5.5 mmol) was added to a pyridinium dichromate (1.68 g, 4.47 mmol) solution in 30 mL of methylene chloride with stirring at 0°C, and then dimenthyl α-hydroxyphosphonate, prepared from dimenthylphosphite (6.3 g, 1.75 mmol) and benzaldehyde (1.86 g, 1.75 mmol) was added. The reaction mixture was stirred at room temperature until completion of the reaction (~4 h), filtered through silica gel, and washed with a small amount of ethyl acetate. After evaporation, a colorless liquid thus obtained was purified by column chromatography.

Yield: 95%, R_f 0.3 (hexane/ethyl acetate = 4:1). $[\alpha]_D^{20}$ 62 (*c* 1.5, $CHCl_3$). Calcd. for $C_{27}H_{43}O_4P$:

P, 6.70%. Found: P, 6.61%. ^{1}H NMR ($CDCl_3$), $\delta = 0.7$–1.0 (m, CH_3); 1.1–2.2 (m, CH_2 + CH); 4.15 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 7.35 (m, C_6H_5). ^{31}P NMR ($CDCl_3$), $\delta_P = -3.5$.

*Di-(1*R*,2*S*,5*R*)-menthyl-o-methoxybenzoylphosphonate(***1b***)*

Compound **1b** was prepared by analogy with compound **1a**. The product was purified by column chromatography (hexane/ethyl acetate as eluent).

Yield: 75%. Calcd. for $C_{28}H_{45}O_5P$: P, 6.29%. Found: P, 6.39%. ^{1}H NMR ($CDCl_3$): $\delta = 0.7$–1.0 (m, CH_3); 1.1–2.2 (m, CH_2 + CH); 3.9 s (OCH_3); 4.15 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 6.6–6.8 (m, C_6H_4); 7.0–7.2 (m, C_6H_4). ^{31}P NMR ($CDCl_3$): $\delta_P = -3.6$.

*Di-(1*R*,2*S*,5*R*)-menthyl-2-fluorobenzoylphosphonate(***1c***)*

Method a. As in the case of **1a**, the product was purified by column chromatography (hexane/ethyl acetate as eluent).

Yield: 80%. $[\alpha]_D^{20}$ −72 (c 1, toluene). ^{1}H NMR ($CDCl_3$): $\delta = 0.6$–0.9 (m, CH_3); 0.8–2.0 (m, CH_2 + CH); 4.0 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 7.4 (m, C_6H_4); 7.43 (m, C_6H_4). Calcd. for $C_{27}H_{42}FO_4P$: P, 6.44%. Found: P, 6.38%. ^{31}P NMR ($CDCl_3$): $\delta_P = -3.1$.

Method b. Prepared similarly to compound **1a**. R_f 0.74 (hexane/ethyl acetate = 5:1).

Yield: 90%. $[\alpha]_D^{20}$ 72 (*c* 1, toluene). Calcd. for $C_{27}H_{42}FO_4P$: P, 6.38%. Found: P, 6.44%. ^{1}H NMR ($CDCl_3$), $\delta = 0.6$–0.9 (m, CH_3); 0.8–2.0 (m, CH_2 + CH); 4.0 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 7.4 (m, C_6H_4). ^{31}P NMR ($CDCl_3$), $\delta_P = -3.1$.

*Di-(1*R*,2*S*,5*R*)-menthyl-(*R*)-1-phenyl-1-hydroxymethylphosphonate((*R*)-***2a***)*

Method a. Sodium borohydride (0.456, 1.2 mmol) was added to a solution of α-ketophosphonate **1a** (4.5 g, 1.0 mmol) in 20 mL of ethanol. After the reaction mixture was left overnight, the solvent was evaporated. The residue was dissolved in diluted hydrochloric acid and extracted with methylene chloride (2 × 20 mL). The solution was filtered, the solvent was evaporated, and the remaining product was recrystallized from hexane or acetonitrile.

Yield: 2.5 g (45%); mp 139°C. $[\alpha]_D^{20}$ −70 (c 1, toluene). ^{31}P NMR ($CDCl_3$), $\delta_P = 23.71$

Method b. Hydroxymethylphosphonate **2a** was prepared from di-(1*R*,2*S*,5*R*)menthylphosphite and benzaldehyde according to the above-mentioned method.

Yield: 50%; mp 139°C. $[\alpha]_D^{20}$ −70 (c 1, toluene).

The compounds **2a** prepared by Methods *a* and *b* were identical.

Calcd. for $C_{27}H_{45}O_4P$: P, 6.27%. Found: P, 6.15%. ^{1}H NMR ($CDCl_3$): $\delta = 0.7$–1.0 (m, CH_3); 1.1–1.23 (m, CH_2 + CH); 3.7 (br, OH); 4.2 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 4.92 (d, CHP, J_{HP} 11); 7.2–7.3 (m, C_6H_5); 7.3–7.5 (m, C_6H_5). ^{13}C NMR: $\delta = 127.99$ (d, *J* 2.5); 127.8 (d, J_{CP} 2.5); 127.3 (d, C_6H_5, J_{CP} 9.6); 71.6 (d, PC, J_{CP} 160); 48.6 (d, CHO^a, J_{CP} 14); 48.5 (d, CHO^b, J_{CP} 13.2); 45.66, s; 42.53, s; 34, s; 31.5, s; 25.31, s; 22.7, s; 21.97, s; 21.13, s; 21.03, s; 15,74, 15.60 (diastereotopic menthyl groups). ^{31}P NMR ($CDCl_3$), $\delta_P = 23.71$.

*Di-(1*R*,2*S*,5*R*)-menthyl-(*S*)-1-phenyl-1-hydroxymethylphosphonate((*S*)-***2a***)*

Method a. To a suspension of sodium borohydride (0.045 g, 1.19 mmol) in 8 mL of THF, L-proline (0.137 g, 1.19 mmol) was added. The mixture was stirred at room temperature for 6 to 12 h. Ketophosphonate **1a** (0.368 g, 0.795 mmol) was then added, and the mixture was stirred for further 24 h at room temperature. The solvent was evaporated and 10 mL of water/ethyl acetate (1:1) mixture was added to the residue. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The extract was washed with 1N HCl, then with sodium carbonate solution, again with water, and finally dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the crystalline solid.

Yield: 0.367 g (70%); mp 112°C–113°C. $[\alpha]_D^{20}$−87.6 (*c* 1.3, $CHCl_3$). Calcd. for $C_{27}H_{45}O_4P$: P, 6.67%. Found: P, 6.38%. ^{1}H NMR ($CDCl_3$): δ = 1.01 (d, CH_3, J_{HH} 6.9); 1.04 (d, CH_3, J_{HH} 6.9); 1.08 (d, CH_3, J_{HH} 6.9); 1.18 (d, CH_3, J_{HH} 6.9); 1.20 (d, CH_3, J_{HH} 6.9); 1.21 (d, CH_3, J_{HH} 6.9); 1.40–2.6 (m, C*H*$_3$ and CH); 2.00 [m, $CH(CH_3)_2$]; 2.4 [m, $CH(CH_3)_2$]; 4.49 (m, OCH); 5.2 (d, CHP, J_{HH} 10.5); 5.10 (br, OH); 7.48 (m, Ar*H*); 7.8 (m, Ar*H*). ^{31}P NMR ($CDCl_3$), $\delta_P = 22.3$.

*Di-(1*R*,2*S*,5*R*)-menthyl-(*R*)-1-(o-methoxyphenyl)-1-hydroxymethylphosphonate((*R*)-***2b***)*

The preparation was as described for compound **2a**. The product was purified by crystallization from hexane and acetonitrile.

Yield: 70%; mp 138°C. $[\alpha]_D^{20}$ −56.4 (c 1, toluene). Calcd. for $C_{28}H_{47}O_5P$: P, 6.27%. Found: P, 6.25%. ^{1}H NMR ($CDCl_3$): $\delta = 0.7$–1.0 (m, CH_3); 1.1–1.23 (m, CH_2 + CH); 3.4 (br, OH); 3.55 (s, OCH_3); 4.0 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 5.17 (d, CHP, J_{HP} 11);

6.6–6.8 (m, C_6H_4); 7.0–7.2 (m, C_6H_4). ^{13}C NMR ($CDCl_3$): $\delta = 157.10$ (d, J 6.5); 129.00 (d, J 2.8); 128.8 (d, J_{CP} 2.8); 125.3 (d, J_{CP} 5.5); 120.6 (d, J_{CP} 2.0); 110.5, 128.8 (d, J_{CP} 2.0, C_6H_5); 66.7 (d, PC, J_{CP} 161); 55 (s, CH_3O); 48.8 (d, CHO[a] J_{CP} 35); 48.5 (d, CHO[b], J_{CP} 34); 43.8, s; 34.09, s; 33.9, s; 31.5, s; 25.24, s; 22.7, s; 21.97, s; 21.87, s; 21.21, s; 21.05; 15,72, 15.62 (diastereotopic menthyl groups). ^{31}P NMR ($CDCl_3$), $\delta_P = 21.49$.

*Di-(1*R*,2*S*,5*R*)-menthyl-(*S*)-1-hydroxy-1-(2-methoxyphenyl)methylphosphonate ((*S*)-**2b**)*

Yield: 74%; mp 116°C–117°C. $[\alpha]_D^{20}$ −75.2 (*c* 0.66, $CHCl_3$). Calcd. for $C_{28}H_{47}O_5P$: C, 67.99%; H, 9.58%; P, 6.26%. Found: C, 68.16%; H, 9.50%; P, 6.27%. ^1H NMR (C_6D_6): $\delta = 0.60$ (d, CH_3, $^3J_{HH}$ 6.9); 0.52 (d, CH_3, $^3J_{HH}$ 6.9); 0.73 (d, CH_3, $^3J_{HH}$ 6.9); 0.79 (m, $2CH_3$); 0.84 (d, CH_3, $^3J_{HH}$ 6.9); 0.92–1.54 (m, CH_2 and CH); 2.14 [m, C*H*$(CH_3)_2$]; 2.40 [m, C*H*$(CH_3)_2$]; 3.59 (s, OCH_3); 4.17 (m, OCH); 4.03 (m, OCH); 4.54 (br, OH); 5.24 d (1H, CHP, J_{HH} 13.2); 6.59 d (1H, ArH, J_{HH} 8.1); 6.80 (t, 1H, ArH, J_{HH} 7.9); 7.04 (t, 1H, ArH, J_{HH} 7.9); 7.60 (d, ArH, J_{HH} 7.5). ^{31}P NMR ($CDCl_3$), $\delta_P = 21.13$.

*Di-(1*R*,2*S*,5*R*)-menthyl-(*R*)-1-(2-fluorophenyl)-1-hydroxymethylphosphonate((*R*)-**2c**)*

The preparation was as described for compound **2a**. The product was purified by crystallization from hexane and acetonitrile.

Yield: 65%; mp 135°C. $[\alpha]_D^{20}$ −68.9 (c 1, toluene). ^1H NMR (DMSO): $\delta = 0.6$–0.9 (m, CH_3); 0.95–1.98 (m, CH_2 + CH); 5.95 (br, OH); 4.05 (dt, OCH, J_{HH} 2.3, J_{HH} 4.1); 4.75 (d, CHP, J_{HP} 11); 7.05 (m, C_6H_5); 7.45 (m, C_6H_5). ^{31}P NMR ($CDCl_3$), $\delta_P = 21.53$.

*Di-(1*R*,2*S*,5*R*)-menthyl-(*S*)-1-(2-fluorophenyl)-1-hydroxymethylphosphonate ((*S*)-**2c**)*

Yield: 97%; mp 137.5°C–138.5°C. $[\alpha]_D^{20}$ −83.7 (*c* 1.3, $CHCl_3$). Calcd. for $C_{27}H_{44}FO_4P$: P, 6.42%. Found: P, 6.38%. ^1H NMR (C_6D_6): $\delta = 0.71$ (d, CH_3, $^3J_{HH}$ 6.9); 0.76 (d, CH_3, $^3J_{HH}$ 6.9); 0.86 (d, CH_3, $^3J_{HH}$ 6.9); 0.91 (d, CH_3, $^3J_{HH}$ 6.9); 1.00–2.25 (m, CH_3 and CH); 1.74 [m, C*H*$(CH_3)_2$]; 2.0 [m, C*H*$(CH_3)_2$]; 4.04 (d, CHP, J_{HH} 22.5); 4.2 (m, OCH), 5.18 (br, OH); 6.9 (t, J_{HH} 8.2, C_6H_4); 7.45 (m, C_6H_4). ^{31}P NMR ($CDCl_3$), $\delta_P = 19.8$.

*(+)-(*R*)-1-Phenyl-1-hydroxymethylphosphonic Acid ((*R*)-**3a**)*

Method a. A solution of hydroxymethylphosphonate **2a** (1 g, 2 mmol) in 50 mL of dioxane was placed in a flask and 25 mL of 6N hydrochloric acid was added. The reaction mixture was then left for 3 days at 80°C. The hydrolysis was monitored by ^{31}P NMR spectroscopy. When the reaction was complete, the solvent was evaporated under reduced pressure, the residue was dissolved in ethanol, followed by the excess addition of cyclohexylamine (~1.5 ml). The precipitate of the dicyclohexylammonium salt was collected by filtration.

Method b. In a round-bottomed flask, NaI (4 equiv.) and trimethylchlorosilane (4 eqiv.) were added to a solution of α-hydroxyphosphonates **3a–c** (1 equiv.) in CH_3CN (10 mL), and the resulting mixture was refluxed for 12 h. The sodium chloride that was precipitated was filtered off. After removal of the solvent under reduced pressure, a solution of ethanol (3 mL) and H_2O (2.5 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. The organic layer was separated and the water phase was evaporated in vacuo.

Yield: 50%; mp 226°C. $[\alpha]_D^{20}$ +14.0 (c = 1, 50% aqueous MeOH) corresponding to the (*R*)-configuration of acid **3a**.

The hydroxyphosphonic acid was dissolved in ethanol, and excess cyclohexylamine was added to obtain a solid precipitate, which was purified by crystallization.

(+)-(*R*)-2α-Cyclohexylammonium salt: mp >200°C. $[\alpha]_D^{20}$ +24.0 (c = 1, $CHCl_3$).

*(–)-(*S*)-1-Phenyl-1-hydroxymethylphosphonic Acid ((*S*)-**3a**)*

Yield: 50%; mp 226°C. $[\alpha]_D^{20}$ −14.0 (c = 1, 50% aqueous MeOH) corresponding to the (*S*)-absolute configuration of acid **3a**.

(–)-(S)-2α-Cyclohexylammonium salt: mp >200°C. $[\alpha]_D^{20}$ −24.0 (c = 1, $CHCl_3$). The dicyclohexylammonium salt of (–)-(*S*)-phenyl(hydroxymethyl)-phosphonic acid has been described elsewhere [8].

*(+)-(*R*)-1-(o-Methoxy)phenyl-1-hydroxymethylphosphonic Acid (*R*)-**3b***

The preparation was as described for compound **3a**. The product was purified by crystallization from hexane and acetonitrile.

(+)-(R)-**3b**-(Cyclohexylammonium salt). Yield: 50%. mp >200°C. $[\alpha]_D^{20}$ +30.0 (c = 1, $CHCl_3$). ^{31}P NMR ($CDCl_3$), $\delta_P = 17.0$

X-ray Crystal Structure Determination of (R)-**2b**

Crystal data: $C_{28}H_{47}O_5P$, $M = 494.63$. Crystal size 0.46 mm × 0.19 mm × 0.17 mm; monoclinic, $P2_1$; $a = 1256.95(12)$ pm, $b = 548.37(6)$ pm, $c = 2087.1(2)$ pm; $\beta = 100.406(3)^\circ$; $U = 1.4149(2)$ nm^3; $Z = 2$; $\mu = 0.131$ mm^{-1}; $D_x = 1.161$ mg/m^3; $T = -130^\circ$C.

Reflections: total 22,952 to $2\theta = 60^\circ$, unique 8210 ($R_{int} = 0.0355$). Final $wR2 = 0.0855$, R1 = 0.0350 for 318 parameters and 1 restraint; $S = 0.999$, max $\Delta\rho = 0.342$ e nm^{-3}.

Data collection and reduction: The crystal was mounted on a glass fiber in inert oil and transferred to the cold gas stream of the diffractometer (Bruker SMART 1000 CCD with LT-3 low temperature attachment; monochromated Mo K_α radiation).

Structure solution and refinement: The structure was solved by direct methods and refined anisotropically on F^2 (program system: SHELXL-97, G.M. Sheldrick, University of Göttingen). Hydrogen atoms were included using a riding model or rigid methyl groups, except for the hydroxyl hydrogen, which was found and refined freely. The Flack parameter refined to −0.01(5). Full details (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Rd., GB-Cambridge CB2 1EZ, under the publication no. CDC-180997. Copies may be obtained free of charge on application to the director of the center (Tele/fax: Int. +12-23-33-60-33; e-mail: deposit@ccdc.cam.ac.uk).

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