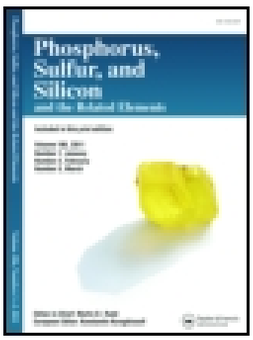

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# Formal synthesis of *P*-chiral [$^{16}$O,$^{17}$O,$^{18}$O]phosphoenol pyruvates by means of the $\alpha$-hydroxyphosphonate-phosphate rearrangement

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**ABSTRACT**

Transesterification of tris(hexafluoroisopropyl) phosphite with racemic 3-methyl-1-phenyl-butane-1,3-diol gave two isomeric hexafluoroisopropyl-substituted 1,2,3-dioxaphosphinanes. These cyclic phosphites were hydrolyzed rapidly and enantioselectively by water catalyzed by HCl. The respective metalated *H*-phosphonates were added to ethyl 3-chloropyruvate and underwent a stereospecific $\alpha$-hydroxyphosphonate-phosphate rearrangement to protected phosphoenol pyruvates. This sequence with oxygen isotope-labeled enantiomers represents an alternative approach to *P*-chiral [$^{16}$O,$^{17}$O,$^{18}$O]phosphoenol pyruvates.

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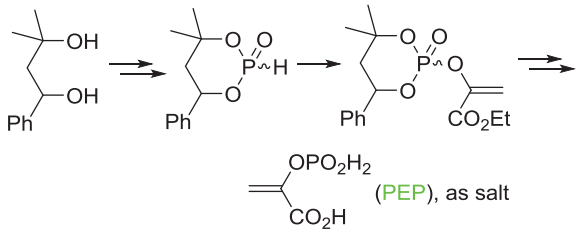
**KEYWORDS**
$\alpha$-Hydroxyphosphonate-phosphate rearrangement; cyclic *H*-phosphonate; tris(hexafluoroisopropyl) phosphite; phosphoenol pyruvate; hydrolysis

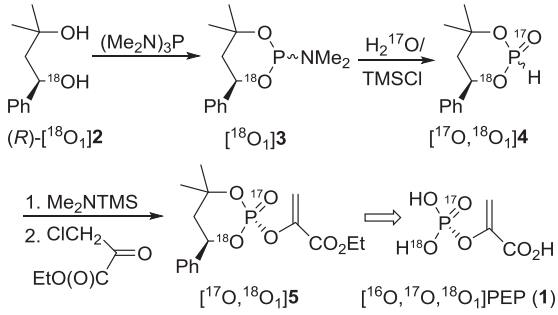
**GRAPHICAL ABSTRACT**




If the chiral $^{18}$O-labeled 1,3-diol and $H_2{}^{17}O$ are used, ($R_P$)- and ($S_P$)-[$^{16}$O,$^{17}$O,$^{18}$O]phosphoenol pyruvate will be obtained.

## Introduction

Phosphoenol pyruvate (PEP) is a high energy compound in living cells produced in the glycolytic cycle. It is used by pyruvate kinase to regenerate ATP from ADP. The phosphorus atom in PEP is a *pro-pro*-chiral center, which can be made chiral by replacing one of its three equivalent $^{16}$O atoms by an $^{17}$O atom and a second one by an $^{18}$O atom.[1,2] In the past many *pro*-chiral, *pro-pro*-chiral phosphorus centers and even the *pro-pro-pro*-chiral center of inorganic phosphate[3,4] have been made chiral by virtue of the oxygen isotopes alone or in combination with sulfur. These compounds have been used to unravel the stereochemistry of enzymes forming and breaking P-O bonds. However, *P*-chiral PEP has never been prepared by chemical methods directly. Lowe et al. developed a method to create a chiral phosphoryl group and attach it to alcohols and ADP.[5] Knowles et al. accessed it as an intermediate in a reaction sequence from *P*-chiral phosphonopyruvate by means of PEP phosphomutase catalyzing the intramolecular migration of the phosphorus atom from the carbon to the oxygen atom.[6] We have recently reported a direct chemical synthesis of the enantiomers of *P*-chiral phosphoenol pyruvate **1** as potassium salts (Scheme 1).[7] In order to summarize the approach, it started with diol (*R*)-[$^{18}$O$_1$]**2** of ee > 99%, which was converted to a roughly 1:1 *cis*/*trans*-mixture of cyclic *H*-phosphonates [$^{17}$O,$^{18}$O$_1$]**4** *via* phosphoramidites [$^{18}$O$_1$]**3** formed in a ratio of at least 1:3.




**Scheme 1.** Synthesis of the enantiomers of *P*-chiral PEP **1**.

The mixture of silylated *H*-phosphonates was allowed to react with ethyl 3-chloropyruvate (Perkow reaction). The

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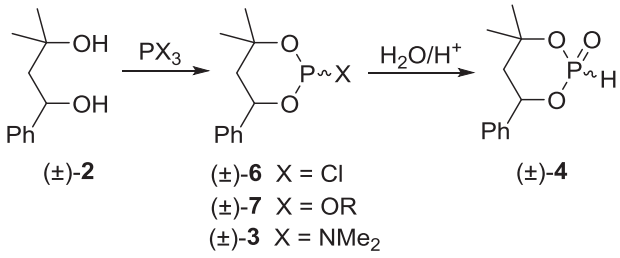
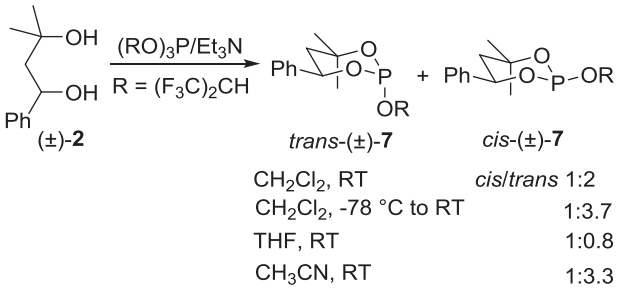



**Scheme 2.** Conversion of 1,3-diol (±)-**2** to cyclic *H*-phosphonates (±)-**4**.




**Scheme 3.** Transesterification of tris(hexafluoroisopropyl) phosphite with 1,3-diol (±)-**2**.

obtained *cis*/*trans*-mixture of protected phosphoenol pyruvates [$^{17}$O,$^{18}$O$_1$]**5** was separated by flash chromatography and the diastereomers were deprotected individually (only one is given in Scheme 1) to give the enantiomers of *P*-chiral PEP **1** as potassium salts.

We envisaged to improve the stereoselectivity for the formation of *H*-phosphonates [$^{17}$O,$^{18}$O$_1$]**4** from diol **2** and to shorten the synthesis by building on the $\alpha$-hydroxyphosphonate-phosphate rearrangement[8,9] in place of the Perkow reaction to generate the protected phosphoenol pyruvates.

## Results and discussion

For simplicity, we performed all experiments with racemic diol (±)-**2** and derivatives thereof as the enantiomers will behave similarly. It is known that 1,3-diols of type **2** react with phosphorus(III) compounds such as $PCl_3$ in the presence of a tertiary amine, $(RO)_3P$, and $(R_2N)_3P$ to give cyclic phosphorochloridites, phosphites, and phosphoramidites (±)-**6**, **(±)-7**, and (±)-**3**, respectively (Scheme 2). The position of X relative to Ph in **3**, **6** and **7** depends very much on X. For X = Cl and OR the *trans*-isomer (Ph = equatorial, X = axial) is thermodynamically more stable than the *cis*-isomer (Ph and X = equatorial). However, for X = $NR_2$ it is the other way round.[10,11] The exchange of X for OH with $H_2O$ and $H_2{}^{17}O$ in the labeled series, has to be performed in the presence of an amine for X = Cl to neutralize the acid and for X = OR, $NR_2$ to speed up the reaction rate.

For **4** the *cis*-isomer is thermodynamically more stable than the *trans*-isomer.[10] Importantly, *H*-phosphonates tautomerize slowly in the presence of water under neutral conditions, but rapidly under acidic conditions.[12] As phosphorochloridites are unstable and difficult to purify, we decided to study cyclic phosphites **7** with X = $OCH(CF_3)_2$. It was hoped that its isomers can be separated and that they are more amenable to hydrolysis than analogs with ordinary alkoxy groups.

Tris(hexafluoroisopropyl) phosphite[13] was prepared and handled under exclusion of moisture and oxygen, as it is easily hydrolyzed to the *H*-phosphonate and oxidized to the respective phosphate. Compared to trialkyl phosphites exchange of hexafluoroisopropoxy groups in the presence of $Et_3N$ proceeded already easily below or at room temperature with diol (±)-**2** to give a mixture of two diastereomeric cyclic phosphites **7** (Scheme 3). When the reaction was performed in $CH_2Cl_2$ at room temperature, two isomeric compounds were formed. They were separated by HPLC and the less polar isomer delivered crystals from hexane with a low melting point (37–38°C), which were amenable to X-ray structure analysis. It proved that the 1,3-substituents in the six-membered ring of (±)-**7**, the phenyl and hexafluoroisopropoxy group, are *trans*-arranged (Figure 1).

Worth mentioning are the differences in bond lengths for the P-O single bonds influenced by the fluorine atoms; P1-O1 = 1.60836(10) Å; P1-O2 = 1.67053(10) Å. The values for P2 are almost the same. The O-C bond lengths vary also. Last but not least the deviations of X-O-Y angles from 120° for O3 and O6 (both higher than 125°) should be noted.

Consequently, the isomer must be *cis*-(±)-**7**. Their ratio of the isomers is determined by the solvent and the reaction temperature. It ranged from 3.7:1 for $CH_2Cl_2$ at –78°C with warming to room temperature in favor of *trans*-(±)-**7** to 0.8:1 in THF at room temperature in favor of *cis*-(±)-**7**. The *trans*-isomer is assumed to be the thermodynamically more stable one.[10,11] To test the thermal configurational stability of *trans*-(±)-**7**, a small sample was bulb-to bulb distilled (80°C / 1 mbar). This isomer is configurationally stable at 80°C during the short period of time needed for vacuum distillation, as the distillate was still homogeneous. Hydrolysis was significant during flash chromatography on silica gel as evidenced by loss of product. The *cis*-isomer is more labile than the *trans*-isomer. Hydrolysis of (±)-**7** in THF containing water was minimal, but addition of TMSCl releasing HCl upon reaction with water increased it very much. Thus, when a mixture of *cis*/*trans*-(±)-**3** was stirred in THF containing 3 equiv. of water and 0.5 equiv. of TMSCl at room temperature for 30 min, no starting material was detected in the reaction mixture by TLC (Scheme 4).

Concentration of the reaction mixture after addition of 1,1,1,3,3,3-hexamethyldisilazane for neutralization of the acid,

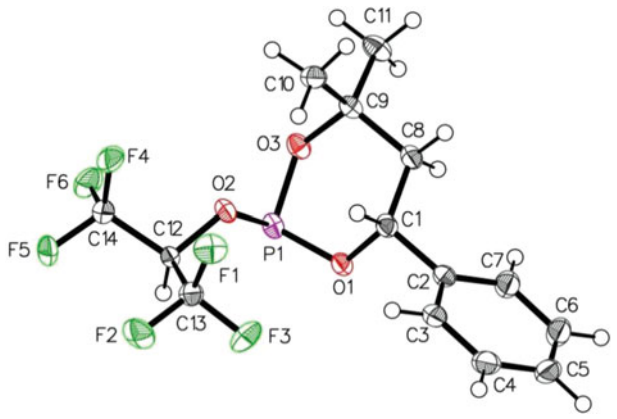
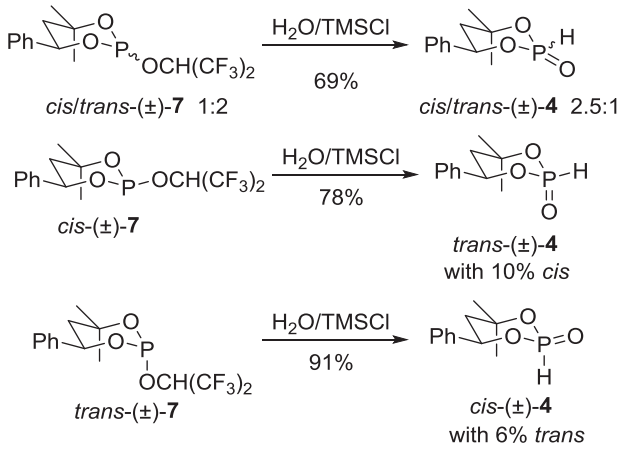


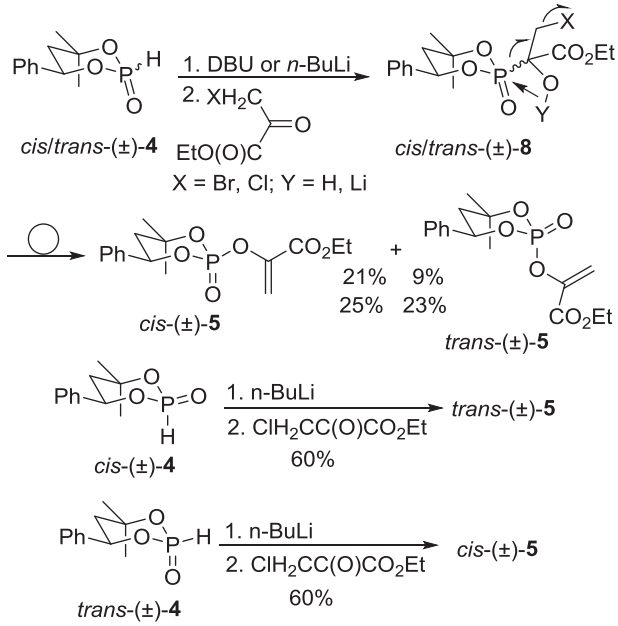

**Figure 1.** Crystal structure of cyclic phosphite *trans*-(±)-**7** drawn with 50% displacement ellipsoids. The second molecule from the asymmetric unit was omitted for clarity.




**Scheme 4.** Acid-catalyzed hydrolysis of cyclic phosphites (±)-**7**.

followed by flash chromatography furnished a *cis*/*trans*-mixture of *H*-phosphonates (±)-**4** in 69% yield. Importantly, when *trans*-(±)-**7** predominated in the starting material by 2:1, *H*-phosphonate *cis*-(±)-**4** was formed preferentially (2.5:1). This result indicated at least a stereoselective inversion of configuration upon hydrolysis. In order to study the behavior of individual homogeneous samples of *cis*- and *trans*-isomer, they were hydrolyzed under the same conditions as their mixture before. As expected, *cis*-(±)-**7** gave preferentially *trans*-(±)-**4** and vice versa, but both in admixture with a small amount of the respective isomer. It is not clear whether pseudorotation[14] interfered with the hydrolytic process or whether partial epimerization of phosphites[15] (±)-**7** or *H*-phosphonates (±)-**4** at phosphorus under the acidic conditions caused the formation of the respective isomer. In any case, hydrolysis did not proceed stereospecifically to deliver just one isomer as envisioned. However, it can be used to prepare oxygen isotope-labeled *H*-phosphonates easily, if $H_2{}^{16}O$ is replaced by $H_2{}^{18}O$ or $H_2{}^{17}O$.

For convenience, the mixture of diastereomeric *H*-phosphonates (±)-**4** needed for the following experiments was prepared by transesterification[8] of 1,3-diol (±)-**2** with bis(2,2,2-trifluoroethyl) phosphite and not by hydrolysis of phosphites (±)-**7**. The first experiment was performed with ethyl 3-bromopyruvate and DBU as base ($pK_a$ in $CH_3CN$: 23.9[16]) in DMF at ambient temperature (Scheme 5). DBU deprotonated the *H*-phosphonates ($pK_a$ in *i*PrOH: 17.4[17]), which attacked the $\alpha$-carbonyl group of pyruvate. The mixture of the *cis*/*trans*-hydroxyphosphonates (±)-**8** formed underwent a DBU-catalyzed $\alpha$-hydroxyphosphonate-phosphate rearrangement[8,9] with expulsion of $Br^-$. The two enol phosphates could be separated by flash chromatography and their spectra were identical to those of the literature.[7] Although the yields for the *cis*- and *trans* isomer (21% and 9%) were low, it was worth testing *n*-BuLi as base and ethyl 2-chloropyruvate[18] as the carbonyl compound at lower temperature. *n*-BuLi converted the mixture of *H*-phosphonates (*cis*/*trans* 1.2:1) to the corresponding lithium salts at −78°C quantitatively. Addition of 3-chloropyruvate induced the formation of the lithiated hydroxyphosphonates (±)-**8**, which rearranged upon slowly warming the reaction mixture to −25°C in the cooling bath. Neither *H*-phosphonate nor phosphonate derived from 3-chloropyruvate and lithiated phosphonate by nucleophilic




**Scheme 5.** Preparation of protected PEP by using the $\alpha$-hydroxyphosphate-phosphate rearrangement.

substitution of chloride could be detected in the crude product by $^1$H NMR spectroscopy.

The 1,3-diol (±)-**2** was also present in the crude product (*cis*-enol phosphate / *trans*-enol phosphate / 1,3-diol (±)-**2** = 1:1:1) and was removed by flash chromatography. The yield of *cis*- and *trans*-enol phosphate increased to acceptable 25% and 23%, respectively. Repetition of the experiment delivered the same yields. To evaluate the stereoselectivity of the reaction, the homogeneous *H*-phosphonates were similarly allowed to react with *n*-BuLi and ethyl 3-chloropyruvate. *H*-Phosphonate *cis*-(±)-**5** containing 1% of *trans*-isomer furnished less polar enol phosphate *trans*-(±)-**5** in 60% yield [crude product: *trans*-(±)-**5** / 1,3-diol (±)-**2** = 1.0:0.30] in admixture with 1% of *cis*-(±)-**5**. However, homogeneous *trans*-*H*-phosphonate gave only the more polar enol phosphate *cis*-(±)-**5** in 56% yield [crude product: *cis*-(±)-**5** / 1,3-diol (±)-**2** = 1.0:0.37 by $^1$H NMR]. Therefore, lithiated *H*-phosphonates do not epimerize under the reaction conditions and are added to the $\alpha$-carbonyl group of ethyl 3-chloropyruvate with retention of configuration at the phosphorus atom. The subsequent rearrangement of the deprotonated $\alpha$-hydroxyphosphonates follows a retentive course. Satisfyingly, each *H*-phosphonate undergoes a stereospecific reaction.

## Conclusion

We have shown that cyclic *cis*- and *trans*-phosphites derived from 1,3-diol (±)-**2** and tris(hexafluoroisopropyl) phosphite are formed and easily hydrolyzed to give cyclic *H*-phosphonates. These convert ethyl 3-chloropyruvate mediated by *n*-BuLi in a stereospecific $\alpha$-hydroxyphosphonate-phosphate rearrangement to protected PEP. When an $^{18}$O-labeled enantiomer of 1,3-diol **2** is utilized for the preparation of cyclic phosphites **7** and $H_2{}^{17}O$ for their hydrolysis, the enantiomers of cyclic *H*-phosphonates *cis*- and *trans*-[$^{17}$O,$^{18}$O$_1$]**4** will result. These can be transformed into protected

(*R*)- and (*S*)-[$^{16}$O,$^{17}$O,$^{18}$O]phosphoenol pyruvate by the $\alpha$-hydroxyphosphonate-phosphate rearrangement. Deprotection by the literature protocol will afford the *P*-chiral phosphoenol pyruvates. The presented sequence is a formal synthesis of (*R*)- and (*S*)-[$^{16}$O,$^{17}$O,$^{18}$O]phosphoenol pyruvate.

## Experimental

$^{1}$H, $^{13}$C (*J*-modulated) and $^{31}$P NMR spectra were recorded in $CDCl_3$ and $CD_2Cl_2$ with a Bruker Avance AV III 400 ($^{1}$H: 400.27 MHz, $^{13}$C: 100.65 MHz, $^{31}$P: 162.03 MHz) and with a Bruker Avance AV III 600 ($^{1}$H: 600.25 MHz, $^{13}$C: 150.93 MHz, $^{31}$P: 242.94 MHz) spectrometer at 25°C. Chemical shifts ($\delta$) are reported in parts per million (ppm) relative to $CHCl_3$ / $CDCl_3$ ($\delta_H$ 7.24, $\delta_C$ 77.0) and $CHDCl_2$ / $CD_2Cl_2$ ($\delta_H$ 5.24, $\delta_C$ 53.5) and external $H_3PO_4$ (85%; $\delta_P$ 0.0); coupling constants (*J*) are given in Hz. Data for $^{1}$H NMR spectra are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constants, and integration. IR spectra were recorded with a Bruker VERTEX 70 IR Spectrometer in ATR mode. HPLC was performed either on a Jasco System with a PU-980 pump, UV 975 and RI 930 detector (in case of analytical determination) or on a Dynamix Model SD-1 with a UV-1 absorbance detector (in case of semipreparative separation using Nucleosil 50–5 column, Ø 4.6 cm × 25 cm). Melting points were measured with a Leica Galen III Thermovar instrument and are uncorrected. Small amounts of liquids were added to reaction mixtures by using a $\mu$L syringe.

Flash (column) chromatography was performed with silica gel 60 (230–400 mesh) and monitored by TLC, conducted on glass-backed 0.25 mm thick silica gel 60 $F_{254}$. Spots were visualized by UV and / or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24} \bullet 4\ H_2O$ (23.0 g) and $Ce(SO_4)_2 \bullet 4\ H_2O$ (1.0 g) in 10% aqueous $H_2SO_4$ (500 mL), followed by heating with a heat gun.

### *cis- and trans-(±)-2-[(1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy]-4,4-dimethyl-6-phenyl-1,3,2-dioxaphosphinane [cis- and trans-(±)-7]*

A mixture of diol (±)-**2** (0.36 g, 2 mmol), tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite[13] (1.117 g, 2.1 mmol, sensitive to oxygen and moisture!) and $Et_3N$ (1 mmol, 0.14 mL) in dry $CH_2Cl_2$ (8 mL) was stirred under argon for 40 min at room temperature and then concentrated under reduced pressure (*trans*/*cis*, 2:1, by $^{31}$P NMR). The crude product was purified by bulb to bulb distillation (65–100°C / 1.4 mbar) to yield a mixture of cyclic phosphites *trans*- and *cis*-(±)-**7** (0.669 g, 89%) as a colorless oil. The isomers were separated by semipreparative HPLC; injection of 1.8 mL of solution (25 mg of mixture of *cis*/*trans*-(±)-**7**/mL); 10% $CH_2Cl_2$ in hexanes (40 mL/min); *trans*-(±)-**7**: $t_r$ = 2.32 min, mp 37–38°C (hexanes); *cis*-(±)-**7**: $t_r$ = 2.77 min, colorless oil.

Alternatively, a rapid flash chromatography (heptane / EtOAc, 7:1, *trans*: $R_f$ = 0.69, *cis*: $R_f$ = 0.58) gave a mixture with the same ratio of the isomers as in the crude product with minimal loss of product. A standard flash chromatography (heptane / $CH_2Cl_2$, 5:1; TLC with heptane / $CH_2Cl_2$, 4:1; *trans*: $R_f$ = 0.52, *cis*: $R_f$ = 0.38) allowed the separation of the isomers, but with losses in yields, especially for the more polar *cis*-isomer.

***trans*-(±)-7**: IR (ATR): $\nu$ = 1375, 1271, 1211, 1191, 1167, 1105, 1020, 1003, 965 cm$^{-1}$. $^{1}$H NMR (400.27 MHz, $CDCl_3$): $\delta$ = 7.39-7.28 (m, 5H), 5.51 (ddd, *J* = 12.0, 3.2, 2.1 Hz, 1H), 4.61 (septd, *J* = 6.4, 5.9 Hz, 1H), 2.20 (dd, *J* = 14.3, 12.0 Hz, 1H), 1.87 (ddd, *J* = 14.3, 3.2, 2.1 Hz, 1H), 1.64 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (150.93 MHz, $CDCl_3$): $\delta$ = 140.7 (d, *J* = 3.0 Hz), 128.6 (2C), 128.2, 125.7 (2C), 121.3 (q with fine structure, *J* = 283.4 Hz, 2C), 78.0 (d, *J* = 9.1 Hz), 70.0 (septd, *J* = 33.4, 23.8 Hz), 68.7 (d, *J* = 3.0 Hz), 46.3 (d, *J* = 3.5 Hz), 32.5 (d, *J* = 4.5 Hz), 28.0. $^{31}$P NMR (162.03 MHz, $CDCl_3$): $\delta$ = 132.0 (sept, *J* = 7.2 Hz). Anal. Calcd for $C_{14}H_{15}F_6O_3P$ (376.23): C, 44.69; H, 4.02. Found: C, 44.78; H, 4.22.

***cis*-(±)-7**: IR (ATR): $\nu$ = 2917, 1375, 1290, 1228, 1197, 1107, 1057, 968 cm$^{-1}$. $^{1}$H NMR (600.25 MHz, $CD_2Cl_2$): $\delta$ = 7.34-7.23 (m, 5H), 5.24 (td, *J* = 12.6, 3.3 Hz, 1H), 4.73 (septd, *J* = 7.4, 6.0 Hz, 1H), 2.69 (dd, *J* = 14.9, 12.6 Hz, 1H), 1.87 (td, *J* = 14.9, 3.3 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR (150.93 MHz, $CD_2Cl_2$): $\delta$ = 141.4, 128.6 (2C), 128.1, 126.1 (2C), 121.5 (q with fine structure, *J* = 284.5 Hz, 2C), 77.5 (d, *J* = 7.6 Hz), 74.0 (d, *J* = 7.4 Hz), 70.4 (septd, *J* = 33.7, 27.2 Hz), 44.6 (d, *J* = 15.7 Hz), 31.2, 28.1 (d, *J* = 1.5 Hz). $^{31}$P NMR (242.99 MHz, $CD_2Cl_2$): $\delta$ = 132.3 (sept, *J* = 7.9 Hz).

### *Test of thermal configurational stability of trans-(±)-7*

A small sample (50 mg) of *trans*-(±)-**7** was bulb to bulb distilled (80°C / 1 mbar). The $^{1}$H and $^{31}$P NMR spectrum recorded in toluene-$d_8$ showed that the distilled sample was still homogeneous and did not contain *cis*-(±)-**7**.

### *Hydrolysis of cyclic phosphites (±)-7 – cis- and trans-(±)-4,4-dimethyl-6-phenyl-1,3,2-dioxaphosphinane-2-oxides [cis- and trans-(±)-4]*

A mixture of phosphites *cis*- and *trans*-(±)-**7** (0.75 g, 2.0 mmol, *trans*/*cis*, 2:1), $H_2O$ (7.2 mmol, 0.13 mL) and TMSCl (0.11 g, 1.0 mmol, 0.12 mL) in dry THF (5 mL) was stirred at room temperature under argon for 30 min. 1,1,1,3,3,3-Hexamethyldisilazane (0.18 g, 1.1 mmol, 0.14 mL) was added (under argon!) and the solution was concentrated under reduced pressure. The crude product was dried (45°C / 1 mbar) for 5 min and then purified by flash chromatography (EtOAc, $R_f$ = 0.50) to yield a crystalline mixture (0.31 g, 69%; *cis*/*trans*, 2.5:1 by $^{1}$H NMR) of cyclic *H*-phosphonates *cis*- and *trans*-**4**. The NMR spectra ($^{1}$H, $^{31}$P) were identical to those of the literature.[8]

Similarly, phosphite *cis*-(±)-**7** (0.15 g, 0.40 mmol) was converted to *H*-phosphonate *trans*-(±)-**4** [0.07 g, 78%, contained 10% of *cis*-(±)-**4**] as colorless solid.

Similarly, phosphite *trans*-(±)-**3** (0.42 g, 1.12 mmol) was converted to *H*-phosphonate *cis*-(±)-**4** [0.23 g, 91%, contained 6% of *trans*-(±)-**4**] as colorless solid.

### *Preparation of enol phosphates (±)-5 using DBU as base*

Ethyl 3-bromopyruvate (0.14 g, 90 $\mu$L, 0.72 mmol) and DBU (0.21 g, 0.20 mL, 2 equiv.) were added to a solution of *H*-phosphonates *cis*- and *trans*-(±)-**4** (0.16 g, 0.71 mmol, *cis*/*trans*, 1.3:1) dissolved in dry DMF (4 mL) at 0°C under argon. The dark colored reaction mixture was stirred for 30 min and concentrated under reduced pressure. The residue was diluted with $CH_2Cl_2$ (5 mL), washed with water (2 × 3 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was flash chromatographed (hexane / EtOAc, 2:1, *trans*-(±)-**5**: $R_f$ = 0.34; *cis*-(±)-**5**: $R_f$ = 0.20) to yield enol phosphate *trans*-(±)-**5** (0.022 g, 9%) and *cis*-(±)-**5** (0.050 g, 21%) as colorless oils. The NMR spectra of the two compounds were identical to the ones reported in the literature.[7]

### *Preparation of enol phosphates (±)-5 using n-BuLi as base*

*n*-BuLi (1.12 mL, 2.5 M solution in hexane; 2.8 mmol, 1.1 equiv.) was dropwise added to a solution of the mixture of *H*-phosphonates (±)-**4** (0.576 g, 2.55 mmol, *cis*/*trans*, 1.2:1) in dry THF (7 mL) under argon at –78°C. After stirring for 3 min, the solution of ethyl 3-chloropyruvate[18] (0.422 g, 2.8 mmol, 1.1 equiv.) in dry THF (3 mL) was added quickly. The reaction mixture was allowed to warm slowly in the cooling bath. When the temperature had risen to –25°C (within 2 h), AcOH (five small drops) was added. The reaction mixture was concentrated under reduced pressure. $CH_2Cl_2$ (25 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL) were added. The organic phase was separated and the aqueous one was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were washed with water (10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure. After recording $^1$H and $^{31}$P NMR spectra of the residue (*cis*-enol phosphate / *trans*-enol phosphate / 1,3-diol (±)-**2**, 1:1:1), it was flash chromatographed ($CH_2Cl_2$ / acetone, 20:1, *trans*: $R_f$ = 0.50; *cis*: $R_f$ = 0.33; 1,3-diol (±)-**2**: $R_f$ = 0.16) to yield enol phosphates *cis*-(±)-**5** (0.221 g, 25%) and *trans*-(±)-**5** (0.200 g, 23%), both as colorless crystals, and 1,3-diol (±)-**2** (0.080 g, 18%) as gum. The NMR spectra of the three compounds were identical to the ones reported in the literature.[7,19]

Similarly, *H*-phosphonate *cis*-(±)-**4** (0.440 g, 1.95 mmol, contained 1% of *trans*-isomer) was converted to homogeneous enol phosphate *trans*-(±)-**5** (0.395 g, 60%).

Similarly, homogeneous *H*-phosphonate *trans*-(±)-**4** (0.534 g, 2.36 mmol) was converted to homogeneous enol phosphate *cis*-(±)-**5** (0.447 g, 56%).

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