# The Phosphonate−Phosphate and Phosphate−Phosphonate Rearrangements and Their Applications, VI[+]

# Metallation of Phosphorylated Aliphatic Alcohols to Configurationally Stable α-Oxyalkyllithium Compounds − Use of the Phosphoryl Group as an Activating Group and Electrophile

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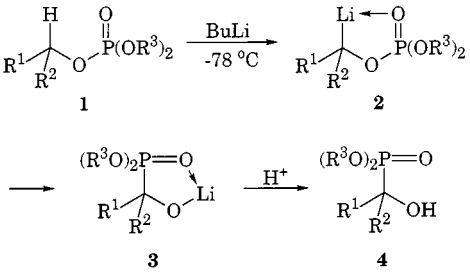
Alkyl diisopropyl phosphates were metallated by *s*BuLi/TMEDA at –78 °C at the alkyl and isopropyl group in a ratio which is strongly influenced by steric effects. The regioselectivity of deprotonation was very high by use of heptadeuterioisopropyl groups, which reflects a high primary kinetic isotope effect ($k_H/k_D \geq 100$). The dipole-stabilized, phosphoryloxy-substituted alkyllithium compounds formed are configurationally stable and rearrange with retention of configuration (phosphate–phosphonate rearrangement).

## Introduction

Organolithium compounds[1] with a heteroatom such as sulfur, phosphorus, selenium or, as found in recent years, nitrogen[2] or oxygen[3] in the α-position are a very important group of intermediates. Still's finding that α-oxyalkyllithium compounds are configurationally stable at low temperature, was a significant discovery in the field of carbanion chemistry.[4] It resulted in a widespread interest in the direct metallation of derivatised alcohols and amines, in the configurational[5] stability of metallated species, in their mechanism of inversion of configuration[6] and in the stereochemical outcome of their reaction with electrophiles.

Primary aliphatic alcohols can be deprotonated after transformation into 2,6-disubstituted benzoates[7,8] or carbamates with a shielded carbonyl group as found by Hoppe et al. The success of the latter derivatives stems from their highly enantioselective metallation by *s*BuLi/(−)-sparteine[3] to α-oxyalkyllithium compounds, which are configurationally stable below −30 °C.

α-Oxy(arylmethyl)lithium compounds **2** ($R^1$ = Ar, $R^2$ = H or alkyl, $R^3$ = alkyl) are intermediates of the phosphate−phosphonate rearrangement (Scheme 1).[9] Benzylic alcohols can be transformed into dialkyl benzyl phosphates **1** which isomerise smoothly to lithiated α-hydroxyphosphonates **3** after metallation. The carbanionic species **2** reacts with the internal electrophile, the phosphoryl group, but does not react with external electrophiles. The reverse process, the phosphonate−phosphate rearrangement is also known and occurs under thermodynamic control.[10] Recently, the range of phosphoryloxy-substituted organolithium compounds accessible by metallation of phosphates was extended significantly.[12] We found that triethyl, tri-*n*-propyl and tri-*n*-butyl phosphate can be deprotonated by *s*BuLi/TMEDA at −78 °C. This finding caused us to study the regioselectivity and the primary kinetic isotope effect of the deprotonation of purely aliphatic phosphates, the configurational stability of the lithiated species, and the stereochemistry of the rearrangement at carbon. Furthermore, we demonstrated that the regioselectivity of metallation can be controlled by the use of deuterium.




Scheme 1. Phosphate−phosphonate rearrangement

## Results and Discussion

### Synthesis of Phosphates and Regioselectivity of Their Metallation

The required unsymmetrical phosphates **6** were obtained by phosphorylation of primary aliphatic alcohols **5** with diisopropyl bromophosphate, prepared from triisopropyl phosphite and bromine at low temperature (Scheme 2). The isopropyl group was used as a protecting group, because metallation at C-2 was considered to be extremely unlikely.

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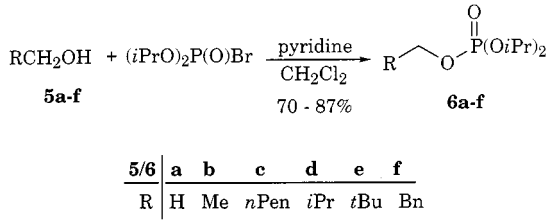
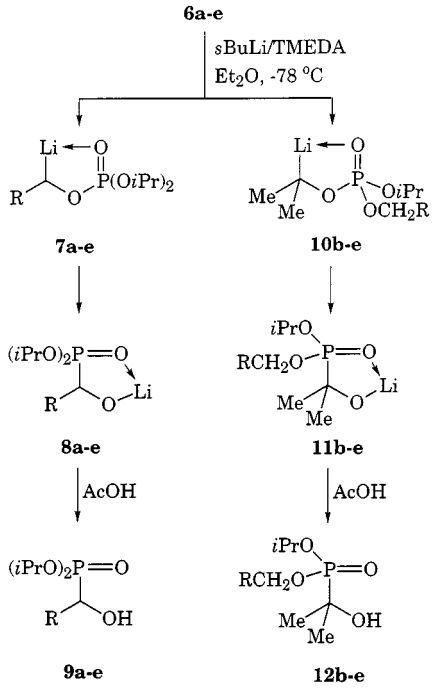



Scheme 2. Preparation of alkyl diisopropyl phosphates from primary aliphatic alcohols and diisopropyl bromophosphate

The phosphates **6a**−**e** were treated with 2 equivalents of *s*BuLi/TMEDA in diethyl ether at −78 °C for 3−5 h (Scheme 3). Extractive work up and flash chromatography furnished the reaction products. The results are compiled in Table 1. As expected, diisopropyl methyl phosphate (**6a**) was deprotonated regioselectively at the methyl group giving the dipole-stabilized[12] α-oxymethyllithium compound **7a**. This species is very likely to be short-lived, because the phosphoryl group migrates intramolecularly (1,2-migration of phosphorus, phosphate−phosphonate rearrangement). The α-hydroxymethylphosphonate **9a** was isolated in 55% yield. Substrates were then selected in which one of the hydrogen atoms of the methyl group of **6a** was replaced by a methyl, *n*-pentyl, isopropyl, or *tert*-butyl group. The increasing bulkiness of the substituents was found to be a simple way of influencing the regioselectivity of metallation. Deprotonation now occurred competitively at the methylene and at the methine groups, resulting in the formation of intermediates **7b**−**e** and **10b**−**e**, respectively. The phosphate−phosphonate rearrangement gave mixtures of the secondary and tertiary α-hydroxyphosphonates **9b**−**e** and **12b**−**e** (see Table 1). The mixture of **9e/12e** could be separated by flash chromatography, while the mixtures of **9c/12c** and **9d/12d** were separated by HPLC chromatography. The ratio changed from 4:1 in favour of the secondary α-hydroxyphosphonate for R = Me to 1:11.5 in favour of the tertiary α-hydroxyphosphonate for R = *t*Bu. Simultaneously, the reaction rate decreased and 25% of starting material was still present for **6e** after a reaction time of 5 h. The ratios of secondary α-hydroxyphosphonate **9** (δ = 24−25) to tertiary α-hydroxyphosphonate **12** (δ = 27−28) could easily be determined from the $^{31}$P NMR spectra. The few examples show that the regioselectivity of metallation is a subtle interplay between acidity and steric effects, especially of substituents at the β-carbon atom. *The deprotonation of the isopropyl group is very surprising. It is to the best of our knowledge the first reported example for the metallation of a protected secondary alcohol (2-propanol) α to the oxygen atom.* Diisopropyl 2-phenylethyl phosphate (**6f**) did not give the isomeric α-hydroxyphosphonate although it was consumed. E2 elimination of diisopropyl phosphate with formation of styrene was facilitated by the phenyl ring, which enhances the acidity of the hydrogen atoms at the β-carbon atom.

The isopropyl groups were replaced in two cases by heptadeuterioisopropyl groups to show whether the regioselectivity could be improved by exploiting the primary kinetic isotope effect (Scheme 4). This approach is interesting for mechanistic reasons, but not for practical ones, although perdeuterated 2-propanol is relatively cheap. Similar considerations have already been used by Hoppe,[13] by our research group[14] and by Clayden[15] to control metallation. Tris(heptadeuterioisopropyl) phosphite needed for the synthesis of the corresponding bromophosphate, was prepared from perdeuterated 2-propanol (D ≥ 98%) analogously to triisopropyl phosphite in 87% yield.[16] The deuterated phosphates **13**, **15**, and **17** of Scheme 4 were prepared according to Scheme 2 except that deuterated components were used. Metallation of phosphate **13** afforded only the secondary α-hydroxyphosphonate **14** in 79% yield. The isomeric tertiary α-hydroxyphosphonate which would result from removal of the α-deuterium of the deuterated isopropyl group could not be detected by $^{31}$P-NMR spectroscopy in the crude product. On the other hand, phosphate−phosphonate rearrangement of phosphate **15** derived from [1,1-$^2H_2$]hexanol produced only the tertiary α-

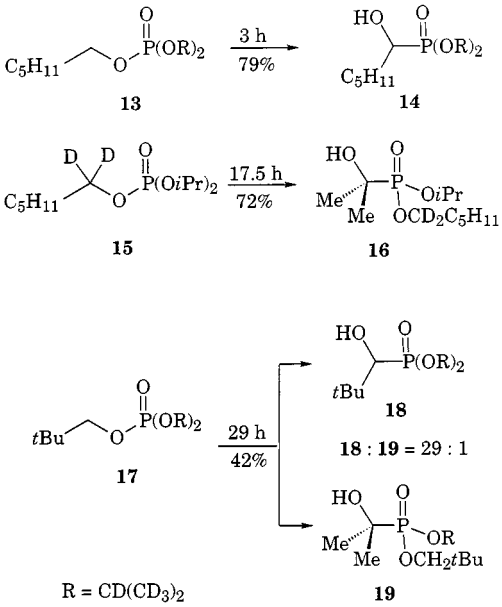



Scheme 3. Rearrangement of alkyl diisopropyl phosphates using *s*BuLi/TMEDA

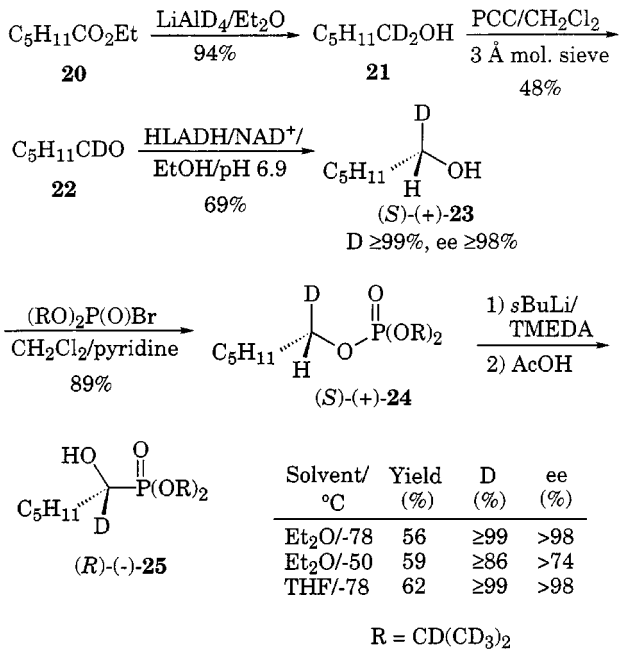
Table 1. Results of phosphate−phosphonate rearrangement of **6a**−**e** with *s*BuLi/TMEDA in $Et_2O$ at −78 °C after quenching with AcOH

| **6** | R | Time [h] | **6** (%)[a] | **9** (%)[a] | **12** (%)[a] | **9/12** | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| **a** | H | 5 | – | 100 | – | 1:0 | 55 |
| **b** | Me | 3 | – | 80 | 20 | 4:1 | 75[c] |
| **c** | *n*Pen | 3 | 6 | 67 | 27 | 2.5:1 | 46[c] |
| **d** | *i*Pr | 3 | 18 | 35 | 47 | 1:1.3 | 60[c] |
| **e** | *t*Bu | 5 | 25 | 6 | 69 | 1:11.5 | 57[d] |

[a] Composition of crude product as determined by $^{31}$P NMR spectroscopy. – [b] Combined yield of **9** und **12**. – [c] Separated by HPLC. – [d] Separated by flash column chromatography.




Scheme 4. Regioselective metallation of specifically deuterated phosphates




Scheme 5. Synthesis and phosphate−phosphonate rearrangement of phosphate (*S*)-(+)-**24**

hydroxyphosphonate **16** in 72% yield. These two substrates demonstrate that metallation can be controlled by use of deuterium as a "protecting group". Bis(heptadeuterioisopropyl) neopentyl phosphate (**17**) produced a 29:1 mixture (by $^{31}$P NMR) of secondary and tertiary α-hydroxyphosphonate, **18** and **19**, respectively. The yield was low (42%) despite a reaction time of 29 h, reflecting the reduced reaction rate. Some starting material (17%) could be recovered unchanged. The primary kinetic isotope effect estimated for this transformation is 334 [11.5:1 (see Table 1)/29:1 = 334], which is very high.

### Configurational Stability of an α-Phosphoryloxy-Substituted Alkyllithium Compound and Stereochemistry of Its Rearrangement

These two aspects were studied for the first time on a nonbenzylic substrate choosing (*S*)-(+)-[1-$^2$H$_1$]hexanol as alcohol which can be prepared chemoenzymatically (Scheme 5).[17] Ethyl hexanoate (**20**) was reduced with $LiAlD_4$ (D ≥ 98%) in diethyl ether to form the dideuterated hexanol **21** (D ≥ 98%) in 94% yield, which was oxidised to the deuterated hexanal **22** (D ≥ 99%, yield 48%) with PCC in the presence of 3 Å molecular sieves.[18] The aldehyde was reduced stereospecifically with horse liver alcohol dehydrogenase/NAD$^+$/EtOH in a phosphate buffer pH 6.9 at 30 °C for 16 h to give (*S*)-(+)-1-deuteriohexanol (**23**) in 69% yield.[19] The absolute configuration of the alcohol was assigned on the basis of precedence for the reduction of other aldehydes.[17,19] Its enantiomeric excess (*ee* ≥ 98%) was determined by derivatisation with (*S*)-(+)-MTPACl/pyridine and $^1$H NMR spectroscopy with decoupling of the hydrogen substituents at C-2. Phosphorylation of the deuterated hexanol **23** with perdeuterated diisopropyl bromophosphate in the same way as hexanol furnished phosphate (*S*)-(+)-**24**.

Metallation of phosphate (*S*)-(+)-**24** was studied at −78 °C in both diethyl ether and THF and at −50 °C in diethyl ether. The results for the two solvents at −78 °C are very similar. As the α-hydroxyphosphonate **25** formed is laevorotatory, it must have an (*R*) configuration.[20] Deuteration was ≥ 99% ($^1$H NMR) and the enantiomeric excess > 98% as determined by $^{31}$P NMR spectroscopy of the corresponding Mosher ester.[20] These data unequivocally prove that the primary kinetic isotope effect at −78 °C is very high ($k_H/k_D \geq 100$), that the intermediate phosphoryloxy-substituted hexyllithium compound is configurationally stable and that it rearranges with retention of configuration. The corresponding benzyllithium compound is configurationally not completely stable and rearranges also with retention of configuration.[14] Increasing the reaction temperature to −50 °C caused a competing deprotonation and dedeuteration, resulting in a deuterium content of ≥ 86% which corresponds to $k_H/k_D = 6.1$. Metallation generates a mixture consisting of 86% of deuterated (*R*)-organolithium compound and 14% of the unlabeled (*S*) enantiomer. This ratio translates itself into the corresponding hydroxyphosphonates **25**, if the organolithium compound is configurationally stable. The calculated enantiomeric excess of 72% fits nicely with the experimental value of 74%. Therefore, the phosphoryloxy-substituted hexyllithium is configurationally stable up to −50 °C.

## Conclusions

It has been shown that metallation of diisopropyl phosphates derived from primary aliphatic alcohols, except methanol, takes place at the alkyl as well as the isopropyl group, although the latter are less acidic. Exclusive or pref-

erential deprotonation at the primary alkyl group was accomplished by the use of heptadeuterioisopropyl instead of isopropyl protecting groups at the phosphorus atom. The coordination of the lithium ion to the P=O group, well-known from the deaggregating effect of HMPA on organolithium reagents, seems to be essential for the deprotonation to proceed (prelithiation complex). It causes an additional acidification of the hydrogen atoms α to the oxygen atoms and facilitates their removal (complex-induced proximity effects).[21] The primary kinetic isotope effect for metallation is low ($k_H/k_D = 6$) at −50 °C and very high ($k_H/k_D \geq 100$) at −78 °C which can only be explained by inferring tunnelling.[22] Very high kinetic isotope effects for metallations were observed by Hoppe et al.[13] as well as by our group[14] and by Claydon et al.[15]. The presumably short-lived alkyllithium compounds were configurationally stable up to at least −50 °C and rearrange, with retention of configuration, into the corresponding α-hydroxyphosphonates (phosphate−phosphonate rearrangement). The phosphoryl group has a double function. It is an activator for the alcohol and an internal electrophile for the carbanion. Surprisingly, the phosphoryl substituent is to date the only group which allows the metallation of even secondary alcohols. Experiments are under way to exploit the potential of these findings.

## Experimental Section

**General:** TLC: Merck precoated TLC plates (0.25 mm), silica gel 60, $F_{254}$; detection: UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24} \cdot 4\,H_2O$ (24 g) and $Ce^{IV}(SO_4)_2 \cdot 4\,H_2O$ (1 g) in $H_2SO_4$ in water (10%, 500 mL), followed by heating with a hot gun. − Flash column chromatography (FC): Merck silica gel 60, 0.040−0.063 mm; eluents: hexane (HE), dichloromethane (DC) and ethyl acetate (EA). − IR: Perkin−Elmer FT 1600 IR-Spectrometer [Si: a solution of the sample in $CH_2Cl_2$ or $CDCl_3$ (NMR sample) was applied to an Si plate and the solvent was allowed to evaporate].[23] − $^1$H and $^{13}$C NMR (*J* modulated) spectra were recorded in $CDCl_3$ with a Bruker AM 400 WB (Bruker AC 250) at 400.13 (250.13) and 100.61 MHz, respectively. $^{31}$P NMR spectra were recorded with the same spectrometer at 161.98 MHz using $H_3PO_4$ (85%) as external standard. In order to obtain undistorted $^{31}$P signal intensities for an accurate integration, adequate relaxation times were used without irradiation during this period to avoid NOE enhancements. − Optical rotation: Perkin−Elmer polarimeter 241 (1-dm cell). − Analytical HPLC: Hibar® Prepacked Column RT 250-4 Customized Packing, Superspher® Si60 (4 μm, Merck), 20 °C, 2 mL/min, 10 μL were injected, pump: Jasco PU 980, detector: Jasco RI 930; semipreparative HPLC: Superspher® Si60 (4 μm, Merck), 250 × 32 mm, 80 mL/min, injection volume: 2 mL, pump: Rainin Dynamax®, Modell SD-1, RI-detector of Knauer; solvent for analytical and semipreparative HPLC: 2-propanol/hexane, 1:20. − Reactions were carried out in freshly distilled, dry solvents. THF was distilled from potassium and diethyl ether from lithium tetrahydroaluminate. TMEDA was heated at reflux for 5 h with $CaH_2$, distilled, and stored over molecular sieves (4 Å). The commercially available *s*BuLi (1.3 M solution in cyclohexane) was stored at +4 °C and used as long as the amount of precipitated LiH was not significant.

**Preparation of Alkyl Diisopropyl and Bis(heptadeuterioisopropyl) Alkyl Phosphates (General Procedure A):** A solution of bromine (1.76 g, 0.57 mL, 11.00 mmol) in dry $CH_2Cl_2$ (10 mL) was added dropwise at −50 °C to a stirred solution of triisopropyl phosphite (2.40 g, 11.50 mmol, 2.85 mL) [tris(heptadeuterioisopropyl) phosphite (2.63 g, 11.50 mmol)] in dry $CH_2Cl_2$ (15 mL) under argon. After 15 min, a solution of alcohol (10 mmol) and dry pyridine (1.6 mL) in dry $CH_2Cl_2$ (10 mL) was added. The cooling bath was removed and the reaction mixture was stirred for 2 h at room temperature. Hydrochloric acid (25 mL, 2 M) was added and stirring was continued for 30 min. The organic phase was separated. The aqueous phase was extracted with $CH_2Cl_2$ (20 mL). The combined organic layers were washed successively with 20 mL each of water and a saturated bicarbonate solution, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by FC and bulb-to-bulb distillation to give phosphates as colourless liquids.

**Phosphate−Phosphonate Rearrangement of Aliphatic Phosphates (General Procedure B):** A stirred solution of phosphate (1 mmol) and TMEDA (0.30 mL, 0.23 g, 2.00 mmol) in dry diethyl ether (8 mL) was cooled to −78 °C under argon. A solution of *s*BuLi (2 mmol) in cyclohexane was added dropwise. After stirring for a few hours (see individual 1-hydroxyphosphonates), a solution of acetic acid (4 mL, 2 M) in dry diethyl ether was added. The cooling bath was removed and the reaction mixture was concentrated in a rotary evaporator. The residue was taken up in water (15 mL) and extracted with dichloromethane (4 × 15 mL). The combined organic phases were washed with water (15 mL), dried with $Na_2SO_4$ and concentrated in vacuo. The residue was purified by FC to give the colourless, oily hydroxyphosphonates.

**Diisopropyl Methyl Phosphate (6a)** was prepared according to General Procedure A from dry methanol (1.92 g, 2.43 mL, 60.00 mmol). The crude product was purified only by bulb-to-bulb distillation [75−80 °C/3 Torr (ref.[24] 32−32 °C/0.05 Torr)] to give 7.13 g (75%) of **6a**.

**Ethyl Diisopropyl Phosphate (6b)** was prepared according to General Procedure A from dry ethanol (1.84 g, 2.35 mL, 40.00 mmol). The crude product was purified by FC (DC/EA, 15:1; $R_f = 0.32$) and bulb-to-bulb distillation [60 °C/0.3 Torr (ref.[25]: 100−112 °C/25 Torr)] to give 5.94 g (70%) of **6b**. − $^1$H NMR (250.13 MHz, $CDCl_3$): δ = 1.331 (dt, $J$ = 7.1, 1.0 Hz, 3 H, $CH_3CH_2$), 1.333 (d, $J$ = 6.3 Hz, 12 H, $Me_2CH$), 4.08 (quint, $J$ = 7.1 Hz, 2 H, $CH_2O$), 4.64 (oct, $J$ = 6.3 Hz, 2 H, CHO).

**Diisopropyl Hexyl Phosphate (6c)** was prepared according to General Procedure A from hexanol (2.04 g, 2.51 mL, 20 mmol). The crude product was purified by bulb-to-bulb distillation (80−81 °C/0.1 Torr) to give 4.63 g (87%). The analytical sample was additionally purified by flash chromatography (PE/EA, 65:35; $R_f = 0.33$) and again by bulb-to-bulb distillation. − IR (film): $\tilde{\nu}$ = 2979 cm$^{-1}$, 2958, 2934, 1386, 1278, 1262, 1003. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (t, $J$ = 6.9 Hz, 3 H, Me), 1.30 (m, 6 H, $CH_2$), 1.30 (d, $J$ = 5.9 Hz, 12 H, $Me_2CH$), 1.64 (quint, $J$ = 6.7 Hz, 2 H, $CH_2$), 3.97 (q, $J$ = 6.7 Hz, 2 H, $CH_2O$), 4.60 (m, 2 H, CHO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.6 (d, $J_{PC}$ = 5.4 Hz), 25.1, 30.2 (d, $J_{PC}$ = 7.6 Hz), 31.3, 67.3 (d, $J_{PC}$ = 6.9 Hz), 72.1 (d, $J_{PC}$ = 6.1 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = −1.8. − $C_{12}H_{27}O_4P$ (266.3): calcd: C 54.12, H 10.21; found C 54.31, H 10.42.

**Isobutyl Diisopropyl Phosphate (6d)** was prepared according to General Procedure A from isobutyl alcohol (0.74 g, 0.92 mL, 10.00 mmol). The crude product was stirred for 2 h with concentrated ammonia (5 mL). Water (5 mL) was added and the product

was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The residue was purified by FC (HE/EA, 2:1; $R_f$ = 0.20, HE/EA, 1:1) and bulb-to-bulb distillation (54−55 °C/0.03 Torr)[26] to give 0.923 g (39%) of **6d**. − IR (Si): $\tilde{\nu}$ = 2979 $cm^{-1}$, 1386, 1376, 1262, 1143, 1180, 1110, 1008. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (d, $J$ = 6.5 Hz, 6 H, $Me_2$CH), 1.26 (d, $J$ = 6.1 Hz, 12 H, $Me_2$CHO), 1.88 (non, $J$ = 6.5 Hz, 1 H, $Me_2CH$), 3.70 (t, $J$ = 6.5 Hz, 2 H, $CH_2O$), 4.56 (oct, $J$ = 6.1 Hz, 2 H, CHO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 18.7, 23.6 (d, $J_{PC}$ = 4.9 Hz), 29.0 (d, $J_{PC}$ = 7.6 Hz), 72.1 (d, $J_{PC}$ = 6.0 Hz), 73.2 (d, $J_{PC}$ = 6.4 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = −1.8.

**Diisopropyl Neopentyl Phosphate (6e)** was prepared according to General Procedure A from neopentanol (0.88 g, 10.00 mmol). The crude product was purified by FC (HE/EA, 3:1; $R_f$ = 0.24, HE/EA, 1:1) and bulb-to-bulb distillation (128−133 °C/24 Torr) to give 1.85 g (73%) of **6e**. − IR (Si): $\tilde{\nu}$ = 2978 $cm^{-1}$, 1386, 1262, 1142, 1110, 1010. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.92 (s, 9 H, $Me_3C$), 1.31 (dd, $J$ = 6.3, 0.6 Hz, 12 H, $Me_2$CH), 3.63 (d, $J$ = 4.4 Hz, 2 H, $CH_2O$), 4.61 (dsept, $J$ = 6.9, 6.3 Hz, 2 H, CHO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 23.6 (d, $J_{PC}$ = 4.6 Hz), 23.7 (d, $J_{PC}$ = 4.6 Hz), 26.1, 32.0 (d, $J_{PC}$ = 8.3 Hz), 72.1 (d, $J_{PC}$ = 6.0 Hz), 76.5 (d, $J_{PC}$ = 6.8 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = −1.8. − $C_{11}H_{25}O_4P$ (252.3): calcd: C 52.37, H 9.99; found C 52.58, H 9.72.

**Diisopropyl 2-Phenylethyl Phosphate (6f)** was prepared from 2-phenylethanol (1.22 g, 1.19 mL, 10.00 mmol) according to General Procedure A. The crude product was purified by FC (HE/EA, 2:1; $R_f$ = 0.21) and bulb-to-bulb distillation (75−80 °C/0.1 Torr) to give 2.03 g (71%) of **6f**. − IR (Si): $\tilde{\nu}$ = 2980 $cm^{-1}$, 2937, 1468, 1455, 1386, 1376, 1263, 1064, 1008. − $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, $J$ = 6.5 Hz, 6 H, Me), 1.27 (d, $J$ = 6.5 Hz, 6 H, Me), 2.97 (t, $J$ = 7.0 Hz, 2 H, $PhCH_2$), 4.17 (q, $J$ = 7.0 Hz, 2 H, $CH_2O$), 4.54 (oct, $J$ = 6.5 Hz, 2 H, CHO), 7.20 (m, 3 H, $H_{arom}$), 7.27 (m, 2 H, $H_{arom}$). − $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 23.6 (d, $J_{PC}$ = 5.0 Hz), 36.8 (d, $J_{PC}$ = 7.4 Hz), 67.6 (d, $J_{PC}$ = 6.1 Hz), 72.3 (d, $J_{PC}$ = 5.9 Hz), 126.6, 128.4, 129.0, 137.3. − $C_{14}H_{23}O_4P$ (286.3): calcd: C 58.73, H 8.10; found C 58.49, H 8.21.

**Bis(heptadeuterioisopropyl) Hexyl Phosphate (13)** was prepared according to General Procedure A from hexanol (0.51 g, 0.63 mL, 5.00 mmol) and a stoichiometric amount of tris(heptadeuterioisopropyl) phosphite. The crude product was stirred for 30 min with concentrated ammonia (2 mL). Then water (5 mL) was added and the product was extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with water (5 mL), dried with $Na_2SO_4$ and purified by FC (HE/EA, 3:1; $R_f$ = 0.26) and bulb-to-bulb distillation (70−75 °C/0.01 Torr) to give 0.707 g (50%) of **13**. − IR (film): $\tilde{\nu}$ = 2959 $cm^{-1}$, 2933, 2234 (C−D), 1269, 1238, 1159, 1017, 994. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (t, $J$ = 6.9 Hz, 3 H, Me), 1.30 (m, 6 H, $CH_2$), 1.63 (quint, $J$ = 6.9 Hz, 2 H, $CH_2$), 3.96 (q, $J$ = 6.9 Hz, 2 H, $CH_2O$). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 13.9, 22.5, 25.1, 30.2 (d, $J_{PC}$ = 7.4 Hz), 31.3, 67.3 (d, $J_{PC}$ = 6.1 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = −1.7.

**1,1-Dideuteriohexyl Diisopropyl Phosphate (15)** was prepared according to General Procedure A from **21** (0.63 g, 6.00 mmol) (D ≥ 98%). The crude product was stirred for 2 h with concentrated ammonia (5 mL). Water (5 mL) was then added and the product was extracted with dichloromethane (2 × 5mL). The combined organic layers were washed with water (5 mL), dried with $Na_2SO_4$ and concentrated in vacuo. The residue was purified by FC (HE/EA, 2:1; $R_f$ = 0.30) and bulb-to-bulb distillation (85−90 °C/0.5 Torr) to give 0.923 g (58%) of **15**. − IR (film): $\tilde{\nu}$ = 2981 $cm^{-1}$, 2958, 2935, 1386, 1265, 1008. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (t, $J$ = 6.9 Hz, 3 H, Me), 1.30 (m, 6 H, $CH_2$), 1.30 (d, $J$ = 5.9 Hz, 12 H, $Me_2$CH), 1.62 (br. t, $J$ = 6.7 Hz, 2 H, $CH_2CD_2$), 4.59 (oct, $J$ = 5.9 Hz, 2 H, CHO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.6 (d, $J_{PC}$ = 4.7 Hz), 25.1, 30.0 (d, $J_{PC}$ = 7.1 Hz), 31.3, 72.1 (d, $J_{PC}$ = 5.9 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = −1.8.

**Bis(heptadeuterioisopropyl) Neopentyl Phosphate (17)** was prepared from neopentanol (0.35 g, 4.00 mmol) in the same way as the unlabeled compound **6e**, bp. 130−135 °C/24 Torr, yield: 0.864 g (81%). − IR (Si): $\tilde{\nu}$ = 2960 $cm^{-1}$, 2235 (C-D), 1367, 1256, 1159, 995. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.92 (s, 9 H, $Me_3C$), 3.62 (d, $J$ = 4.4 Hz, 2 H, $CH_2O$). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 26.0, 32.0 (d, $J_{PC}$ = 8.3 Hz), 76.5 (d, $J_{PC}$ = 6.8 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = −1.7.

**1,1-Dideuteriohexan-1-ol (21):** A solution of ethyl hexanoate (5.05 g, 5.80 mL, 35.00 mmol) in dry diethyl ether was added dropwise within 30 min to a stirred and cooled (0 °C) suspension of 0.97 g (23.00 mmol, 98% D) of $LiAlD_4$ in 35 mL of dry diethyl ether under argon.[27] After refluxing for 2 h, the reaction mixture was cooled to 0 °C and cold water (40 mL) and $H_2SO_4$ (10%, 60 mL) were added carefully. The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with brine (2 × 40 mL) and a saturated aqueous solution of bicarbonate (2 × 40 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was bulb-to-bulb-distilled (65−70 °C/15 Torr) to give 3.41 g (94%) of **21**[27] as a colourless liquid; $R_f$ = 0.32, HE/EA, 7:1; D ≥ 98% (by $^1$H NMR). − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (t, $J$ = 6.9 Hz, 3 H, Me), 1.28 (m, 6 H, $CH_2$), 1.52 (overlapping t and s, $J$ = 6.9 Hz, 3 H, $CH_2CD_2O$, OH). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.3, 31.6, 32.5, 62.3 (quint, $J_{DC}$ = 21.4 Hz, $CD_2$).

**1-Deuteriohexanal (22):** PCC (9.11 g, 42.00 mmol) was added to a vigorously stirred and water-cooled mixture of **21** (1.76 g, 16.90 mmol) and 3-Å molecular sieves (17 g) in dry dichloromethane (90 mL) under argon. After stirring for 1 h at room temperature, diethyl ether (250 mL) was added. The solution was decanted and the residue was washed with diethyl ether (4 × 50 mL). The solutions were filtered through silica gel (100 g) in a glass column. The filtrate was concentrated in a rotary evaporator (bath temperature: 20 °C). The residue was bulb-to-bulb-distilled (70−75 °C/64 Torr) to yield 0.82 g (48%) of **22**[27] as a colourless liquid; D ≥ 99% ($^1$H NMR). − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.87 (t, $J$ = 6.9 Hz, 3 H, Me), 1.29 (m, 4 H, $CH_2$), 1.61 (m, 2 H, $CH_2$), 2.39 (t, $J$ = 7.4 Hz, 2 H, $CH_2CDO$).

**(*S*)-(+)-1-Deuteriohexanol [(*S*)-(+)-23]:** The reduction of **22** was carried out according to ref.[19] with a minor modification. $NAD^+$ (0.120 g), HLADH (0.030 g), hexanal (0.795 g) in 1,4-dioxane (11 mL, from Na) were added to phosphate buffer (1440 mL, 10 mM, pH 6.9) containing freshly distilled 1,4-dioxane (25 mL, from Na) and dry ethanol (66 mL). After shaking gently at 30 °C in an incubator for 16 h, the reaction mixture was cooled and divided into two halves, of which one was extracted with diethyl ether (4 × 225 mL). The combined organic phases were washed with water (400 mL), dried with $MgSO_4$ and concentrated in vacuo. Both fractions were combined and purified by bulb-to-bulb distillation (40−90 °C/15 Torr) to furnish a solution of (*S*)-(+)-**23** in dioxane. FC (HE/EA, 7:1; $R_f$ = 0.32) and another bulb-to-bulb distillation (65−70 °C/15 Torr) gave 0.559 g (69%) of pure (*S*)-(+)-**23**[27]

as a colourless liquid; D ≥ 99%; $[\alpha]_D^{20} = +0.34$ ($c = 20.05$, acetone) {ref.[27]: reduction of **22** with baker's yeast; $[\alpha]_D^{225} = +0.31$ (neat, 1 dm)}; *ee* ≥ 98% by $^1$H NMR of Mosher ester. It was prepared in 92% yield from 0.02 g (0.19 mmol) of (*S*)-(+)-**23** and 1.5 equiv. of (*S*)-(+)-MTPACl and purified by FC (HE/DC, 4:1; $R_f = 0.25$). For comparison a sample of racemic [1-$^2H_1$]hexanol obtained by reduction of hexanal with $NaBD_4$ was esterified as well.

**(*S*)-(+)-1-Deuteriohexyl Bis(heptadeuterioisopropyl) Phosphate [(*S*)-(+)-24]** was prepared according to General Procedure A from of (*S*)-(+)-**23** (0.40 g, 3.88 mmol). The crude product was purified by FC (HE/EA, 3:1; $R_f = 0.26$) and bulb-to-bulb distillation (70−75 °C/0.01 Torr) to yield 0.972 g (89%) of (*S*)-(+)-**24**; $[\alpha]_D^{20} = +0.054$ ($c = 16.505$, acetone). − IR (film): $\tilde{\nu} = 2958$ cm$^{-1}$, 2862, 2234 (C−D), 1238, 1159, 991. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.85 (t, $J = 6.9$ Hz, 3 H, Me), 1.30 (m, 6 H, $CH_2$), 1.63 (q, $J = 7.0$ Hz, 2 H, $CH_2$), 3.94 (tq, $J = 7.0$, 1.5 Hz, 1 H, CHDO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 13.9, 22.5, 25.1, 30.1 (d, $J_{PC} = 7.2$ Hz), 31.3, 67.0 (dt, $J_{PC} = 6.2$ Hz, $J_{DC} = 22.5$ Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = −1.7.

**Diisopropyl 1-Hydroxymethylphosphonate (9a)** was prepared from **6a** (0.29 g, 1.50 mmol) (reaction time of 5 h) according to General Procedure B, except that water (1 mL) and ethyl acetate (20 mL) were added to the residue after concentration of the reaction mixture. The aqueous phase was extracted with another 15 mL of ethyl acetate. The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuo. The residue was purified by FC (DC/EA, 1:4, $R_f = 0.16$) to give 0.16 g (55%) of **9a** identical by TLC and $^1$H NMR spectroscopy to an authentic sample.[28]

**Diisopropyl 1-Hydroxyethylphosphonate (9b) and Ethyl Isopropyl 1-Hydroxy-1-methylethylphosphonate (12b)** were prepared by General Procedure B from **6b** (0.21 g, 1.00 mmol); reaction time: 3 h. FC (DC/EA, 1:4; $R_f = 0.20$) gave 0.14 g (67%) of an inseparable mixture of **9b/12b**. The two isomers could also not be separated by HPLC. The signals of the major phosphonate in the $^1$H and $^{13}$C NMR spectra are identical with those reported for **9b**.[29] − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 24.8. − **9b** and **12b**: $^1$H NMR ($CDCl_3$, 400.3 MHz, mixture): δ = 1.33 (m, 12 H, $Me_2$CH of **9b/12b**), 1.40 (dd, $J = 17.0$, 7.0 Hz, 0.8 × 3 H, C$H_3$CHP of **9b**), 1.42 (br. d, $J = 15.7$ Hz, 0.2 × 6 H, $Me_2$CP of **12b**), 3.96 (dq, $J = 7.3$, 3.3 Hz, 0.8 H, CHP of **9b**), 4.16 (m, 1.4 H, OH of **9b/12b** and $OCH_2$ of **12b**), 4.72 (m, 1.8 H, OCH); $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 27.5 (**12b**). − $^{13}$C NMR (100.6 MHz, $CDCl_3$, mixture; only signals for **12b** are given): δ = 16.5 (d, $J_{PC} = 5.4$ Hz), 23.8 (d, $J_{PC} = 5.4$ Hz), 24.1 (d, $J_{PC} = 3.9$ Hz), 24.9 (d, $J_{PC} = 5.4$ Hz), 25.0 (d, $J_{PC} = 4.6$ Hz), 62.5 (d, $J_{PC} = 6.9$ Hz), 69.1 (d, $J_{PC} = 163.7$ Hz), 71.3 (d, $J_{PC} = 7.6$ Hz).

**Diisopropyl 1-Hydroxyhexylphosphonate (9c) and Hexyl Isopropyl 1-Hydroxy-1-methylethylphosphonate (12c)** were prepared by General Procedure B from **6c** (0.27 g, 1.00 mmol); reaction time: 3 h. FC (DC/EA; 3:2) gave 0.123 g (46%) of a mixture of **9c/12c**. The two isomers were separated by semipreparative HPLC; **9c**: $t_R$ = 4.8 min; **12c**: $t_R = 5.5$ min. − **9c**: $R_f = 0.28$ (DC/EA, 3:2). The $^1$H and $^{13}$C NMR spectra are identical with those reported for **9c**.[20] − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 24.4. − **12c**: $R_f = 0.28$ (DC/EA, 3:2). − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.82 (t, $J = 7.0$ Hz, 3 H, Me), 1.26 (m, 6 H, $CH_2$), 1.27 (d, $J = 6.4$ Hz, 6 H, $Me_2$CH), 1.35 (d, $J = 15.1$ Hz, 3 H, $Me_2$CP), 1.36 (d, $J = 15.1$ Hz, 3 H, $Me_2$CP), 1.60 (quint, $J = 7.0$ Hz, 2 H, C$H_2$CH$_2$O), 3.18 (br. s, 1 H, OH), 4.01 (m, 2 H, $CH_2$O), 4.70 (oct, $J = 6.4$ Hz, 1 H, CHO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.8 (d, $J_{PC} = 5.4$ Hz,), 24.2 (d, $J_{PC} = 3.1$ Hz), 25.0 (d, $J_{PC} = 4.6$ Hz), 25.1 (d, $J_{PC} = 4.6$ Hz), 25.2, 30.5 (d, $J_{PC} = 5.6$ Hz), 31.3, 66.6 (d, $J_{PC} = 7.7$ Hz), 69.4 (d, $J_{PC} = 163.4$ Hz), 71.4 (d, $J_{PC} = 7.7$ Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 27.3.

**Diisopropyl 1-Hydroxy-2-methylpropylphosphonate (9d) and Isobutyl Isopropyl 1-Hydroxy-1-methylethylphosphonate (12d)** were prepared by General Procedure B from **6d** (0.24 g, 1.00 mmol); reaction time: 3 h; $R_f = 0.20$ (HE/EA, 1:1). The components were separated by HPLC: 0.030 g (13%) **6d** ($t_R = 7.3$ min), 0.061 g (26%) of **9d** ($t_R = 7.8$ min) and 0.083 g (34%) of **12d** ($t_R = 8.7$ min). − **9d**: The $^1$H and $^{13}$C NMR spectra were identical with those reported.[20] − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 24.4. − **12d**: IR (film): $\tilde{\nu} = 3316$ cm$^{-1}$, 2975, 1469, 1375, 1236, 1180, 996. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (t, $J = 6.5$ Hz, 6 H, $Me_2$CHCH$_2$), 1.27 (d, $J = 6.0$ Hz, 6 H, $Me_2$CH), 1.37 (d, $J = 15.1$ Hz, 3 H, $Me_2$CP), 1.38 (d, $J = 15.1$ Hz, 3 H, $Me_2$CP), 1.88 (non, $J = 6.5$ Hz, 1 H, $Me_2$C*H*CH$_2$), 3.47 (br. s, 1 H, OH), 3.78 (m, 2 H, $CH_2$), 4.70 (m, 1 H, CHO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 18.7 (d, $J_{PC} = 3.8$ Hz), 23.8 (d, $J_{PC} = 5.4$ Hz), 24.2 (d, $J_{PC} = 3.1$ Hz), 25.0 (d, $J_{PC} = 4.6$ Hz), 25.1 (d, $J_{PC} = 4.6$ Hz), 29.2 (d, $J_{PC} = 5.4$ Hz), 69.4 (d, $J_{PC} = 163.7$ Hz), 71.39 (d, $J_{PC} = 7.7$ Hz), 72.4 (d, $J_{PC} = 7.6$ Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 27.2.

**Diisopropyl 1-Hydroxy-2,2-dimethylpropylphosphonate (9e) and Isopropyl Neopentyl 1-Hydroxy-1-methylethylphosphonate (12e)** were prepared by General Procedure B from **6e** (0.25 g, 1.00 mmol); reaction time: 5 h. FC (HE/EA, 1:1) gave 0.046 g (18%) of **6e**, 0.013 g (5%) of **9e**, 0.123 g (49%) of **12e** and 0.008 g of mixture of **9e/12e**; combined yield of **9e/12e**: 0.144 g (57%). − **9e**: $R_f = 0.26$ (HE/EA, 1:1). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 24.0. The $^1$H and $^{13}$C NMR spectra agree with the ones reported.[30] − **12e**: $R_f = 0.24$ (HE/EA, 1:1). − IR (film): $\tilde{\nu} = 3313$ cm$^{-1}$, 2976, 1467, 1375, 1237, 1179, 1141, 998. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (s, 9 H, $Me_3$C), 1.27 (d, $J = 6.4$ Hz, 6 H, $Me_2$CH), 1.34 (d, $J = 14.8$ Hz, 3 H, $Me_2$CP), 1.37 (d, $J = 15.3$ Hz, 3 H, $Me_2$CP), 3.65 (A part of an ABP system, $J_{AB} = 9.4$ Hz, $J_{PH} = 4.4$ Hz, 1 H, $CH_2$O), 3.68 (B part of an ABP system, $J_{AB} = 9.4$ Hz, $J_{PH} = 4.4$ Hz, 1 H, $CH_2$O), 4.70 (oct, $J = 6.4$ Hz, 2 H, OCH). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 23.8 (d, $J_{PC} = 5.2$ Hz), 24.3 (d, $J_{PC} = 2.8$ Hz), 25.1 (d, $J_{PC} = 4.4$ Hz), 25.2 (d, $J_{PC} = 4.8$ Hz), 26.1, 69.5 (d, $J_{PC} = 164.0$ Hz), 71.3 (d, $J_{PC} = 7.6$ Hz), 75.5 (d, $J_{PC} = 8.1$ Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 27.1. − $C_{11}H_{25}O_4P$ (252.3): calcd: C 52.37, H 9.99; found C 52.63, H 9.80.

**Bis(heptadeuterioisopropyl) 1-Hydroxyhexylphosphonate (14)** was prepared by General Procedure B from **13** (0.28 g, 1.00 mmol); reaction time: 3 h. FC (HE/EA, 1:1, $R_f = 0.20$) gave 0.223 g (79%) of **14**, D ≥ 99% ($^1$H NMR). − IR (film): $\tilde{\nu} = 3316$ cm$^{-1}$, 2956, 2860, 2232 (C-D), 1235, 1157, 1072, 986. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (t, $J = 6.9$ Hz, 3 H, Me), 1.30 (m, 5 H, $CH_2$), 1.65 (m, 3 H, $CH_2$), 2.90 (br. s, 1 H, OH), 3.73 (dt, $J = 9.8$, 4.2 Hz, 1 H, CHP). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.5 (d, $J_{PC} = 13.2$ Hz), 31.3, 31.5, 68.2 (d, $J_{PC} = 161.1$ Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 24.6.

**1,1-Dideuteriohexyl Isopropyl 1-Hydroxy-1-methylethylphosphonate (16)** was prepared by General Procedure B from **15** (0.27 g, 1.00 mmol), reaction time: 17.5 h; FC (HE/EA, 1:1; $R_f = 0.20$) gave 0.193 g (72%) of **16**. − IR (film): $\tilde{\nu} = 3317$ cm$^{-1}$, 2959, 2934, 1376, 1238, 1192, 1178, 1142, 1000. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.85 (t, $J = 6.7$ Hz, 3 H, Me), 1.27 (m, 6 H, $CH_2$), 1.298 (d, $J = 6.4$ Hz, 3 H, $Me_2$CH), 1.301 (d, $J = 6.4$ Hz, 3 H, $Me_2$CH), 1.38 (d, $J = 15.3$ Hz, 3 H, $Me_2$CP), 1.39 (d, $J = 15.3$ Hz, 3 H, $Me_2$CP), 1.62 (br. t, $J = 7.4$ Hz, 2 H, $CH_2CD_2$), 3.30 (br. s, 1 H,

OH), 4.71 (oct, $J$ = 6.4 Hz, 1 H, CHO). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.8 (d, $J_{PC}$ = 5.3 Hz), 24.2 (d, $J_{PC}$ = 3.0 Hz), 25.0 (d, $J_{PC}$ = 4.7 Hz), 25.0 (d, $J_{PC}$ = 4.9 Hz), 25.1, 30.3 (d, $J_{PC}$ = 5.6 Hz), 31.3, 69.3 (d, $J_{PC}$ = 163.5 Hz), 71.2 (d, $J_{PC}$ = 7.7 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 27.4.

**Bis(heptadeuterioisopropyl) 1-Hydroxy-2,2-dimethylpropylphosphonate (18) and Heptadeuterioisopropyl Neopentyl 1-Hydroxy-1-(trideuteriomethyl)-2,2,2-trideuterioethylphosphonate (19)** were prepared by General Procedure B from **17** (0.27 g, 1.00 mmol), reaction time: 29 h; FC (HE/EA, 1:1; $R_f$ = 0.26) gave 0.057 g (21%) of recovered **17** and 0.112 g (42%) of **18**, containing 3.3% of **19** (by $^{31}$P NMR, δ = 27.1). − IR (film): $\tilde{\nu}$ = 3324 cm$^{-1}$, 2956, 2231 (C−D), 1233, 1157, 1073, 1012, 982. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.01 (s, 9 H, $Me_3C$), 2.32 (t, $J$ = 6.8 Hz, 1 H, OH), 3.40 (t, $J$ = 6.8 Hz, 1 H, CHP). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 24.1.

**(−)-Bis(heptadeuterioisopropyl) 1-Deuterio-1-hydroxyhexylphosphonate [(*R*)-(−)-25]** was prepared by General Procedure B from (*S*)-(+)-**24** (0.28 g, 1.00 mmol) in diethyl ether or THF at −78 °C and in diethyl ether at −50 °C as shown in Scheme 5; reaction time: 3 h; FC (HE/EA, 1:1, $R_f$ = 0.20). The reaction in diethyl ether at −78 °C gave 0.101 g (36%) of recovered (*S*)-(+)-**24** and 0.157 g (56%) of (*R*)-(−)-**25** with D ≥ 99%; *ee* ≥ 98% [only one signal in $^{31}$P NMR spectrum of (*R*)-MTPA ester, δ = 17.23], $[\alpha]_D^{20}$ = −16.48 (*c* = 1.505, acetone) [ref.[20] for unlabeled (*S*) enantiomer: $[\alpha]_D^{20}$ = +14.74 (*c* = 1.2, acetone)]. − In THF as solvent: yield: 0.173 g (62%), D ≥ 99%, *ee* ≥ 98%, $[\alpha]_D^{20}$ = −16.78 (*c* = 1.43, acetone). − IR (film): $\tilde{\nu}$ = 3314 cm$^{-1}$, 2956, 2931, 2232 (C-D), 1235, 1157, 1074, 1047, 986. − $^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (t, $J$ = 6.9 Hz, 3 H, Me), 1.31 (m, 5 H, $CH_2$), 1.64 (m, 3 H, $CH_2$), 2.96 (br. s, 1 H, OH). − $^{13}$C NMR (100.61 MHz, $CDCl_3$): δ = 14.0, 22.5, 25.4 (d, $J_{PC}$ = 13.1 Hz), 31.2, 31.5, 67.7 (dt, $J_{PC}$ = 160.2 Hz, $J_{DC}$ = 22.1 Hz). − $^{31}$P NMR (161.98 MHz, $CDCl_3$): δ = 24.5.

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[1] A. Krief, *Tetrahedron* **1980**, *36*, 2531−2540; *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed., vol. E 19d (Carbanionen), Thieme Verlag, Stuttgart, **1993**.
[2] P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552−560; R. E. Gawley, *Curr. Org. Chem*. **1997**, *1*, 71−94.
[3] D. Hoppe, T. Hense, *Angew. Chem*. **1997**, *109*, 2376−2410; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2282−2316.
[4] W. C. Still, C. Sreekumar, *J. Am. Chem. Soc*. **1980**, *102*, 1201−1202.
[5] R. W. Hoffmann, J. Lanz, R. Metternich, G. Tarara, D. Hoppe, *Angew. Chem*. **1987**, *99*, 1196−1197; *Angew. Chem. Int. Ed. Engl*. **1987**, *26*, 1145: R. W. Hoffmann, W. Klute, *Chem. Eur. J.* **1996**, 2, 694−700.
[6] V. K. Aggarwal, *Angew. Chem*. **1994**, *106*, 185−187; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 175;
[7] P. Beak, L. G. Carter, *J. Org. Chem.* **1981**, *46*, 2363−2373.
[8] R. Schlecker, D. Seebach, W. Lubosch, *Helv. Chim. Acta* **1978**, *41*, 512−526.
[9] F. Hammerschmidt, S. Schmidt, *Chem. Ber*. **1996**, *129*, 1503−1508.
[10] F. Hammerschmidt, *Monatsh. Chem.* **1993**, *124*, 1063−1069.
[11] F. Hammerschmidt, S. Schmidt, *Monatsh. Chem.* **1997**, *128,* 1173−1180.
[12] P. Beak, D. B. Reitz, *Chem. Rev.* **1978**, *78*, 275−316.
[13] D. Hoppe, M. Paetow, F. Hintze, *Angew. Chem*. **1993**, *105,* 430−432; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 394.
[14] F. Hammerschmidt, A. Hanninger, *Chem. Ber.* **1995**, *128*, 823−830.
[15] J. Clayden, J. H. Pink, N. N. Westlund, F. X. Wilson, *Tetrahedron Lett.* **1998**, *39*, 8377−8380.
[16] A. H. Ford-Moore, B. J. Perry, *Org. Synth., Coll. Vol.* **1967**, *IV*, 955−956.
[17] J. B. Jones, I. J. Jakovac, *Can. J. Chem.* **1982**, *60*, 19−28.
[18] J. Herscovici, M.-J. Egron, K. Antonakis, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1967−1973.
[19] E. Caspi, C. R. Eck, *J. Org. Chem.* **1977**, *42*, 767−768; C. A. Townsend, A. S. Neese, A. B. Theis, *J. Chem. Soc., Chem. Commun.* **1982**, 116−118; F. Hammerschmidt, *Liebigs Ann. Chem.* **1988**, 955−960.
[20] M. Drescher, F. Hammerschmidt, H. Kählig, *Synthesis* ***1995,*** 1267−1272.
[21] P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356−363.
[22] T. H. Lowry, K. Schueller Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper Collins Publishers, New York, **1987**, p. 232−244.
[23] W. Mikenda, *Vib. Spectrosc*. **1992**, *3*, 327−330.
[24] W. Dabkowski, J. Michalski, C. Radziejewski, Z. Skrzypczynski, *Chem. Ber.* **1982**, *115*, 1636−1643.
[25] I. Dostrovsky, M. Halaman, *J. Chem. Soc*. **1953**, 502−507.
[26] N. N. Lebedev, B. V. Mamzurin, V. P. Savel′yanov, *J. Gen. Chem. USSR* **1985**, *55*, 482−485.
[27] S. Lifson, C. Andreola, N. C. Peterson, M. M. Green, *J. Am. Chem. Soc.* **1989**, *111*, 8850−8858.
[28] F. Hammerschmidt, H. Kählig, N. Müller, *J. Chem. Soc., Perkin Trans. 1* **1991**, 365−369.
[29] Y.-F. Li, F. Hammerschmidt, *Tetrahedron: Asymmetry* **1993**, *4*, 109−120.
[30] F. Wuggenig, F. Hammerschmidt, *Monatsh. Chem.* **1998**, *129*, 423−436.

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