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# Determination of Absolute Configuration of α-Hydroxyphosphonates by $^{31}P$ NMR Spectroscopy of Corresponding Mosher Esters

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**Abstract:** (*R*)-MTPA esters of α-hydroxyphosphonates **1a-h** of known absolute configuration were prepared and their $^{31}P$ NMR spectra were recorded. The chemical shifts of the $^{31}P$ signals of the derivatized (*S*)-alcohols are consistently downfield relative to the signals of the corresponding (*R*)-alcohols. A variety of racemic and diastereomeric α-hydroxyphosphonates **1i-o** and their (*R*)-MTPA esters were prepared. The $^{31}P$ chemical shift differences are large enough to securely assign absolute configurations to α-hydroxyphosphonates.

## Introduction

The phenomenon of the chemical shift nonequivalence of diastereomeric esters has been commonly used for determination of the absolute configuration and enantiomeric purity.[1] The method using optically active α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA; Mosher acid) is especially useful and has been employed most widely.[1,2] This procedure, however, is not applicable when the $^{1}H$ NMR signals of the respective diastereomers are not sufficiently separated, or when the crucial signals overlap with other resonances. In such cases, one of the most popular techniques uses NMR spectra of other nuclei (e. g. $^{19}F$ NMR).

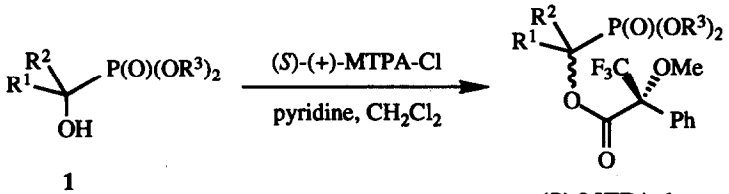
Optically active α-hydroxyphosphonates are attractive starting materials for α-aminophosphonic acids. They are accessible by chemical resolution,[3-5] asymmetric reduction,[6] stereoselective opening[7] of homochiral dioxane acetals with triethylphosphite, enantioselective addition of phosphite to aldehydes,[8,9] and by enzymatic enantioselective esterification[10] or hydrolysis of corresponding esters.[11] Their absolute configuration was determined by X-ray analysis,[4,5] chemical correlation with α-aminophosphonic acids of known configuration,[5,7] Horeau's method,[11,12] and $^{1}H$ NMR spectroscopy of Mosher esters.[11]

In our previous paper[11] we reported on the use of $^{1}H$ NMR spectroscopy of MTPA esters of α-hydroxyphosphonates to assign their absolute configurations. Horeau's method caused problems in assigning S, M, and L to the substituents.[11] Sometimes $^{1}H$ NMR spectroscopy of MTPA esters was not an acurate method to determine the enantiomeric purity, if relevant signals were overlapping with others. The phosphorus atom in the phosphonate part is certainly an auxiliary to determine the absolute configuration and enantiomeric purity[13] since the chemical shift dispersion is usually large and spectra are simple when broad-band proton

decoupling is used. This paper discloses our results on the determination of absolute configuration of α-hydroxyphosphonates by derivatisation with Mosher reagent and $^{31}P$ NMR spectroscopy.

## Results and Discussion

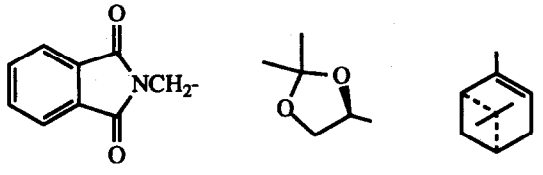
Mosher esters (*R*)-**MTPA-1a-f** of racemic α-hydroxyphosphonates **1a-f** and one or both of their corresponding enantiomers with enantiomeric excesses of up to 99% and of known absolute configuration were prepared in high yield (about 95%) according to a literature procedure[11] (Scheme 1; only the (*R*)-MTPA esters of racemic α-hydroxyphosphonates are given in the scheme and the experimental part). Four deuteriated




**1** (*R*)-**MTPA-1**

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (±)-**1a** | Ph | H | Me |
| (±)-**1b** | Ph | H | iPr |
| (±)-**1c** | Me | H | Me |
| (±)-**1d** | Me | H | iPr |
| (±)-**1e** | (*E*)-MeCH=CH | H | Me |
| (±)-**1f** | $BnOCH_2$ | H | Me |
| (1*S*,2*R*)-**1g** | BnOCH(Me) | D | iPr |
| (1*R*,2*S*)-**1g** | BnOCH(Me) | D | iPr |
| (1*R*,2*R*)-**1h** | BnOCH(Me) | D | iPr |
| (1*S*,2*S*)-**1h** | BnOCH(Me) | D | iPr |
| (±)-**1i** | Et | H | Me |
| (±)-**1j** | iPr | H | Et |
| (±)-**1k** | n-$C_5H_{11}$ | H | Et |
| (±)-**1l** | $PhCH_2CH_2$ | H | iPr |
| (±)-**1m** | see below | H | Et |
| **1n** | see below | H | Me |
| **1o** | see below | H | Me |

$R^1$ in (±)-**1m** and **2e**: $R^1$ in **1n** and **2f**: $R^1$ in **1o** and **2g**:

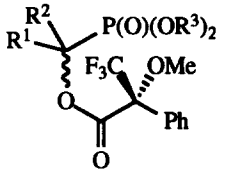



**Scheme 1** Preparation of Mosher esters from α-hydroxyphosphonates **1a-o**

α-hydroxyphosphonates **1g-h** of known configuration[14] with 98% ee were derivatized similarly as well.

The mixtures of diastereomeric esters obtained did not show any separation on TLC. Their $^{1}H$ and $^{31}P$ NMR spectra were recorded. The $^{31}P$ NMR data, obtained with broad-band proton decoupling, are summarized in Table 1.

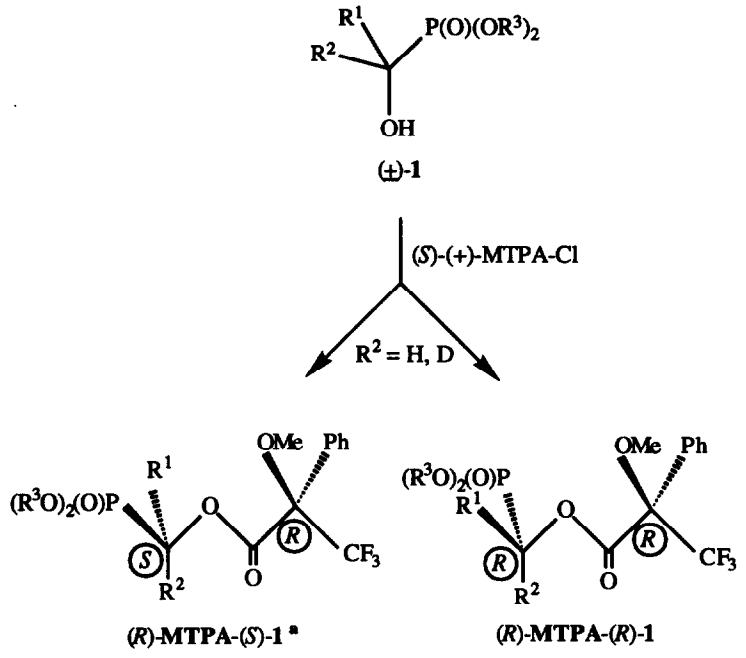
**Table 1** $^{31}P$ NMR data of Mosher esters of α-hydroxyphosphonates of known absolute configuration




(*R*)-MTPA-1

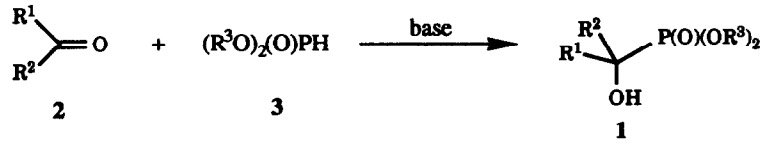
| (*R*)-Mosher ester | $R^1$ | $R^2$ | $R^3$ | Chemical shifts δ (ppm) (*S*) | (*R*) at C-1 | Δδ [δ(*S*)-δ(*R*)] |
|---|---|---|---|---|---|---|
| (*R*)-**MTPA-(±)-1a** | Ph | H | Me | 19.17 | 18.87 | 0.30 |
| (*R*)-**MTPA-(±)-1b** | Ph | H | iPr | 14.72 | 14.36 | 0.36 |
| (*R*)-**MTPA-(±)-1c** | Me | H | Me | 22.68 | 22.26 | 0.42 |
| (*R*)-**MTPA-(±)-1d** | Me | H | iPr | 18.04 | 17.53 | 0.51 |
| (*R*)-**MTPA-(±)-1e** | (*E*)-MeCH=CH | H | Me | 19.93 | 19.60 | 0.33 |
| (*R*)-**MTPA-(±)-1f** | $BnOCH_2$ | H | Me | 19.69 | 18.92 | 0.77 |
| (*R*)-**MTPA-(1*S*,2*R*)-1g** | BnOCH(Me) | D | iPr | 15.17 | 15.10 | 0.07 |
| (*R*)-**MTPA-(1*R*,2*R*)-1h** | BnOCH(Me) | D | iPr | | | |
| (*R*)-**MTPA-(1*S*,2*S*)-1h** | BnOCH(Me) | D | iPr | 15.65 | 14.14 | 1.51 |
| (*R*)-**MTPA-(1*R*,2*S*)-1g** | BnOCH(Me) | D | iPr | | | |

On the basis of the generally accepted conformation model for Mosher esters (Scheme 2), the trifluoromethyl group and the carbinyl hydrogen ($R^2$ = H, D) are eclipsed with the carbonyl oxygen.[15] The phosphorus atom in the (*R*)-MTPA ester will be shielded by the phenyl group when the chiral alcohol has (*R*)-configuration at C-1 relative to the alcohol having (*S*)-configuration. The chemical shift of the phosphorus signal in the $^{31}P$ NMR spectra of the (*R*)-MTPA derivatives of (*R*)-alcohols will consequently be upfield (smaller value in δ) as compared with those of the (*S*)-alcohols. The results support this prediction. The shift differences [δ(*S*)-δ(*R*)] range from 0.30 to 1.51 ppm. Only in the case of deuteriated α-hydroxyphosphonates (1*S*,2*R*)-**1g** and (1*R*,2*R*)-**1h** the shift difference is very small (0.07 ppm), probably because of the benzyloxy group and (*R*)-configuration at C-2.




**Scheme 2** Conformation model of Mosher esters derived from α-hydroxyphosphonate (±)-**1**
a) (*R*)-**MTPA**-(*S*)-**1** is indicating that it is the ( *R*)-MTPA ester of (*S*)-**1**.

To see whether the shift differences for (*R*)-MTPA esters of other α-hydroxyphosphonates are also large enough to securely assign the absolute configuration, some more were prepared and their $^{31}P$ NMR spectra were recorded. Achiral aldehydes **2a-e** and two chiral aldehydes, 2,3-isopropylidene-D-glyceraldehyde (**2f**) and (*R*)-(-)-myrtenal (**2g**), were treated under base catalysis with phosphites **3a-c** (Scheme 3). Sodium methoxide or ethoxide in dry ether were used as a reaction medium at -35°C for aldehydes **2a-d** and **2g** according to a general procedure given in ref..[11] 1,8-Diazabicyclo[5.4.0]undec-7-ene and triethylamine in methylene chloride were the bases for aldehydes **2e** and **2f**, respectively. The chiral aldehydes **2f** and **2g** afforded mixtures of diastereomeric α-hydroxyphosphonates (**1n**: 65/35; **1o**: 50/50), which could not be separated by flash chromatography. α-Hydroxyphosphonates **1i-o** were derivatized with (*S*)-(+)-MTPA-Cl to yield the corresponding diastereomeric Mosher esters. The chemical shifts of their $^{31}P$ NMR spectra are compiled in Table 2. The shift differences range from 0.40 to 1.09 ppm. On the basis of the arguments presented before, the $^{31}P$ NMR signals at lower field in the spectra of the diastereomeric mixtures are assigned to the (*R*)-MTPA esters derived from the α-hydroxyphosphonates with (*S*)-configuration at C-1.




2 3 1

| | | | | | |
|---|---|---|---|---|---|
| **2a** | $R^1$ = Et, $R^2$ = H | **3a** | $R^3$ = Me | **1i** | $R^1$ = Et, $R^2$ = H, $R^3$ = Me |
| **2b** | $R^1$ = iPr, $R^2$ = H | **3b** | $R^3$ = Et | **1j** | $R^1$ = iPr, $R^2$ = H, $R^3$ = Et |
| **2c** | $R^1$ = n-$C_5H_{11}$, $R^2$ = H | **3c** | $R^3$ = iPr | **1k** | $R^1$ = n-$C_5H_{11}$, $R^2$ = H, $R^3$ = Et |
| **2d** | $R^1$ = $PhCH_2CH_2$, $R^2$ = H | | | **1l** | $R^1$ = $PhCH_2CH_2$, $R^2$ = H, $R^3$ = iPr |
| **2e** | $R^1$ = see Scheme 1, $R^2$ = H | | | **1m** | $R^1$ = see Scheme 1, $R^2$ = H, $R^3$ = Et |
| **2f** | $R^1$ = see Scheme 1, $R^2$ = H | | | **1n** | $R^1$ = see Scheme 1, $R^2$ = H, $R^3$ = Me |
| **2g** | $R^1$ = see Scheme 1, $R^2$ = H | | | **1o** | $R^1$ = see Scheme 1, $R^2$ = H, $R^3$ = Me |

**Scheme 3** Preparation of racemic and diastereomeric α-hydroxyphosphonates

**Table 2** Assignment of configuration at C-1 of Mosher esters, prepared from racemic, diastereomeric (for **1n** and **1o**) α-hydroxyphosphonates, on the basis of $^{31}P$ NMR chemical shifts

| | Chemical shifts δ (ppm) | | Δδ |
|---|---|---|---|
| Mosher ester | (*S*) | (*R*) at C-1 | [δ(*S*)-δ(*R*)] |
| (*R*)-MTPA-(±)-**1i** | 22.21 | 21.77 | 0.44 |
| (*R*)-MTPA-(±)-**1j** | 19.33 | 18.93 | 0.40 |
| (*R*)-MTPA-(±)-**1k** | 19.90 | 19.43 | 0.47 |
| (*R*)-MTPA-(±)-**1l** | 17.42 | 17.01 | 0.41 |
| (*R*)-MTPA-(±)-**1m** | 16.18 | 15.72 | 0.46 |
| (*R*)-MTPA-**1n** | 19.17[a] | 18.08 | 1.09 |
| (*R*)-MTPA-**1o** | 19.55 | 18.64 | 0.91 |

a) Major diastereomer in mixture of Mosher esters

It is demonstrated that $^{31}P$ NMR shift data can be used easily to determine the absolute configuration of α-hydroxyphosphonates by derivatisation with (*R*)- or (*S*)-MTPA-Cl. It is suggested that this method is also applicable to α-hydroxyphosphinates and α-hydroxyphosphane oxides.

**Experimental**

$^1$H NMR spectra were recorded on a Bruker AM 400 WB (400 MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in ppm relative to internal standard TMS and coupling constants in Hz. $^{31}$P NMR spectra were recorded on the same spectrometer (162 MHz) using 85% $H_3PO_4$ as external standard. IR spectra were run on a Perkin Elmer 1600 FT-IR spectrometer as films obtained by applying a solution from the NMR sample to a silicon plate and allowing the solvent to evaporate.[16] Silica gel 60 Merck (0.040-0.063 mm) was used for flash chromatography. TLC was carried out on 0.2 mm thick Merck plates, silica gel 60 $F_{254}$. Spots were visualized by UV and/or dipping into a solution of 24 g of $(NH_4)_6Mo_7O_{24}.4H_2O$ and 1 g of $Ce(SO_4)_2.4H_2O$ in 500 ml 10% $H_2SO_4$ in water, followed by heating on a hot plate at 200 °C. Melting points were determined on a Reichert Thermovar instrument and were uncorrected. (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride from JPS Chimie (Switzerland) {$[\alpha]_D^{20}$ = + 136.5 ( c = 5.2, $CCl_4$), ee ≥ 99.5%} was used. Abbreviations used: methylene chloride = MC; ethyl acetate = EA; diastereomer = d..

**(1*R*)- and (1*S*)-Dimethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-phenylmethylphosphonate [(*R*)-MTPA-(±)-1a]:**

$R_f$ = 0.64 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2957, 2854, 1757, 1496, 1454, 1270, 1182, 1032 cm$^{-1}$. $^1$H NMR: δ 3.50, 3.59, 3.64, 3.67 (4x3H, 4xd, J = 10.8, $P(OMe)_2$), 3.48, 3.58 (2x3H, 2xq, J = 1.0, OMe in MTPA), 6.30, 6.32 (2x1H, 2xd, J = 13.3, CHP), 7.33-7.51 (4x5H, m, aromatic-H). $^{31}$P NMR: δ 19.17, 18.87.

**(1*R*)- and (1*S*)-Diisopropyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-phenylmethylphosphonate [(*R*)-MTPA-(±)-1b]:**

$R_f$ = 0.64 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2983, 2935, 1758, 1453, 1388, 1266, 1181, 1106 cm$^{-1}$. $^1$H NMR: δ 1.08, 1.11, 1.12, 1.19, 1.20, 1.24, 1.25, 1.28 (8x3H, 8xd, J = 6.4, $P(OCH\underline{Me}_2)_2$), 3.49, 3.62 (2x3H, 2xq, J = 1.0, OMe in MTPA), 4.59, 4.65 (2x2H, 2xm, $P(O\underline{C}HMe_2)_2$), 6.18, 6.20 (2x1H, 2xd, J = 13.8, CHP), 7.39 (4x5H, m, aromatic-H). $^{31}$P NMR: δ 14.72, 14.36.

**(1*R*)- and (1*S*)-Dimethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-ethylphosphonate [(*R*)-MTPA-(±)-1c]:**

$R_f$ = 0.55 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2958, 2855, 1757, 1452, 1252, 1184, 1123, 1033 cm$^{-1}$. $^1$H NMR: δ 1.49, 1.58 (2x3H, 2xdd, J = 6.9, 16.2, $C\underline{H}_3CH$), 3.569, 3.571 (2x3H, 2xbr s, OMe in MTPA), 3.62, 3.70, 3.77, 3.78 (4x3H, 4xd, J = 10.8, $P(OMe)_2$), 5.49 (2x1H, m, CHP), 7.49 (2x5H, m, aromatic-H). $^{31}$P NMR: δ 22.68, 22.26.

**(1*R*)- and (1*S*)-Diisopropyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-ethylphosphonate [(*R*)-MTPA-(±)-1d]:**

$R_f$ = 0.56 (M:EA = 10:1); oil. IR: $\upsilon_{max}$ 2984, 2940, 1757, 1452, 1388, 1249, 1172, 1108, 1060, 1005 cm$^{-1}$. $^1$H NMR: δ 1.21, 1.23, 1.25, 1,27, 1.31, 1.32x3 (8x3H, 8xd, J = 6.4, $P(OCH\underline{Me}_2)_2$), 1.45, 1.54

(2x3H, 2xdd, J = 6.9, 16.2, $CH_3CH$), 3.57, 3.59 (2x3H, 2xq, J = 1.0, OMe in MTPA), 4.61, 4.73 (2x2H, 2xm, $P(OCHMe_2)_2$), 5.43 (2x1H, m, CHP), 7.50 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 18.04, 17.53.

**(1*R*)- and (1*S*)-Dimethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-(2E)-butenylphosphonate [(*R*)-MTPA-(±)-1e]:**

$R_f$ = 0.59 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2958, 2855, 1756, 1670, 1452, 1269, 1172, 1123, 1032, 967 $cm^{-1}$. $^1H$ NMR: δ 1.70, 1.76 (2x3H, 2xm, MeCH=), 3.54, 3.56 (2x3H, 2xq, J = 1.0, OMe in MTPA), 3.58, 3.67, 3.75x2 (4x3H, 4xd, J = 10.8, $P(OMe)_2$), 5.49, 5.60 (2x1H, 2xm, MeCH=CH), 5.82 (2x1H, 2 overlapping dd, CHP), 5.85, 6.02 (2x1H, 2xm, MeCH=), 7.37-7.56 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 19.93, 19.60.

**(1*R*)- and (1*S*)-Dimethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-2-benzyloxyethylphosphonate [(*R*)-MTPA-(±)-1f]:**

This mixture of Mosher esters was prepared from α-hydroxyphosphonate (±)-1f[5], $R_f$ = 0.38 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2958, 2855, 1759, 1453, 1365, 1272, 1184, 1122, 1038 $cm^{-1}$. $^1H$ NMR: δ 3.559, 3.564 (2x3H, 2xq, J = 1.0, OMe in MTPA), 3.60, 3.71, 3.76, 3.78. (4x3H, 4xd, J = 10.8, $P(OMe)_2$), 3.79-3.97 (2x2H, m, $OCH_2CHP$), 4.44, 4.56 (2x2H, 2xAB system, J = 11.8, $PhCH_2O$), 5.78, 5.91 (2x1H, m, CHP), 7.19-7.60 (4x5H, m, aromatic-H). $^{31}P$ NMR: δ 19.69, 18.92.

**(1*S*, 2*R*)-Diisopropyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-2-benzyloxy-[1-$^2H_1$]propylphosphonate [(*R*)-MTPA-(1*S*,2*R*)-1g]:[5]**

$^1H$ NMR: δ 1.22, 1.25, 1.31x2, 1.34 (5x3H, 5xd, J = 6.4, $CH_3CHCD$, $P(OCHMe_2)_2$), 3.57 (3H, q, J = 1.0, OMe in MTPA), 4.01 (1H, dq, J = 4.0, 6.2, $CH_3CHCD$), 4.54 (2H, AB system, J = 11.2, $PhCH_2O$), 4.76 (2x1H, m, $P(OCHMe_2)_2$), 7.26-7.62 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 15.17.

**(1*R*, 2*S*)-Diisopropyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-2-benzyl-oxy [1-$^2H_1$]propylphosphonate [(*R*)-MTPA-(1*R*,2*S*)-1g]:**

$^1H$ NMR: δ 1.17, 1.22, 1.26, 1.31, 1.36 (5x3H, 5xd, J = 6.2, $CH_3CHCD$, $P(OCHMe_2)_2$), 3.60 (3H, q, J = 1.0, OMe in MTPA), 4.07 (1H, dq, J = 2.0, 6.2, $CH_3CHCD$), 4.48, 4.63 (2x1H, 2xm, $P(OCHMe_2)_2$), 4.58 (2H, AB system, J = 11.0, $PhCH_2O$), 7.24-7.65 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 14.14.

**(1*R*, 2*R*)-Diisopropyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-2-benzyloxy-[1-$^2H_1$]propylphosphonate [(*R*)-MTPA-(1*R*,2*R*)-1h]:**

$R_f$ = 0.46 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2983, 2937, 1755, 1498, 1453, 1387, 1259, 1173, 1106, 995 $cm^{-1}$. $^1H$ NMR: δ 1.14, 1.20, 1.27, 1.28, 1.35 (5x3H, 5xd, J = 6.4, $CH_3CHCD$, $P(OCHMe_2)_2$), 3.54 (3H, br s, OMe in MTPA), 4.04 (1H, dq, J = 4.4, 6.4, $CH_3CHCD$), 4.55 (2H, AB system, J = 11.8, $PhCH_2O$), 4.61, 4.69 (2x1H, 2xm, $P(OCHMe_2)_2$), 7.22-7.60 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 15.10.

**(1*S*, 2*S*)-Diisopropyl 1-[(R)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-2-benzyl-oxy [1-$^2H_1$]propylphosphonate [(*R*)-MTPA-(1*S*,2*S*)-1h]:**[5]

$^1$H NMR: δ 1.19, 1.26, 1.265, 1.28, 1.31 (5x3H, 5xd, J = 6.2, C$\underline{H}_3$CHCD, P(OCH$\underline{Me}_2$)$_2$), 3.58 (3H, q, J = 1.0, OMe in MTPA), 3.97 (1H, dq, J = 4.0, 6.2, CH$_3$C$\underline{H}$CD), 4.39 (2H, AB system, J = 11.5, PhC$\underline{H}_2$O), 4.72 (2x1H, m, P(OC$\underline{H}$Me$_2$)$_2$), 7.20-7.65 (2x5H, m, aromatic-H). $^{31}$P NMR: δ 15.65.

**Dimethyl 1-hydroxypropylphosphonate [(±)-1i]:**

This compound was prepared according to a literature procedure.[11] Propanal (**2a**) (0.116 g, 2 mmol) was treated with dimethyl phosphite (0.220 g, 2 mmol) in the presence of a catalytic amount of saturated sodium methoxide solution in methanol (2 drops) at -35°C in ether (10 ml) to afford phosphonate (±)-**1i** (0.204 g, 61%) by flash chromatography ($R_f$ = 0.08, PE:EA = 1:5); oil. IR: $\upsilon_{max}$ 3318, 2961, 2855, 1460, 1216, 1120, 1032, 980 cm$^{-1}$. $^1$H NMR: δ 1.08 (3H, t, J = 7.4, C$\underline{H}_3$CH$_2$), 1.77 (2H, m, CH$_3$C$\underline{H}_2$), 3.80, 3.82 (2x3H, 2xd, J = 10.3, P(OMe)$_2$), 3.84 (1H, m, CHP). Elemental analysis: $C_5H_{13}O_4P$ Calcd. C, 35.72; H, 7.79; Found C, 35.94; H, 7.97%.

**(1*R*)- and (1*S*)-Dimethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-propyl-phosphonate [(*R*)-MTPA-(±)-1i]:**

$R_f$ = 0.25 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2958, 2855, 1755, 1452, 1269, 1172, 1122, 1037 cm$^{-1}$. $^1$H NMR: δ 0.88, 1.03 (2x3H, 2xt, J = 7.4, C$\underline{H}_3$CH$_2$), 1.88 (2x2H, m, CH$_3$C$\underline{H}_2$), 3.56, 3.59 (2x3H, 2xq, J = 1.0, OMe in MTPA), 3.62, 3.71, 3.766, 3.768 (4x3H, 4xd, J = 10.8, P(OMe)$_2$), 5.38 (2x1H, m, CHP), 7.50 2x5H, m, aromatic-H). $^{31}$P NMR: δ 22.21, 21.77.

**Diethyl 1-hydroxy-2-methylpropylphosphonate [(±)-1j]:**

Isobutanal (**2b**) (0.72 g, 10 mmol) and diethyl phosphite (1.38 g, 10 mmol) were dissolved in dry ether (20 ml). A saturated solution of sodium ethoxide in ethanol (50 µl) was added at -35°C. The reaction was worked up according to a literature procedure[11] to afford α-hydroxyphosphonate (±)-**1j** (0.994 g, 47%) after purification by flash chromatography ($R_f$ = 0.18, MC:EA = 5:1); oil. IR: $\upsilon_{max}$ 3314, 2982, 1470, 1392, 1216, 1165, 1029, 967 cm$^{-1}$. $^1$H NMR: δ 1.062, 1.068 (2x3H, 2xd, J = 6.9, (C$\underline{H}_3$)$_2$CH), 1.34 (2x3H, t, J = 7.4, P(OCH$_2$C$\underline{H}_3$)$_2$), 2.09 (1H, m, (CH$_3$)$_2$C$\underline{H}$), 3.13 (1H, t, J = 6.4, OH), 3.65 (1H, q, J = 6.4, CHP), 4.17 (2x2H, m, P(OC$\underline{H}_2$CH$_3$)$_2$). Elemental analysis: $C_8H_{19}O_4P$ Calcd. C, 45.71; H, 9.11; Found C, 45.84; H, 9.00%.

**(1*R*)- and (1*S*)-Diethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-2-methyl-propylphosphonate [(*R*)-MTPA-(±)-1j]:**

$R_f$ = 0.45 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2984, 1753, 1452, 1393, 1371, 1245, 1170, 1123, 1054, 1023, 970 cm$^{-1}$. $^1$H NMR: δ 0.92, 1.00, 1.05, 1.08 (4x3H, 4xd, J = 6.9, (C$\underline{H}_3$)$_2$CH), 1.23, 1.27, 1.28, 1.31 (4x3H, 4xt, J = 6.9, P(OCH$_2$C$\underline{H}_3$)$_2$), 2.32 (2x1H, m, (CH$_3$)$_2$C$\underline{H}$), 3.55, 3.61 (2x3H, 2x br s, OMe in MTPA), 3.92-4.19 (4x2H, m, P(OC$\underline{H}_2$CH$_3$)$_2$), 5.30 (2x1H, m, CHP), 7.38-7.64 (2x5H, m, aromatic-H). $^{31}$P NMR: δ 19.33, 18.93.

**Diethyl 1-hydroxyhexylphosphonate [(±)-1k]:**

Hexanal (**2c**) (5.0 g, 50 mmol) and diethyl phosphite (6.9 g, 50 mmol) were dissolved in dry ether (20 ml). A saturated solution of sodium ethoxide in ethanol (0.25 ml) was added at -35°C. After workup, according to a literature procedure,[11] the crude material was purified by flash chromatography to afford the α-hydroxyphosphonate (±)-**1k** (10.94 g, 92%, $R_f$ = 0.27, MC:EA = 5:3) which was bulb to bulb distilled (125-130°C/0.005 mmHg); oil. IR: $\upsilon_{max}$ 3313, 2933, 2861, 1458, 1393, 1229, 1028, 969 $cm^{-1}$. $^1H$ NMR: δ 0.89 (3H, t, J = 6.9, $C\underline{H}_3CH_2CH_2$), 1.31 (3x2H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.335, 1.339 (2x3H, 2xt, J = 6.9, $P(OCH_2C\underline{H}_3)_2$), 1.71 (2H, m, $C\underline{H}_2CHP$), 3.45 (1H, br s, OH), 3.85 (1H, m, CHP), 4.16 (2x2H, m, $P(OC\underline{H}_2CH_3)_2$). Elemental analysis: $C_{10}H_{23}O_4P$ Calcd. C, 50.41; H, 9.73; Found C, 50.62; H, 9.71%.

**(1*R*)- and (1*S*)-Diethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]hexylphosphonate [(*R*)-MTPA-(±)-1k]:**

$R_f$ = 0.70 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2958, 1754, 1452, 1250, 1170, 1123, 1024, 974 $cm^{-1}$. $^1H$ NMR: δ 0.82, 0.87 (2x3H, 2xt, J = 6.9, $C\underline{H}_3CH_2CH_2$), 1.23, 1.27. 1.28, 1.32 (4x3H, 4xt, J = 7.4, $P(OCH_2C\underline{H}_3)_2$), 1.23 (6x2H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.88 (2x2H, m, $C\underline{H}_2CHP$), 3.55, 3.61 (2x3H, 2xq, J = 1.0, OMe in MTPA), 3.93-4.19 (4x2H, m, $P(OC\underline{H}_2CH_3)_2$), 5.42 (2x1H, m, CHP), 7.38-7.61 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 19.90, 19.43.

**Diisopropyl 1-hydroxy-3-phenylpropylphosphonate [(±)-1l]:**

Yield: 71%, m.p. 70-72°C (recrystallized from petroleum ether / methylene chloride). IR: $\upsilon_{max}$ 3318, 2978, 1455, 1386, 1231, 1107, 989 $cm^{-1}$. $^1H$ NMR: δ 1.28, 1.317, 1.323, 1.33 (4x3H, 4xd, J = 6.4, $P(OCH\underline{Me}_2)_2$), 2.01 (2H, m, $BnC\underline{H}_2$), 2.73 (1H, dt, J = 8.9, 14.3, PhC<u>Ha</u>), 2.95 (2H, m, OH, PhC<u>Hb</u>), 3.77 (1H, m, CHP), 4.73 (2x1H, m, $P(OC\underline{H}Me_2)_2$), 7.17-7.30 (5H, m, aromatic-H). Elemental analysis: $C_{15}H_{25}O_4P$ Calcd. C, 59.99; H, 8.39; Found C, 60.20; H, 8.27%.

**(1*R*)-and (1*S*)-Diisopropyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-3-phenylpropylphosphonate [(*R*)-MTPA-(±)-1l]:**

$R_f$ = 0.71 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2982, 1756, 1455, 1388, 1259, 1171, 1107, 990 $cm^{-1}$. $^1H$ NMR: δ 1.23x4, 1.28x2, 1.30, 1.32 (8x3H, 8xd, J = 6.4, $P(OCH\underline{Me}_2)_2$), 2.14 (2x2H, m, $BnC\underline{H}_2$), 2.62 (2x2H, m, $PhC\underline{H}_2$), 3.58, 3.64 (2x3H, 2xbr s, OMe in MTPA), 4.64, 4.72 (2x2H, 2xm, $P(OC\underline{H}Me_2)_2$), 5.42 (2x1H, m, CHP), 7.05-7.68 (4x5H, m, aromatic-H). $^{31}P$ NMR: δ 17.42, 17.01.

**Diethyl 1-hydroxy-2-phthalimidoethylphosphonate [(±)-1m]:**

1,8-Diazabicyclo[5.4.0]undec-7-ene (10 drops) was added to a cooled solution (-30°C) of crude **2e**, prepared by Swern oxidation[17] of 2-phthalimidoethanol[18] (5.73 g, 30 mmol) and **3b** (4 ml) under argon. The reaction mixture was allowed to warm to room temperature overnight. The solution was washed with 2N HCl and water, dried ($Na_2SO_4$) and concentrated. The residue was heated in an air bath up to 70°C/0.1 mm to remove volatile material and then crystallized from MC / hexane. The crude (±)-**1m** obtained was recrystallized from MC / tert.-butyl methyl ether to afford (±)-**1m** (5.8 g) and the mother liquor was purified by flash chromatography (MC:EA = 3:1) to give another 0.65 g of (±)-**1m**; total yield 6.45 g (66%), $R_f$ = 0.15 (MC:EA

= 5:1), m.p. 118-120°C. IR: $\upsilon_{max}$ 3285, 2986, 1774, 1718, 1396, 1216, 1102, 1024, 967 $cm^{-1}$. $^1H$ NMR: δ 1.29, 1.32 (2x3H, 2xt, J = 6.9, $P(OCH_2\underline{C}H_3)_2$), 3.69 (1H, br s, OH), 3.98 (1H, right part of ABXP system, the left part is overlapping with $P(OCH_2)$, NCH), 4.14 (5H, m, $P(OCH_2\underline{C}H_3)_2$, NCH), 4.25 (1H, m, CHP), 7.69-7.85 (4H, m, aromatic-H). Elemental analysis: $C_{14}H_{18}NO_6P$ Calcd. C, 51.38; H, 5.54; Found C, 51.59; H, 5.29%.

**(1*R*)- and (1*S*)-Diethyl 1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]-2-phthalimidoethylphosphonate [(*R*)-MTPA-(±)-1m]:**

$R_f$ = 0.28 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2986, 1758, 1721, 1396, 1370, 1273, 1243, 1172, 1125, 1023, 980 $cm^{-1}$. $^1H$ NMR: δ 1.29, 1.30, 1.34, 1.39 (4x3H, 4xt, J = 7.4, $P(OCH_2\underline{C}H_3)_2$), 3.48, 3.51 (2x3H, 2xq, J = 1.0, OMe in MTPA), 3.98-4.35 (6x2H, m, $P(O\underline{C}H_2CH_3)_2$, $NCH_2$), 5.92 (2x1H, 2 overlapping ddd, CHP), 7.08-7.84 (2x4H and 2x5H, m, aromatic-H). $^{31}P$ NMR: δ 16.18, 15.72.

**(1*R*, 2*R*)- and (1*S*, 2*R*)-Dimethyl 2,3-O-isopropylidene-1,2,3-trihydroxypropylphosphonate (1n):**

A solution of dimethyl phosphite (0.132 g, 1.2 mmol), 2,3-O-isopropylidene-D-glyceraldehyde (**2f**) (0.13 g, 1.0 mmol), and triethylamine[19] (2 drops) in benzene (5 ml) was heated at 60-80°C for 4.5 h. The volatile materials were removed under reduced pressure. The residue was purified by flash chromatography ($R_f$ = 0.10, MC:EA = 1:2) to afford the α-hydroxyphosphonate **1n** (0.114 g, 47%) as a mixture of diastereomers; oil. IR: $\upsilon_{max}$ 3288, 2988, 1458, 1372, 1222, 1157, 1055 $cm^{-1}$. $^1H$ NMR: (two diastereomers, ratio: 35:65). δ 1.33 and 1.41 (major diastereomer), 1.35 and 1.42 (minor d.) (4x3H, 4xbr s, $(CH_3)_2C$), 3.00 (minor d.) (1H, t, J = 8.0, OH), 3.61 (major d.) (1H, br d, J = 10.0, OH), 3.788 and 3.795 (major d.), 3.796 and 3.81 (minor d.) (4x3H, 4xd, J = 10.3, $P(OMe)_2$), 3.85 (minor d.) (1H, m, CHP), 3.90 (minor d.) (1H, dd, J = 6.6, 8.4, $H_{3a}$), 4.06 (4x1H, m, minor d. $H_{3b}$; major d. $H_{3a}$, $H_{3b}$ and CHP), 4.33 (major d.) (1H, m, C<u>H</u>CHP), 4.41 (minor d.) (1H, m, C<u>H</u>CHP). After decoupling of $^{31}P$: δ 1.33 and 1.41 (major d.), 1.35 and 1.42 (minor d.) (4x3H, 4xbr s, $(CH_3)_2C$), 3.00 (minor d.) (1H, d, J = 6.8, OH), 3.61 (major d.) (1H, br s, OH), 3.788 and 3.795 (major d.), 3.796 and 3.81 (minor d.) (4x3H, 4xbr s, $P(OMe)_2$), 3.85 (minor d.) (1H, dd, J = 5.0, 6.8, CHP), 3.90 (minor d.) (1H, dd, J = 6.6, 8.4, $H_{3a}$), 4.06 (4x1H, m, minor d. $H_{3b}$; major d. $H_{3a}$, $H_{3b}$ and CHP), 4.33 (major d.) (1H, q, J = 5.8, C<u>H</u>CHP), 4.41 (minor d.) (1H, dt, J = 5.0, 6.6, C<u>H</u>CHP). Elemental analysis: $C_8H_{17}O_6P$ Calcd. C, 40.01; H, 7.13; Found C, 40.22; H, 6.98%.

**(1*R*,2*R*)- and (1*S*,2*R*)-Dimethyl 2,3-O-isopropylidene-2,3-dihydroxy1-1-[(*R*)-2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy]propylphosphonate [(*R*)-MTPA-1n]:**

$R_f$ = 0.16 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2925, 2855, 1758, 1452, 1373, 1268, 1172, 1121, 1036 $cm^{-1}$. $^1H$ NMR: (two diastereomers, ratio: 37:63) δ 1.19 and 1.30 (major diastereomer), 1.35 and 1.41 (minor d.) (4x3H, 4xs, $(CH_3)_2C$), 3.59 and 3.71 (minor d.), 3.79 and 3.80 (major d.) (4x3H, 4xd, J = 10.8, $P(OMe)_2$), 3.586 (major d.), 3.63 (minor d.) (2x3H, 2xq, J = 1.0, OMe in MTPA), ca. 3.80 (major d.) (1H, dd, overlapping with OMe, $H_{3a}$), 3.99 (major d.) (1H, dd, J = 7.4, 6.4, $H_{3b}$), 4.10 (minor d.) (2H, AB part of ABX system, J = 9.2, 6.4, 5.4, $H_{3a}$ and $H_{3b}$), 4.51 (2H, m, overlapping signals of H-2 of major and minor d.), 5.50 (1H, minor d.) (1H, dd, J = 8.4, 9.4, CHP), 5.72 (major d.) (1H, dd, J = 3.9, 10.3, CHP), 7.38-7.65 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 19.17, 18.08 (ratio: 61:39).

**(1*R*)- and (1*S*)-Dimethyl 1-hydroxy-1-{(1′*R*, 5′*R*)-6′,6′-dimethylbicyclo[3.1.1]hept-2′-en-2′-yl}-methylphosphonate (1o):**

Yield: 94%, $R_f$ = 0.18 (PE:EA = 1:5); oil; ratio of diastereomers: ca. 1:1. IR: $\upsilon_{max}$ 3300, 2986, 2953, 2914, 2831, 1467, 1366, 1236, 1187, 1037 $cm^{-1}$. $^1H$ NMR: δ 0.86, 0.87 (2x3H, 2xs, $CH_3$), 1.20, 1.21 (2x1H, 2xd, J = 8.9), 1.30 (2x3H, s, $CH_3$), 2.10 (2x1H, m), 2.33 (2x3H, m), 2.44 (2x1H, m), 3.12 (2x1H, m), 3.79, 3.93 (4x3H, 2xd, J = 10.3, $P(OMe)_2$), 4.37 (2x1H, 2 overlapping dd, CHP), 5.70 (2x1H, m, =CH). Elemental analysis: $C_{12}H_{21}O_4P$ Calcd. C, 55.38; H, 8.13; Found C, 55.52; H, 8.21%.

**(1*R*)- and (1*S*)-Dimethyl 1-[(*R*)-2′′-methoxy-2′′-(trifluoromethyl)phenylacetyloxy]-1-{(1′*R*, 5′*R*)-6′,6′-dimethylbicyclo[3.1.1]hept-2′-en-2′-yl}-methylphosphonate [(*R*)-MTPA-1o]:**

$R_f$ = 0.32 (MC:EA = 10:1); oil. IR: $\upsilon_{max}$ 2956, 1758, 1452, 1270, 1183, 1122, 1036 $cm^{-1}$. $^1H$ NMR: δ 0.69, 0.86, 1.23, 1.30 (4x3H, 4xs, $C(CH_3)_2$), 1.14, 1.80 (2x1H, 2xd, J = 7.9, 8.9), 2.09 (2x1H, m), 2.23 - 2.47 (2x4H, m), 3.55, 3.58 (2x3H, 2xq, J = 1.0, OMe in MTPA), 3.57, 3.68, 3.74, 3.75 (4x3H, 4xd, J = 10.8, $P(OMe)_2$), 5.64, 5.80 (2x1H, 2xm, =CH), 5.76 (2x1H, d, J = 12.8, CHP), 7.38-7.59 (2x5H, m, aromatic-H). $^{31}P$ NMR: δ 19.55, 18.64.

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