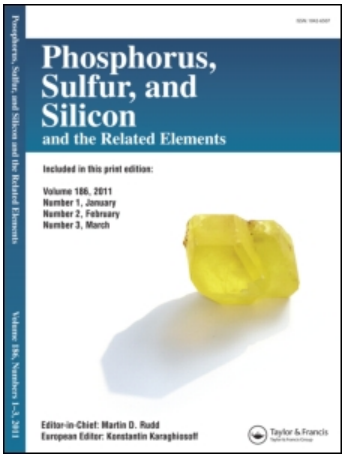

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ENZYMES IN ORGANIC CHEMISTRY 7.[1] EVALUATION OF HOMOCHIRAL t-BUTYL(PHENYL)PHOSPHINOTHIOIC ACID FOR THE DETERMINATION OF ENANTIOMERIC EXCESSES AND ABSOLUTE CONFIGURATIONS OF α-SUBSTITUTED PHOSPHONATES

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ENZYMES IN ORGANIC CHEMISTRY 7.[1] EVALUATION OF HOMOCHIRAL t-BUTYL(PHENYL)PHOSPHINOTHIOIC ACID FOR THE DETERMINATION OF ENANTIOMERIC EXCESSES AND ABSOLUTE CONFIGURATIONS OF α-SUBSTITUTED PHOSPHONATES

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α-Hydroxy-, α-acetoxy-, α-chloroacetoxy-, α-azido-, α-phthalimidooxy-, and α-aminooxy-phosphonates are investigated by ^{1}H and ^{31}P NMR spectroscopy in the presence of homochiral *t*-butyl(phenyl)phosphinothioic acid as chiral solvating agent. The ^{31}P NMR shift differences for the diastereomeric complexes of α-hydroxyphosphonates are large (0.10 – 0.30 ppm) and allow the determination of their enantiomeric excess and the cautious assignment of their absolute configuration.

Keywords: α-Substituted phosphonates; enantiomeric excess; absolute configuration; *t*-butyl(phenyl)phosphinothioic acid

INTRODUCTION

α-Substituted phosphonic acids and their derivatives have become increasingly important because of their biological activity.[2] The phosphonic acid group is considered an isosteric replacement for the carboxyl group and

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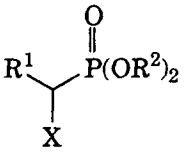
this concept has been used extensively, especially in the field of amino acids. α-Hydroxyphosphonates[3] accessible by a number of methods are convenient starting materials for the synthesis of other α-substituted phosphonates. We have found that lipases FAP 15[4] and AP 6[1] (from *Rhizopus oryzae* and *Aspergillus niger,* respectively) and protease Chirazyme P-2[5] hydrolyse in a biphasic buffered system α-acetoxy- and α-chloroacetoxyphosphonates enantioselectively. We were therefore looking for a simple and rapid method for the determination of the enantiomeric excesses of α-hydroxyphosphonates and other α-substituted phosphonates derived from them. Published methods for the determination of the ee involve HPLC[3] on chiral, stationary phases or the preparation of diastereomeric derivatives such as camphanoate[6], Mosher[7] and O-methyl mandelate[3b] esters and NMR spectroscopy. The latter esters allow also the assignment of the absolute configuration.

RESULTS AND DISCUSSION

In this paper, we report on the application of (*S*)-(-)-*t*-butyl(phenyl)phosphinothioic acid[8] (**6**) as a chiral solvating agent (CSA)[9] for the direct determination of the enantiomeric excess of various α-substituted phosphonates, especially α-hydroxyphosphonates and their respective acetates and chloroacetates, by ^{31}P (161.98 MHz) and ^{1}H NMR (400.13 MHz) spectroscopy (Figure 1). These types of phosphonates of varying optical purity are routinely obtained by enzymatic resolution[1] of α-acetoxy- or α-chloroacetoxyphosphonates. Homochiral *t*-butyl(phenyl)phosphinothioic acid was prepared by a modified literature procedure from commercially available dichlorophenylphosphine, *t*-butylmagnesium chloride, and sulfur after hydrolytic workup, followed by a simple resolution with 1-phenylethylamine.[8,10,11] It has previously been used for the determination of the enantiomeric purity of phosphinic amides, phosphinates, thiophosphinates, phosphine oxides, thiophosphonates, and phosphonic amides, having a stereogenic phosphorus atom, sulfoxides, various amines, alcohols, and thioalcohols.[11] Recently, this CSA has been introduced by Zymanczyk et al.[12] for the determination of enantiomeric excesses of secondary α-hydroxyphosphonates and independently by us[13] for tertiary α-hydroxyphosphonates. As derivatisation is avoided, using a CSA is a very rapid and clean method. Application of ^{31}P NMR

spectroscopy permits the evaluation of the enantiomeric excess of chiral nonracemic compounds in crude products obtained by enzymatic resolution.



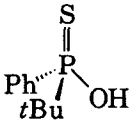
1 X = OH

2 X = OAc, $OC(O)CH_2Cl$, $OC(O)C_3H_7$, OC(O)OMe

3 X = N_3, R^2 = *i*Pr

4 X = Phthalimidooxy, R^2 = *i*Pr

5 X = ONH_2, R^2 = *i*Pr



(*S*)-(-)-**6**

1	R^1	R^2
a	Ph	*i*Pr
b	Me	*i*Pr
c	C_5H_{11}	Et
d	(*E*)-CH_3CH=CH	Me
e	$(CH_3)_2CH$	*i*Pr
f	$(CH_3)_3C$	*i*Pr
g	$(CH_3)_2CHCH_2$	*i*Pr
h	$PhCH_2$	Et
i	PhC≡C	*i*Pr
j	*c*$C_6H_{11}CH_2CH_2$	Et
k	$(CH_3)_2CH$	$CH_2CMe_2CH_2$
l	*c*C_3H_5	*i*Pr
m	*c*C_4H_7	*i*Pr
n	*c*C_5H_9	*i*Pr
o	*c*C_6H_{11}	*i*Pr
p	*c*C_7H_{13}	*i*Pr
q	*c*C_8H_{15}	Et
r	*o*MeC_6H_4	Me
s	*o*$MeOC_6H_4$	*i*Pr
t	1-Naphthyl	Me
u	2-Thienyl	Et
v	3-Thienyl	*i*Pr
w	2-Furyl	*i*Pr
x	3-Pyridyl	*i*Pr
y	2-Pyridyl	*i*Pr

2	R^1	R^2	X
a	Ph	*i*Pr	OAc
b	Me	*i*Pr	OAc
c	(*E*)-CH_3CH=CH	Me	OAc
d	1-Naphthyl	Me	OAc
e	2-Thienyl	*i*Pr	OAc
f	3-Thienyl	*i*Pr	OAc
g	Ph	*i*Pr	$ClCH_2CO_2$
h	Me	*i*Pr	$ClCH_2CO_2$
i	C_5H_{11}	Et	$ClCH_2CO_2$
j	$(CH_3)_2CH$	*i*Pr	$ClCH_2CO_2$
k	$(CH_3)_3C$	*i*Pr	$ClCH_2CO_2$
l	$(CH_3)_2CHCH_2$	*i*Pr	$ClCH_2CO_2$
m	*c*$C_6H_{11}CH_2CH_2$	Et	$ClCH_2CO_2$
n	*c*C_3H_5	*i*Pr	$ClCH_2CO_2$
o	*c*C_4H_7	*i*Pr	$ClCH_2CO_2$
p	*c*C_5H_9	*i*Pr	$ClCH_2CO_2$
q	*c*C_6H_{11}	*i*Pr	$ClCH_2CO_2$
r	*c*C_8H_{15}	Et	$ClCH_2CO_2$
s	*o*MeC_6H_4	Me	$ClCH_2CO_2$
t	2-Thienyl	*i*Pr	$ClCH_2CO_2$
u	Me	*i*Pr	$C_3H_7CO_2$
v	(*E*)-CH_3CH=CH	Me	$MeOCO_2$

3	R^1
a	$PhCH_2$
b	*c*C_6H_{11}

4/5	R^1
a	Me
b	$PhCH_2CH_2$

FIGURE 1 α-Substituted phosphonates investigated by NMR spectroscopy using (-)-*t*-butyl(phenyl)phosphinothioic acid as chiral solvating agent

Zymanczyk-Duda et al. recorded the ^{31}P NMR spectra in $CDCl_3$ as the only solvent and investigated only a limited number of six diethyl α-hydroxyphosphonates, mostly derived from substituted benzaldehydes, and two diethyl β-hydroxy- phosphonates. In order to fully assess the scope of the reagent, we first studied the observed shift differences for ^{31}P and ^{1}H NMR signals as function of the solvent ($CDCl_3$ and C_6D_6) and concentration of the CSA (*S*)-(-)-**6** (1.2 and 2 equiv.) for two representative α-hydroxyphosphonates, racemic diisopropyl α-hydroxyphenylmethylphosphonate (**1a**) and diisopropyl α-hydroxyethylphosphonate (**1b**) and their respective acetates **2a** and **2b** and chloroacetates **2g** and **2h** (Figure I). Weighed samples of these compounds and the required amounts of the shift reagent were dissolved in $CDCl_3$ and C_6D_6 and the spectra were recorded. The results are given in Tables I and II. The ratios of CSA (*S*)-(-)-**6** (δ = 95 - 98 ppm) and phosphonate as determined by ^{31}P NMR spectroscopy agreed normally within ±5% with the desired ratio of 1.2 or 2, respectively.

TABLE I Chemical shifts and shift differences for phosphorus resonances of α-hydroxyphosphonates **1a** and **1b**, their corresponding α-acetoxy- and α-chloroacetoxyphosphonates **2a**, **2g** and **2b**, **2h** in $CDCl_3$ and C_6D_6 at two different concentrations (1.2 and 2 equiv.) of CSA (*S*)-(-)-**6**

Phosphonate	*Solvent*	*CSA (equiv.)*	δ *(ppm)*	δ *(ppm)*	Δδ *(Hz)*	Δδ *(ppm)*
1a	$CDCl_3$	1.2	19.90	19.74	26.2	0.16
1a	$CDCl_3$	2.0	19.84	19.65	30.5	0.19
1a	C_6D_6	1.2	20.40	20.21	31.4	0.19
1a	C_6D_6	2.0	20.35	20.14	33.6	0.21
2a	$CDCl_3$	1.2	16.19	-	0.0	0.00
2a	$CDCl_3$	2.0	16.10	16.08	3.1	0.02
2a	C_6D_6	1.2	16.57	16.53	7.0	0.04
2a	C_6D_6	2.0	16.46	16.41	8.3	0.05
2g	$CDCl_3$	1.2	14.92	14.91	2.4	0.01
2g	$CDCl_3$	2.0	14.85	14.84	1.8	0.01
2g	C_6D_6	1.2	15.27	15.23	5.9	0.04
2g	C_6D_6	2.0	15.19	15.15	6.9	0.04
1b	$CDCl_3$	1.2	24.45	24.23	33.3	0.21
1b	$CDCl_3$	2.0	24.42	24.19	37.9	0.23
1b	C_6D_6	1.2	25.08	24.85	37.7	0.23

Phosphonate	*Solvent*	*CSA (equiv.)*	δ *(ppm)*	δ *(ppm)*	Δδ *(Hz)*	Δδ *(ppm)*
1b	C_6D_6	2.0	25.04	24.78	40.1	0.25
2b	$CDCl_3$	1.2	19.89	-	0.0	0.00
2b	$CDCl_3$	2.0	19.81	-	0.0	0.00
2b	C_6D_6	1.2	20.11	20.09	3.5	0.02
2b	C_6D_6	2.0	20.04	20.01	4.0	0.03
2h	$CDCl_3$	1.2	18.42	-	0.0	0.00
2h	$CDCl_3$	2.0	18.37	-	0.0	0.00
2h	C_6D_6	1.2	18.66	-	0.0	0.00
2h	C_6D_6	2.0	18.63	-	0.0	0.00

TABLE II Chemical shifts and shift differences for 1-H resonances of α-hydroxyphosphonates **1a** and **1b**, their corresponding α-acetoxy- and α-chloroacetoxyphosphonates **2a, 2g** and **2b, 2h** in $CDCl_3$ and C_6D_6 at two different concentrations (1.2 and 2 equiv.) of CSA (*S*)-(-)-**6**

Phosphonate	*Solvent*	*CSA (equiv.)*	δ *(ppm)*	δ *(ppm)*	Δδ *(Hz)*	Δδ *(ppm)*
1a	$CDCl_3$	1.2	5.04	4.83	87.1	0.22
1a	$CDCl_3$	2.0	5.06	4.81	98.0	0.25
1a	C_6D_6	1.2	5.21	5.02	76.0	0.10
1a	C_6D_6	2.0	5.22	5.02	81.2	0.20
2a	$CDCl_3$	1.2	6.08	-	0.0	0.00
2a	$CDCl_3$	2.0	6.08	-	0.0	0.00
2a	C_6D_6	1.2	6.45	6.44	5.4	0.01
2a	C_6D_6	2.0	6.45	6.43	6.0	0.02
2g	$CDCl_3$	1.2	6.116	6.113	1.2	0.003
2g	$CDCl_3$	2.0	6.120	6.115	1.7	0.004
2g	C_6D_6	1.2	6.39	6.38	5.9	0.01
2g	C_6D_6	2.0	6.40	6.38	6.9	0.02
1b	$CDCl_3$	1.2	4.00	3.83	65.5	0.16
1b	$CDCl_3$	2.0	4.01	3.82	76.4	0.19
1b	C_6D_6	1.2	4.12	3.97	60.1	0.15
1b	C_6D_6	2.0	4.14	3.98	64.0	0.16
2b	$CDCl_3$	1.2	5.16	-	0.0	0.00
2b	$CDCl_3$	2.0	5.16	-	0.0	0.00
2b	C_6D_6	1.2	5.43	-	0.0	0.00
2b	C_6D_6	2.0	5.42	-	0.0	0.00

Phosphonate	*Solvent*	*CSA (equiv.)*	δ *(ppm)*	δ *(ppm)*	Δδ *(Hz)*	Δδ *(ppm)*
2h	$CDCl_3$	1.2	5.22	-	0.0	0.00
2h	$CDCl_3$	2.0	5.22	-	0.0	0.00
2h	C_6D_6	1.2	5.34	-	0.0	0.00
2h	C_6D_6	2.0	5.35	-	0.0	0.00

Several general trends are evident in the ^1H and ^{31}P NMR spectra. Firstly, the shift differences increase by going from $CDCl_3$ to C_6D_6 as solvent and the effect is much more pronounced for the α-acetoxy- and α-chloroacetoxyphosphonates (±)-**2a**, **2b** and **2g**, **2h** than for the α-hydroxyphosphonates (±)-**1a** and **1b**. α-Acetoxyphosphonate (±)-**2a** shows only one phosphorus resonance, if 1.2 equiv. of CSA and $CDCl_3$ as solvent were used. The same is true for (±)-**2b** for both concentrations of shift reagent. α-Chloroacetoxyphosphonate (±)-**2g** shows only one ^{31}P NMR signal for both solvents and concentrations of the CSA. Secondly, the ^{31}P NMR shift differences vary between 0.16 – 0.21 and 0.21 – 0.25 ppm for the racemic α-hydroxyphosphonates (±)-**1a** and **1b**, respectively. The signals are well separated and allow an accurate integration. The shift differences, if there is one at all, for the α-acetoxy- and α-chloroacetoxyphosphonates (±)-**2g** and **2h** are very small, 0.02 – 0.05 ppm, too small for a satisfactory individual integration of the resonances.

The ^1H NMR spectra show characteristic signals for the diastereomeric complexes of phosphonates and CSA (*S*)-(-)-**6** (Table II). Only the resonances for the CHP hydrogens are given. The general trends are similar to those observed for the ^{31}P NMR signals. Based on these results and in contrast to Zymanczyk-Duda et al. deuterated benzene was used as solvent throughout this investigation. 20 μmol of phosphonate were dissolved routinely in 0.6 ml of a standard solution containing either 1.2 equiv. of *t*-butyl(phenyl)phosphinothioic acid for α-hydroxyphosphonates or 2 equiv. for all other α-substituted phosphonates. A large number of phosphonates **1–5**, having predominantly a hydroxy or an acyloxy and in a limited number of cases also an azido, a phthalimidooxy or an aminooxy group as α-substitutent, were tested with *t*-butyl(phenyl)phosphinothioic acid (*S*)-(-)-**6** as CSA. $R^{[1]}$ is covering a wide range of substitutents: alkyl, branched alkyl, cycloalkyl (from cyclopropyl to cyclooctyl), alkenyl, alkynyl, aryl and heteroaryl. The data are compiled in Table III. The assigment

of resonances to the (*R*) or (*S*) configurated phosphonate was made by using chiral, nonracemic compounds of known configuration, if such samples were available.

TABLE III Chemical shifts and shift differences of phosphorus and selected proton resonances of phosphonates recorded in C_6D_6 using CSA (*S*)-(-)-**6** (1.2 equiv. for α-hydroxyphosphonates **1**, 2 equiv. for all other phosphonates **2** – **5**)

Phospho-nate	*^{31}P NMR resonances*					*^{1}H NMR resonances*			
	δ *(R)*[a]	δ *(S)*[a]	$\Delta\delta^b$ *(Hz)*	$\Delta\delta^b$ *(ppm)*	*signal*	δ *(R)*[a]	δ *(S)*[a]	$\Delta\delta^b$ *(Hz)*	$\Delta\delta^b$ *(ppm)*
1a	20.29	20.10	30.9	0.19	CHP	4.10	4.20	-41.1	-0.10
1b	25.08	24.85	37.7	0.23	CHP	3.97	4.12	-60.1	-0.15
1c	26.31	26.10	34.1	0.21	-	-	-	-	-
1d[c]	25.25	25.11	22.7	0.14	CHP	4.48	4.59	-48.3	-0.12
1e	24.38	24.11	44.3	0.27	CHP	3.65	3.86	-85.4	-0.21
1f	24.17	23.87	49.0	0.30	CHP	3.59	3.84	-101.2	-0.25
1g	25.15	24.91	39.2	0.24	CHP	4.07	4.26	-77.0	-0.19
1h[c]	25.11	24.92	30.5	0.19	CHP	4.17	4.30	54.4	0.14
1i[c]	16.73	16.63	15.8	0.10	CHP	4.98	5.12	55.4	0.14
1j	26.30	26.11	30.2	0.19	-	-	-	-	-
1kc	22.45	22.22	36.9	0.23	-	-	-	-	-
1l	23.23	23.03	31.5	0.20	CHP	3.18	3.39	-83.2	-0.21
1m	24.32	24.03	45.6	0.28	CHP	3.73	3.92	-75.6	-0.19
1n	24.49	24.21	45.3	0.28	CHP	3.72	3.90	-72.6	-0.18
1o	24.52	24.20	51.8	0.32	CHP	3.74	3.92	-73.6	-0.18
1p	24.72	24.40	51.0	0.32	CHP	3.81	4.01	-77.8	-0.19
1q	26.47	26.18	46.7	0.29	-	-	-	-	-
1r	24.63	24.49	23.0	0.14	CHP	5.33	5.51	-72.4	-0.18
1s	21.29	21.14	24.6	0.15	CHP	5.73	5.90	-68.9	-0.17
1t	23.92	23.85	11.0	0.07	CHP	5.92	6.13	-84.7	-0.21
1u	20.16	19.96	31.9	0.20	CHP	5.26	5.44	-70.4	-0.18
1v	19.98	19.80	29.3	0.18	CHP	5.06	5.23	-67.2	-0.17
1w	18.39	18.27	19.5	0.12	CHP	5.10	5.23	-51.2	-0.13
1x	18.79	18.68	18.0	0.11	CHP	4.85	5.05	-77.5	-0.19
1y[c]	18.02	17.89	20.6	0.13	CHP	4.48	4.59	-48.3	-0.12
2a	16.46	16.41	8.3	0.05	CHP	6.45	6.43	6.0	0.02
2b	19.91	19.88	4.1	0.03	CHP	5.42	5.42	0.0	0.00
					CH_3CP	1.32	1.35	-11.3	-0.03

Phospho-nate	*^{31}P NMR resonances*					*^{1}H NMR resonances*			
	δ *(R)*[a]	δ *(S)*[a]	Δδ[b] *(Hz)*	Δδ[b] *(ppm)*	*signal*	δ *(R)*[a]	δ *(S)*[a]	Δδ[b] *(Hz)*	Δδ[b] *(ppm)*
2c[c]	21.59	21.54	8.9	0.06	-	-	-	-	-
2d	20.95	20.92	4.8	0.04	Ar-H	8.32	8.34	-8.4	-0.02
					OMe	3.43	3.34	36.0	0.09
2e	14.93	14.92	2.3	0.014	CHP	6.73	6.73	0.0	0.00
					Thienyl-H	7.26	7.31	-22.6	-0.06
2f[c]	16.00	15.97	4.4	0.03	CHP	6.533	6.538	-2,0	-0.005
2g	15.19	15.15	6.9	0.04	CHP	6.37	6.40	-14.0	-0.03
					CH_2Cl[d]	3.66	3.59	31.2	0.08
2h[c]	18.63	18.63	0.0	0.00	CHP	5.35	5.35	0.0	0.00
					CH_2Cl[d]	3.59	3.54	18.0	0.05
2i	20.22	20.20	2.9	0.02	CHP	5.32	5.30	6.4	0.02
					CH_2Cl[d]	3.37	3.44	-29.3	-0.07
2j	17.47	17.48	-2.6	-0.02	CHP	5.270	5.277	-2.9	-0.007
					CH_2Cl[d]	3.61	3.70	−35.1	-0.09
2k	16.91	16.96	-8.9	-0.06	CHP	5.26	5.24	7.8	0.02
					CH_2Cl[d]	3.62	3.69	-29.5	-0.07
2l	18.30	18.30	0.0	0.00	CHP	5.61	5.60	4.0	0.01
					CH_2Cl[d]	3.61	3.71	-42.0	-0.11
2m	20.25	20.25	0.0	0.00	CHP	5.49	5.48	5.2	0.01
					CH_2Cl[d]	3.55	3.61	-28.0	-0.07
2n	16.73	16.76	-3.9	-0.02	CHP	4.73	4.76	-9.8	-0.03
					CH_2Cl[d]	3.63	3.70	-28.0	-0.07
2o	17.17	17.17	0.0	0.00	CHP	5.400	5.395	2.0	0.005
					CH_2Cl[d]	3.62	3.72	-38.4	-0.10
2p	17.51	17.51	0.0	0.00	CHP	5.40	5.39	5.4	0.01
					CH_2Cl[d]	3.62	3.73	-44.4	-0.11
2q	17.59	17.59	0.0	0.00	CHP	5.33	5.35	-5.9	-0.02
					CH_2Cl[d]	3.64	3.75	-41.6	-0.11
2r	20.11	20.09	2.0	0.02	CH_2Cl[d]	3.66	3.59	24.8	0.06
2s	20.07	20.09	-3.6	-0.02	CHP	6.564	6.559	1.9	0.005
					CH_2Cl[d]	3.48	3.53	-19.7	-0.05
2t	13.74	13.74	0.0	0.00	CHP	6.58	6.62	-16.0	-0.04
					CH_2Cl[d]	3.54	3.59	-22.4	-0.06
2u[c]	19.94	19.97	4.2	0.03	CHP	5.47	5.47	0.0	0.00
					CH_3CP	1.34	1.38	-16.7	-0.04
2v[c]	20.47	20.53	10.7	0.07	$CH_3CH{=}CH$	1.39	1.34	18.7	0.05
3a	19.99	20.04	8.1	0.05	CHP	3.92	3.85	30.76	0.08

Phospho-nate	^{31}P NMR resonances					^{1}H NMR resonances			
	δ (R)[a]	δ (S)[a]	Δδ[b] (Hz)	Δδ[b] (ppm)	signal	δ (R)[a]	δ (S)[a]	Δδ[b] (Hz)	Δδ[b] (ppm)
3b	18.01	17.90	16.5	0.12	CHP	3.55	3.47	32.2	0.08
4a	17.05	16.92	20.9	0.13	CHP	4.99	4.94	17.5	0.05
4b	16.74	16.55	31.8	0.20	CHP	5.09	5.02	29.0	0.07
5a	21.62	21.60	2.5	0.02	CHP	4.07	4.11	-16.4	-0.04
5b	21.55	21.48	12.0	0.07	CHP	4.01	4.04	-14.4	-0.03

[a] Assignment of absolute configurations was made on the basis of spectra of chiral, non-racemic phosphonates. For racemic compounds the higher value of the phosphorus resonances and lower value of the proton resonances is given first. This sequence does not imply an assignment of configuration. –
[b] $\Delta\delta = \delta_{(R)} - \delta_{(S)}$ for compounds of known configuration; $\Delta\delta = |\delta_{(R)} - \delta_{(S)}|$ for racemic compounds and other signals than CHP. –
[c] Racemic phosphonate. –
[d] Calculated value for δ_A (at lower field) of AB system of CH_2Cl group

The general trends detectable in Table I and II are substantiated by the data of Table III. The ^{31}P NMR spectra of the α-hydroxy-, α-azido- and α-phthalimidooxyphosphonates **1a-1y**, **3a**, **b**, and **4a,b**, respectively, normally show large shift differences (0.10 – 0.30 ppm), those of the α-acyloxy- and α-aminooxyphosphonates **2** and **5** show only small shift differences (0.00 – 0.07 ppm), which in 7 out of 24 cases is zero. The ^{1}H NMR spectra of all phosphonates provide in the majority of cases separate resonances for the individual diastereomeric complexes, sometimes well separated, noteably for 1-H of α-hydroxyphosphonates with shift differences of 0.10 – 0.25 ppm. The shift differences for 1-H of the other phosphonates, especially of the α-acyloxyphosphonates, are at best 0.08 ppm, except 0.13 ppm for **3a**. For reasons of comparison the values of δ(1-H) have been listed inTable III, although other signals show in many cases much larger shift differences, e. g. the AB systems of the $ClCH_2$ groups of chloroacetates, methyl or aromatic or heteroaromatic hydrogens. Careful inspection of the spectra normally allows to find appropriate signals with adequate shift differences.

The determination of the ee was carried out with samples of known optical purity, which has been obtained by ^{31}P NMR spectroscopy of Mosher esters (Table IV). The values obtained by integration of satisfactorily separated ^{31}P and/or ^{1}H NMR signals agree within experimental error and correspond to the known values.

TABLE IV Determination of ee of chiral, non-racemic α-substituted phosphonates of known ee using CSA (*S*)-(-)-**6** and ^{31}P NMR and / or ^{1}H NMR spectroscopy

Phosphonate		*ee with (S)-(-)-6*	
	ee[a]	*^{31}P NMR*	*^{1}H NMR*
1c	70	71	-
1e	60	62	64
1f	98	≥98	≥98
1g	96	97	-
1j	82	84	-
1l	71	73	75
1m	92	91	94
1n	86	85	85
1o	94	94	95
1p	75	77	78
1q	17	17	-
1r	48[b]	48	50
1t	89	89	90
1u	88	89	87
1v	35	36	35
1w	62	60	60
1x	77	75	76
2a	33	33	31
2e	61	-	62
2i	64	-	70[c]
2j	55	-	60[c]
2k	41	45	40[c]
3a	65[d]	64	65
3d	90[d]	89	89

[a] Ee determined by ^{31}P NMR spectroscopy of Mosher esters. –
[b] Determined from $[\alpha]^{20}_{D}$. –
[c] Old samples with partial hydrolysis of chloroacetates. –
[d] Ee of starting α-hydroxyphosphonates used for preparation of azides

The second objective of this investigation was the evaluation of (*S*)-(-)-*t*-butyl(phenyl)phosphinothioic acid for the determination of the absolute configuration of α-substituted phosphonates. Inspection of Table III reveals that the phosphorus of the complexes of all (*R*) configurated α-hydroxyphosphonates **1** with (*S*)-(-)-*t*-butyl(phenyl)phosphinothioic acid resonate consistently at lower field than those of the (*S*) configurated phosphonates, if two signals are observed. This finding is in

agreement with observations for chiral, non-racemic tertiary benzylic phosphonates reported earlier.[13] The contrary is true for the ^1H NMR signals for the α-protons. It is therefore justified to cautiously assign absolute configurations, if the shift differences are large and the conclusions drawn from the ^1H NMR and ^{31}P NMR spectra are complementary. Nevertheless, it will be necessary to use an independant method to substantiate the results. For all other α-substituted phosphonates **2** – **5** no general conclusions can be drawn.

Zymanczyk-Duda et al. reported in their paper that racemic diethyl 2-hydroxypropylphosphonate shows one signal for phosphorus in the ^{31}P NMR spectrum recorded in $CDCl_3$ in the presence of 1 equiv. of (*S*)-(-)-*t*-butyl(phenyl)phosphinothioic acid. We used C_6D_6 as solvent and two equiv. of CSA and detected two signals ($\delta = 28.43$ and 28.37 ppm) with a small shift difference ($\Delta\delta = 8.6$ Hz or 0.053 ppm). The signal at lower field was again corresponding to the (*R*)-2-hydroxypropylphosphonate.

Finally, we applied this method to the reaction products of the enzymatic resolution of (±)-diethyl 1-chloroacetoxyhexylphosphonate (**2i**) in a buffered biphasic system with protease Chirazyme P-2. The crude product as obtained after workup is a mixture of the 1-hydroxyphosphonate **1c** and the corresponding chloroacetate **2i** of opposite configuration. Until now the conversion was determined by ^1H NMR spectroscopy of the mixtures, which were then separated by flash chromatography and the chloroacetate was hydrolysed chemically. The two α-hydroxyphosphonates were derivatised with (*S*)-(+)-MTPA-Cl and the Mosher esters formed were investigated by ^{31}P NMR spectroscopy to determine the ee and the absolute configurations. The data thus found for this experiment were: 47% conversion; the α-hydroxyphosphonate obtained by enzymatic hydrolysis had *(R)* configuration and 70% ee, and the α-hydroxyphosphonate obtained by chemical hydrolysis had *(S)* configuration and 62% ee. Now 20 mg of crude product were dissolved with 2 equiv. of (*S*)-(-)-*t*-butyl(phenyl)phosphinothioic acid in C_6D_6 and the ^1H and ^{31}P NMR spectrum were recorded (compare **1c** and **2i** in Table III). As four diastereomeric complexes are present in the benzene solution, the ^1H NMR spectrum is complex. Nevertheless, the AB systems of the CH_2Cl groups of the diastereomeric chloroacetate complexes are well separated and can be used to determine the ee (63%). The ^{31}P NMR spectrum shows between

20 to 27 ppm just four signals, two pairs of singlets of different intensity. From the integration of the two pairs of signals the conversion was calculated to be 47%. For the α-hydroxyphosphonate the signal at lower field is stronger and therefore has *(R)* configuration and the ee is found to be 71%. For the α-chloroacetoxyphosphonate the signal at higher field is stronger and as the shift difference is only small, the ee cannot be determined from the relative intensities of the two signals. If it is desired or necessary, the ee and the configuration of the chloroacetate can be determined after hydrolysis to the corresponding α-hydroxyphosphonate. These data are obtained easily and they agree within experimental error with those obtained from the Mosher esters. This investigation has been extended to other mixtures. Analytical samples from crude pro- ducts from enzymatic resolutions should best be investigated with the CSA as soon as possible. If it is necessary to keep them for a few days, they should be stored at –4 °C to minimize hydrolysis of the chloroacetates, which will give erroneous results.

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EXPERIMENTAL

TLC: Merck precoated TLC plates (0.25 mm), silica gel 60, F_{254}; detection: UV and/or dipping the TLC plates into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (24 g) and of $Ce(SO_4)_2\cdot 4H_2O$ (1 g) in 10% H_2SO_4 (500 ml) in water, followed by heating with a hot gun. – ^1H and ^{13}C NMR spectra (*J* modulated) were recorded in C_6D_6 or $CDCl_3$ using tetramethylsilane as internal standard on a Bruker AM 400 WB at 400.13 and 100.61 MHz, respectively. ^{31}P NMR spectra were recorded on the same spectrometer at 161.97 MHz using H_3PO_4 (85%) as external standard. In order to get undistorted ^{31}P signal intensities for an accurate integration, adequate relaxation times were used without irradiation during this period to avoid NOE enhancements. The sweep width in general was kept small to obtain a suitable resolution for signals resonating close together – IR

spectra were run on a Perkin Elmer 1600 FT-IR spectrometer. – Flash chromatography: Merck silica gel 60, 0.040–0.063 mm. – Optical rotation: Perkin-Elmer polarimeter 241 (1 dm cell). – Melting points were measured with a Reichert Thermovar instrument and are uncorrected. – Reactions were carried out in dry solvents under an argon atmosphere. Diethyl ether was distilled from lithium aluminum hydride.

The synthesis of compounds **1a**, **1b**, **2a**, and **2b** is described in ref. 14, that of **1c**, **1e**, and **1g** in ref. 15, that of **1d** and **2c** in ref. 18, **2v** in ref. 19, that of **1f**, **1l-1q**, **2j-2l**, **2n-2r**, and **3b** in ref. 1, **1h** and **3a**, in ref. 20, that of **1j**, **2m**, **4a**, **4b**, **5a**, **5b** in ref. 21, and that of **1r-1y and 2d-2f** in ref. 4

Compounds **2g, 2h, 2i, 2s,** and **2t** were prepared by chloroacetylation of the corresponding α-hydroxyphosphonates using chloroacetic anhydride/pyridine.[1] – Racemic and optically active diethyl 2-hydroxypropylphosphonate[22] were prepared by hydrogenolysis of the corresponding benzyl ethers in ethanol on Pd/C (10%) in a Parr apparatus at 3.4 bar.

Preparation of *t*-butyl(phenyl)phosphinothioic acid (*S*)-(-)-6:

It was prepared according to a literature procedure with some modifications.[10] The crude *t*-butylphenylphosphine oxide was not distilled, but treated immediately with sulfur in toluene. After concentration in vacuo, the residue was dissolved in diethyl ether and water was added. The phosphinothioic acid was extracted into the aqueous layer by stirring and adding solid $NaHCO_3$ until the evolution of CO_2 ceased. The organic phase was removed. The aqueous phase was acidified with conc. HCl. The phosphinothioic acid liberated was extracted with diethyl ether and crystallised from diethyl ether/hexane to yield (±)-***6***, which was resolved with (*S*)-(-)-1-phenylethylamine[8]. The recovered acid from the mother liquor was resolved similarly with (*R*)-(+)-1-phenylethylamine.

(±)-Diisopropyl 1-hydroxy-3-phenyl-2-propynylphosphonate [(±)-1i]:

This α-hydroxyphosphonate was prepared according to a literature procedure[15] starting from 11 mmol of the aldehyde, except that the reaction was carried out at –40 °C and worked up already after 2 h. Crystallisation of the crude product from ethyl acetate gave 2.0 g (68%) of (±)-**1i**; m.p. 112–113 °C; $R_f = 0.36$ [CH_2Cl_2/ethyl acetate (5:3)]. IR (Nujol): ν = 3260 cm^{-1}, 1232, 1066, 1018, 992. – ^1H NMR: δ = 1.34 and 1.345 (2d,

J = 6.5 Hz, each 3H, CH_3), 1.36 (d, J = 6.5 Hz, 6H, CH_3), 4.71 (dd, J = 3.4, 6.2 Hz, 1H, OH), 4.85 (m, 3H, OCH, CHP), 7.29 (m, 3H, H_{arom}), 7.44 (m, 2H, H_{arom}). – ^{13}C NMR: δ = 23.76 (d, J_{PC} = 4.3 Hz, CH_3), 23.86 (d, J_{PC} = 3.6 Hz, CH_3), 24.09 (d, J_{PC} = 3.8 Hz, CH_3), 24.22 (d, J_{PC} = 3.1 Hz, CH_3), 59.82 (d, J_{PC} = 170.1 Hz, CHP), 72.57 (d, J_{PC} = 7.6 Hz, OCH), 72.80 (d, J_{PC} = 6.9 Hz, OCH), 84.06 (d, J_{PC} = 3.8 Hz, *C*CHP), 87.14 (d, J_{PC} = 10.7 Hz, *C*CCHP), 122.36 (d, J_{PC} = 3.8 Hz, iC_{arom}), 128.22 (mC_{arom}), 128.60 (pC_{arom}), 131.78 (d, J_{PC} = 3.1 Hz, oC_{arom}). – $C_{15}H_{21}O_4P$ (296.31): calcd. C 60.80, H 7.14; found C 60.93, H 7.03.

(±)-2,2 -Dimethylpropane-1,3-diyl 1-hydroxy-2-methylpropylphosphonate [(±)-*1k*]:

Phosphazene base *t*-butylaminotris(dimethylamino)phosphorane (0.1 ml) was added dropwise to a stirred and cooled solution (0 °C) of 1.58 g (22 mmol) of freshly distilled isobutyraldehyde and 3.0 g (20 mmol) of cyclic phosphite[23] in 15 ml of dry diethyl ether under an argon atmosphere.[15] The reaction was exothermic and after a few minutes crystals formed. The mixture was kept for 30 min in the cooling bath and for 30 min at room temperature, then 15 ml of hexane were added. After standing for 18 h at 4 °C, the crystals were collected, washed with a cold mixture (1:1) of diethyl ether and hexane and dried to yield 4.05 g (92%) of α-hydroxyphosphonate (±)-**1k**; the analytical sample was recrystallised from chloroform/hexane, m.p. 150–151 °C (lit.[24] m.p. 157 °C), R_f = 0.15 [CH_2Cl_2/ethyl acetate (1:1)] ; the ^1H and ^{13}C NMR data agree with those reported in the literature.

(±)-Diisopropyl 1-butyryloxyethylphosphonate [(±)-2u]:

A solution of 4.2 g (20 mmol) of 1-hydroxyethylphosphonate (±)-**1b** and 2.66 g (25 mmol, 2.6 ml) butyryl chloride in 20 ml of dry pyridine was left for 18 h at room temperature. Pyridine was removed in vacuo (40 °C/0.05 mm) and CH_2Cl_2 (70 ml) and 2N HCl were added to the residue. The mixture was stirred for 40 min. The organic phase was removed, dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was purified by flash chromatography [CH_2Cl_2/ethyl acetate (5:1), R_f = 0.42] and bulb to bulb distillation (80–90 °C/0.001 mm) to give 5.14 g (92%) of ester (±)-**2u** as an oil. – IR (film): ν = 2980 cm^{-1}, 2938, 1746, 1376, 1247,

1175, 1107, 986. - ^{1}H NMR: $\delta = 0.96$ (t, $J = 7.3$ Hz, 3H, CH_3), 1.32, 1.325, 1.338, and 1.34 (four d, $J = 6.5$ Hz, each 3H, CH_3), 1.43 (dd, $J = 7.0$, 16.7 Hz, 3H, CH_3CP), 1.67 (sex, J = 7.3 Hz, 2H, $(O)CCCH_2$), 2.34 (t, $J = 7.3$ Hz, $(O)CCH_2$), 4.75 (m, 2H, OCH), 5.21 (dq, $J = 7.0$, 9.0 Hz, 1H, CHP). – $C_{12}H_{25}O_5P$ (280.30): calcd. C 51.42, H 8.99; found C 51.58, H 8.89.

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