Enzymes in Organic Chemistry, Part 4:[1] Enantioselective Hydrolysis of 1-Acyloxy(aryl)methyl- and 1-Acyloxy(heteroaryl)methylphosphonates with Lipases from *Aspergillus niger* and *Rhizopus oryzae*. A Comparative Study

Gerhard Eidenhammer, Friedrich Hammerschmidt*

Institut für Organische Chemie der Universität Wien, Währingerstraße 38, A-1090 Wien, Austria

Fax +43(1)313672280

Dedicated to Prof. Dr. P.K. Claus on the occasion of his 60th birthday

Received 19 December 1995

Racemic 1-acyloxy(aryl)methyl- and 1-acyloxy(heteroaryl)methylphosphonates (±)-**4** are prepared and tested for kinetic resolution by lipases AP 6 and FAP 15. Both enzymes proved to be useful in terms of broadness of application, reaction rate and enantiomeric excess. In general, reaction rates are higher with lipase AP 6 than with FAP 15. (*S*)-α-Hydroxyphosphonates (−)-**3** are formed on enzymatic hydrolysis of α-acyloxyphosphonates (±)-**4**. Lipase FAP 15 gives products with higher enantiomeric excesses. 1-Acetoxy-(2-methoxyphenyl)methylphosphonates are either not kinetically resolved or are saponified with very low enantioselectivity.

In the preceding paper[1] we reported on the enzyme-catalyzed hydrolysis of α-acetoxy- and α-chloroacetoxyalkylphosphonates using lipase from *Aspergillus niger* (lipase AP 6). The reaction proceeds enantioselectively in a biphasic system and affords chiral, nonracemic α-hydroxyphosphonates with straight chain alkyl groups of up to ten carbon atoms. Chloroacetates are hydrolyzed much more easily than acetates and the enantiomeric excess is normally higher with diisopropyl than diethyl phosphonates.

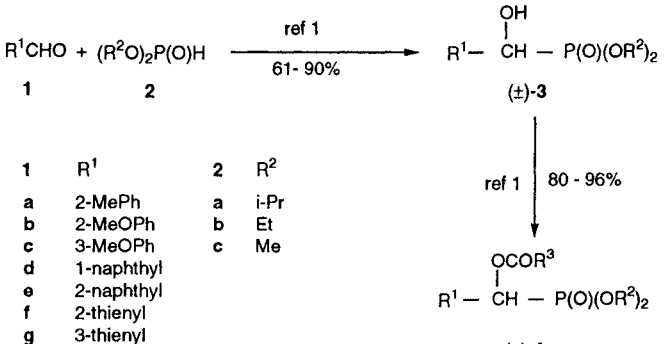
We have extended these investigations to 1-acyloxy(aryl)- and 1-acyloxy(heteroaryl)methylphosphonates and tested two enzymes, lipases AP 6 and FAP 15 (from *Rhizopus oryzae*) and the results of these studies are disclosed in this paper. The latter enzyme proved to be useful in the resolution of α-acyloxyphosphonates derived from acetaldehyde, crotonaldehyde, and benzaldehyde, but interestingly not from other aliphatic aldehydes.[1]

The α-hydroxyphosphonates (±)-**3a–m** used as starting materials were prepared by base-catalyzed addition of phosphites **2a–c** [preferentially diisopropyl phosphite **(2a)**] to aromatic or heteroaromatic aldehydes **1a–j** (Abramov reaction) as reported previously (Scheme 1, Tables 1 and 3).[1]

The addition proceeded cleanly to afford α-hydroxyphosphonates (±)-**3**, which were esterified with or without prior isolation and purification by crystallization or flash chromatography to yield α-acyloxyphosphonates (±)-**4** (Scheme 1, Tables 2 and 3). The aromatic α-hydroxyphosphonates (±)-**3a–g** were transformed into acetates[2] and chloroacetates[3] (±)-**4a–h**, the heteroaromatic ones (±)-**3h–m** to acetates (±)-**4i–n** only. Purification by bulb to bulb distillation or flash chromatography afforded the products in excellent yield. When 1-naphthaldehyde **(1d)** and dimethyl phosphite were allowed to react under standard conditions for 72 hours instead of 16–18 hours, only dimethyl (1-naphthyl)methylphosphate **(5)** was isolated in 75% yield (Scheme 2).

A close examination of product formation as a function of time revealed that α-hydroxyphosphonate (±)-**3f** crystallized out rapidly from diethyl ether used as solvent. When stirring of the initially formed suspension was continued at room temperature, the reaction mixture became homogenous gradually, because α-hydroxyphosphonate (±)-**3f** isomerized to phosphate **5** (phosphonate-phosphate rearrangement),[4] catalyzed by the phosphazene base P_1-*t*-Bu [*tert*-butylamino-tris(dimethylamino)phosphorane] used for the Abramov reaction. This side reaction was not observed with diisopropyl phosphite. It could be suppressed by simply carrying out the reaction at 0°C and keeping the reaction time short (TLC, 1 h).

We were especially interested in the influence of a substituent in the phenyl ring and the size of the aromatic

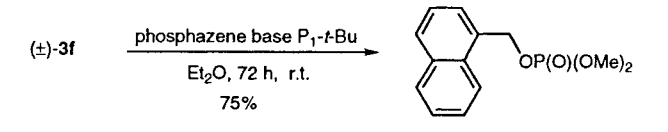


1	R^1	2	R^2
a	2-MePh	a	i-Pr
b	2-MeOPh	b	Et
c	3-MeOPh	c	Me
d	1-naphthyl		
e	2-naphthyl		
f	2-thienyl		
g	3-thienyl		
h	2-furyl		
i	2-pyridyl		
j	3-pyridyl		

3	R^1	R^2
a	2-MePh	i-Pr
b	2-MePh	Me
c	2-MeOPh	i-Pr
d	3-MeOPh	i-Pr
e	1-naphthyl	i-Pr
f	1-naphthyl	Me
g	2-naphthyl	i-Pr
h	2-thienyl	i-Pr
i	2-thienyl	Et
j	3-thienyl	i-Pr
k	2-furyl	i-Pr
l	2-pyridyl	i-Pr
m	3-pyridyl	i-Pr

4	R^1	R^2	R^3
a	2-MePh	i-Pr	CH_2Cl
b	2-MePh	Me	CH_3
c	2-MeOPh	i-Pr	CH_3
d	2-MeOPh	i-Pr	CH_2Cl
e	3-MeOPh	i-Pr	CH_2Cl
f	1-naphthyl	i-Pr	CH_3
g	1-naphthyl	Me	CH_3
h	2-naphthyl	i-Pr	CH_3
i	2-thienyl	i-Pr	CH_3
j	2-thienyl	Et	CH_3
k	3-thienyl	i-Pr	CH_3
l	2-furyl	i-Pr	CH_3
m	2-pyridyl	i-Pr	CH_3
n	3-pyridyl	i-Pr	CH_3

Scheme 1



Scheme 2 **5**

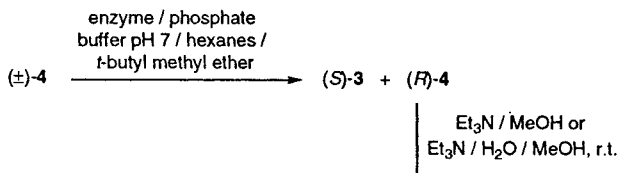
Table 1. α-Hydroxyphosphonates (±)-**3** Prepared

Product	Yield[a] (%)	mp[b] (°C)	R_f[c]	IR[d] ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	87 (C)	90–92	0.32	3264, 1237, 1176, 1011	1.07 [d, 3H, J = 6.3, $(CH_3)_2$CHO], 1.27, 1.28 [2d, 3H each, J = 6.1, $(CH_3)_2$CHO], 1.30 [d, 3H, J = 6.3, $(CH_3)_2$CHO], 2.38 (s, 3H, CH_3), 3.60 (br s, 1H, OH), 4.62 [m, 2H, $(CH_3)_2CHO$], 5.19 (d, 1H, J = 11.3, PCH), 7.18, 7.65 (2m, 4H, ArH)
3b	81 (C)	95–96	0.18	3292, 1237, 1043	2.35 (s, 3H, CH_3), 3.62, 3.67 (2d, 3H each, J = 10.3, OCH_3), 4.52 (br s, 1H, OH), 5.28 (d, 1H, J = 10.8, PCH), 7.18, 7.65 (2m, 4H, ArH)
3c	82 (C)	71–73	0.22	3300, 1247, 991	1.03, 1.25, 1.31 [3d, 3H, each, J = 6.1, $(CH_3)_2$CHO], 1.32 [d, 3H, J = 6.3, $(CH_3)_2$CHO] 3.56 (br s, 1H, OH), 3.85 (s, 3H, OCH_3), 4.53, 4.73 [2dsept, 1H each, J = 6.1, 7.1, $(CH_3)_2CHO$], 5.33 (d, 1H, J = 12.7, PCH), 6.88, 6.98, 7.26, 7.52 (4m, 4H, ArH)
3d	81 (C)	63–64	0.38	3281, 1602, 1232, 993	1.16 [d, 3H, J = 6.3, $(CH_3)_2$CHO], 1.26 [d, 6H, J = 6.1, $(CH_3)_2$CHO], 1.28 [d, 3H, J = 6.3, $(CH_3)_2$CHO], 3.82 (s, 3H, OCH_3), 4.49 (m, 1H, OH), 4.64 [m, 2H, $(CH_3)_2CHO$], 4.94 (dd, 1H, J = 5.5, 11.3, PCH), 6.83, 7.07, 7.23 (3m, 4H, ArH)
3e	61 (A)	125–126	0.31	3254, 1211, 1064, 1001	0.86 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 1.20, 1.22 [2d, 3H each, J = 5.9, $(CH_3)_2$CHO] 1.27 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 2.50 (br s, 1H, OH), 4.53, 4.63 [2dsept, 1H each, $(CH_3)_2CHO$], 5.80 (d, 1H, J = 11.8, PCH), 7.50, 7.83, 8.10 (3m, 7H, ArH)
3f	77 (A)	110–112	0.15	3279, 1237, 1030	3.53, 3.67 (2d, 3H each, J = 10.8, OCH_3), 4.08 (dd, 1H, J = 4.4, 9.8, OH), 5.88 (dd, 1H, J = 4.4, 11.3, CHP), 7.51, 7.86, 8.06 (3m, 7H, ArH)
3g	72 (A)	108–110	0.30	3279, 1234, 993	1.14 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 1.24, 1.26 [2d, 3H each, J = 5.9, $(CH_3)_2$CHO] 1.27 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 3.67 (br s, 1H, OH), 4.63 [m, 2H, $(CH_3)_2CHO$], 5.13 (d, 1H, J = 10.8, PCH), 7.47, 7.61, 7.82, 7.96 (4m, 7H, ArH)
3h	80 (A)	67–68	0.31	3262, 1222, 993	1.18, 1.28 [2d, 3H, 6H, J = 6.4, $(CH_3)_2$CHO], 1.29 [d, 3H, J = 5.9, $(CH_3)_2$CHO], 3.70 (br s, 1H, OH), 4.70 [m, 2H, $(CH_3)_2CHO$], 5.15 (d, 1H, J = 10.3, PCH), 6.96, 7.16, 7.26 (3m, 3H, ArH)
3i	61 (B)	oil[e]	0.27	3262, 1222, 1028, 974	1.26, 1.30 (2t, 3H each, J = 6.9, CH_3), 1.90 (br s, 1H, OH), 4.09 (m, 4H, CH_2) 5.22 (d, 1H, J = 10.8, PCH), 7.00, 7.18, 7.30 (3m, 3H, ArH)
3j	86 (A)	42–44	0.30	3288, 1232, 990	1.16, 1.25, 1.29 [3d, 3H each, J = 5.9, $(CH_3)_2$CHO], 1.31 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 2.93 (dd, 1H, J = 5.4, 8.4, OH), 4.66 [m, 2H, $(CH_3)_2CHO$], 5.04 (dd, 1H, J = 5.4, 10.3, PCH), 7.21, 7.30, 7.39 (3m, 3H, ArH)
3k	84 (C)	57–58	0.26	3280, 1225, 994	1.17 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 1.31, 1.32 [2d, 3H each, J = 5.9, $(CH_3)_2$CHO], 1.33 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 3.79 (t, 1H, J = 7.4, OH), 4.65, 4.74 [2m, 1H each, $(CH_3)_2CHO$], 4.93 (dd, 1H, J = 7.4, 13.3, PCH), 6.37, 6.51, 7.41 (3m, 3H, ArH)
3l	86 (B)	oil[e]	0.29	3278, 1237, 994	1.07, 1.24, 1.32, 1.37 [4d, 3H each, J = 6.3, $(CH_3)_2$CHO], 4.54, 4.80 [2dsept, 1H each, J = 6.3, 7.2, $(CH_3)_2CHO$], 5.05 (dd, 1H, J = 3.3, 11.3, PCH), 5.24 (br s, 1H, OH), 7.25, 7.57, 7.71, 8.56 (4m, 4H, ArH)
3m	90 (C)	50–51	0.10	3260, 1236, 990	1.14 [d, 3H, J = 6.4, $(CH_3)_2$CHO], 1.18 [d, 3H, J = 5.9, $(CH_3)_2$CHO], 1.20, 1.22 [d, 3H each, J = 6.4, $(CH_3)_2$CHO], 4.62 [m, 2H, $(CH_3)_2CHO$], 4.95 (d, 1H, J = 11.8, PCH), 6.18 (br s, 1H, OH), 7.22, 7.84, 8.41, 8.57 (4m, 4H, ArH)

[a] Yields after purification of crude product by crystallization (Method A), flash chromatography (Method B), crystallization and flash chromatography of mother liquor (Method C). Satisfactory microanalyses obtained: C ± 0.25, H ± 0.27.
[b] Compounds were crystallized from hexanes containing a small amount of CH_2Cl_2 or EtOAc for **3e** and **3m**.
[c] CH_2Cl_2/EtOAc = 5 : 3.
[d] See experimental.
[e] Purified by bulb to bulb distillation; **3i**: bp 170–180 °C/0.01 Torr; **3l**: bp 150–160 °C/0.01 Torr.

system on the rate of hydrolysis and the enantioselectivity of the kinetic resolution of α-acyloxyphosphonates. It was anticipated that substituents in the ortho position would have a pronounced influence on the reaction parameters. To prove this, 2-methyl- and 2-methoxybenzaldehydes (**1a** and **1b**) and for comparison 3-methoxybenzaldehyde (**1c**) were used as aldehydes. Also, 1- and 2-naphthaldehydes (**1d** and **1e**) were derivatised to α-hydroxyphosphonates (±)-**3e–g** to study the effect of large, planar substituents on the enzymatic hydrolysis. The 2- and 3-thienylcarbaldehydes (**1f** and **1g**), furfural (**1h**) and 2- and 3-pyridinecarbaldehydes (**1i** and **1j**) were used as heteroaromatic precursors for α-hydroxyphosphonates (±)-**3h–m**.

1-Acyloxyphosphonates (±)-**4** were hydrolyzed on a 1 mmol scale under argon at room temperature (22–31 °C) in a well stirred biphasic system (hexanes/*tert*-butyl methyl ether, phosphate buffer) as previously reported (Scheme 3, Table 4).[1,2]



Scheme 3

The pH was kept constant by automatic addition of 0.5 N sodium hydroxide using an autotitrator. With the exception of (±)-**4m** and **4n** hydrolysis was stopped by addition of 1 N hydrochloric acid to adjust the pH to 4 at a

Table 2. α-Acycloxyphosphonates (±)-**4** Prepared

Product	Yield[a] (%)	bp (°C/0.01 Torr)	IR (film) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	87	–[b]	1770, 1258, 1157, 998	1.00, 1.28 [2d, 3H, 6H, J= 6.3, $(CH_3)_2CHO$], 1.30 [d, 3H, J= 6.1, $(CH_3)_2CHO$], 2.49 (s, 3H, CH_3), 4.14 (AB system, 2H, J= 15.0, CH_2Cl), 4.57, 4.70 [2m, 1H each, $(CH_3)_2CHO$], 6.30 (d, 1H, J= 14.0, PCH), 7.20, 7.56 (2m, 4H, ArH)
4b	89	–[c]	1748, 1264, 1231, 1032	2.17 (s, 3H, $COCH_3$), 2.48 (s, 3H, CH_3), 3.61, 3.74 (2d, 3H each, J= 10.4, OCH_3), 6.37 (d, 1H, J= 13.8, PCH), 7.22, 7.55 (2m, 4H, ArH)
4c	97	180	1752, 1253, 1221, 995	1.04, 1.25 [2d, 3H each, J= 6.4, $(CH_3)_2CHO$], 1.27, 1.29 [2d, 3H each, J= 5.9, $(CH_3)_2CHO$], 2.11 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 4.54, 4.72 [2dsept, 1H each, J= 6.4, 7.4, $(CH_3)_2CHO$], 6.64 (d, 1H, J= 13.8, PCH), 6.85, 6.95, 7.27, 7.55 (4m, 4H, ArH)
4d	92	–[c]	1771, 1495, 1254, 1157, 1105, 1000	1.05 [d, 3H, J= 6.1, $(CH_3)_2CHO$], 1.27, 1.29 [2d, 3H each, J= 6.6, $(CH_3)_2CHO$], 1.31 [d, 3H, J= 6.4, $(CH_3)_2CHO$], 3.87 (s, 3H, OCH_3), 4.13 (AB system, 2H, J= 15.1, CH_2Cl), 4.56, 4.74 [2m, 1H each, $(CH_3)_2CHO$], 6.71 (d, 1H, J= 13.2, PCH), 6.88, 6.98, 7.31, 7.56 (4m, 4H, ArH)
4e	95	–[c]	1770, 1602, 1258, 1159, 995	1.11 [d, 3H, J= 6.1, $(CH_3)_2CHO$], 1.25 [d, 3H, J= 6.3, $(CH_3)_2CHO$], 1.29, 1.30 [2d, 3H each, J= 6.1, $(CH_3)_2CHO$], 3.81 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2Cl), 4.65 [m, 2H, $(CH_3)_2CHO$], 6.09 (d, 1H, J= 13.7, PCH), 6.88, 7.06, 7.26 (3m, 4H, ArH)
4f	95	200	1751, 1374, 1258, 1223, 993	0.75 [d, 3H, J= 6.4, $(CH_3)_2CHO$], 1.21, 1.26 [2d, 3H each, J= 5.9, $(CH_3)_2CHO$], 1.28 [d, 3H, J= 6.4, $(CH_3)_2CHO$], 2.10 (s, 3H, $COCH_3$), 4.47, 4.71 [2dsept, 1H each, J= 5.9, 6.3, $(CH_3)_2CHO$], 6.91 (d, 1H, J= 14.8, PCH), 7.49, 7.56, 7.82, 8.29 (4m, 7H, ArH)
4g	89	–[c]	1751, 1265, 1223, 1040	2.17 (s, 3H, $COCH_3$), 3.47, 3.72 (2d, 3H each, J= 10.7, OCH_3), 6.98 (d, 1H, J= 14.0, PCH), 7.53, 7.82, 8.22 (3m, 7H, ArH)
4h	95	190–200	1750, 1374, 1260, 1224, 1105, 999	1.06 [d, 3H, J= 6.4, $(CH_3)_2CHO$], 1.23, 1.27 [2d, 3H each, J= 5.9, $(CH_3)_2CHO$], 1.29 [d, 3H, J= 6.4, $(CH_3)_2CHO$], 2.21 (s, 3H, $COCH_3$), 4.57, 4.67 [2dsept, 1H each, J= 6.4, 7.4, $(CH_3)_2CHO$], 6.23 (d, 1H, J= 14.3, PCH), 7.46, 7.61, 7.81, 7.93 (4m, 7H, ArH)
4i	95	130	1755, 1374, 1260, 1220, 994	1.05, 1.21, 1.23, 1.24 [4d, 3H each, J= 5.9, $(CH_3)_2CHO$], 2.04 (s, 3H, $COCH_3$), 4.59, 4.67 [2dsept, 1H each, J= 5.9, 7.4, $(CH_3)_2CHO$), 6.27 (d, 1H, J= 14.3, PCH), 6.91, 7.19, 7.24 (3m, 3H, ArH)
4j	96	165–170	1756, 1261, 1024, 974	1.24, 1.31 (2t, 3H each, J= 6.9, CH_3CH_2O), 2.14 (s, 3H, $COCH_3$), 4.10 (m, 4H, CH_3CH_2O), 6.41 (d, 1H, J= 14.3, PCH), 7.00, 7.26, 7.33 (3m, 3H, ArH)
4k	95	150	1753, 1374, 1259, 1223, 1000	1.09, 1.23 [2d, 3H each, J= 6.4, $(CH_3)_2CHO$], 1.28, 1.29 [2d, 3H each, J= 5.9, $(CH_3)_2CHO$], 2.13 (s, 3H, $COCH_3$), 4.60, 4.63 [2m, 1H each, $(CH_3)_2CHO$], 6.20 (d, 1H, J= 13.8, PCH), 7.23, 7.27, 7.42 (3m, 3H, ArH)
4l	95	150	1756, 1375, 1262, 1218, 999	1.14, 1.29, 1.30, 1.31 [4d, 3H each, J= 5.9, $(CH_3)_2CHO$], 2.06 (s, 3H, $COCH_3$), 4.67, 4.74 [2m, 1H each, $(CH_3)_2CHO$], 6.18 (d, 1H, J= 15.8, PCH), 6.35, 6.58, 7.40 (3m, 3H, ArH)
4m	98	180	1754, 1374, 1257, 1218, 1105, 1004	1.17, 1.27 [2d, 3H each, J= 6.1, $(CH_3)_2CHO$], 1.30 [d, 3H, J= 6.3, $(CH_3)_2CHO$], 1.31 [d, 3H, J= 5.9, $(CH_3)_2CHO$], 2.21 (s, 3H, $COCH_3$), 4.66, 4.75 [2dsept, 1H each, J= 6.3, 7.4, $(CH_3)_2CHO$], 6.20 (d, 1H, J= 14.6, PCH), 7.23, 7.52, 7.70, 8.60 (4m, 4H, ArH)
4n	90	–[c]	1752, 1374, 1263, 1223, 1004	1.14 [d, 3H, J= 6.0, $(CH_3)_2CHO$], 1.26 [d, 3H, J= 6.3, $(CH_3)_2CHO$], 1.30 [d, 6H, J= 6.4, $(CH_3)_2CHO$], 2.18 (s, 3H, $COCH_3$), 4.68 [m, 2H, $(CH_3)_2CHO$], 6.08 (d, 1H, J= 14.6, PCH), 7.31, 7.85, 8.58, 8.69 (4m, 4H, ArH)

[a] Yields after bulb to bulb distillation. Satisfactory microanalyses obtained: C ± 0.44, H ± 0.29.
[b] Purified by flash chromatography (R_f 0.68, CH_2Cl_2/EtOAc, 5 : 3); mp 50–51 °C.
[c] Purified by flash chromatography with CH_2Cl_2/EtOAc 5 : 1, for **4n** CH_2Cl_2/acetone, 5 : 1. Solvent for TLC: CH_2Cl_2/EtOAc 5 : 3; **4b**: R_f 0.49, **4d**: R_f 0.59, **4e**: R_f 0.63; for **4n**: CH_2Cl_2/acetone, 3 : 1, R_f 0.39.

conversion of normally 45%. Passage of the reaction mixture through Celite and extractive workup furnished a mixture of unreacted ester (+)-**4** and α-hydroxyphosphonate (−)-**3**, which were separated by flash chromatography easily. The conversion as calculated from the ^{1}H NMR spectrum of the crude material agreed well with the value obtained from the consumption of base (see Table 4). Chloroacetates and acetates (+)-**4** were saponified chemically under mild conditions in anhydrous methanol (with 10% of water for acetates) and triethylamine at room temperature.[2] The hydrolysis of acetates was complete in 24–48 h (TLC), the hydrolysis of chloroacetates in about 16 h. Dimethyl acetoxyphosphonate (+)-**4g** could not be hydrolyzed smoothly by this method. The reaction did not go to completion probably caused by partial demethylation at phosphorus. To overcome these difficulties, the esters (+)-**4g** and (+)-**4b** were treated with sodium methoxide in methanol at −20 °C for 3–5 h (TLC). The low temperature was selected to prevent the well known cleavage of α-hydroxyphosphonates into phosphites and aldehydes under basic conditions (retro-Abramov reaction), which after readdition would lead to partial or full racemization of the α-hydroxyphosphonates. To test whether this process is actually taking place, optically active phosphonate (−)-**3f** $\{[\alpha]_D^{20}$ −88.1 (c = 0.9, acetone)$\}$ was esterified with acetic anhydride/pyridine in 83% yield and then hydrolyzed with sodium methoxide in methanol to give again phosphonate (−)-**3f** in 85% yield with $[\alpha]_D^{20}$ −84.9 (c = 0.6, acetone). Thus the extent of racemization, if it occurs at all, is low.

Table 3. ^{13}C NMR Data of Selected Compounds **3** and **4**

Product	^{13}C NMR ($CDCl_3$/TMS) δ, J (Hz)
3b	16.36 (CH_3), 53.47 (d, J = 7.6, OCH_3), 53.83 (d, J = 6.9, OCH_3), 66.94 (d, J = 161.0, CHP), 126.11 (d, J = 3.1, C_{ar}), 127.20 (d, J = 4.6, C_{ar}), 128.00 (d, J = 3.1, C_{ar}), 130.20 (d, J = 2.3, C_{ar}), 134.91 (d, J = 1.5, C_{ar}), 135.64 (d, J = 7.6, C_{ar})
3f	53.65 (d, J = 7.6, OCH_3), 53.84 (d, J = 7.6, OCH_3), 67.21 (d, J = 161.0, CHP), 123.30 (C_{ar}), 125.37 (d, J = 3.0, C_{ar}), 125.56 (d, J = 6.1, C_{ar}), 125.71 (C_{ar}), 126.27 (C_{ar}), 128.76 (C_{ar}), 128.95 (d, J = 3.0, C_{ar}), 130.71 (d, J = 6.1, C_{ar}), 132.47 (d, J = 2.3, C_{ar}), 133.61 (d, J = 1.5, C_{ar})
3g	23.56 [d, J = 5.3, $(CH_3)_2CHO$], 23.84 [d, J = 4.6, $(CH_3)_2CHO$], 24.09 [d, J = 3.1, $(CH_3)_2CHO$], 24.10 [d, J = 3.1, $(CH_3)_2CHO$], 71.12 (d, J = 161.0, CHP), 71.64 [d, J = 7.6, $(CH_3)_2CHO$], 71.95 [d, J = 7.6, $(CH_3)_2CHO$], 125.24 (d, J = 4.6, C_{ar}), 125.84 (d, J = 1.5, C_{ar}), 125.91 (C_{ar}), 126.13 (C_{ar}), 127.51 (d, J = 1.5, C_{ar}), 127.57 (d, J = 1.5, C_{ar}), 128.00 (C_{ar}), 132.97 (d, J = 2.3, C_{ar}), 133.04 (d, J = 3.1, C_{ar}), 134.13 (d, J = 2.3, C_{ar})
3i	16.36 (d, J = 5.3, CH_3CH_2O), 16.40 (d, J = 5.3, CH_3CH_2O), 63.35 (d, J = 6.9, CH_3CH_2O), 63.61 (d, J = 6.9, CH_3CH_2O), 67.04 (d, J = 166.3, PCH), 125.80 (d, J = 3.1, C_{ar}), 126.18 (d, J = 7.7, C_{ar}), 126.83 (d, J = 2.3, C_{ar}), 139.34 (C_{ar})
3m	23.55 [d, J = 5.3, $(CH_3)_2CHO$], 23.80 [d, J = 5.3, $(CH_3)_2CHO$], 23.81 [d, J = 3.1, $(CH_3)_2CHO$], 24.00 [d, J = 3.1, $(CH_3)_2CHO$], 68.52 (d, J = 164.8, PCH), 71.69 [d, J = 7.6, $(CH_3)_2CHO$], 72.09 [d, J = 7.3, $(CH_3)_2CHO$], 122.97 (d, J = 3.1, C_{ar}), 133.59 (C_{ar}), 134.97 (d, J = 4.6, C_{ar}), 148.46 (d, J = 6.9, C_{ar}), 148.51 (d, J = 3.8, C_{ar})
4c	20.92 ($COCH_3$), 23.25 [d, J = 6.1, $(CH_3)_2CHO$], 23.79 [d, J = 5.3, $(CH_3)_2CHO$], 24.04 [d, J = 3.1, $(CH_3)_2CHO$], 24.22 [d, J = 3.1, $(CH_3)_2CHO$], 55.66 (OCH_3), 64.29 (d, J = 177.0, PCH), 71.56 [d, J = 6.9, $(CH_3)_2CHO$], 71.77 [d, J = 6.9, $(CH_3)_2CHO$], 110.57 (d, J = 2.3, C_{ar}), 120.53 (d, J = 3.1, C_{ar}), 122.61 (d, J = 1.5, C_{ar}), 129.14 (d, J = 3.8, C_{ar}), 129.66 (d, J = 2.3, C_{ar}), 156.86 (d, J = 6.1, C_{ar}), 169.19 (d, J = 9.2, CO)
4e	23.42 [d, J = 5.9, $(CH_3)_2CHO$], 23.78 [d, J = 5.4, $(CH_3)_2CHO$], 24.02 [d, J = 3.5, $(CH_3)_2CHO$], 24.20 [d, J = 3.0, $(CH_3)_2CHO$], 40.67 (CH_2Cl), 55.25 (OCH_3), 72.21 [d, J = 8.4, $(CH_3)_2CHO$], 72.41 (d, J = 172.4, PCH), 72.42 [d, J = 7.9, $(CH_3)_2CHO$], 113.35 (d, J = 5.9, C_{ar}), 114.77 (d, J = 2.5, C_{ar}), 120.47 (d, J = 6.4, C_{ar}), 129.38 (d, J = 2.0, C_{ar}), 134.19 (d, J = 2.0, C_{ar}), 159.49 (d, J = 2.0, C_{ar}), 165.92 (d, J = 8.9, CO)
4f	20.92 ($COCH_3$), 23.03 [d, J = 6.1, $(CH_3)_2CHO$], 23.81 [d, J = 5.3, $(CH_3)_2CHO$], 24.06 [d, J = 2.4, $(CH_3)_2CHO$], 24.19 [d, J = 3.1, $(CH_3)_2CHO$], 67.56 (d, J = 174.7, PCH), 71.88 [d, J = 6.9, $(CH_3)_2CHO$], 72.17 [d, J = 6.9, $(CH_3)_2CHO$], 124.12 (C_{ar}), 125.13 (d, J = 3.1, C_{ar}), 125.76 (C_{ar}), 126.13 (C_{ar}), 126.89 (d, J = 6.1, C_{ar}), 128.54 (C_{ar}), 129.24 (d, J = 3.1, C_{ar}), 130.07 (C_{ar}), 131.12 (d, J = 5.3, C_{ar}), 133.57 (d, J = 1.0, C_{ar}), 169.40 (d, J = 9.4, CO)
4h	20.92 ($COCH_3$), 23.45 [d, J = 5.3, $(CH_3)_2CHO$], 23.76 [d, J = 5.4, $(CH_3)_2CHO$], 24.06 [d, J = 3.1, $(CH_3)_2CHO$], 24.17 [d, J = 3.8, $(CH_3)_2CHO$], 71.10 (d, J = 172.4, PCH), 71.95 [d, J = 6.8, $(CH_3)_2CHO$], 72.01 [d, J = 6.9, $(CH_3)_2CHO$], 125.59 (d, J = 4.6, C_{ar}), 126.20 (C_{ar}), 126.36 (C_{ar}), 127.54 (d, J = 6.9, C_{ar}), 127.63 (C_{ar}), 128.00 (d, J = 2.3, C_{ar}), 128.10 (C_{ar}), 131.23 (d, J = 2.3, C_{ar}), 132.91 (d, J = 2.3, C_{ar}), 133.25 (d, J = 2.3, C_{ar}), 169.36 (d, J = 9.4, CO)
4i	20.59 ($COCH_3$), 23.18 [d, J = 5.3, $(CH_3)_2CHO$], 23.59 [d, J = 5.3, $(CH_3)_2CHO$], 23.82 [d, J = 3.1, $(CH_3)_2CHO$], 24.02 [d, J = 3.8, $(CH_3)_2CHO$], 65.93 (d, J = 177.8, PCH), 71.97 [d, J = 7.6, $(CH_3)_2CHO$], 72.20 [d, J = 6.9, $(CH_3)_2CHO$], 126.50 (d, J = 2.3, C_{ar}), 126.74 (d, J = 2.3, C_{ar}), 128.50 (d, J = 8.4, C_{ar}), 135.07 (C_{ar}), 168.97 (d, J = 8.4, CO)
4j	16.27 (d, J = 5.9, CH_3CH_2O), 16.41 (d, J = 5.9, CH_3CH_2O), 20.79 ($COCH_3$), 63.53 (d, J = 7.6, CH_3CH_2O), 63.60 (d, J = 6.9, CH_3CH_2O), 65.85 (d, J = 177.8, PCH), 126.86 (d, J = 2.3, C_{ar}), 127.05 (d, J = 3.1, C_{ar}), 128.62 (d, J = 7.6, C_{ar}), 139.00 (C_{ar}), 169.19 (d, J = 8.4, CO)
4k	20.85 ($COCH_3$), 23.40 [d, J = 6.1, $(CH_3)_2CHO$], 23.75 [d, J = 6.3, $(CH_3)_2CHO$], 24.04 [d, J = 3.8, $(CH_3)_2CHO$], 24.18 [d, J = 3.0, $(CH_3)_2CHO$], 66.83 (d, J = 176.3, PCH), 71.95 [d, J = 6.9, $(CH_3)_2CHO$], 72.09 [d, J = 6.9, $(CH_3)_2CHO$], 124.92 (d, J = 9.2, C_{ar}), 125.72 (C_{ar}), 127.54 (d, J = 4.6, C_{ar}), 134.02 (d, J = 1.5, C_{ar}), 169.31 (d, J = 8.4, CO)
4l	20.68 ($COCH_3$), 23.41 [d, J = 5.3, $(CH_3)_2CHO$], 23.78 [d, J = 4.6, $(CH_3)_2CHO$], 23.98 [d, J = 3.8, $(CH_3)_2CHO$], 24.16 [d, J = 3.1, $(CH_3)_2CHO$], 63.85 (d, J = 180.0, PCH), 72.17 [d, J = 7.6, $(CH_3)_2CHO$], 72.42 [d, J = 6.9, $(CH_3)_2CHO$], 110.73 (C_{ar}), 111.61 (d, J = 6.1, C_{ar}), 143.29 (d, J = 2.0, C_{ar}), 147.03 (C_{ar}), 169.26 (d, J = 8.0, CO)

The enantiomeric excesses and the absolute configurations of α-hydroxyphosphonates **3** obtained by enzymatic hydrolysis of (±)-**4** were determined routinely by esterification with (*S*)-(+)-MTPA-Cl in pyridine and the use of ^1H and ^{31}P NMR spectroscopy.[5,6] The methoxy groups of the Mosher acid part of the derivatives of α-hydroxyphosphonates (*S*)-**3** resonate at lower field than the corresponding signals of the derivatives of (*R*)-**3** (Table 5). The same trend is observed for the phosphorus signals in the ^{31}P NMR spectra.[6] The enantiomeric excesses were determined from the integrals of appropriate signals in the ^1H or more conveniently in the ^{31}P NMR spectra. The shift differences range from 0.22 to 0.56 for the phosphorus signals and from 0.07 to 0.17 for the methoxy signals (Table 5).

α-Acyloxyphosphonates with ortho substituents in the phenyl ring are generally hydrolyzed more slowly by lipases AP 6 and FAP 15 than the parent compounds[2] (Table 4, entries 1–8). The reaction rate is zero for ester (±)-**4a** with FAP 15 and too small for preparative purposes for ester (±)-**4c** with both enzymes (Entries 1, 5, and 6).

In general, dimethyl α-acyloxyphosphonates are hydrolyzed more rapidly by both enzymes than the more bulky diisopropyl phosphonates. The same also holds for chloroacetates versus acetates. The enantioselectivity is higher for lipase FAP 15 than AP 6. The enantiomeric excesses for α-acyloxyphosphonate (±)-**4** derived from *o*-methoxybenzaldehyde are very low as compared to those derived from *o*-methylbenzaldehyde (Entries 7 and 8 vs Entries 1 and 2). The strong influence of the ortho methoxy group might be a combination of a steric effect and its possible involvement in hydrogen bonding at the active site of the enzymes. If the methoxy group is moved into the meta position, its detrimental effect is alleviated and the rate of hydrolysis and the ee increase (Entry 9).

Table 4. Enzymatic Hydrolysis of (±)-**4**

Entry	Substrate	Enzyme, mg	Temp (°C)	Time (h); Conversion (%)	Produced Alcohol				Recovered Ester	Alcohol from Recovered Ester			
					Yield (%)	ee[b] (%)	Configuration	$[\alpha]_D(c)$[c]	$[\alpha]_D(c)$[c]	Yield[d] (%)	ee[b] (%)	Configuration	$[\alpha]_D(c)$[c]
1	**4a**	FAP 15, 145	24	22.5; 0	not worked up								
2	**4a**	AP 6, 114	24	19.7; 45/43	38	55 (54)	(*S*)	−28.2 (1.3)	+15.2 (2.4)	46	38 (41)	(*R*)	+22.7 (1.4)
3	**4b**	FAP 15, 103	26	53.6; 46/36	28	95 (95)	(*S*)	−71.9 (1.0)	+25.1 (1.7)	50	52 (51)	(*R*)	+38.6 (1.1)
4	**4b**	AP 6, 78	25	24.0; 45/44	30	74 (72)	(*S*)	−60.5 (1.3)	+21.5 (2.2)				
5	**4c**	FAP 15, 86	25	14.0; 5	not worked up								
6	**4c**	AP 6, 106	22	15.0; 11	not worked up								
7	**4d**	FAP 15, 125	25	17.5; 45/40	33	14 (14)	(*S*)	−7.4 (1.1)	+3.6 (1.7)	45	9 (9)	(*R*)	+5.4 (3.5)
8	**4d**	AP 6, 31	23	3.3; 45/45	42	7 (7)	(*S*)	−1.9 (1.4)	+1.5 (1.5)				
9	**4e**	AP 6, 5	23	1.8; 45/46	32	85	(*S*)	−16.4 (1.0)	+31.5 (2.3)	41	70	(*R*)	+12.8 (1.0)
10	**4f**	FAP 15, 97	31	66.0; 8	6	94 (98)	(*S*)	−91.2 (1.0)	+6.4 (0.9)				
11	**4f**	AP 6, 80	31	16.5; 0	not worked up								
12	**4g**	FAP 15, 104	24	65.7; 46/47	28	92 (93)	(*S*)	−97.4 (1.2)	+28.9 (0.9)				
13	**4g**	AP 6, 118	23	24.0; 45/34	29	79 (89)	(*S*)	−87.6 (1.0)	+13.9 (1.2)	57	47 (49)	(*R*)	+48.9 (1.1)
14	**4h**	FAP 15, 100	30	18.5; 0	not worked up								
15	**4h**	AP 6, 60	30	23.3; 44/45	38	91 (92)	(*S*)	−30.4 (0.9)	+44.7 (0.9)	38	78 (78)	(*R*)	+27.8 (0.9)
16	**4i**	FAP 15, 97	27	23.5; 41/33	28	92 (93)	(*S*)	−7.3 (1.3)	+35.2 (1.2)	40	58 (62)	(*R*)	+5.4 (2.3)
17	**4i**	AP 6, 70	25	2.7; 45	38	79 (76)	(*S*)	−5.6 (1.1)	+28.7 (1.2)	42	61 (62)	(*R*)	+5.5 (3.2)
18	**4j**	FAP 15, 48	24	14.7; 45/42	38	87 (88)	(*S*)	−10.2 (2.2)	+34.4 (1.4)	40	65 (64)	(*R*)	+7.3 (1.5)
19	**4k**	FAP 15, 102	26	16.0; 28/22	26	96[e]	(*S*)	−20.7 (1.0)	+20.4 (1.9)				
20	**4k**	AP 6, 13	21	15.3; 42	22	82 (82)	(*S*)	−17.5 (1.1)	+20.0 (1.4)	40	36 (35)	(*R*)	+6.8 (1.4)
21	**4l**	FAP 15, 90	28	17.2; 45/42	34	91 (93)	(*S*)	−15.8 (1.2)	+48.1 (1.3)	26	67 (66)	(*R*)	+13.0 (1.0)
22	**4l**	AP 6, 24	29	5.3; 45/45	30	89 (87)	(*S*)	−16.1 (1.1)	+41.2 (1.2)	37	63 (61)	(*R*)	+11.3 (1.0)
23	**4m**	FAP 15, 92	23	38.7; 46/44	39	14 (12)	(*S*)	−7.5 (1.6)	+33.3 (1.4)				
24	**4m**	FAP 15, 76	22	42.0; 40/42	30	33 (32)	(*S*)	−18.7 (2.6)	+26.6 (1.2)				
25	**4n**	FAP 15, 84	23	20.3; 20/21	18	52[e]	(*S*)	−20.4 (2.5)	+6.8 (2.0)				
26	**4n**	AP 6, 35	22	4.9; 45/45	40	77 (77)	(*S*)	−30.2 (1.0)	+27.8 (2.1)	34	66 (65)	(*R*)	+26.2 (1.1)

[a] Conversion determined from 0.5 N NaOH consumed/conversion determined by ^{1}H NMR.
[b] ee as determined by ^{1}H NMR spectroscopy (by ^{31}P NMR spectroscopy).
[c] In 2 mL acetone solution at 20 °C; concentration was rounded to the nearest tenth.
[d] Yield of ester after enzymatic hydrolysis multiplied by yield of chemical hydrolysis.
[e] Calculated on the basis of the data of Entries 20 and 26, respectively.

Table 5. Assignment of Configuration at C-1 of Diastereomeric Mosher Esters, Prepared from α-Hydroxyphosphonates **3** on the Basis of ^1H (for the Methoxy Group of MTPA) and ^{31}P NMR Chemical Shifts

Mosher Ester of	Chemical Shift, δ		Δδ($^1H/^{31}P$)
	(*S*) ($^1H/^{31}P$)	(*R*) ($^1H/^{31}P$) at C-1 of **3**	
3a	3.60/15.44	3.47/15.11	0.13/0.33
3b	3.59/19.64	3.49/19.42	0.10/0.22
3c	3.61/15.25	3.50/14.90	0.10/0.35
3d	3.63/14.58	3.50/14.20	0.13/0.38
3e	3.65/15.01	3.48/14.70	0.17/0.31
3f	3.64/14.62	3.48/14.26	0.14/0.36
3g	3.56/19.25	3.40/19.03	0.16/0.22
3h	3.58/13.30	3.45/12.91	0.13/0.39
3i	3.58/15.19	3.48/14.91	0.10/0.28
3j	3.61/14.25	3.47/13.93	0.14/0.32
3k	3.58/12.36	3.47/11.80	0.11/0.56
3l	3.64/13.54	3.57/13.10	0.07/0.44
3m	3.61/13.57	3.49/13.20	0.12/0.37

Diisopropyl 1-acetoxy-(1-naphthyl)methylphosphonate [(±)-**4f**] was hydrolyzed only very slowly by lipase FAP 15 and was not a substrate for lipase AP 6 (Entries 10 and 11). In contrast, dimethyl α-acyloxyphosphonate (±)-**4g** is kinetically resolved by both enzymes and the enantiomeric excesses are high (Entries 12 and 13). The 2-naphthyl derivative (±)-**4h** is hydrolyzed by lipase AP 6 only, the ee being 91% (Entries 14 and 15). From racemic α-acyloxyphosphonates with either aromatic or heteroaromatic substituents those with *S*-configuration were hydrolyzed preferentially.

1-Acetoxy(heteroaryl)methylphosphonates (±)-**4i–4n** are good substrates for both enzymes, with the exception of (±)-**4k** and **4n** (lipase FAP 15) (Entries 16–26). When compared on the basis of crude commercially available enzymes, lipase AP 6 hydrolyzes these substrates at least ten times more rapidly than lipase FAP 15. The enantiomeric excesses are very high and vary between 80 and 95% at a conversion of 41–45% being slightly higher for products obtained with FAP 15. The enantioselective hydrolysis of 1-acetoxy-(2-pyridyl)methylphosphonate (±)-**4m** furnished configurationally unstable hydroxyphosphonate (−)-**3l**, which racemized even when stored in the refrigerator. Purification and determination of the ee by optical rotation and derivatization with Mosher acid chloride had to be done in the shortest time possible to get the data reported in Table 4 (Entry 24). Chemical hydrolysis of ester (+)-**4m** afforded racemic α-hydroxyphosphonate **3l**. The α-hydrogen of **3l** is fairly acidic. Thus, 50% of the hydrogen was exchanged for deuterium within 8 days as proven by ^1H NMR spectroscopy, when a sample of (±)-**3l** dissolved in methanol-d_4 was allowed to stand at room temperature. When (−)-**3l** with $[\alpha]_D^{20}$ −7.5 (c = 1.6, acetone) was reesterified with acetyl chloride/pyridine in dichloromethane at −50°C, ester (−)-**4m** with $[\alpha]_D^{20}$ −11.0 (c = 1.3, acetone) was isolated. This specific optical rotation is smaller than that of ester (+)-**4m** isolated from the enzymatic hydrolysis (Table 4, Entries 23 and 24). If there has been no racemization of α-hydroxyphosphonate (−)-**3m**, the ee of (+)-**4m** obtained by reesterification should be higher than that of α-acetoxyphosphonate (+)-**4m** obtained by enzymatic hydrolysis at a conversion of less than 50% (see Table 4). These two experiments clearly underline the ease of racemization which could be facilitated by an intramolecular hydrogen bond between the hydroxy group and the pyridine nitrogen because α-hydrogen of a protonated pyridine should be more acidic than that of a neutral pyridine. Additional support for this assumption is given by the fact that the corresponding acetate (+)-**4m**, missing such a hydrogen bond, does not racemize as its optical rotation remains constant within a few days. Also, 1-hydroxy-(3-pyridyl)methylphosphonate (−)-**3m** does not racemize. The very mild conditions for the enzymatic hydrolysis underlines the utility of lipases to prepare even α-hydroxyphosphonates very prone to racemization.

In summary, lipases AP 6 and FAP 15 are very useful enzymes to generate chiral, non-racemic α-hydroxyphosphonates with aryl and heteroaryl substituents. The (*S*)-α-acyloxyphosphonates are saponified much more easily than their enantiomers. Surprisingly, lipase FAP 15 which does not hydrolyze α-acyloxyphosphonates derived from aliphatic aldehydes,[1] shows a high enantioselectivity with planar substituents and even tolerates an α-naphthyl substituent.

All starting materials and enzymes were obtained from commercial suppliers and were generally used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on Bruker spectrometers AM 400 WB and AC 250. ^{31}P NMR spectra were recorded on a AM 400 WB 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. IR spectra were run on a Perkin Elmer 1600 FT-IR spectrometer; liquid samples were measured as films between NaCl plates, solid samples were dissolved in $CHCl_3$ (Uvasol) and applied to a silicon plate.[7] Optical rotations were measured at 20°C on a Perkin Elmer 241 polarimeter in acetone solution in a 1 dm cell. TLC was carried out on 0.25 mm Merck plates, silica gel 60 F_{254}. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualized by dipping into a solution of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (23 g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1 g) in 10% H_2SO_4 in water (500 mL) followed by heating on a hot plate. A Metrohm 702 SM Titrino instrument was used as an autotitrator. (*S*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride [JPS Chimie; $[\alpha]_D^{20}$ +136.5 (c = 5.2, CCl_4), ee > 99.5%] was used for derivatization of α-hydroxyphosphonates.

Substituted dialkyl 1-hydroxymethylphosphonates (±)-**3** were prepared as reported in the preceding paper.[1] The crude product was purified by crystallization (Method A), flash chromatography (Method B) or crystallization and flash chromatography of mother liquor (Method C) (Table 1). Compounds (±)-**3e–g**[8], **3h**[9], **3i**[10], **3k**[9], **4i**[11], **4j**[11], and **4l**[11] have been reported in the literature, but have not been characterized adequately. Mosher esters of (*S*)- and (*R*)-**3** were prepared as reported in our earlier publication.[1]

Substituted dialkyl 1-(acetoxy)methylphosphonates (±)-**4** were prepared according to a literature procedure.[2] The crude products obtained after removal of volatile materials in vacuo were purified by bulb to bulb distillation or flash chromatography (Table 2). Substituted dialkyl 1-(chloroacetoxy)methylphosphonates were prepared by the method used for the esterification of diisopropyl 1-hydroxy-2-phenylethylphosphonate with chloroacetic anhydride/pyridine in dichloromethane (Table 2).[3]

Enzymatic Hydrolysis of Esters 4; General Procedure:
Esters (±)-**4** (1 mmol) were hydrolyzed enzymatically with phosphate buffer (17 mL) in a mixture of solvents (for acetates: hexanes/*tert*-butyl methyl ether, 3:1; for chloroacetates, 1:1, 4 mL) and lipase AP 6 or FAP 15 (Table 4).[2] The reaction was not stopped by the addition of 1 N HCl, when acetates (±)-**4m** and **4n** were hydrolyzed. In these cases EtOAc was replaced by CH_2Cl_2 for extraction and by acetone as eluents for flash chromatography. Acetates (except **4b** and **4g**) were hydrolyzed within 24–48 h (followed by TLC) by a known procedure except that water (0.5 mL) was added to the methanolic solution.[2] Chloroacetates recovered from enzymatic resolution were hydrolyzed within about 16 h by the same procedure except that no water was added.

Chemical Hydrolysis of Acetates (+)-4b and (+)-4g:
A solution of (+)-**4b** or (+)-**4g** in anhydr. MeOH (5 mL) was cooled to −20 °C and an equivalent amount of NaOMe in MeOH (0.2 mmol/mL) added. After 3–5 h (TLC), AcOH (1.5 equiv) was added. The solvent was removed in vacuo and the residue was purified by flash chromatography.

Dimethyl (1-Naphthyl)methylphosphate (5):
1-Naphthaldehyde (1.72 g, 11 mmol) was allowed to react with dimethyl phosphite (1.1 g, 10 mmol) in the presence of base for 72 h and worked up according to the method used for the preparation of α-hydroxyphosphonates.[1] The product was purified by flash chromatography; yield: 1.984 g (75%); R_f 0.49 (CH_2Cl_2/EtOAc, 5:3). IR (film): ν = 2955, 1512, 1463, 1282, 1236, 1186, 1170, 1040 cm^{-1}. ^1H NMR (400 MHz): δ = 3.69 (d, J = 11.3 Hz, 6H, OCH_3), 5.53 (d, J = 7.9 Hz, 2H, CH_2), 7.45, 7.55, 7.87, 8.10 (4 m, 7H, H_{arom}).

Acetylation of (−)-Diisopropyl 1-Hydroxy-(2-pyridyl)methylphosphonate (3l):
1-Hydroxyphosphonate (−)-**3l** {0.092 mmol; $[\alpha]_D^{20}$ −7.5 (c = 1.635, acetone)} obtained by enzymatic hydrolysis of **4m** with FAP 15 was dissolved in anhydr. CH_2Cl_2 (3 mL) and treated with acetyl chloride (0.46 mmol)/pyridine (0.69 mmol) at −50 °C. The mixture was allowed to warm up to room temperature in a cooling bath (18 h). Water (3 mL) and CH_2Cl_2 (10 mL) were added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), evaporated and the residue was purified by flash chromatography (CH_2Cl_2/acetone, 6:1); yield: 88%, $[\alpha]_D^{20}$ −11.0 (c = 1.275, acetone).

We thank the Fonds zur Förderung der wissenschaftlichen Forschung (projects no. P10566-CHE and 6537C) for support of this work and Amano Enzyme Limited (UK) for lipases AP 6 and FAP 15.

(1) For Part 3, Drescher, M.; Hammerschmidt, F.; Kählig, H. *Synthesis* **1995**, 1267.
(2) Li, Y.-F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109.
(3) Drescher, M.; Li, Y.-F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933.
(4) Hammerschmidt, F. *Monatsh. Chem.* **1993**, *124*, 1063.
(5) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.
(6) Hammerschmidt, F.; Li, Y.-F. *Tetrahedron* **1994**, *50*, 10253.
(7) Mikenda, W. *Vib. Spectrosc.* **1992**, *3*, 327.
(8) Borisov, G. *Compt. Rend. Acad. Bulgare Sci.* **1964**, *17*, 633; *Chem. Abstr.* **1965**, *62*, 11847.
(9) Abramov, V.S.; Kapustina, A.S. *Zh. Obshch. Khim.* **1957**, *27*, 173; *Chem. Abstr.* **1957**, *51*, 12878.
(10) Utkin, Y.E.; Sergeeva, A.S.; Tarasov, V.; Promonenkov, V.K.; Ivin, S.Z. *Zh. Obshch. Khim.* **1967**, *37*, 2710; *Chem. Abstr.* **1968**, *69*, 67473.
(11) Abramov, S.V.; Shergina, I.V. *Zh. Obshch. Khim.* **1968**, *38*, 866; *Chem. Abstr.* **1968**, *69*, 52219.