Enzymatic Resolution of Medium-Ring Lactones. Synthesis of (*S*)-(+)-Phoracantholide I

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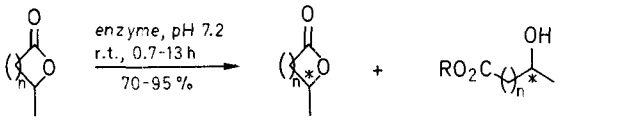
The horse liver and pig liver esterase hydrolysis of racemic medium ring lactones gives with excellent enantiomeric excess the *S*- (or *R*) lactones and the corresponding *R*- (or *S*) hydroxy acids. This is the first general method to obtain optically pure medium ring lactones. Application to the preparation of (*S*)-(+)-Phoracantholide I is reported.

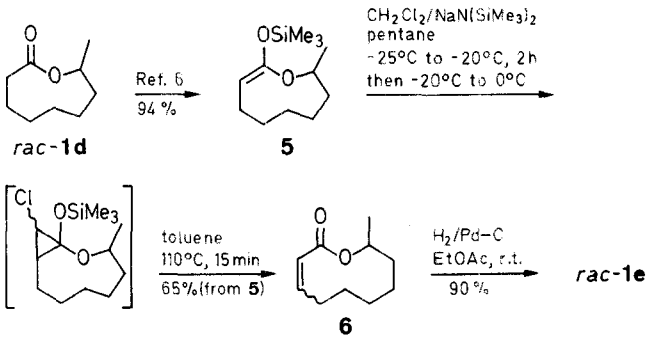
We have recently reported the kinetic enzymatic hydrolysis of some racemic γ-butyrolactones, δ-valerolactones, and ε-caprolactones substituted by an aliphatic chain in γ, δ and ε position, respectively, using lipases or esterases, leading to optically active lactones with moderate enantiomeric excess.[1] In these lactones we observed a rough improvement of the enzymatic resolution with the lengthening of the chain. Lipase-catalyzed synthesis of optically active lactones from racemic hydroxy acid has been also reported.[2]

We wish to report here the results obtained with the racemic medium ring lactones **1a–e**, substituted by a methyl group α to the oxygen atom using pig liver esterase (PLE)[3] and horse liver esterase (HLE).[4] Resolution of racemic lactones **1a–e** was performed at room temperature in a buffer solution of sodium dihydrogenphosphate at pH 7.2. To check the absence of spontaneous hydrolysis, the racemic lactones **1a–e** were stirred in the buffer solution for 15 minutes before adding HLE or PLE (no pH change). Immediately after the enzyme addition, the hydrolysis began and the pH was automatically maintained at 7.2 by addition of a 2 M sodium hydroxide solution (pH stat). When the desired conversions were reached, the remaining optically active lactones **1a–e** were extracted with ether. The aqueous layers containing the sodium salts **2a–e** were acidified (pH 2) and antipodal lactone of (*S*)-**1a** [(*R*)-**1a**] or the hydroxy acids **3b–e** were also extracted with ether. Our results are reported in Table 1.



1-4	a	b	c	d	e
n	3	4	5	6	7

The racemic lactone **1a** was prepared from ethyl 5-oxo-hexanoate by reduction of the carbonyl group and acidic lactonization. Racemic lactones **1b–d** were obtained from the corresponding 2-methylcycloalkanones by Baeyer–Villiger oxidation using *m*-chloroperoxybenzoic acid. The racemic lactone **1e** (racemic phorocantholide I[5]) was obtained in four steps by a new ring expansion method starting from the racemic lactone **1d**. The silyl enol ether **5** prepared[6] from (±)-8-nonanolide (**1d**), underwent addition of chlorocarbene[7] to give an intermediate bicyclic adduct, which rearranged into a *E*/*Z*-mixture of α,β-unsaturated lactones **6** by heating in toluene. The hydrogenation of the lactone **6** gave the racemic phoracantholide I [(±)-**1e**].



As shown in Table 1, the optically active lactones **1** can be obtained (except *R*-**1b**) with high optical purity. The hydroxy acids **3d–e** are obtained with an equivalent optical purity, while

Table 1. Enzymatic Hydrolysis of Racemic Lactones **1a–e**

Substrate	Reaction Conditions				Optically Active Lactone **1**			Hydroxyacid **3**		
	Enzyme	conversion (%)	Time (h)	Substrate[a] / Enzyme	Yield (%)	ee (%)	Configuration	Yield (%)	ee (%)	Configuration
(±)-**1a**	PLE	63	1.0	1.00	97	70	*S*-**1a**	79[b]	40	*R*
(±)-**1a**	HLE	60	0.7	2.00	90	95	*S*-**1a**	83[b]	64	*R*
(±)-**1b**	PLE	65	3.2	1.10	86	83	*R*-**1b**	79	44	*S*
(±)-**1b**	HLE	62	4.5	1.30	80	76	*R*-**1b**	84	47	*S*
(±)-**1c**	PLE	>53	13.0	1.00	70	>95	*S*-**1c**	65	84	*R*
(±)-**1c**	HLE	>69	10.7	0.77	74	>95	*S*-**1c**	71	42	*R*
(±)-**1d**	PLE	50	3.3	1.00	78	>95	*S*-**1d**	80	>95	*R*
(±)-**1d**	HLE	50	3.0	1.00	94	>95	*S*-**1d**	80	>95	*R*
(±)-**1e**	HLE	50	12.0	0.80	88	>99	*S*-**1e**	80	>99	*R*

[a] Weight/Weight.

[b] The lactone *R*-**1a** was isolated instead the hydroxy acid.

the hydroxy acids **3a–c** show a medium enantiomeric excess. However, the hydroxy acids **3a–c** should be isolated with better optical purity for a rate of conversion lower than 50%. A recent paper shows that these acids can be obtained by a lipase-catalyzed hydrolysis of linear esters.[8] Except for the 6-heptanolide (**1b**), the *R* enantiomers have been substrates for these two enzymes (Table 1). The hydrolysis of the racemic phoracantholide I led to the (*S*)-(+)-phoracantholide (ee > 99%).[9] Its antipode can be prepared by lactonization[10] of the hydroxy acid **3e**.

The enantiomeric excess (ee) of the optically active lactones **1a–e** were determined by ^{1}H-NMR of the corresponding diols **7a–e** in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III) [Eu(hfc)$_3$] (Table 2). These diols were prepared by double addition of methyllithium to the lactones.[11] The ee's of hydroxy acids **3b–e** were determined using the same technique on the corresponding hydroxy esters **4b–e** (obtained from acids **3** by reaction with diazomethane). The ee of lactones (*R*)- and (*S*)-**1a**, and (*S*)-**1e** were also confirmed by comparison of their optical rotations with those reported in the literature (Table 3).

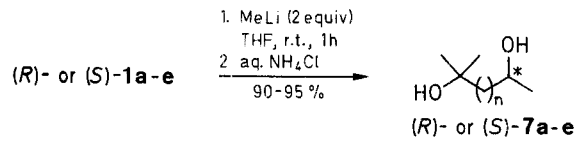
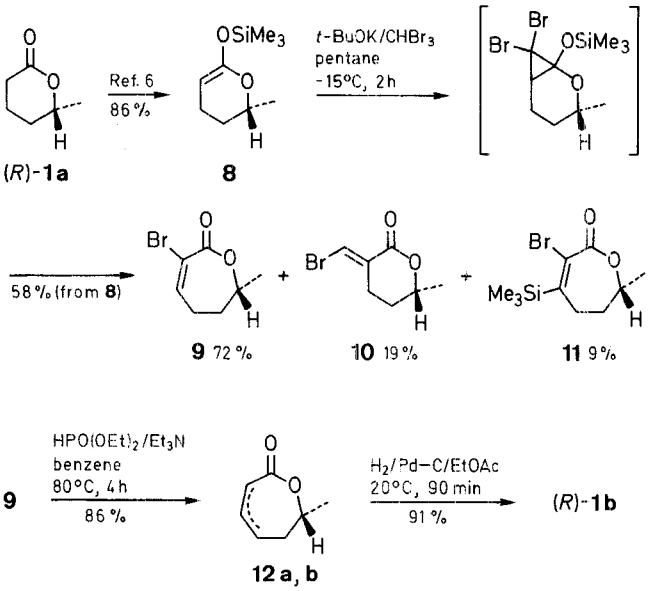


Table 2. Chemical Shifts of the Geminal Dimethyl Groups in (±)-**7a–e** in the Presence of Eu(hfc)$_3$

Compound	Eu(hfc)$_3$ (mol%)	δ (CDCl$_3$)	
		S	*R*
7a	35	3.07–3.30	3.16–3.18
7b	50	4.85–4.92	4.82–4.96
7c	80	7.14–7.27	7.18–7.25
7d	100	8.71–8.81	–
7e	90	7.21–7.33	7.23–7.30

The absolute configurations of the known lactones (*R*)- and (*S*)-**1a** and (*S*)-**1e** were deduced from the sign of their optical rotations. In the other cases, the absolute configurations were obtained by chemical correlation. The (*R*)-(+)-lactone *R*-**1a** was transformed in four steps by ring expansion into the (*R*)-(+)-lactone **1b** via its silyl enol ether **8**. The latter reacted readily with dibromocarbene and the subsequent spontaneous rearrangement gave the unsaturated lactone **9** as the major product beside two other lactones **10** and **11**. The lactone **9** was treated with diethylphosphite[12] to give an isomer mixture **12**, which was hydrogenated to afford *R*-**1b**.



The absolute configuration of lactone (*R*)-**1c** was obtained by an analogous procedure. The silyl enol ether **13** derived from the (*R*)-(+)-lactone **1b** was treated with chlorocarbene to give the intermediate bicyclic product as an isomeric mixture, which upon heating in xylene led to the unsaturated lactones **14a, b**. Catalytic hydrogenation of this mixture furnished the (*R*)-(−)-lactone (*R*)-**1c**.

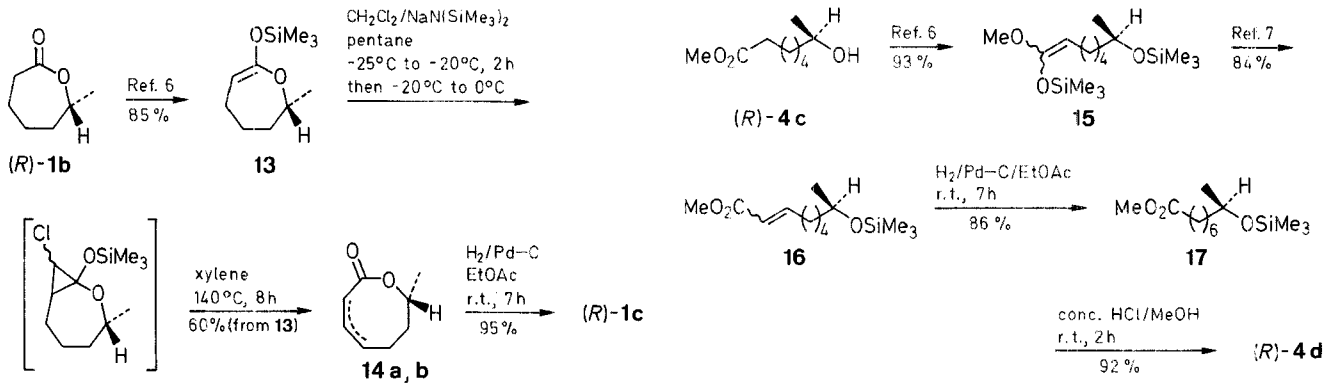
Table 3. Compounds **1**, **3**, **4**, and **7** Prepared

Product[a]	Molecular Formula[b] or Lit. $[\alpha]_D^{20}$	$[\alpha]_D^{20}$ (*c*, solvent)	IR (neat) ν (cm^{-1})	^{1}H-NMR (250 MHz, CDCl$_3$/TMS) δ, *J* (Hz)	^{13}C-NMR (62 MHz, CDCl$_3$/TMS) δ	MS (70 eV) *m/z* (%)
(*S*)-**1a**	−40.7°[18] (ee = 94) (*c* = 2.2, EtOH)	−41.7° (ee = 95) (*c* = 2.2, EtOH) −49.4° (*c* = 1, THF)	1750 (CO)	1.38 (d, 3H, *J* = 6.1); 1.41–1.65 (m, 1H); 1.74–2.00 (m, 3H); 2.35–2.65 (m, 2H); 4.36–4.52 (m, 1H)	18.59, 21.77, 29.30, 29.66, 77.07, 172.12	114 (M$^+$, 4.7); 70 (100)
(*R*)-**1a**	+43.4°[18] (ee = 100) (*c* = 2.1, EtOH)	+33.3° (ee = 64) (*c* = 1, THF)				
(*R*)-**1b**	+25.0°[19] (ee = 100) (*c* = 1.8, CHCl$_3$)	+24.5° (ee = 83) (*c* = 1, THF)	1730 (CO)	1.38 (d, 3H, *J* = 6.1); 1.46–1.76 (m, 3H); 1.80–2.01 (m, 3H); 2.51–2.74 (m, 2H); 4.37–4.52 (m, 1H)	22.45, 22.78, 28.12, 34.69, 36.11, 76.72, 175.65	128 (M$^+$, 0.9); 55 (100)
(*S*)-**1c**	$C_8H_{14}O_2$ (142.2)	+67.8° (ee = 95) (*c* = 2.2, THF)	1730 (CO)	1.30–2.00 (m, 8H); 1.35 (d, 3H, *J* = 6.2); 2.41–2.64 (m, 2H); 4.66–4.82 (m, 1H)	21.53, 23.92, 26.18, 28.85, 32.18, 38.88, 74.84, 176.55	143 (M$^+$ + 1, 0.5); 98 (100)

Table 3. (continued)

Product[a]	Molecular Formula[b] or Lit. $[\alpha]_D^{20}$	$[\alpha]_D^{20}$ (*c*, solvent)	IR (neat) ν (cm^{-1})	^{1}H-NMR (250 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	^{13}C-NMR (62 MHz, $CDCl_3$/TMS) δ	MS (70 eV) *m/z* (%)
(*S*)-**1d**	$C_9H_{16}O_2$ (156.2)	+45.5° (ee = 95) (*c* = 1, THF)	1740 (CO)	1.20–2.05 (m, 10H); 1.26 (d, 3H, *J* = 6.4); 2.21–2.35 (m, 1H); 5.01–5.15 (m, 1H)	20.62, 21.78, 23.86, 24.91, 29.34, 35.04, 35.62, 71.47, 175.47	156 (M^+, 2); 68 (100)
(*S*)-**1e**	+34.8°[9] (ee = 89) (*c* = 0.68, $CHCl_3$)	+40.3° (ee = 99) (*c* = 0.67, $CHCl_3$) +42.6° (*c* = 0.9, THF)	1730 (CO)	0.95–2.25 (m, 13H); 1.27 (d, 3H, *J* = 6.6); 2.42–2.56 (m, 1H); 4.94–5.08 (m, 1H)	19.39, 20.61, 23.37, 23.95, 24.20, 27.07, 35.15, 72.57, 174.03	170 (M^+, 1.7); 55 (100)
(*S*)-**3b**	$C_7H_{14}O_3$ (146.2)	+4.2° (ee = 44) (*c* = 1.2, THF)	3500–2500 (OH,[c] 1715 (CO)	1.20 (d, 3H, *J* = 6.2); 1.30–1.77 (m, 6H); 2.58 (t, 2H, *J* = 7.4); 3.70–3.90 (m, 1H); 6.08–6.50 (m, 2H)		131 ($M^+ - 15$; 0.4); 73 (100)
(*R*)-**3c**	$C_8H_{16}O_3$ (160.2)	−7.5° (ee = 84) (*c* = 1.7, THF)	3660–2500 (OH),[c] 1717 (CO)	1.20 (d, 3H, *J* = 6.3); 1.25–1.75 (m, 8H); 2.37 (t, 2H, *J* = 7.4); 3.72–3.90 (m, 1H); 5.7–6.5 (m, 2H)	23.14, 24.57, 25.21, 28.92, 33.69, 38.75, 68.04, 178.80	145 ($M^+ - 15$, 0.3); 73 (100)
(*R*)-**3d**	$C_9H_{18}O_3$ (174.2) (*c* = 1, THF)	−8.6° (ee = 95) (*c* = 1, THF)	3660–2400 (OH),[c] 1715 (CO)	1.19 (d, 3H, *J* = 6.1); 1.23–1.72 (m, 10H); 2.35 (t, 2H, *J* = 7.5); 3.72–3.90 (m, 1H); 5.55–6.15 (m, 2H)		159 ($M^+ - 15$, 0.5); 73 (100)
(*R*)-**3e**	−8.13°[10] (ee = 95) (*c* = 0.11, $CHCl_3$)	−7.2° (ee = 99) (*c* = 1, THF)	3660–2400 (OH),[c] 1715 (CO)	1.20 (d, 3H, *J* = 6.1); 1.24–1.72 (m, 12H); 2.36 (t, 2H, *J* = 7.3); 3.70–3.89 (m, 1H); 5.50–6.35 (m, 2H)		144 ($M^+ - 44$, 25); 45 (100)
(*S*)-**4b**	$C_8H_{16}O_3$ (160.2)	+4.1° (ee = 44) (*c* = 0.9, THF)	3420 (OH)	1.19 (d, 3H, *J* = 6.1); 1.28–1.73 (m, 7H); 2.34 (t, 2H, *J* = 7.3); 3.68 (s, 3H); 3.71–3.88 (m, 1H)		145 ($M^+ - 15$, 1.4); 87 (100)
(*R*)-**4c**	$C_9H_{18}O_3$ (174.2)	−8.0° (ee = 84) (*c* = 1, THF)	3400 (OH)	1.20 (d, 3H, *J* = 6.1); 1.27–1.72 (m, 9H); 2.32 (t, 2H, *J* = 7.4); 3.68 (s, 3H); 3.72–3.88 (m, 1H)		159 ($M^+ - 15$, 1.3); 87 (100)
(*R*)-**4d**	$C_{10}H_{20}O_3$ (188.3)	−8.6° (ee = 95) (*c* = 1, THF)	3420 (OH)	1.19 (d, 3H, *J* = 6.1); 1.23–1.72 (m, 11H); 2.32 (t, 2H, *J* = 7.5); 3.68 (s, 3H); 3.72–3.88 (m, 1H)		173 ($M^+ - 15$, 0.7); 87 (100)
(*R*)-**4e**	$C_{11}H_{22}O_3$ (202.3)	−7.9° (ee = 99) (*c* = 1, THF)	3400 (OH)	1.19 (d, 3H, *J* = 6.1); 1.23–1.72 (m, 13H); 2.31 (t, 2H, *J* = 7.5); 3.68 (s, 3H); 3.71–3.88 (m, 1H)		187 ($M^+ - 15$, 1.4); 87 (100)
(*S*)-**7a**	$[\alpha]_D$ not reported[20]	+7.7° (ee = 95) (*c* = 1, THF)	3630 (free OH); 3360 (OH)	1.21 (d, 3H, *J* = 6.3); 1.23 (s, 6H, CH_3); 1.35–1.57 (m, 6H); 1.60 (br s, 2H); 3.76–3.90 (m, 1H)		131 ($M^+ - 15$, 0.4); 59 (100)
(*R*)-**7b**	$[\alpha]_D$ not reported[20]	−10.0° (ee = 83) (*c* = 1, THF)	3360 (OH)	1.20 (d, 3H, *J* = 6.1); 1.21 (s, 6H); 1.28–1.55 (m, 10H); 3.71–3.89 (m, 1H)	23.48, 24.28, 26.23, 29.19 (2C), 39.22, 43.82, 67.95, 70.93	145 ($M^+ - 15$, 0.4); 59 (100)
(*S*)-**7c**	$C_{10}H_{22}O_2$ (174.2)	+8.6° (ee = 95) (*c* = 1.2, THF)	3360 (OH)	1.19 (d, 3H, *J* = 6.1); 1.21 (s, 6H); 1.25–1.54 (m, 12H); 3.72–3.88 (m, 1H)	23.37, 24.18, 25.62, 29.10 (2C), 30.04, 39.15, 43.75, 67.91, 70.91	141 ($M^+ - 33$, 9.6); 59 (100)
(*S*)-**7d**	$C_{11}H_{24}O_2$ (188.3)	+8.4° (ee = 95) (*c* = 1, THF)	3380 (OH), 3620 (free OH)	1.20 (d, 3H, *J* = 6.1); (s, 6H); 1.25–1.55 (m, 14H); 3.71–3.86 (m, 1H)		155 ($M^+ - 33$, 6.5); 59 (100)
(*S*)-**7e**	$C_{12}H_{26}O_2$ (202.3)	+9.2° (ee = 99) (*c* = 0.54, THF)	3670 (free OH)[c]	1.19 (d, 3H, *J* = 6.1); 1.21 (s, 6H); 1.25–1.55 (m, 16H); 3.72–3.87 (m, 1H)		169 ($M^+ - 33$, 13.8); 59 (100)

[a] For yields, mp or bp, see experimental.
[b] Satisfactory microanalyses obtained: C ±0.39, H ±0.37. Exceptions: (*S*)-**1c**, C +0.44; **4b**, C +0.53.
[c] Recorded in CCl_4 solution.



This procedure could not be applied to the transformation of the eight-membered lactones to nine-membered lactones due to the difficulty in preparing the corresponding silyl enol ether (only the α-trimethylsilyllactone was obtained). The chemical correlation was accomplished starting from the linear (*R*)-(−) ester **4c**. This ester was transformed in three steps[7] into the homologue α,β-unsaturated ester **16**, which led after catalytic hydrogenation and hydrolysis to the (*R*)-(−)-saturated ester **4d**.

Optical rotations at Na-D line were measured at 20 °C using a Perkin-Elmer 241 polarimeter. Mass spectra were obtained using a Nermag R-10-10 spectrometer (70 eV). IR spectra were recorded using a Perkin-Elmer 682 IR spectrophotometer. ^{1}H- and ^{13}C-NMR were recorded using a Bruker 250 AM spectrometer. The enzymatic hydrolysis were monitored with a pH meter E 512 Metrohm-Herisan. PLE and HLE (acetone powders) were purchased from Sigma.

(±)-5-Hexanolide [(±)-1a]:

To a suspension of $NaBH_4$ (6.3 g, 0.167 mmol) in EtOH (500 mL) at

Table 4. Compounds **5**, **6**, **8**–**17** Prepared

Product[a]	Molecular Formula[b]	IR (neat) ν(cm^{-1})	^{1}H-NMR (250 MHz, $CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) m/z (%)
5	$C_{12}H_{24}O_2Si$ (228.4)	1680 (C=C)	0.23 (s, 9H); 1.16–1.87 (m, 9H); 1.26 (d, 3H, J = 6.7); 2.23–2.43 (m, 1H); 3.91 (t, 1H, J = 7.3); 4.25 (m, 1H)	228 (M$^+$, 5.4); 75 (100)
Z-**6**	$C_{10}H_{16}O_2$ (168.2)	1720 (C=O)	1.10–1.85 (m, 8H); 1.31 (d, 3H, J = 6.2); 2.00–2.19 (m, 1H); 2.70–2.88 (m, 1H); 5.09–5.25 (m, 1H); 5.85 (m, 1H); 6.32 (m, 1H, $J_{2,3}$ = 11.5)	168 (M$^+$, 0.8); 81 (100)
E-**6**	$C_{10}H_{16}O_2$ (168.2)	1740 (C=O)	0.94–1.60 (m, 5H); 1.33 (d, 3H, J = 6.4); 1.60–2.03 (m, 4H); 2.47–2.60 (m, 1H); 4.73–4.89 (m, 1H); 6.09–6.30 (m, 2H, $J_{2,3}$ = 16.6)[c]	168 (M$^+$, 2.5); 81 (100)
8	$C_9H_{18}O_2Si$ (186.3)	1697 (C=C)	0.22 (s, 9H); 1.30 (d, 3H, J = 6.0); 1.37–1.56 (m, 1H); 1.69–1.83 (m, 1H); 1.90–2.20 (m, 2H); 3.76–3.83 (m, 1H); 3.97–4.15 (m, 1H)	186 (M$^+$, 32.5); 73 (100)
9	$C_7H_9BrO_2$ (205.1)	1740 (C=O)	1.44 (d, 3H, J = 6.3); 1.99 (m, 2H); 2.41 (m, 2H); 4.53 (m, 1H); 6.94 (t, 1H, J = 6.5)	206 (M$^+$, 7.5); 208 (M$^+$, 6.7); 53 (100)
10	$C_7H_9BrO_2$ (205.1)	1730 (C=O) 1604 (C=C)	1.42 (d, 3H, J = 6.4); 1.70 (m, 1H); 2.02 (m, 1H); 2.44 (m, 1H); 2.74 (m, 1H); 4.45 (m, 1H); 7.80 (t, 1H, J = 2.6)	206 (M$^+$, 19.9); 204 (M$^+$, 19.6); 81 (100)
11	$C_{10}H_{17}BrO_2Si$ (277.2)	1715 (C=O)	0.31 (s, 9H); 1.40 (d, 3H, J = 6.2); 1.70 (m, 1H); 2.00 (m, 1H); 2.61 (m, 1H); 2.77 (m, 1H); 4.37 (m, 1H)	263 (M$^+$ − 15, 44.8); 261 (M$^+$ − 15, 48.9); 75 (100)
12a	$C_7H_{10}O_2$ (126.2)	1732 (C=O) 1664 (C=C)	1.40 (d, 3H, J = 6.3); 2.27–2.58 (m, 2H); 3.05 (m, 1H); 3.61–3.71 (m, 1H); 4.83–5.00 (m, 1H); 5.47–5.74 (m, 2H)	126 (M$^+$, 8.1); 54 (100)
12b	$C_7H_{10}O_2$ (126.2)	1700 (C=O) 1640 (C=C)	1.42 (d, 3H, J = 6.8); 1.94–2.14 (m, 2H); 2.40–2.54 (m, 2H); 4.52 (m, 1H); 5.99 (m, 1H); 6.41 (m, 1H)	126 (M$^+$, 4); 39 (100)
13	$C_{10}H_{20}O_2Si$ (200.4)	1685 (C=C)	0.22 (s, 9H); 1.20–2.12 (m, 6H); 1.30 (d, 3H, J = 6.3); 4.00–4.16 (m, 2H)	200 (M$^+$, 17.6); 55 (100)
14a	$C_8H_{12}O_2$ (140.2)	1733 (C=O) 1660 (C=C)	1.38 (d, 3H, J = 6.4); 1.57–1.87 (m, 4H); 1.96–2.15 (m, 1H); 2.20–2.43 (m, 1H); 3.14–3.36 (m, 2H); 4.68–4.87 (m, 1H); 5.55 (m, 1H); 5.73 (m, 1H)	140 (M$^+$, 0.5); 54 (100)
14b	$C_8H_{12}O_2$ (140.2)	1725 (C=O) 1648 (C=C)	1.28 (d, 3H, J = 6.1); 1.51–1.94 (m, 4H); 2.05–2.27 (m, 1H); 2.42–2.61 (m, 1H); 4.75–4.93 (m, 1H); 5.76 (m, 1H); 6.24 (m, 1H, $J_{2,3}$ = 12.8)	140 (M$^+$, 1.4); 68 (100)
E-**15**	$C_{15}H_{34}O_3Si_2$ (318.6)	1685 (C=C)	0.11 (s, 9H); 0.22 (s, 9H); 1.13 (d, 3H, J = 6.2); 1.20–1.63 (m, 6H); 1.96 (m, 2H); 3.51 (s, 3H); 3.66 (t, 1H, J = 6.8); 3.70–3.82 (m, 1H)	318 (M$^+$, 0.1); 73 (100)
Z-**15**	$C_{13}H_{26}O_3Si$ (258.4)	1732 (C=O) 1649 (C=C)	0.11 (s, 9H); 1.13 (d, 3H, J = 6.1); 1.18–1.57 (m, 6H); 2.58–2.73 (m, 2H); 3.65–3.85 (m, 1H); 3.71 (s, 3H); 6.24 (m, 1H)	243 (M$^+$ − 15, 5.9); 117 (100)
E-**16**	$C_{13}H_{26}O_3Si$ (258.4)	1733 (C=O) 1663 (C=C)	0.11 (s, 9H); 1.13 (d, 3H, J = 6.3); 1.20–1.58 (m, 6H); 2.13–2.28 (m, 2H); 3.65–3.85 (m, 1H); 3.73 (s, 3H); 5.83 (d, 1H, J = 15.7); 6.97 (m, 1H)	243 (M$^+$ − 15, 9.9); 117 (100)
17	$C_{13}H_{28}O_3Si$ (260.5)	1749 (C=O)	0.11 (s, 9H); 1.10–1.70 (m, 10H); 1.13 (d, 4H, J = 6); 2.31 (t, 2H, J = 7.1); 3.67 (s, 3H); 3.69–3.82 (m, 1H)	245 (M$^+$ − 15, 9.6); 117 (100)

[a] For yields, mp or bp, see experimental.
[b] Satisfactory microanalyses obtained: C ±0.37, H ±0.21. Exception: **15**, C +0.45.
[c] Measured in C_6D_6.

0°C is added dropwise over 1.5 h ethyl 5-oxohexanoate[13] (24 g, 0.152 mol). After 2 h at this temperature, the mixture is hydrolyzed with 2N HCl (100 mL). Then EtOH is evaporated, and water is added (100 mL). Continuous extraction with Et_2O (500 ml, 10 h), drying of the organic layer (Na_2SO_4), and evaporation give the crude ethyl 5-hydroxyhexanoate. To this are added benzene (500 mL) and TsOH (0.4 g). After refluxing overnight (Dean-Stark), the mixture is washed with 10% $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated. Distillation of the residue gives (±)-**1a**; yield: 13.8 g (80%); bp 42–50°C/0.065 mbar. For spectra, see *R*- or *S*-**1a** (Table 3).

(±)-6-Heptanolide [(±)-1b]:

To a solution of 2-methylcyclohexanone (3 g, 26.7 mmol) in CH_2Cl_2 (100 mL) is added 3-chloroperoxybenzoic acid (16.2 g, 42%, 40 mmol). After stirring for 5 h, 10% $NaHCO_3$ (300 mL) and water (100 mL) are added, and the organic layer separated. The aqueous layer is extracted with CH_2Cl_2 (2 × 100 mL), the organic fractions are combined and washed with brine (2 × 50 mL). The organic phase is dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow liquid, which is purified by distillation; yield: 2.6 g (76%); bp 46–47°C/0.1 mbar (Lit.[14] bp 94°C/6.5 mbar). For spectra, see (*R*)-**1b** (Table 3).

(±)-7-Octanolide [(±)-1c]:

The above procedure is performed with 2-methylcycloheptanone[15] (8.1 g, 64 mmol) in refluxing CH_2Cl_2 for 11 h to afford (±)-**1c**; yield: 6.7 g (73%); bp 34–36°C/0.13 mbar. For spectra, see (*S*)-**1c** (Table 3).

(±)-8-Nonanolide [(±)-1d]:[16]

The above procedure is also performed with 2-methylcyclooctanone[15] (1.4 g, 10 mmol) in refluxing CH_2Cl_2 for 7 days to afford (±)-**1d**; yield: 0.78 g (50%); bp 50–51°C/0.65 mbar. For the spectra see (*S*)-**2d** (Table 3).

(±)-9-Decanolide [(±)-Phoracantholide I; (±)-1e]:

2,3,4,5,6,7-Hexahydro-2-methyl-9-trimethylsiloxyoxocine (**5**): This is prepared by the general procedure[6] from (±)8-nonanolide(±)-**1d** (8.35 g, 53.4 mmol); yield: 11.47 g (94%); bp 50–51°C/0.05 mbar (Table 4).

Preparation of 2-decene-9-olide (**6**) *from* **5**: To a stirred solution of trimethylsilyl enol ether **5** (0.193 g, 4 mmol) and CH_2Cl_2 (1.54 mL, 24 mmol) in pentane (10 mL) at −25 to −20°C under argon is added in 2 h solid sodium bis(trimethylsilyl)amide (3.67 g, 20 mmol). After 10 min, Et_3N (2.22 mL, 16 mmol) is added. After 15 min the temperature is raised to 0°C, and the mixture is quenched with cold water (15 mL). Extraction with Et_2O (3 × 10 mL), drying (Na_2SO_4), and concentration give a residue, which is immediately refluxed in toluene (8 mL) for 15 min. After the removal of solvent, the two isomers of **6** are isolated by column chromatography on silica gel using *n*-hexane/ether (95:5 to 50:50) as eluent.

(±)-(*Z*)-*2-Z-Decene-9-olide* (*Z*-**6**); yield: 209 mg (31%); oil

(±)-(*E*)-*2-E-Decene-9-olide* (*E*-**6**); yield: 228 mg (34%); solid mp 44°C.

Conversion of **6** *to* (±)-**1e**: To a solution of a mixture of *E*- and *Z*-lactones **6** (3 g, 17.8 mmol) in EtOAc (50 mL) is added 10% Pd/C (0.2 g). After complete hydrogenation (1 bar, 7 h), the mixture is filtered, concentrated, and distilled to give (±)-**1e**; yield: 2.79 g (92%); bp 42°C/0.09 mbar. For spectra see (*S*)-**1e** (Table 3).

Enzymatic Resolution of Racemic Lactones (±)-1a–e to Optically Active Lactones (*R*)- or (*S*)-1a–e; General Procedure:

In an Erlenmeyer flask are placed the buffer NaH_2PO_4 (0.1 M adjusted to pH 7.2; 10 mL), the racemic lactone (±)-**1** (1 g) and 15 min later, the crude enzyme HLE or PLE (1 g). The reaction starts immediately. After NaOH consumption corresponding to 50–60% conversion has been noted, ice (2 g) and Celite (1 g) are added. After stirring for 5 min, the mixture is filtered over Celite, the cake is washed with Et_2O (2 × 5 mL), and the aqueous phase is extracted with Et_2O [17 mL, followed by TLC (Et_2O/*n*-hexane: 50/50)]. The organic phase is washed with 10% $NaHCO_3$ (5 mL), dried (Na_2SO_4), and concentrated to give the optically active lactones (*R*)- or (*S*)-**1a–e**. The aqueous layer combined with washing solution is heated 5 min at 70°C. After cooling, Celite (1 g) and 2 N HCl (2 mL) are added, and the mixture is filtered. The filtrate is extracted with Et_2O [15 mL, followed by TLC (Et_2O)]. The combined Et_2O extract is dried (Na_2SO_4), and concentrated to give the optically active hydroxy acids **2b–e** [or the lactone (*R*)-**1a**]. The results are reported in Table 1.

Preparation of Diols 7a–e; General Procedure:

(*R*)- or (*S*)-Lactone **1** (1 mmol) is added over 1 h to CH_3Li (2 mmol) in THF (1 mL) at room temperature. After 15 min, the mixture is quenched with 10% aq. NH_4Cl (4 mL) and extracted with Et_2O (3 × 5 mL). The organic phase is dried (Na_2SO_4) and concentrated (Table 3).

Absolute Configuration of the Optically Active Lactone 1b:

(*R*)-*3,4-Dihydro-2-methyl-6-trimethylsiloxy-2H-pyrane* (**8**): This is prepared from (*R*)-5-hexanolide [(*R*)-**1a**; 1.68 g, 14.7 mmol, ee = 64%] by the general procedure;[6] yield: 2.47 g (90%); bp 75–77°C/20 mbar.

Preparation of (*R*)-2-bromo-2-heptene-6-olide **9** *from* **8**:[17]

To a stirred solution of (*R*)-3,4-dihydro-2-methyl-6-trimethylsiloxy-2*H*-pyrane (**8**; 3.20 g, 17.3 mmol) and tribromomethane (8.74 g, 34.6 mmol) in pentane (25 mL) at −15°C is added during 2 h solid KOBu-*t* (3.70 g, 33 mmol). After 15 min, the mixture is warmed to room temperature and 90 min later water (20 mL) is added. Extraction with Et_2O (3 × 10 mL), drying (Na_2SO_4), and concentration gives a residue, which is purified by flash chromatography (SiO_2, *n*-hexane/EtOAc, 85:15). The following three products are isolated.

(*R*)-*2-Bromo-3-trimethylsilyl-2-heptene-6-olide* (**11**): yield: 218 mg (4.6%); oil; R_f (*n*-hexane/EtOAc, 80:20) = 0.51, $[\alpha]_D^{20}$ + 9.5° (*c* = 1.11, THF); ee = 64%.

(*R*)-*2-[(E)-Bromomethylene]-5-hexanolide* (**10**); yield: 392 mg (11%); mp 35–38°C; R_f (*n*-hexane/EtOAc 80:20) = 0.30; $[\alpha]_D^{20}$ + 35.6° (*c* = 1.16, THF); ee = 64%.

(*R*)-*2-Bromo-2-heptene-6-olide* (**9**); yield: 1.48 g (42%); mp 41–43°C; R_f (*n*-hexane/EtOAc, 80:20) = 0.23, $[\alpha]_D^{20}$ + 42.2° (*c* = 1.06, THF); ee = 64%.

Conversion of **9** *to* (*R*)-(+)-*6-heptanolide* (**1b**): A mixture of (*R*)-2-bromo-2-heptene-6-olide (**9**; 1.3 g, 6.3 mmol), diethylphosphite[12] (1.5 g, 16.6 mmol), Et_3N (3.5 mL, 25.3 mmol) and benzene (10 mL) is refluxed for 4 h. After cooling, Et_2O is added (20 mL), and the mixture is filtered. Concentration of the ethereal solution affords a residue containing the two isomers **12a** and **12b**, which are separated by flash chromatography (SiO_2, *n*-hexane/EtOAc, 80:20).

(R)-(+)-3-Heptene-6-olide (**12a**); yield: 595 mg (74.9%); R_f (*n*-hexane/EtOAc, 65:35) = 0.29; $[\alpha]_D^{20}$ + 23° (*c* = 1.025, THF); ee = 64%.

(R)-(+)-2-Heptene-6-olide (**12b**); yield: 93 mg (11.7%); R_f (*n*-hexane/EtOAc, 65:35) = 0.21; $[\alpha]_D^{20}$ + 21.6° (*c* = 1.01 THF); ee = 64%.

The mixture of these two unsaturated lactones is hydrogenated as reported for (±)-**1e** to give (*R*)-**1b**; yield: 636 mg (91%); $[\alpha]_D^{20}$ + 17.2° (*c* = 1, THF); ee = 64%.

Absolute Configuration of the Optically Active Lactone 1c:

(*R*)-*2-Methyl-2,3,4,5-tetrahydro-7-trimethylsiloxyoxepine* (**13**): This is prepared from (*R*)-6-heptanolide [(*R*)-**1b**; 5.1 g, 39.8 mmol, ee = 64%] using the general procedure;[6] yield: 6.5 g (82%); bp 92–94°C.

Preparation of (*R*)-*2-Octene-7-olide* (**14a**) *and* (*R*)-*3-octene-7-olide* (**14b**) *from* **13**:

The procedure described for the preparation of lactone **6** is used (Et_3N is not necessary). Reaction of the silyl enol ether **13** (5.1 g, 25.4 mmol, ee = 64%) with chlorocarbene gives an adduct, which is refluxed in xylene for 8 h. After flash chromatography (SiO_2, *n*-hexane/ether, 95:5 to 50:50) the two lactones **14a** and **14b** are isolated.

(*R*)-(−)-*3-Octene-7-olide* (**14a**); yield: 227 mg (6%); $[\alpha]_D^{20}$ − 20.7° (*c* = 0.965, THF); ee = 64%.

(*R*)-(−)-*2-Octene-7-olide* (**14b**); yield: 2.05 g (58%); $[\alpha]_D^{20}$ − 10.3° (*c* = 0.99, THF); ee = 64%.

Conversion of **14** *to* (*R*)-(−)-*7-Octanolide* [(*R*)-**1c**]: The procedure described for the preparation of (±)-**1e** is used. From the mixture of lactones **14a** and **14b** (1:9) (204 mg, 1.45 mmol), (*R*)-**1c** is obtained; yield: 173 mg (84%); $[\alpha]_D^{20}$ − 46.8° (*c* = 0.98, THF); ee = 64%.

Absolute Configuration of the Optically Active Lactone (*S*)-1d:

(*R*)-*1,7-Bis-trimethylsiloxy-1-methoxy-1-octene* (**15**): This is prepared from methyl (*R*)-7-hydroxyoctanoate (**4c**; 1.27 g, 7.3 mmol, ee = 70%) using the general procedure;[6] yield: 2.16 g (93%, *E*/*Z*, 90 = 10); bp 71–72°C/0.08 mbar.

Preparation of Methyl (*R*)-*8-Trimethylsiloxy-2-nonenoate* (**16**) *from* **15**: Compound **16** is prepared using the procedure described for the synthesis of **6**. After the carbene addition to (*R*)-1,7-bis-trimethylsilyloxy-1-methoxy-1-octene (965 mg, 3 mmol, ee = 70%), the crude reaction mixture is refluxed in benzene for 5 h. The benzene is distilled off

and the two isomers *E*-**16** and *Z*-**16** are isolated by column chromatography on SiO_2, (Et_2O/*n*-hexane, 7:93).

Methyl (R)-8-Trimethylsiloxy-2(E)-nonenoate (E-16): yield: 586 mg (75%); R_f (*n*-hexane/Et_2O, 85:15) = 0.31; $[\alpha]_D^{20} - 10.2°$ (c = 1.03, THF); ee = 70%.

Methyl (R)-8-Trimethylsiloxy-2(Z)-nonenoate (Z-16): yield: 64 mg (9%); R_f (hexane/Et_2O, 85:15) = 0.41.

Conversion of **16** to Methyl (*R*)-8-Trimethylsiloxynonanoate **(17)**: The procedure used for (±)-**1e**, performed with the *E*/*Z* mixture of unsaturated esters **16** (286 mg, 1.1 mmol, ee = 70%) affords methyl (*R*)-8-trimethylsilyloxynonanoate **(17)**; yield: 246 mg (86%); $[\alpha]_D^{20} - 9.6°$ (c = 0.98 THF); ee = 70%.

Conversion of **17** *to Methyl (R)-8-Hydroxynonanoate* **(4d)**:
A solution of the silyl ether **17** (286 mg, 1.1 mmol) in MeOH (10 mL) is stirred with a trace of conc. HCl for 2 h. MeOH is removed and the product is isolated by extraction with Et_2O; yield: 190 mg (92%); $[\alpha]_D^{20} - 5.4°$ (c = 1.15, THF); ee = 70%.

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(1) Blanco, L., Guibé-Jampel, E., Rousseau, G. *Tetrahdron Lett.* **1988**, *29*, 1915.
(2) Gutman, A.L., Zuobi, K., Boltansky, A. *Tetrahedron Lett.* **1987**, *28*, 3861.
Zhi-Wei, G., Ngooi, T.K., Scilimati, A., Fülling, G., Sih, C.J. *Tetrahedron Lett.* **1988**, *29*, 5583.
(3) Use of PLE in asymmetric synthesis, see: Kuhn, T., Tamm, C. *Tetrahedron Lett.* **1989**, *30*, 693 for a leading reference.
(4) Use of HLE in asymmetric synthesis, see: Ref. 1 and Guibé-Jampel, E., Rousseau, G., Blanco, L. *Tetrahedron Lett.* **1989**, *30*, 67.
(5) Suginome, H., Yamada, S. *Tetrahedron* **1987**, *43*, 3371, and references cited therein.
(6) Corey, E.J., Gross, A.W. *Tetrahedron Lett.* **1984**, *25*, 495.
(7) Slougui, N., Rousseau, G. *Tetrahedron* **1985**, *41*, 2643.
(8) Scilimati, A., Ngooi, T.K., Sih, C.J. *Tetrahedron Lett.* **1988**, *29*, 4927.
(9) Kitahara, T., Kosehi, K., Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 389.
(10) Naoshima, Y., Hasegawa, H. *Chem. Lett.* **1987**, 2379.
(11) Jakovac, I.J., Jones, J.B. *J. Org. Chem.* **1979**, *44*, 2165.
(12) Hirao, T., Fujihara, Y., Kurokawa, K., Ohshiro, Y., Agawa, T. *J. Org. Chem.* **1986**, *51*, 2830.
(13) Chong, R., Clezy, P.S. *Aust. J. Chem.* **1967**, *20*, 123.
(14) Starcher, P.S., Phillips, B. *J. Am. Chem. Soc.* **1958**, *80*, 4079.
(15) Girard, C., Conia, J.M. *Tetrahedron Lett.* **1974**, 3327.
(16) Still, W.C., Galynker, I. *Tetrahedron* **1981**, *37*, 3981.
(17) Amice, P., Blanco, L., Conia, J.M. *Synthesis* **1976**, 196.
(18) Seebach, D., Renaud, P. *Helv. Chim. Acta* **1985**, *68*, 2342.
(19) Pirkle, W.H., Adams, P.E. *J. Org. Chem.* **1979**, *44*, 2169.
(20) Mori, K., Senda, S. *Tetrahedron* **1985**, *41*, 541.