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Lipase-Catalyzed Synthesis of (5*R*,6*S*)-6-Acetoxyalkan-5-olides – Homologues of the Mosquito Oviposition Attractant Pheromone

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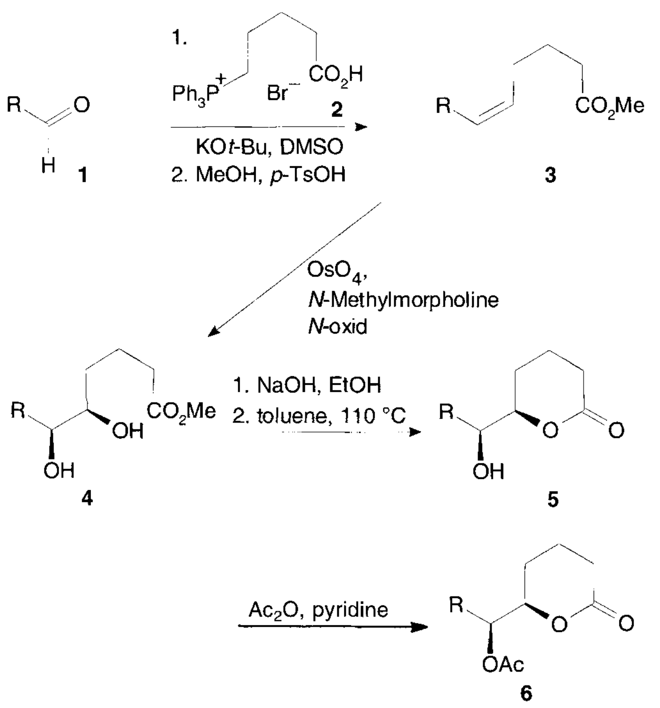
Dedicated to Prof. Dr. habil. Helmut Dorn on the Occasion of his 70th Birthday

Abstract. Sixteen homologous (5*R**,6*S**)-6-hydroxyalkan-5-olides *rac*-**5** and their acetoxy derivatives *rac*-**6** were synthesized from the corresponding methyl (*Z*)-alk-5-enoates **3** by osmium(VIII) oxide catalyzed *cis*-hydroxylation to the dihydroxy esters *rac*-**4** and hydrolysis of these esters followed by lactonization. Pancreatin-catalyzed lactonization of the dihydroxy esters *rac*-**4** afforded enantiomerically enriched hydroxy lactones *ent*-**5**, five of which were obtained enantiomerically pure by recrystallization. Acetylation of the 6-hydroxyalkan-5-olides *rac*-**5** by vinyl acetate catalyzed by the lipase SP 526 provided enantiomerically enriched 6-acetoxyalkan-5-olides **6** with an enantiomeric excess of more than 90% in nine cases. These compounds are known as mosquito oviposition attractant pheromone (**6h**) or its homologues.

Lipases represent that class of enzymes, which has found the broadest application in enantiomer-differentiating formation or hydrolysis of carbon–oxygen bonds [2–6]. *In vivo* destinated for the hydrolysis of acyl glycerides or the acylation of glycerol, many lipases exhibit *in vitro* frequently a low substrate specifity combined with a high enantiotopic or enantiomer selectivity. This last mentioned fact is one of the reasons for the extensive and successful use of these chiral biocatalysts in organic synthesis. Although a lipase in general accepts a broad variety of structurally related substances as substrates, it is of great interest for the design of lipase-catalyzed carbon–oxygen bond formation or fission to enlarge the knowledge about the relation betweeen the structure of a series of homologous compounds and their relative suitability as substrates in a lipase-catalyzed enantiomer-selective acylation or solvolysis reaction. In recent years several investigations directed to this aim have been performed [7–11].

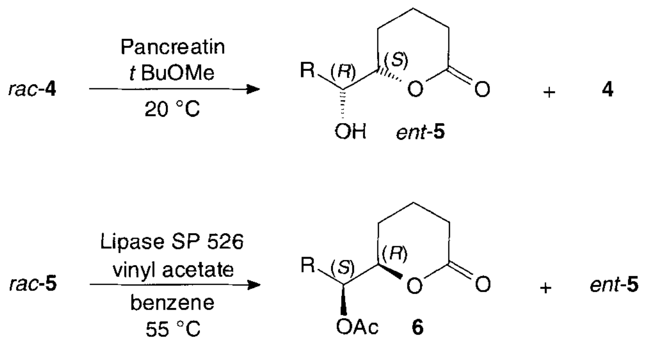
Reporting here on the results obtained in connection with the lipase-catalyzed lactonization of the 16 racemic methyl *syn*-5,6-dihydroxyalkanoates *rac*-**4** and the lipase-catalyzed acetylation of the 16 racemic 6-hydroxyalkan-5-olides *rac*-**5** we like to contribute to the important problem of the substrate specifity of lipases. This investigation originated from the interest in the synthesis of a series of homologues of (5*R*,6*S*)-6-acetoxyhexadecan-5-olide (**6h**), the main component of the mosquito oviposition attractant pheromone [12–13].

The substrates *rac*-**5a**–**p** and *rac*-**6a**–**p** for these lipase-catalyzed reactions were prepared according to Scheme 1 in analogy to procedures elaborated originally for *rac*-**5h** and *rac*-**6h** [14]. The Wittig reaction of the aldehydes **1a**–**p** with (4-carboxybutyl)triphenylphosphonium bromide **2** [15] and the subsequent esterification with methanol afforded the (*Z*)-configurated esters **3a**–**p** in a yield of 36–98 % containing 7–13 % of the corresponding (*E*)-isomer. Only *rac*-**3l** was obtained as pure (*Z*)-isomer (Table 1). The *cis*-dihydroxylation of **3a**–**p** with a catalytic amount of osmium(VIII) oxide and *N*-methylmorpholine *N*-oxide [16] provided the *syn*-dihydroxy esters *rac*-**4a**–**p** in a yield of 15–96% containing 0–24% of the corresponding *anti*-diastereomer. The crystalline esters *rac*-



Scheme 1 Synthesis of the racemic δ-lactones *rac*-**5** and *rac*-**6** (Only one enantiomer of the racemic compounds is depicted in this scheme. The meaning of R is explained in the Tables)

4b–**m** and *rac*-**4p** could be obtained in diastereomerically pure form by recrystallization from hexane/diethyl ether (Table 2). The lactonization of the dihydroxy esters *rac*-**4a–p** afforded the hydroxy lactones *rac*-**5a–p** in a yield of 44–92% (Table 3). Acetylation of these lactones with acetanhydride in pyridine provided the acetoxy lactones *rac*-**6a–p**.



Scheme 2 Lipase-catalyzed enantioselective lactonization of *rac*-**4** and acetylation of *rac*-**5** (The meaning of R is explained in the Tables)

On the basis of our previous experience in the enzyme-catalyzed enantiomer-selective lactonization of dihydroxy esters [14,17] the diols *rac*-**4a–p** were cyclized in *tert*-butyl methyl ether in the presence of pancreatin (Scheme 2). In all cases enantiomerically enriched (5*S*,6*R*)-6-hydroxyalkan-5-olides *ent*-**5a–p** were obtained. The *e.e.* were in the order of 51–89%. The enantiomeric ratio *E* [18] reached values of 4–25 (Table 4). Best results were obtained for lactone *ent*-**5n** with a 2-dimethylpropyl side chain (34% yield [1]), 88% *e.e.*, *E* = 25). In contrast to this result, hydroxy lactones with short side chains such as ethyl (*ent*-**5a**), propyl (*ent*-**5b**), isopropyl (*ent*-**5k**), and *tert*-butyl (*ent*-**5l**) reveal low enantiomeric ratios (*E* = 4–6) and correspondingly low *e.e.* If the enantiomerically enriched lactones were crystalline like *ent*-**5f–j**, enantiomerically pure (5*S*,6*R*)-6-hydroxyalkan-5-olides could be obtained by recrystallization.

A significantly higher enantiomer selectivity was found for the acetylation of the lactones *rac*-**5a–p** with vinyl acetate to the (5*R*,6*S*)-6-acetoxyalkan-5-olides **6a–p** with lipase SP 526 as biocatalyst (Table 5 and 6). The highest enantiomeric ratios (*E*>100) were observed for the substrates *rac*-**5k**, *rac*-**5m**, and *rac*-**5p** with branched side chains, such as isopropyl, 2-methylpropyl and cyclohexyl. The obtained acetoxy lactones **6k**, **6m**, and **6p** were nearly enantiomerically pure. The other hydroxy lactones *rac*-**5** with unbranched side chains from ethyl to tridecyl were converted into the corresponding 6-acetoxyalkan-5-olides **6** with *e.e.* of 67–95% and enantiomeric ratios *E* of 10–58.

The absolute configuration of the enantiomerically enriched hydroxy lactones **5e** [19] and **5h**/*ent*-**5h** [20] as well as the acetoxy lactones **6e** [19] and **6h**/*ent*-**6h** [20] was assigned according to the literature. For all other enantiomerically enriched lactones the HPLC pattern was compared with that of the known compounds. It was assumed that the eluation order of all homologues is the same and thus allows an assignment of the absolute configuration to the unknown compounds. The HPLC-data are given in Tables 4 and 6.

Comparing the results obtained by the enantiomer-selective lactonization of the dihydroxy esters *rac*-**4a–p** it can be stated that pancreatin accepted all 16 homologous compounds as substrates (Table 4 and Scheme 2). The enantiomeric ratio *E*, however, was in no case higher than 25. In the enzyme-catalyzed acetylation of the hydroxy lactones *rac*-**5a–p** the lipase SP 526 revealed to be more sensitive to the structure of the substrate. Lactones *rac*-**5l** and *rac*-**5n** with a quarternary carbon in the side chain were not accepted as substrate. Lactones *rac*-**5k**, *rac*-**5m**, and *rac*-**5p** with a tertiary carbon in the side chain were exellent substrates. In these cases an enantiomeric ratio *E*>100 was observed and the acetylation products were obtained with an *e.e.* > 98%. Surprisingly, the lactone *rac*-**5o** also bearing a tertiary carbon in the side chain was not accepted as substrate by SP 526. The lactones *rac*-**5a–j** with an un-

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[1]) All yields of enantiomerically pure or enriched compounds are related to an obtainable maximum yield of 100 %.

branched side chain were accepted as substrates throughout, the enantiomeric ratio E, however, was significantly lower than in the three optimal cases with a tertiary carbon in the side chain (Table 5, Scheme 2).

In conclusion, using the SP 526-catalyzed acetylation of *rac*-**5a–p** the homologues **6a, 6d, 6g, 6i–k, 6m,** and **6p** of the mosquito oviposition attractant pheromone **6h** could be prepared with an *e.e.* > 90%. The biocatalytical reaction performed with a series of 16 homologous 6-hydroxyalkan-5-olides was most enantioselective with three substrates bearing a tertiary carbon in the side chain. Furthermore, the homologues *ent*-**5f**, *ent*-**5g**, *ent*-**5i**, and *ent*-**5j** of the deacetylated pheromone enantiomer *ent*-**5h** could be obtained in enantiomerically pure form by the pancreatin-catalyzed lactonization of the corresponding dihydroxy esters *rac*-**4** and subsequent recrystallization.

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Experimental

Melting points (corrected): Boëtius micromelting point apparatus . – Optical rotations were measured at the sodium D-line in a 1-dm cell with a Perkin-Elmer 241 polarimeter. – ^{13}C NMR: 75 MHz, Varian Gemini 300, solvent $CDCl_3$ with hexamethyldisiloxane as internal standard. – HPLC: 6200 pump (Merck-Hitachi), spectral photometer (Knauer), RI detector (Merck), and data system (Auswert 2, ZIOC Berlin). – The enzymes were obtained from Novo Nordisk A/S, Bagsvaerd, Denmark (lipase SP 526, 25 KLU/g) and from Fa. Belger, Kleinmachnow, Germany (pancreatin, 6 x NF, 360 U/g triolein as a substrate, 5.4% H_2O).

Methyl (Z)-Alk-5-enoates (3a–p) (General Procedure)

Potassium *tert*-butoxide (11.2 g, 100 mmol) was added at 15 °C to a solution of (4-carboxybutyl)triphenylphosphonium bromide (**2**) (22.2 g, 50.0 mmol) in dry DMSO (90 ml). The

Table 1 Yields and analytical data of the methyl (*Z*)-alk-5-enoates (**3a–p**)

3	R	Yield (%)	*Z/E* ratio	Formula Mol. mass	%C calcd. found	%H calcd. found	^{13}C NMR δ (ppm)
a	CH_3CH_2	72	92/8	$C_9H_{16}O_2$ 156.2	69.19 68.95	10.32 10.17	14.29, 20.49, 24.87, 26.39, 33.41, 51.44, 127.7, 132.8, 174.1
b	$CH_3(CH_2)_2$	63	89/11	$C_{10}H_{18}O_2$ 170.3	70.55 70.91	10.66 10.63	13.79, 22.82, 24.90, 26.55, 29.29, 33.47, 51.46, 128.6, 130.9, 174.2
c	$CH_3(CH_2)_3$	78	93/7	$C_{11}H_{20}O_2$ 184.3	71.70 70.95	10.94 11.18	13.90, 22.27, 24.82, 26.44, 26.85, 31.80, 33.38, 51.37, 128.2, 131.0, 174.1
d	$CH_3(CH_2)_4$	95	90/10	$C_{12}H_{22}O_2$ 198.3	72.69 71.98	11.18 11.03	14.08, 22.58, 24.74, 26.52, 27.19, 29.38, 31.53, 33.66, 41.47, 128.3, 131.2, 174.2
e	$CH_3(CH_2)_5$	98	91/9	$C_{13}H_{24}O_2$ 212.3	73.55 73.16	11.39 11.22	14.11, 22.66, 24.91, 26.55, 27.25, 29.00, 29.68, 31.79, 33.48, 51.46, 128.3, 131.2, 174.2
f	$CH_3(CH_2)_7$	79	90/10	$C_{15}H_{28}O_2$ 240.4	74.95 74.86	11.74 11.93	14.10, 22.69, 24.89, 26.52, 27.23, 29.19-29.70 (4 signals), 31.91, 33.44, 51.42, 128.3, 131.2, 174.1
g	$CH_3(CH_2)_8$	79	90/10	$C_{16}H_{30}O_2$ 254.4	75.55 75.73	11.89 11.86	14.11, 22.68, 24.88, 26.52, 27.22, 29.17-29.69 (5 signals), 31.91, 33.45, 51.44, 128.3, 131.2, 174.1
h	$CH_3(CH_2)_9$	84	93/7	$C_{17}H_{32}O_2$ 268.4	76.07 75.80	12.02 11.97	14.10, 22.68, 24.88, 26.52, 27.22, 29.33-29.63(6 signals), 31.90, 33.46, 51.44, 128.3, 131.2, 174.1
i	$CH_3(CH_2)_{10}$	83	91/9	$C_{18}H_{34}O_2$ 282.5	76.54 76.45	12.13 12.28	14.28, 22.85, 25.04, 26.68, 27.39, 29.51-29.81 (7 signals) 32.08, 33.61, 51.61, 128.4, 131.3, 174.3
j	$CH_3(CH_2)_{12}$	36	87/13	$C_{20}H_{38}O_2$ 310.5	77.36 77.30	12.34 12.10	14.13, 22.70, 24.89, 26.53, 27.23, 29.16-29.70 (9 signals), 31.93, 33.46, 51.45, 128.3, 131.2, 174.2
k	$(CH_3)_2CH$	79	90/10	$C_{10}H_{18}O_2$ 170.3	70.55 70.18	10.66 10.39	23.11, 24.97, 26.42, 26.58, 33.40, 51.40, 125.9, 138.6, 174.1
l	$(CH_3)_3C$	94	100/0	$C_{11}H_{20}O_2$ 184.3	71.70 71.63	10.94 10.94	25.30, 27.60, 31.10, 33.10, 33.52, 51.45, 127.49, 140.73, 174.04
m	$(CH_3)_2CHCH_2$	80	90/10	$C_{11}H_{20}O_2$ 184.3	71.70 71.43	10.94 11.10	13.79, 22.81, 24.89, 26.54, 29.28, 33.47, 51.46, 128.5, 130.9, 174.2
n	$(CH_3)_3CCH_2$	90	93/7	$C_{12}H_{22}O_2$ 198.3	72.69 72.14	11.18 11.09	24.87, 26.54, 29.24, 31.15, 33.51, 41.09, 51.42, 127.82, 129.8, 174.1
o	$(CH_3CH_2)_2CH$	98	91/9	$C_{12}H_{22}O_2$ 198.3	72.69 72.84	11.18 10.99	11.87, 25.07, 27.07, 28.26, 33.55, 40.70, 51.46, 128.6, 135.6, 174.2
p	*c*-C_6H_{11} [a]	62	93/7	$C_{13}H_{22}O_2$ 210.3	74.25 73.98	10.54 10.36	25.05, 25.96, 26.04, 26.74, 33.31, 33.45, 36.29, 51.48, 126.5, 137.2, 174.2

[a] *c*-C_6H_{11} = cyclohexyl.

Table 2 Yields and analytical data of the methyl (5*R**,6*S**)-5,6-dihydroxyalkanoates (*rac*-**4a–p**)

4	R	Yield (%)	*syn/anti* ratio	*m.p.* (°C)	Formula Mol. mass	%C calcd. found	%H calcd. found	^{13}C NMR δ(ppm)
a	CH_3CH_2	67	92/8	–	$C_9H_{18}O_4$ 190.2	56.82 56.81	9.54 9.75	10.42, 21.24, 24.39, 30.41, 33.77, 51.61, 73.89, 76.16, 174.4
b	$CH_3(CH_2)_2$	62	89/11	38–40 a)	$C_{10}H_{20}O_4$ 204.3	58.80 58.50	9.87 9.88	14.09, 19.18, 21.23, 30.46, 33.54, 33.78, 51.63, 74.14, 74.36, 174.3
c	$CH_3(CH_2)_3$	67	93/7	66–68 a)	$C_{11}H_{22}O_4$ 218.3	60.52 60.34	10.16 10.32	14.05, 21.26, 22.75, 28.20, 30.44, 31.15, 33.18, 51.63, 74.15, 74.68, 174.4
d	$CH_3(CH_2)_4$	75 b)	90/10	90–91 a)	$C_{12}H_{24}O_4$ 232.3	62.04 62.30	10.41 10.69	14.32, 21.76, 23.09, 26.20, 31.00, 32.00, 32.35, 33.94, 51.08, 74.51, 74.92, 173.9
e	$CH_3(CH_2)_5$	96	92/8	85–86 a)	$C_{13}H_{26}O_4$ 246.4	63.38 63.32	10.64 10.85	14.05, 21.20, 22.59, 25,95, 29.31, 30.43, 31.42, 31.76, 33.76, 51.59, 74.09, 74.64, 174.3
f	$CH_3(CH_2)_7$	83	90/10	87–88 a)	$C_{15}H_{30}O_4$ 274.4	65.66 65.73	11.02 11.25	14.10, 21.26, 22.66, 26.05, 29.29–29.70 (3 sig.), 30.40, 31.44, 31.87, 33.77, 51.61, 74.14, 74.68, 174.4
g	$CH_3(CH_2)_8$	64	90/10	86–87 a)	$C_{16}H_{32}O_4$ 288.4	66.63 66.70	11.18 11.39	14.09, 21.23, 22.66, 26.03, 29.30–29.68 (4 sig.), 30.39, 31.43, 31.87,33.76, 51.60, 74.11, 74.67, 174.3
h	$CH_3(CH_2)_9$	64	93/7	91–93 a)	$C_{17}H_{34}O_4$ 302.5	67.51 67.69	11.33 11.33	14.10, 21.22, 22.67, 26.02, 29.32–29.68 (5 sig.), 30.42, 31.44, 31.89, 33.76, 51.59, 74.11, 74.66, 174.3
i	$CH_3(CH_2)_{10}$	95	91/9	98–100 a)	$C_{18}H_{36}O_4$ 316.5	68.31 68.23	11.47 11.78	14.20, 21.29, 22.76, 26.09, 29.42–29.70 (6 sig.), 30.51, 31.51, 31.99, 33.84, 51.69, 74.18, 74.73, 174.4
j	$CH_3(CH_2)_{12}$	39	87/13	101–102 a)	$C_{20}H_{40}O_4$ 344.5	69.72 69.84	11.70 12.14	14.13, 21.22, 22.70, 26.02, 29.37–29.68 (8 sig.), 30.46, 31.45, 31.93, 33.78, 52.62, 74.11, 74.67, 174.3
k	$(CH_3)_2CH$	47	90/10	35–38 a)	$C_{10}H_{20}O_4$ 204.3	58.80 58.83	9.87 10.01	18.62, 19.00, 21.11, 29.56, 29.93, 33.80, 51.64, 71.87, 79.82, 174.5
l	$(CH_3)_3C$	40	100/0	46–49 a)	$C_{11}H_{22}O_4$ 218.3	60.52 60.70	10.16 10.11	21.02, 26.75, 31.62, 33.76, 34.31, 51.58, 72.05, 82.53, 174.4
m	$(CH_3)_2CHCH_2$	55	90/10	32–34 a)	$C_{11}H_{22}O_4$ 218.3	60.52 60.66	10.16 10.45	21.26, 21.67, 23.78, 24.54, 30.47, 33.77, 40.30, 51.62, 72.59, 74.46, 174.3
n	$(CH_3)_3CCH_2$	75	93/7	–	$C_{12}H_{24}O_4$ 232.3	62.04 61.85	10.41 10.74	21.73, 30.18–30.61 (5 sig.), 33.89, 45.55, 51.07, 72.41, 75.66, 173.9 b)
o	$(CH_3CH_2)_2CH$	15 c)	76/24	–	$C_{12}H_{24}O_4$ 232.3	62.04 61.70	10.41 10.70	10.60, 10.69, 20.56, 21.09, 21.14, 30.02, 33.83, 41.76, 51.63, 71.87, 75.79, 174.4
p	c-C_6H_{11}	27	84/16	65–67	$C_{13}H_{24}O_4$ 244.3	63.90 63.56	9.90 10.14	21.54, 26.34, 26.53, 26.87, 28.96, 29.49, 30.22, 33.93, 39.91, 51.04, 71.59, 78.95, 173.9 b)

a) Diastereomerically pure compounds obtained by recrystallization. b) Spectrum measured in benzene. c) After a reaction time of 3 days.

mixture was stirred for 20 min under nitrogen. Then an alkanal **1** (25.0 mmol) was added and stirring was continued for 45 min at 20 °C. The resulting mixture was diluted with ethyl acetate (100 ml) and water (100 ml). The organic phase was separated and extracted with water (2 x 30 ml). The aqueous phase and the aqueous extracts were combined, acidified with 4N H_2SO_4 to pH 2, and then extracted with ethyl acetate (3 x 40 ml). After drying of the organic extracts with $MgSO_4$ and evaporation of the solvent under reduced pressure, the solid by-products were removed by filtration after dilution with diethyl ether (50 mL). The filtrate was again concentrated under reduced pressure and the residual oil was refluxed for 4–8 h in methanol (50 ml) in the presence of *p*-toluenesulfonic acid (30 mg). After concentration under reduced pressure the residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (4:3) as eluent. The methyl esters **3a–p** were obtained as colorless oils. According to HPLC on RP-18 these esters were contaminated with 0–13% of the corresponding *E*-isomer. Yields and analytical data are accumulated in Table 1.

Methyl (5*R**,6*S**)-5,6-Dihydroxyalkanoates (*rac*-4a–p) (General Procedure)

A solution of a methyl ester **3** (27.2 mmol) in acetone (50 ml) was combined with a mixture prepared by addition of a solution of OsO_4 (21.6 g, 0.085 mmol) in *tert*-butanol (1.1 ml) to a solution of *N*-methylmorpholine *N*-oxide monohydrate (3.90 g, 28.9 mmol) in acetone (140 ml) and water (10 ml). This mixture was stirred at 22 °C for 12 h and then reduced with 1N Na_2SO_3 (20 ml), neutralized with 1 N H_2SO_4 and filtered. Acetone was removed from the filtrate by evaporation under reduced pressure and the acidity of the residue was adjusted to pH 2. The mixture was diluted with water (50 ml) and

Table 3 Yields and analytical data of the (5*R**,6*S**)-6-hydroxyalkan-5-olides (*rac*-**5a–p**)

5	R	Yield (%)	React. time (h)	*m.p.* (°C)	Formula Mol. mass	%C calcd. found	%H calcd. found	^{13}C NMR δ (ppm)
a	CH_3CH_2	69	1.5	–	$C_8H_{14}O_3$ 158.2	60.74 60.12	8.92 8.98	10.28, 18.29, 21.25, 24.82, 29.80, 73.75, 83.25, 172.0
b	$CH_3(CH_2)_2$	84	3	–	$C_9H_{16}O_3$ 172.2	62.77 62.59	9.36 9.69	13.98, 18.35, 19.09, 21.21, 29.83, 33.80, 72.07, 83.54, 171.8
c	$CH_3(CH_2)_3$	88	3	–	$C_{10}H_{18}O_3$ 186.3	64.49 64.22	9.74 10.07	14.00, 18.35, 21.22, 22.63, 28.03, 29.81, 31.48, 72.34, 83.54, 171.9
d	$CH_3(CH_2)_4$	85	3	–	$C_{11}H_{20}O_3$ 200.3	65.97 65.67	10.07 10.20	14.01, 18.35, 21.21, 22.56, 25.55, 29.32, 29.80, 31.70, 72.38, 83.48, 171.8
e	$CH_3(CH_2)_5$	92	3	–	$C_{12}H_{22}O_3$ 214.3	67.25 66.77	10.35 10.58	14.07, 18.35, 21.21, 22.60, 25.84, 29.22, 29.81, 31.73, 31.77, 72.34, 83.52, 171.8
f	$CH_3(CH_2)_7$	70	2	51–53	$C_{14}H_{26}O_3$ 242.4	69.38 69.29	10.81 11.00	14.09, 18.32, 21.16, 22.64, 25.86, 29.23-29.78 (4 signals), 31.72, 31.83, 72.33, 83.48, 171.8
g	$CH_3(CH_2)_8$	79	2	49–51	$C_{15}H_{28}O_3$ 256.4	70.27 70.23	11.01 11.30	14.10, 18.33, 21.15, 22.66, 25.88, 29.29-29.78 (5 signals), 31.73, 31.86, 72.31, 83.52, 171.8
h	$CH_3(CH_2)_9$	84	2.5	65–67	$C_{16}H_{30}O_3$ 270.4	71.07 71.24	11.18 11.44	14.07,18.38, 21.36, 22.67, 25.87, 29.31-29.80, (6 signals), 31.85, 31.91, 72.49, 83.40, 171.6
i	$CH_3(CH_2)_{10}$	80	2	64–65	$C_{17}H_{32}O_3$ 284.4	71.78 71.81	11.34 11.68	14.12, 18.35, 21.19, 22.70, 25.89, 29.35-29.81 (7 signals); 31.73, 31.91, 72.37, 83.48, 171.8
j	$CH_3(CH_2)_{12}$	44	3	70–71	$C_{19}H_{36}O_3$ 312.5	73.03 72.93	11.61 11.83	14.14, 18.36, 21.18, 22.70, 25.89, 29.37-29.80 (9 signals), 31.73, 31.93, 72.38, 83.47, 171.7
k	$(CH_3)_2CH$	83	3.5	–	$C_9H_{16}O_3$ 172.2	62.77 62.92	9.36 9.60	18.34, 18.48, 18.90, 21.17, 29.23, 29.85, 77.30, 81.58, 171.9
l	$(CH_3)_3C$	38 a)	–	–	$C_{10}H_{18}O_3$ 186.3	64.49 64.32	9.74 9.78	18.46, 22.62, 26.70, 29.68, 34.06, 79.78, 81.87, 172.0
m	$(CH_3)_2CHCH_2$	73	4	50–52	$C_{10}H_{18}O_3$ 186.3	64.49 64.74	9.74 10.14	18.37, 21.15, 21.73, 23.53, 24.56, 29.80, 40.53, 70.38, 83.89, 171.8
n	$(CH_3)_3CCH_2$	92	3	55–57	$C_{11}H_{20}O_3$ 200.3	65.97 65.58	10.07 10.33	18.37, 20.87, 29.61-30.15 (5 signals), 45.03, 69.83, 84.53, 171.7
o	$(CH_3CH_2)_2CH$	8 a)	–	–	$C_{11}H_{20}O_3$ 200.3	65.97 65.67	10.07 10.21	10.50, 18.38, 20.34, 21.09, 21.51, 29.83, 40.89, 73.45, 81.57, 171.9
p	*c*-C_6H_{11}	27 a)	–	95–97	$C_{12}H_{20}O_3$ 212.3	67.90 67.65	9.50 9.52	18.34, 21.02, 25.67, 25.95, 26.27, 28.76, 29.02, 29.83, 38.75, 76.25, 81.32, 172.0

a) These lactones were obtained together with the corresponding dihydroxy esters *rac*-**4** by the dihydroxylation reaction. They were separated by flash chromatography.

extracted with ethyl acetate (1 x 100, 2 x 40 ml). The combined extracts were dried with $MgSO_4$ and concentrated under reduced pressure.The residue, containing also the *anti*-diol, could be in most cases recrystallized from hexan/diethyl ether (1:1) to afford the pure *syn*-diol *rac*-**4**. Yields and analytical data are compiled in Table 2.

(5*R**,6*S**)-6-Hydroxyalkan-5-olides (*rac*-5a–p) (General Procedure)

A dihydroxy ester *rac*-**4** (1.0 g) was dissolved in ethanol (30 ml) and stirred with an equimolar amount of 1N aqueous NaOH for 2 h. After acidification to pH 2 with 1N H_2SO_4 the mixture was concentrated under reduced pressure and distributed between ethyl acetate (30 ml) and water (30 ml). The water phase was extracted with ethyl acetate (2×30 ml). The combined extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was refluxed in toluene for 1.5–4 h. After concentration under reduced pressure the residue was purified by flash chromatography on silica gel with nitromethane/ethyl acetate (2:1) as eluent to afford the lactones *rac*-**5a**–**p**. Yields and analytical data are accumulated in Table 3.

(5*S*,6*R*)-6-Hydroxyalkan-5-olides (*ent*-5a–p) by Pancreatin-Catalyzed Lactonization of the Diols (*rac*-4a–p) (General Procedure)

Pancreatin (200 mg/0.33 mmol *rac*-**4**) and anhydrous Na_2SO_4 (100 mg) were added to a solution of a dihydroxy ester *rac*-**4** (100 mg) in *tert*-butyl methyl ether (6 ml). The mixture was stirred at 22 °C for 28–78 h. The enzyme was removed by filtration and the filtrate concentrated under reduced pressure. The residue was separated by flash chromatography on silica gel with nitromethane/ethyl acetate (2:1) into the diol **4** and the lactone *ent*-**5**. The crystalline lactones could be obtained

Table 4 Yields and analytical data of the enantiomerically enriched (5*S*,6*R*)-6-hydroxyalkan-5-olides (*ent*-**5a–p**) obtained by pancreatin-catalyzed lactonization of *rac*-**4a–p**

ent-**5**/ **5**	R	Reaction time (h)	Yield of *ent*-**5**/**5** (%)	e.e. of *ent*-**5** (%)	Enantio meric ratio E	$[\alpha]_D^{20}$	c a)	*m.p.* (°C)	HPLC eluent system b)	R_t of **5** (min)	R_t of *ent*-**5** (min)
a	CH_3CH_2	53	33	60	5	5.8	1.0	–	A	7.5	10.5
b	$CH_3(CH_2)_2$	34	20	64	6	9.7	0.7	–	B	7.9	10.4
c	$CH_3(CH_2)_3$	48	28	70	7	9.7	0.9	–	B	6.7	8.1
d	$CH_3(CH_2)_4$	40	32	74	9	16.0	2.0	–	B	5.8	6.7
e	$CH_3(CH_2)_5$	45	27	80	12	9.9	1.0	–	B	5.3	6.7
f	$CH_3(CH_2)_7$	35	32	77	11	11.7	1.0	59–60 c)	B	5.8	7.2
g	$CH_3(CH_2)_8$	55	34	75	10	11.7	1.0	66–68 c)	A	7.3	9.3
h	$CH_3(CH_2)_9$	78	30	77	12	11.9	0.7	65–67 c)	B	4.5	5.2
i	$CH_3(CH_2)_{10}$	53	25	89	23	14.3	1.0	76–77 c)	C	4.7	5.3
j	$CH_3(CH_2)_{12}$	60	28	78	11	9.1	1.0	80–81 c)	C	4.3	4.8
k	$(CH_3)_2CH$	48	28	61	5	–3.4	1.0	–	B	7.6	11.3
l	$(CH_3)_3C$	28	36	51	4	–8.8	1.0	–	B	6.4	8.4
m	$(CH_3)_2CHCH_2$	48	26	81	13	17.5	1.0	–	B	5.7	6.7
n	$(CH_3)_3CCH_2$	48	34	88	25	11.2	1.0	–	A	8.0	9.8
o	$(CH_3CH_2)_2CH$	48	43	63	7	–	–	–	B	6.4	9.1
p	*c*-C_6H_{11}	40	29	69	7	–	–	–	B	6.1	9.1

a) g/100 ml in $CHCl_3$. b) HPLC was performed on Chiralcel AS. Eluent system A: hexane/isopropanol (9:1); B: hexane/isopropanol (8:2); C: heptane/ethanol (9:1). c) Enantiomerically pure compounds obtained by recrystallization.

Table 5 Yields and analytical data of the enantiomerically enriched (5*R*,6*S*)-6-acetoxyalkan-5-olides (**6a–p**) obtained by SP 526-catalyzed acetylation of *rac*-**5a–p** with vinyl acetate

6/ *ent*-**6**	React. time (h)	Yield of **6**/*ent*-**6** (%)	*e.e.* of **6** (%)	*E*	$[\alpha]_D^{20}$	c a)
a	10	41	91	40	-50.9	1.0
b	20	48	67	10	-29.6	2.0
c	14	39	89	31	-45.9	0.9
d	8	38	93	58	-45.1	1.1
e	12	48	79	19	-35.4	2.0
f	20	41	87	27	-33.8	2.0
g	20	33	92	37	- 6.0	1.0
h	20	25	95	53	-35.0	0.7
i	20	33	90	29	-11.8	0.9
j	20	16	95	46	-11.5	0.9
k	20	15	99	>100	- 4.0	1.0
l	35	–	–	–	–	–
m	35	23	98	>100	-68.9	0.9
n	35	–	–	–	–	–
o	35	–	–	–	–	–
p	41	22	99	>100	-11.2	1.0

a) g/100 ml in $CHCl_3$.

as enantiomerically pure compounds by recrystallization from hexane/diethyl ether (1:1). The enantiomeric excess was determined by HPLC. The results are gathered inTable 4.

(5*R**,6*S**)-6-Acetoxyalkan-5-olides (*rac*-6a–p) (General Procedure)

Acetic anhydride (0.58 g, 5.70 mmol) was added to the solution of a lactone *rac*-**5** (0.57 mmol) in pyridine (10 ml). The mixture was heated to reflux for 2.5 h, cooled to ambient temperature, and poured onto ice (10 g) to afford the corresponding lactone *rac*-**6** as a colorless oil in a yield of 40–96%. Elemental analyses and NMR data are given in Table 5.

(5*R*,6*S*)-6-Acetoxyalkan-5-olides (6a–p) by Lipase-Catalyzed Acetylation of the Hydroxy Lactones *rac*-5a–p. (General Procedure)

Lipase SP 526 (100 mg/0.37 mmol *rac*-**5**) was added to the solution of a hydroxy lactone *rac*-**5** (100 mg) in benzene (12 ml). The mixture was stirred with vinyl acetate (tenfold equimolar amount) at 55 °C for 8–41 h. The reaction was stopped by removal of the enzyme. The filtrate was concentrated under reduced pressure and the residue separated by flash chromatography on silica gel with nitromethane/ethyl acetate (2:1) as eluent. The enantiomeric excesses were determined by HPLC. Yields and analytical data are summarized in Table 6.

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Table 6 HPLC data of the enantiomerically enriched (5*R*,6*S*)-6-acetoxyalkan-5-olides (**6a–p**) and (*ent*-**6a–p**) as well as elemental analyses and ^{13}C NMR of *rac*-**6a–p**

6/ *ent-***6**	HPLC eluent system [a]	R_t of **6** (min)	R_t of *ent*-**6** (min)	Formula Mol. mass	%C calcd. found	%H calcd. found	^{13}C NMR δ (ppm)
a	A	13.8	11.9	$C_{10}H_{16}O_4$ 200.2	59.98 60.07	8.05 8.16	9.58, 18.22, 20.98, 22.66, 23.50, 29.61, 75.37, 80.14, 170.5, 170.8
b	B	14.0	11.8	$C_{11}H_{18}O_4$ 214.3	61.66 61.26	8.47 8.25	13.85, 18.25, 18.38, 21.02, 23.48, 29.63, 31.63, 74.00, 80.56, 170.5, 170.9
c	B	10.6	9.9	$C_{12}H_{20}O_4$ 228.3	63.13 63.20	8.83 8.82	13.87, 18.19, 20.98, 22.43, 23.43, 27.34, 29.17, 29.56, 74.19, 80.45, 170.4, 170.8
d	D	7.7	7.1	$C_{13}H_{22}O_4$ 242.3	64.44 63.55	9.15 9.27	13.97, 18.26, 21.04, 22.46, 23.51, 24.91, 29.47, 29.63, 31.55, 74.28, 80.5, 170.4, 170.8
e	B [b])	17.2	26.6	$C_{14}H_{24}O_4$ 256.3	65.60 64.86	9.44 9.54	14.00, 18.23, 21.00, 22.51, 23.46, 25.18, 29.0, 29.5, 29.6, 31.6, 74.3, 80.5, 170.4, 170.8
f	B	8.6	7.9	$C_{16}H_{28}O_4$ 284.4	67.57 67.64	9.92 10.03	14.08, 18.24, 21.01, 22.62, 23.47, 25.24, 29.8–29.6 (5 signals), 31.8, 743, 80.5, 170.4, 170.8
g	A	10.4	9.5	$C_{17}H_{30}O_4$ 298.4	68.42 68.07	10.13 10.17	14.09, 18.24, 21.07, 22.65, 23.48, 25.2, 29.3–29.6 (6 signals), 31.8, 74.2, 80.5, 170.5, 170.9
h	A	11.1	9.7	$C_{18}H_{32}O_4$ 312.5	69.19 69.43	10.32 10.42	14.09, 18.24, 21.02, 22.65, 23.48, 25.2, 29.3–29.6 (7 signals), 31.9, 74.3, 80.5, 170.5, 170.8
i	C	5.9	5.4	$C_{19}H_{34}O_4$ 326.5	69.90 69.78	10.50 10.55	14.10, 18.24, 21.02, 22.67, 23.50, 25.3, 29.3–29.6 (8 signals), 31.9, 74.3, 80.5, 170.5, 170.9
j	C	5.4	5.1	$C_{21}H_{38}O_4$ 354.5	71.14 70.78	10.80 10.72	14.14, 18.26, 21.06, 22.70, 23.50, 25.3, 29.4–29.7 (10 signals), 31.9, 74.3, 80.5, 170.5, 170.9
k	B	13.5	9.7	$C_{11}H_{18}O_4$ 214.3	61.66 61.41	8.47 8.28	16.51, 18.19, 19.25, 20.82, 23.75, 28.10, 29.73, 77.41, 78.52, 170.3, 170.7
l		–	–	$C_{12}H_{20}O_4$ 228.3	63.13 63.40	8.83 8.80	18.19, 20.75, 24.39, 26.44, 29.51, 34.45, 79.15, 79.88, 170.0, 170.5
m	E [b])	9.8	12.5	$C_{12}H_{20}O_4$ 228.3	63.13 62.87	8.83 8.71	18.27, 21.06, 21.69, 23.37, 23.48, 24.41, 29.60, 38.24, 72.63, 81.03, 170.5, 170.9
n		–	–	$C_{13}H_{22}O_4$ 242.3	64.44 64.17	9.15 9.29	18.23, 21.33, 33.55, 29.53-29.85 (5 signals), 42.07, 72.10, 81.74, 170.6, 170.8
o		–	–	$C_{13}H_{22}O_4$ 242.3	64.44 64.22	9.15 9.42	11.18, 11.56, 18.20, 20.87, 22.16, 24.01, 29.70, 40.72, 74.84, 78.37, 170.2, 170.7
p	B	14.8	8.5	$C_{14}H_{22}O_4$ 254.3	66.12 65.83	8.72 8.62	18.22, 20.84, 23.55, 25.82, 26.04. 26.21, 27.01, 29.74, 37.82, 76.80, 78.1, 170.2, 170.7

[a]) HPLC was performed on Chiralcel AS. Eluent system A: hexane/isopropanol (9:1); B: hexane/isopropanol (8:2); C: heptane/ethanol (9:1); D: heptane/ethanol (8:2); E: hexane/isopropanol (5:5). [b]) HPLC was performed on Chiralcel OF. On this column we found for *rac*-**6h**: R_t = 6.3 min (**6h**) and 10.0 min (*ent*-**6h**).

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