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Lipase-Catalyzed Resolution of Racemic 2-Alkyl Substituted 1-Alkanols[1]

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Abstract: (*R*)-2-alkyl-1-alkanols (*R*)-**1** with high optical purities were obtained by lipase-catalyzed esterification of the racemic substrates (*R,S*)-**1** with vinyl acetate in dichloromethane. The alcohols (*R*)-**1** were oxidized without racemization to the corresponding carboxylic acids (*R*)-**4**. The enriched (*S*)-acetates (*S*)-**3** either were saponified to the alcohols (*S*)-**1** which are substrates for a second lipase-catalyzed transesterification to give (*S*)-**1** in high optical purity or were racemized and applied once again in the kinetic resolution to prepare (*R*)-**1**.

Introduction

Optically active 2-alkyl carboxylic acids as well as the corresponding primary alcohols are important intermediates in the synthesis of biologically active compounds and for the preparation of liquid crystals. (*S*)-2-Methyl-1-hexanol and (*S*)-2-methyl-1-decanol, for example, have been used as chiral building blocks for the synthesis of the pheromones of the european pine saw fly[3] and of the peach leaf miner moth.[4] (*S*)-2-Methyl pentanoic acid was used for the synthesis of (*S*)-4-methyl-3-heptanone, the pheromone of the leaf-cutting ant Atta texana.[5a,b] (*S*)-(+)-Manicone and (*S*)-(-)-normanicone, the mandibular gland constituents of myrmicine ants, were prepared starting from (*S*)-2-methyl-1-butanol.[5c]
For the preparation of chiral ferroelectric liquid crystals, 2-methyl-1-carboxylic acids and the corresponding primary alcohols were used in recent times.[6]

The first preparations of optically active 2-methyl carboxylic acids were accomplished by classical racemate separations with quinine,[7] with D- and L-valine,[8] with (*R*)- and (*S*)-α-phenylethylamine[4b,9] and with L-phenylglycinol.[10] The optical yields in stereoselective syntheses, using chiral auxiliaries, were generally not satisfying for the preparation of optically active 2-methyl carboxylic acids.[11] Starting from chiral 1,2-epoxides, the reaction with trimethylaluminium leads to optically active 2-methyl-1-alkanols with inversion of configuration and optical yields of 83-89% ee.[12]

In the last decade, increasing attention has been given to the use of enzymes for the preparation of chiral compounds. For the kinetic resolution of racemic secondary alcohols many examples are described in the literature.[13] However, this is not the case for primary alcohols. Whereas 3-substituted primary alcohols were easily transesterified with methyl propionate in presence of porcine pancreatic lipase (PPL) with high optical yields, the comparable 2-substituted primary alcohols in contrary react very slowly and only with poor optical yields.[14]

During the time this work was in progress, the lipase-catalyzed kinetic resolution of 2-methyl-4-hexen-1-ol and other 2-methyl-1-alkanols through transesterification with vinyl acetate was described by E. Santaniello et al.[15] Also the kinetic resolution of 2-methyl-2-phenyl-1-alcohols was successfully accomplished by lipase-catalyzed transesterifications.[16]

The kinetic resolution of 2-alkyl substituted carboxylic acids with lipases so far was not yet successfully achieved. This is true for the lipase-catalyzed hydrolysis of 2-methyl carboxylates[10,15a] as well as for the enantioselective esterification of racemic carboxylic acids[17a] or the enantioselective acidolysis of racemic 2-methyl alkanoates with carboxylic acids.[17b]

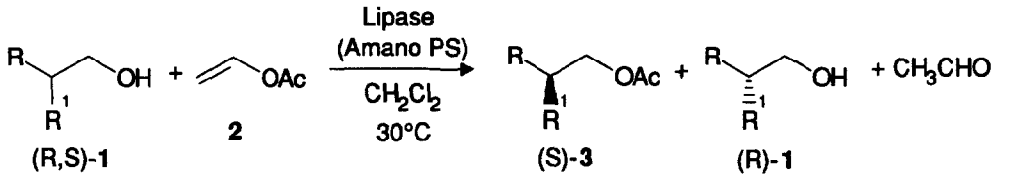
The present publication describes the preparation of optically active (*R*)- and (*S*)-2-alkyl-1-alkanols (*R*)-**1** and (*S*)-**1**, respectively, by lipase-catalyzed transesterification with vinyl acetate, the oxidation of the alcohols (*R*)-**1** to the corresponding carboxylic acids (*R*)-**4** and the racemization of the optically enriched alcohols (*S*)-**1**.

Preparation of Optically Pure (*R*)-2-Alkyl-1-alkanols (*R*)-1 and (*R*)-2-Alkyl Carboxylic Acids (*R*)-4

First we have investigated the lipase-catalyzed hydrolysis of 2-ethyl hexyl esters of various carboxylic acids. Although we tried eight commercially available lipases, the conversion rates in all cases were rather low and the optical yields of the 2-ethyl-1-hexanol isolated very poor (0 to 38% ee). The highest enantioselectivities were obtained with lipases from Pseudomonas species (PFL from Fluka, Amano P and Amano PS from Amano). The variation of the acyl moiety in the ester - acetate, butyrate, isobutyrate, capronate and laureate - gave no better conversion rates nor higher optical purities of the obtained 2-ethyl-1-hexanol.

Since the lipase-catalyzed hydrolysis of racemic esters of 2-ethyl-1-hexanol was not satisfying for the preparation of the optically pure alcohol, we have investigated the lipase-catalyzed transesterification of racemic 2-alkyl-1-alkanols. From the esters used for transesterifications - trifluoroethyl butyrate, trichloroethyl butyrate, vinyl butyrate, trifluoroethyl acetate and vinyl acetate - the vinyl acetate in dichloromethane as solvent gave the highest optical yield and comparable rates of conversion like the other esters investigated. Therefore we concentrated our efforts in the preparation of optically active 2-alkyl-1-alkanols to the transesterification of racemic 2-alkyl-1-alkanols with vinyl acetate. As solvents for the lipase-catalyzed transesterifications besides the dichloromethane we have examined *n*-hexane, diisopropyl ether, cyclohexane, benzene and vinyl acetate. From all applied solvents the highest enantioselectivity with $E^{18} = 6.7$ was obtained with dichloromethane in comparison to E = 4.5 for hexane, E = 2.8 for diisopropyl ether, E = 2.2 for cyclohexane, E = 1.5 for benzene and E = 1.7 for vinyl acetate.

The lipase-catalyzed resolution of the racemic 2-alkyl substituted primary alcohols **1** with vinyl acetate **2** in dichloromethane yielded the (*R*)-alcohols (*R*)-**1** with optical purities between 96-99% ee by driving the extent of conversion between 60 to 80% applying the equations for the enantioselectivity of enzymes for two competing enantiomers[13a,18] (Table 1).



	a	b	c	d	e	f	g	h
R:	C_3H_7	C_4H_9	C_4H_9	C_6H_{13}		C_8H_{17}		
R^1:	CH_3	CH_3	C_2H_5	CH_3	CH_3	CH_3	CH_3	CH_3

Table 1. Lipase-Catalyzed Esterification of Racemic 2-Alkyl-1-alkanols (*R,S*)-**1** (0.5 M solution) with Vinyl Acetate **2** (2.0 M solution) in Dichloromethane at 30°C

substrates (*R,S*)-**1**	reaction time [h]	conversion [%][a]		(*R*)-**1** yield [%]	ee [%][b]	E[c]		(*S*)-**3** yield [%]	ee [%][d]
a	6	80.2	**a**	16.8	98	5.9	**a**	72.4	28.7
b	7.25	74.6	**b**	22.1	99	8.7	**b**	70.3	33.7
c	12	74.8	**c**	22.9	97.5	7.3	**c**	69.1	33.7
d	5.5	78.0	**d**	20.5	96.2	5.7	**d**	73.9	27.4
e	5	67.9	**e**	28.9	97.9	11.1	**e**	64.3	48.6
f	5.75	70.0	**f**	26.0	98.1	9.9	**f**	67.7	42.4
g	5	63.2	**g**	32.8	96.1	13.0	**g**	60.6	57.1
h	4.75	69.0	**h**	24.8	97.3	9.7	**h**	62.2	48.7

[a] Determined by gas chromatography. - [b] Determined by capillary gas chromatography after Jones oxidation to the corresponding acids (R)-4. - [c] See Ref.[13a,18] - [d] See b) after alkaline hydrolysis and oxidation to (S)-4.

The enantioselectivity E calculated[18] with values in a range of E = 5 to 13 depends on the length of the aliphatic chain R in the substrates. E raises with increasing length of R in the series of the 2-methyl substituted alkanols **1a,b,f**. 2-Methyl-1-octanol **1d**, however, deviates with an enantioselectivity of E = 5.7. A double bond in the residue R of the substrate clearly increases the enantioselectivity compared with the corresponding saturated alcohol (**1a,h** and **1b,g**). A greater enantioselectivity is also achieved with the branched rest R (**1e**) in comparison to the unbranched compound **1b**.

The ee values of the obtained alcohols (*R*)-**1** were determined by gas chromatography on β-cyclodextrin phases[19] after analytical Jones oxidation according to Sonnet[4c,20] to the corresponding (*R*)-carboxylic acids (*R*)-**4**. This oxidation proceeds without racemization, which is also confirmed by our own experiments.[2]

In collaboration with M. Reuss and M. Indlekofer,[21] for the lipase-catalyzed optical resolution of racemic 2-methyl-1-pentanol (*R,S*)-**1a** by transesterification with vinyl acetate, a mechanistic model has been developed for the double-substrate reaction sequence treating both enantiomers as competing substrates. The model is based upon a ping-pong mechanism with alternative substrates involving an acyl-enzyme intermediate. The model successfully predicts the evolution of the enantiomeric excess of substrate (ee_R) and the degree of conversion with time for batch experiments with various initial concentrations of vinyl acetate and (*R,S*)-**1a** and is in excellent agreement with the definition of the enantioselectivity E proposed by C. J. Sih.[13a,18]

For the preparation of optically active 2-alkyl carboxylic acids **4** in larger amounts the Jones oxidation is unsuitable due to various side reactions.[22] According to the oxidation of (*S*)-alcohols described in the literature[12] the aliphatic (*R*)-2-alkyl substituted alkanols (*R*)-**1a-d,f** were oxidized to the corresponding (*R*)-2-alkyl carboxylic acids **4a-d,f** in 3 N sulfuric acid with an excess of $KMnO_4$ at 10-15°C without racemization. The crude products were purified by column chromatography to give the optically pure carboxylic acids (*R*)-**4** in chemical yields comparable to those in Ref.[12] (Table 2).

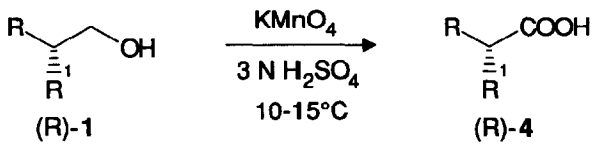


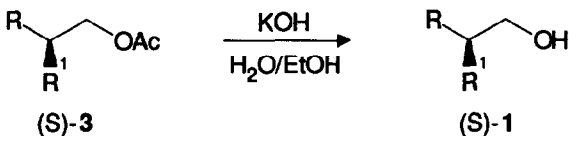
Table 2. Preparative Oxidations of (*R*)-**1a-d,f** with $KMnO_4$ in 3 N Sulfuric Acid at 10-15°C to the Corresponding Acids (*R*)-**4a-d,f**

(*R*)-**1**	ee [%][a]	H_2SO_4 [ml]	(*R*)-**4**	yield [%]	ee [%][a]	$[\alpha]_D^{20}$ (c, $CHCl_3$)
a	94.6	50	**a**	55.6	94.8	-16.55 (4.20)[b]
b	96.7	50	**b**	69.1	96.4	-18.05 (5.12)[b]
c	93.5	50	**c**	68.8	92.4	-7.43 (3.62)[c]
d	94.1	40	**d**	73.3	93.7	-15.60 (4.14)[d]
f	97.5	25	**f**	68.4	96.5	-14.91 (3.22)[e]

[a] Determined by capillary gas chromatography on β-cyclodextrin phases. - [b] Ref.[7a,11a] - [c] Ref.[7c,23] - [d] Ref.[9b] - [e] Ref.[11c]

Preparation of (*S*)-2-Alkyl-1-alkanols (*S*)-1 with High Optical Purity

The acetates (*S*)-**3**, isolated in the enzyme-catalyzed esterification, were saponified with potassium hydroxide in aqueous ethanol to the corresponding (*S*)-alcohols **1** as shown in Table 3 for the compounds (*S*)-**3a-d, f.**



(S)-3 (S)-1

Table 3. Preparative Alkaline Hydrolysis of (*S*)-**3a-d,f** with Potassium Hydroxide in Aqueous Ethanol at Room Temperature

substrates (*S*)-3	reaction time [h]	products (*S*)-1	yield [%]	ee[a] [%]	$[\alpha]_D^{20}$ (c, solvent)
a	24	**a**	84.9	26.9	-3.46 (neat)
b	24	**b**	88.9	44.4	-5.60 (15.9, diethyl ether)
c	24	**c**	92.5	45.8	+1.69 (neat)
d	24	**d**	93.4	38.4	-4.79 (12, CH_2Cl_2)
f	22	**f**	91.0	44.7	-4.66 (16, CH_2Cl_2)

[a] Determined after Jones oxidation to the acids (*S*)-**4** by capillary gas chromatography.

The optically active (*R*)-alcohols **1** could be obtained by lipase-catalyzed esterification with conversion rates between 60-80% as shown above. Since the lipase favors the (*S*)-alcohols as substrates in these reactions, the (*S*)-acetates **3** are formed preferably in chemical yields up to 60-70%. But according to the concept for competing enantiomers,[18] with an enantioselectivity of E = 10 only optical purities of approximately 80% ee for (*S*)-**3** can be achieved even by driving the conversion rate below 10%.

The (*S*)-acetates or (*S*)-alcohols therefore can only be obtained in a higher optical purity by a second lipase-catalyzed kinetic resolution with the enriched (*S*)-alcohols (*S*)-**1**. We were able to prepare the (*S*)-2-methyl-1-alkanols (*S*)-**1a,b,f**, which are interesting intermediates in the synthesis of pheromones, by a twofold enzyme-catalyzed esterification with vinyl acetate **2** in optical purities of 91-94% ee and total yields of 13-23% referred to the starting racemic alcohols (Table 4).

In the first step, the (*S*)-acetates **3** were enriched to an optical yield of 63-67% ee by lipase-catalyzed resolution of the racemic alcohols (*R,S*)-**1** with a conversion rate between 40-50%. After purification by column chromatography, distillation and alkaline hydrolysis these enriched (*S*)-alcohols were converted in a second enzyme-catalyzed esterification with a degree of conversion between 50-60% to give (*S*)-**3** with an optical yield of 91-94% ee, leaving the unreacted (*S*)-alcohols with ee values of 17-41%. As shown in Table 4, the experimentally obtained enantiomeric excesses of (*S*)-**1f** correlate very well with the expected theoretical data.[18a]

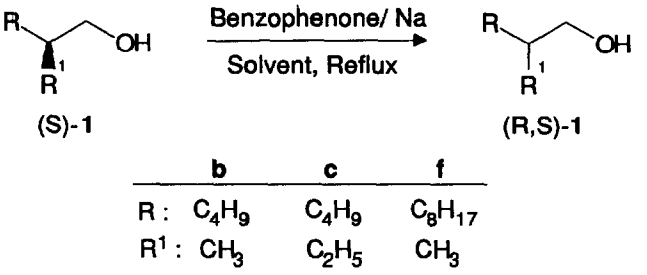
Table 4. Twofold Lipase-Catalyzed Esterification of Racemic Alcohols (*R,S*)-**1a,b,f** with Vinyl Acetate **2** to (*S*)-2-Alkyl Alkanols (*S*)-**1a,b,f** in Dichloromethane at 30°C

substrate [ee%]	conv. [%]	(*S*)-**3**				(*R*)-**1** [(*S*)-**1**]				(*S*)-**1**
			yield [%]	ee [%][a]	E		yield [%]	ee [%][b]	E	yield [%][c]
(*R,S*)-**1a**	40.6	**a**	35.3	66.7	7.7	**a**	53.7	42.8	6.6	-
(*S*)-**1a** [66.7]	49.2		44.4	90.6	-		-	[40.8]	-	12.7
(*R,S*)-**1b**	49.7	**b**	47.1	63.1	8.2	**b**	46.8	62.2	8.1	-
(*S*)-**1b** [63.1]	51.5		46.3	93.6	-		-	[34.5]	-	16.3
(*R,S*)-**1f**	49.7	**f**	45.8	65.9[d]	9.4	**f**	48.5	66.9	10.2	-
(*S*)-**1f** [65.9]	62.0		58.3	92.1[d]	-		-	[17.3]	-	23.0

[a] After saponification and Jones oxidation to (*S*)-**4**. - [b] After Jones oxidation to (*R*)-**4**. - [c] Total yield over the sequence (*R,S*)-**1**→(*S*)-**3**→(*S*)-**1**→(*S*)-**3**→(*S*)-**1**. - [d] Theoretical data[18a]: 67% ee and 93 - 94% ee.

Racemization of the Enriched (*R*)- and (*S*)-2-Alkyl-1-Alkanols

In the lipase-catalyzed resolution of the racemic alcohols (*R,S*)-**1** the enriched (*S*)-acetates **3** were formed in relatively high yields besides the (*R*)-2-alkyl-1-alkanols. On the other side, the enriched (*R*)-alcohols were obtained as by-products in the preparation of the optically pure (*S*)-alcohols. If only one enantiomer is needed, the unwanted enantiomer has to be isomerized, so that it could be applied again in the enzyme-catalyzed resolution after racemization. The racemization of (*S*)-2-methyl-1-butanol with catalytic amounts of sodium and benzophenone without a solvent has been described in the literature.[24] Since the rate of racemization strongly depends on the temperature, we have modified the method by using various solvents under reflux conditions.



The (*S*)-alkyl alcohols **1b,c** and **f** were racemized in toluene within 5 to 6 hours to give the racemic substrates in approximately 90% yield. However, in heptane, where the reaction temperature is only 12°C lower than in toluene, the reaction time is much longer and the yield is lower (Table 5).

Table 5. Preparative Racemization of (*S*)-**1b,c,f** in Various Solvents in the Presence of Sodium and Benzophenone (each 5 mol%)

(*S*)-**1**	ee [%][a)]	solvent	time [h]	temp. [°C]	(*R,S*)-**1**	yield [%]	ee [%][a)]
b	44.4	toluene	6	110	**b**	86.4	0
c	45.8	toluene	6	110	**c**	89.0	0
c	45.8	heptane	32	98	**c**	82.1	0
f	44.7	toluene	5	110	**f**	92.2	0

[a)] Determined by capillary gas chromatography on β-cyclodextrin phases.

Experimental

Materials and Methods: The racemic alcohols (*R,S*)-**1a,c** were purchased from Aldrich; (*R,S*)-**1b,d-f** were prepared according to Ref.,[25,26e] (*R,S*)-**1h** to Ref.,[26d] and (*R,S*)-**1g** to Ref.[10] Lipase from *Pseudomonas species* (Amano PS, 30 Units/mg). All solvents were purified and dried as described in the literature. Optical rotations were performed in a Perkin-Elmer polarimeter 241 LC. Gas chromatography for determination of conversions: Hewlett Packard 5700 A with FID, Spectra Physics minigrator, 30 ml/min nitrogen, glass columns 2.3 m x 2 mm, phases OV 17, 101, 225. Capillary GC for determination of enantiomeric excess: a) Carlo Erba Fractovap 4160 with FID, Spectra Physics minigrator, 0.4-0.5 bar hydrogen, columns 20 and 50 m, phase OV 1701 with 10% permethylated β-cyclodextrin. b) Carlo Erba MRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.4-0.5 bar hydrogen, columns 20 and 50 m, phase OV 1701 with 10% permethylated β-cyclodextrin.

*Lipase-catalyzed esterification of 2-alkyl-1-alkanols (R,S)-***1**: 300 Units/mmol **1** of the lipase is given at 30°C with stirring to a solution of the racemic alcohol (*R,S*)-**1** (50.0 mmol) and vinyl acetate (0.20 mol) in absolute dichloromethane (total volume 100 ml). The conversion was followed by gas chromatography. In addition, the enantiomeric excess of the substrate **1** was determined after Jones oxidation of a sample of the reaction mixture containing approximately 10 µl **1**. After the given time (Table 1) the enzyme is filtered off and the filtrate is concentrated and chromatographed on silica gel with petroleum ether/ethyl acetate (9:1) and after elution of (*S*)-**3** with ethyl acetate. The solvents are removed and the residue is distilled through a Vigreux column in vacuo to give the optically active alcohols (*R*)-**1**.[3,4a,7b,c,10,15a,26]

(*R,S*)-**1**		(*R*)-**1**			(*S*)-**3**		
	g		yield g	$[\alpha]_D^{20}$ (c, solvent)		yield g	$[\alpha]_D^{20}$ (c, CH_2Cl_2)
a	5.11	**a**	0.86	+12.10 (neat)[7b,26a]	**a**	5.22	-0.085 (neat)
b	5.81	**b**	1.28	+14.22 (6.96, ether)[4a]	**b**	5.56	-0.23 (23.2)
c	6.51	**c**	1.49	-3.70 (neat)[7c,26b]	**c**	5.95	+1.37 (14.5)
d	7.21	**d**	1.48	+11.17 (4.7,CH_2Cl_2)	**d**	6.89	-0.33 (21.0)
e	6.51	**e**	1.88	+12.39 (2.30,$CHCl_3$)[26c]	**e**	5.54	-0.65 (19.5)
f	8.62	**f**	2.24	+9.86 (4.29, CH_2Cl_2)[3a]	**f**	7.26	-0.40 (20.6)
g	5.71	**g**	1.87	+2.67 (6.32, CH_2Cl_2)[15a]	**g**	4.73	+2.32 (22.8)
h	5.01	**h**	1.24	+2.64 (neat)[26d]	**h**	4.42	+1.05 (16.8)

Elemental analyses data of compounds (*R*)-**1** and (*S*)-**3**

	(*R*)-**1** emp. formula (mol. weight)	calcd. found	C	H		(*S*)-**3** emp. formula (mol. weight)	C	H
a	$C_6H_{14}O$		70.53	13.81	**a**	$C_8H_{16}O_2$	66.63	11.18
	(102.2)		70.51	13.56		(144.2)	66.90	10.95
b	$C_7H_{16}O$		72.35	13.88	**b**	$C_9H_{18}O_2$	68.31	11.47
	(116.2)		72.30	13.93		(158.2)	68.52	11.49
c	$C_8H_{18}O$		73.78	13.93	**c**	$C_{10}H_{20}O_2$	69.72	11.70
	(130.2)		74.02	13.78		(172.3)	69.61	11.52
d	$C_9H_{20}O$		74.93	13.97	**d**	$C_{11}H_{22}O_2$	70.92	11.90
	(144.3)		74.93	14.09		(186.3)	70.68	11.82
e	$C_8H_{18}O$		73.78	13.93	**e**	$C_{10}H_{20}O_2$	69.72	11.70
	(130.2)		73.61	13.72		(172.3)	69.76	11.63
f	$C_{11}H_{24}O$		76.68	14.04	**f**	$C_{13}H_{26}O_2$	72.85	12.23
	(172.3)		76.73	13.90		(214.3)	72.30	11.89
g	$C_7H_{14}O$		73.63	12.36	**g**	$C_9H_{16}O_2$	69.19	10.32
	(114.2)		73.41	12.35		(156.2)	69.39	10.14
h	$C_6H_{12}O$		71.95	12.08	**h**	$C_8H_{14}O_2$	67.57	9.92
	(100.2)		71.86	12.07		(142.2)	67.88	10.07

Preparative oxidation of (R)-1 to the carboxylic acids (R)-4: To the cooled solution of (*R*)-**1** in 3 N sulfuric acid (Table 2) the 1.6 fold amount of $KMnO_4$ is added in portions so that the temperature does not exceed 15°C. The reaction mixture is warmed up to room temperature and stirred for 4 h. The manganese dioxide formed is dissolved with $NaHSO_3$ and the mixture is extracted three times with 100 ml diethyl ether. The combined ether phases are extracted with 10% sodium hydroxide solution. With cooling the extract is acidified with 10% HCl and extracted three times with 100 ml diethyl ether. The combined extracts are dried with $MgSO_4$, concentrated and the residue is chromatographed on silica gel with petroleum ether/ethyl acetate (1:1) to give the (*R*)-acids **4a-f**.[7a,c,9b,11a,c]

(*R*)-**1**	g (mmol)	$KMnO_4$ g (mmol)	(*R*)-**4**	yield g	elemental analyses emp. formula (mol. weight)	calcd. found	C	H
a	1.02 (10.0)	2.53 (16.0)	**a**	0.65	$C_6H_{12}O_2$		62.04	10.41
					(116.2)		61.84	10.37
b	1.16 (10.0)	2.53 (16.0)	**b**	0.90	$C_7H_{14}O_2$		64.58	10.84
					(130.2)		64.42	10.94
c	1.30 (10.0)	2.53 (16.0)	**c**	0.99	$C_8H_{16}O_2$		66.63	11.18
					(144.2)		66.41	11.20
d	1.15 (8.0)	2.02 (12.8)	**d**	0.93	$C_9H_{18}O_2$		68.31	11.47
					(158.2)		68.49	11.38
f	0.86 (5.0)	1.26 (8.0)	**f**	0.64	$C_{11}H_{22}O_2$		70.92	11.90
					(186.3)		71.13	11.98

Saponification of the acetates (S)-3 to the alcohols (S)-1: (*S*)-**3** is stirred in aqueous ethanol for 24 h at room temperature with the 1.5 fold amount of potassium hydroxide. The solvent is removed and the residue is diluted with 50 - 100 ml water and extracted twice with 250 ml diethyl ether. The extracts are washed with 20 - 50 ml water, dried with $MgSO_4$, concentrated and the product is distilled through a Vigreux column.

(*S*)-3	g (mmol)	KOH g (mmol)	ethanol/H_2O (ml)	(*S*)-1	yield g
a	14.42 (100.0)	8.41 (150.0)	150/20	**a**	8.68
b	15.82 (100.0)	8.41 (150.0)	150/20	**b**	10.34
c	17.22 (100.0)	8.41 (150.0)	150/20	**c**	12.05
d	9.31 (50.0)	4.21 (75.0)	75/20	**d**	6.74
f	5.35 (25.0)	2.10 (37.5)	50/10	**f**	3.92

*Preparation of (S)-alcohols (S)-***1**[3,4a,26a] *in high optical purity by twofold resolution*: The lipase-catalyzed esterification, work-up and saponification were carried out as described above. The conversion was followed by ^1H NMR spectroscopy.

substrate g (mol)	2 g (mol)	lipase [U/mmol **1**]	CH_2Cl_2 ml	time [h]	(*S*)-3 yield g	$[\alpha]_D^{20}$ (c,CH_2Cl_2)	(*S*)-1[a] yield g (%)	(*R*)-1 yield g	(*S*)-1 ee [%]
(*R,S*)-**1a**							32.4		
102.2 (1.0)	172.2 (2.0)	75	1000	7.5	50.9	-	(89.8)	54.9	-
(*S*)-**1a**						-0.66	12.3		not isol.
30.6 (0.3)	51.6 (0.6)	150	300	5	19.2	(10.1)	(90.3)	-	40.8
(*R,S*)-**1b**							4.7		
11.3 (0.1)	34.4 (0.4)	300	200	2.25	7.4	-	(87.5)	5.44	-
(*S*)-**1b**						-1.25	1.1		not isol.
2.9 (0.025)	8.6 (0.1)	150	50	3.25	1.8	(3.20)	(85.6)	-	34.5
(*R,S*)-**1f**							3.7		
8.6 (0.05)	17.2 (0.2)	300	100	2.5	4.9	-	(93.4)	4.2	-
(*S*)-**1f**						-1.55	0.8		not isol.
1.7 (0.01)	3.4 (0.04)	300	20	2.5	1.2	(3.35)	(89.4)	-	17.3

[a] By saponification of the isolated acetates (S)-3.

*Preparative racemization of (S)-***1**: (*S*)-**1** is given to a solution of sodium and benzophenone in toluene or heptane and then the reaction mixture is refluxed. After the given time (Table 5) 50 ml water are added and the mixture is extracted three times with 100 ml diethyl ether. The combined extracts are washed with 50 ml water and dried with $MgSO_4$. The solvents are removed and the racemic alcohol (*R,S*)-**1** is distilled through a Vigreux column in vacuo.

(*S*)-1	g (mmol)	sodium mg (mol%)	benzophenone mg (mol%)	solvents (ml)	(*R,S*)-1	yield g
b	2.32 (20.0)	23.0 (5.0)	182.2 (5.0)	toluene (40)	**b**	2.01
c	2.60 (20.0)	23.0 (5.0)	182.2 (5.0)	toluene (40)	**c**	2.32
c	1.30 (10.0)	11.5 (5.0)	91.1 (5.0)	heptane (20)	**c**	1.07
f	1.72 (10.0)	11.5 (5.0)	91.1 (5.0)	toluene (20)	**f**	1.59

Analytical determination of the enantiomeric excess (ee): The Jones reagent is prepared from 10.0 g CrO_3 and 10 ml conc. sulfuric acid, refilled with water to 40 ml total volume (2.5 M CrO_3).

a) 10 µl of the alcohol **1** (either the pure product or in the reaction mixture) are dissolved in 2 ml acetone and treated with cooling with 60 µl Jones reagent. After 10 min the reaction mixture is diluted with 5 ml water and extracted with 5 ml diethyl ether. The ether solution is extracted with 2 ml 10% sodium hydroxide solution. The aqueous phase is acidified with cooling with 10% HCl and then extracted with 5 ml diethyl ether. The extract is filtered through a small silica gel column and the enantiomeric excess of **4** is determined from the filtrate by capillary gas chromatography on OV 1701 phases with 10% permethylated β-cyclodextrin (column 50 m).

b) 100 µl (*S*)-**3** in 2 ml of a 2 M solution of KOH in 90% ethanol are allowed to stand at room temperature for 18 h. Then the mixture is diluted with 5 ml water, extracted with 20 ml diethyl ether and the organic phase is concentrated. The crude (*S*)-alcohols are treated as described in a).

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