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Optimized double kinetic resolution for the preparation of (*S*)-solketal

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Abstract: The lipase AK (lipase from *Pseudomonas sp.*)-catalysed alcoholysis of racemic solketal (2,2-dimethyl-1,3-dioxolane-4-methanol) esters and acylation of solketal in organic solvents proceeded with E=20–25. This enabled the preparation of the more reactive (*S*)-enantiomer with more than 30% total isolated yield (based on the racemate) and 95% *ee* by a double kinetic resolution strategy consisting of enzymatic acylation–chemical saponification–enzymatic acylation or enzymatic alcoholysis–enzymatic acylation sequences. Numerical calculations and theoretical plots for the optimal termination conversions for the 1st and 2nd resolution steps as well as for the final yields as the function of E is considered. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

In the enzymatic kinetic resolution of a racemic mixture, the faster reacting enantiomer prevails in the product fraction while the slower reacting enantiomer is enriched in the substrate fraction. Enantiomeric excess values for the substrate (ee_S) and product (ee_P) of an irreversible reaction can be quantitatively expressed by enantiomeric ratio $E = [\ln((1 - ee_S)/(1 + ee_S/ee_P))] / [\ln((1 + ee_S)/(1 + ee_S/ee_P))]$ at any conversion (c) which equals to $c = [(ee_S)/(ee_S + ee_P)]$.[1] The constant E is also the ratio of the specificity constants, and in the case of racemic substrates the ratio of initial rates of the faster to slower reacting enantiomer. Even with moderate E values ee_S=100% is achievable when the conversion approaches to 100%. For the product, the maximal enantiopurity is obtained at the opposite end of the conversion scale, the value of the highest ee_P being dictated by $(E - 1 + E \cdot ee_0 + ee_0) / (E + 1 + E \cdot ee_0 - ee_0)$, where ee_0=0 and ee_0>0 for racemic and nonracemic substrates, respectively.[2] Examination of the equation reveals that the maximal ee_P is higher for ee_0>0 than for ee_0=0. Accordingly, the faster reacting enantiomer with high enantiopurity can be obtained by subjecting the isolated enantiomerically enriched product of the first enzymatic resolution to the second. The benefits of the double kinetic resolution strategy as to ee_P and the overall yield of the product enantiomer were indisputably shown previously using enzymatic acetylation followed by enzymatic hydrolysis.[3]

Solketal, 2,2-dimethyl-1,3-dioxolane-4-methanol or 1,2-isopropylidene glycerol (**1**, Scheme 2) with one stereogenic center is a versatile C_3-synthon.[4] Its biocatalytic resolution has been widely studied in order to transform the easily available racemate to the high-valued antipodal chirons.[5–16] In such efforts solketal was previously shown to be the best candidate among the various acetal and ketal protected glycerols.[17] Accordingly, the less reactive (*R*)-solketal was previously obtained at 38% yield and over 99% *ee* using the (*S*)-selective lipase AK (lipase from *Pseudomonas sp.*)-catalysed butyrylation; for the more reactive (*S*)-enantiomer double kinetic resolution strategy was used.[16]

Owing to the synthetic value of enantiopure solketal a double resolution strategy was further studied in this work for obtaining the more reactive (*S*)-enantiomer. By combining lipase AK-catalysed alcoholysis with the previously presented acylation the four routes of Scheme 1 clearly become possible

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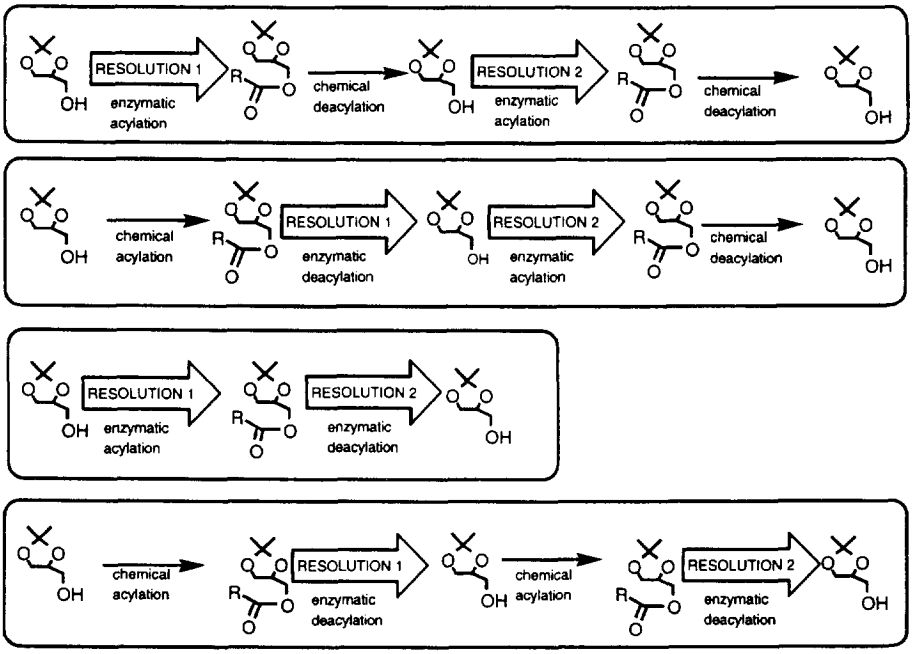
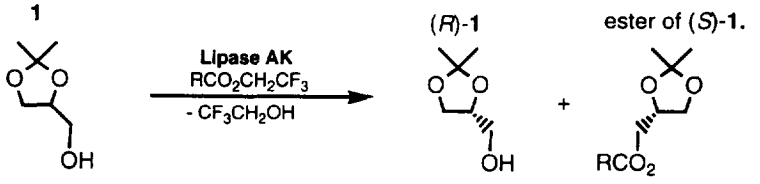
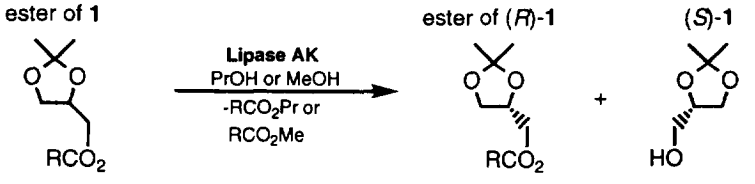
for the preparation of (*S*)-solketal. For the demand of high enantioselectivity in the acylation step of a double kinetic resolution, attention was paid to the nature of an acyl donor (Scheme 2). The lipase AK-catalysed alcoholysis of various solketal esters (Scheme 3) was also studied in order to learn about the equilibrium nature and enantioselectivity of the reaction. Finally, for the maximal theoretical chemical yield of the faster reacting enantiomer, numerical calculations were performed in order to find the optimal termination conversions for the 1st and 2nd resolution steps. The calculations allow the creation of plots with predictive power for practical resolutions.



Scheme 1.



Scheme 2.



Scheme 3.

Table 1. Enzymatic acylation of racemic solketal with 2,2,2-trifluoroethyl esters[a]

Ester	Catalyst (mg ml^{-1})	Time (h)	Conversion (%)	E
Acetate	10	1	19	5
Chloroacetate	10	no reaction		
Propionate	10	2	21	8
Butyrate	10	2	50	13
Butyrate[b]	10/25[c]/50[d]	1/1[c]/1[d]	30/27[c]/18[d]	13/22[c]/20[d]
3-Methylbutyrate	100/100[c]	8/16[c]	36/31[c]	16/27[c]
Hexanoate	10	1	58	14
Decanoate	10	1	37	6
Laurate[b]	10	1	73	5
Bentsoate	100	25	20	7

[a]Conditions: racemic solketal (0.1M), an acyl donor (0.2M) and the enzyme preparation (10% lipase AK adsorbed on Celite) in diisopropyl ether were shaken at 23 °C. [b]Vinyl ester as an acyl donor. [c]Acylation at 0°C. [d]Solketal (0.5M) and vinyl butyrate (1.0M) at 0°C.

Results and discussion

Acylation

For the lipase AK-catalysed acylation of solketal the structural effects of an achiral acyl donor on *E* were studied by varying the acyl part of 2,2,2-trifluoroethyl esters (Scheme 2, Table 1). Clearly 2,2,2-trifluoroethyl hexanoate, 3-methylbutyrate and butyrate afford comparable and acceptable enantioselectivities. Even though enantioselectivity in the case of the higher carboxylic acid esters stays moderate (E=5−7), the reactions proceed at considerable rates. This enables the preparation of chemically pure solketal esters under mild conditions and the synthesis of optically active lipid intermediates with enantiopure solketal as a starting material. Butyrate as an economic acyl donor was chosen for the preparative scale acylations. Moreover, because the alcohol part of the ester has not an effect on *E* vinyl butyrate was used in the place of the 2,2,2-trifluoroethyl ester in order to ensure irreversible acyl transfer.

Alcoholysis

The alcoholysis of various racemic solketal esters in diisopropyl ether was conducted in the presence of lipase AK at 23°C (Scheme 3, Tables 2 and 3). As expected, the alcoholysis of primary alcohol esters is reversible and stops at an equilibrium conversion. Quantitative expressions relating ee_S, ee_P, c and the apparent equilibrium constant (K) have been introduced for reversible resolutions.[18] Accordingly, ee_S goes through a maximum with conversion corresponding to the situation where the faster reacting enantiomer is reaching the equilibrium while the reaction of the slower reacting enantiomer to the product is still proceeding (Figure 1a). For the initial screenings (Table 2) the need to determine the K value of a reaction was avoided by determining the E value at low conversions where the reaction still practically behaves irreversibly. The enantioselectivity for the propanolysis of solketal carboxylates (Table 2) is approximately the same as in the acylation of solketal by the corresponding 2,2,2-trifluoroethyl carboxylate (Table 1). This is plausible as the reactions proceed through the same diastereomeric tetrahedral intermediates. Accordingly, the propanolyses of solketal butyrate and hexanoate lead to the highest E values. Similarly reactions in diisopropyl ether are favoured.

In the next experimental set propanol was replaced with methanol and enantioselectivity at different

Table 2. Alcoholysis of solketal esters with 1-propanol by lipase AK[a]

Ester	Solvent	Catalyst (mg ml^{-1})	Time (h)	Conversion (%)	*E*
Acetate	*i*-Pr_2O	50	1	11	5
Propionate	*i*-Pr_2O	50	3	24	8
Butyrate	*i*-Pr_2O	50	2	19	12
Hexanoate	*i*-Pr_2O	50	1	16	12
Decanoate[b]	*i*-Pr_2O	50	1	37	7
Stearate[b]	*i*-Pr_2O	50	1		7[c]
Butyrate	THF	20	1	3	11
Butyrate	Et_2O	20	1	2	10
Butyrate	Bu_2O	20	1	4	7
Butyrate	PhMe	20	11	9	12
Butyrate	t-Am-OH	20	11	19	6
Butyrate	MeCN	20	11	3	6

[a]Conditions: solketal ester (0.1M), 1-propanol (0.4M) and the enzyme preparation (10% lipase AK adsorbed on Celite) in the given solvent were shaken at 23 °C.[b] Nucleophile methanol (0.8M).[c]From the extrapolated value of $(1+ee_P)/(1- ee_P)$ at time=0.

Table 3. Enzymatic methanolysis of racemic solketal butyrate and hexanoate[a]

Ester	Ester (M)	Methanol (M)	Catalyst (mg ml^{-1})	Temperature (°C)	Time (h)	Conversion (%)	*E*
Butyrate	0.1	0.1	50	23	1.0	20	11
Butyrate	0.1	0.2	50	23	1.0	18	12
Butyrate	0.1	0.4	50	23	1.0	14	13
Butyrate	0.1	0.4	100	0	2.3	23	26
Butyrate	0.1	0.8	50	23	1.0	11	13
Butyrate	0.1	0.8	100	0	1.7	12	26
Butyrate	0.5	4.0	100[b]	0	14.5	32	21
Hexanoate	0.1	0.8	50	23	1.8	23	14
Hexanoate	0.1	0.8	50	0	1.6	13	24
Hexanoate	0.5	4.0	250	23	1.0	18	13
Hexanoate	0.5	4.0	125	0	2.3	14	22
Hexanoate	0.1	0.8	12.5[b]	23	1.8	9	13
Hexanoate	0.1	0.8	12.5[b]	0	1.7	5	21
Hexanoate	0.5	4.0	62.5[b]	23	1.2	11	12
Hexanoate	0.5	4.0	62.5[b]	0	2.6	11	20

[a]Conditions: solketal ester, methanol and the enzyme preparation (10% lipase AK adsorbed on Celite) in i-Pr_2O at 23 °C. [b]Lipase AK (40%) adsorbed on Celite.

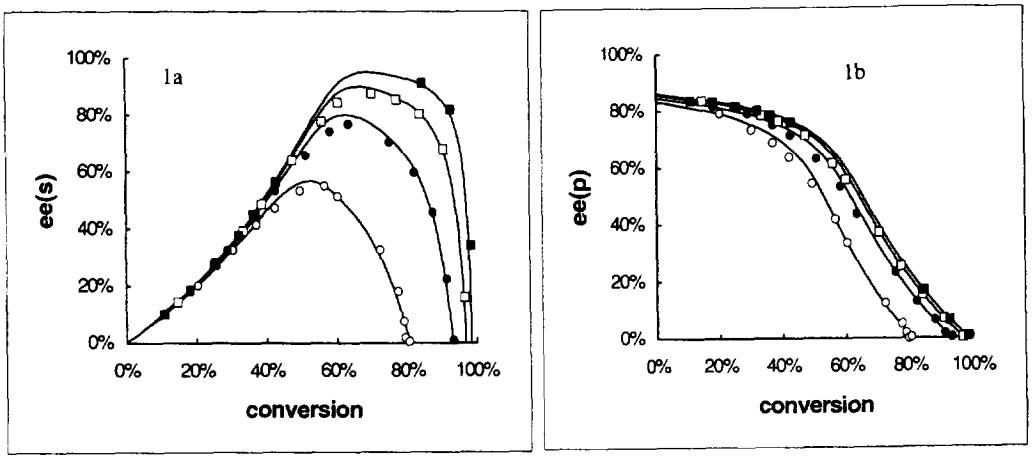


Figure 1. Conversion *vs.* ee_S (**1a**) and ee_P (**1b**) for the lipase AK-catalysed methanolysis of racemic solketal butyrate (0.1 M) in *i*-Pr_2O at 23°C for 0.1 (o), 0.2 (•), 0.4 (□) and 0.8 M (■) methanol. Solid lines for the theoretical curves.

concentrations of alcohol and either solketal butyrate or hexanoate was studied (Table 3). For 0.1 M solketal butyrate in diisopropyl ether at 23°C the use of 0.1, 0.2, 0.4 and 0.8 M methanol resulted in the equilibrium conversions of 81, 93, 97 and 99%, respectively. The corresponding E values were 11, 12, 13 and 13. The experimental *ee*-values as the function of %-conversion are shown in Figure 1 together with the theoretical graphs (solid lines).[19] The use of high alcohol to ester ratio enables the shift of an equilibrium more to the product side leading to higher ee_S at the maximum. The theoretical lines in Figure 1 slightly deviate from the experimental points particularly at the middle conversion range. It is probable, that a ping-pong bi–bi mechanism should be used instead of the uni–uni mechanism which is behind the theoretical graphs. The ping-pong bi–bi mechanism includes the effect of the second substrate and the corresponding product (methanol and methyl butyrate in the present case).[20] The rate equations for the ping-pong bi–bi mechanism cannot be directly integrated and numerical methods for the task has to be used.[21] Because the deviations between the experimental and theoretical points in Figure 1 are small and the correct calculation would increase the labour, we deliberately relied on the uni–uni assumption as a coarse tool in analyzing the resolution data.

The favourable effect of low temperature on enantioselectivity is clear according to the results of Table 3. Moreover, the kinetic resolutions proceed at acceptable E in concentrated solutions (0.5 and 4.0 M with respect to ester and methanol, respectively) allowing high yields per volume in the subsequent preparative resolutions. The use of solketal hexanoate as the substrate results in greater solubility and boiling point differences between the unreacted ester and produced solketal compared to the lower carboxylic acid esters of solketal. These differences are useful in the isolation step after the resolution.

Double kinetic resolution.

The highest ee_P [dictated by $(E-1)/(E+1)$] of conventional kinetic resolution will be obtained when the conversion approaches zero. For enhancing ee_P from this limiting value double kinetic resolution must be used. In that case, the highest ee_P is dictated by $(E_1E_2-1)/(E_1E_2+1)$, E_1 and E_2 referring to the enantiomeric ratios of the 1st and 2nd resolution step, respectively.[22] When the desired ee_P is adjusted between $(E-1)/(E+1)$ and $(E_1E_2-1)/(E_1E_2+1)$ it becomes intuitively obvious that the desired ee_P is achieved with various combinations of termination conversions for the 1st and 2nd resolution steps but the possible equivalence of the final yield remains obscure. In order to find an answer, the conversion of the 2nd resolution at desired ee_P was calculated at various conversions of the 1st resolution using $E_1=E_2=20$ (a basic program is shown in the experimental part). The results are plotted in Figure 2a.

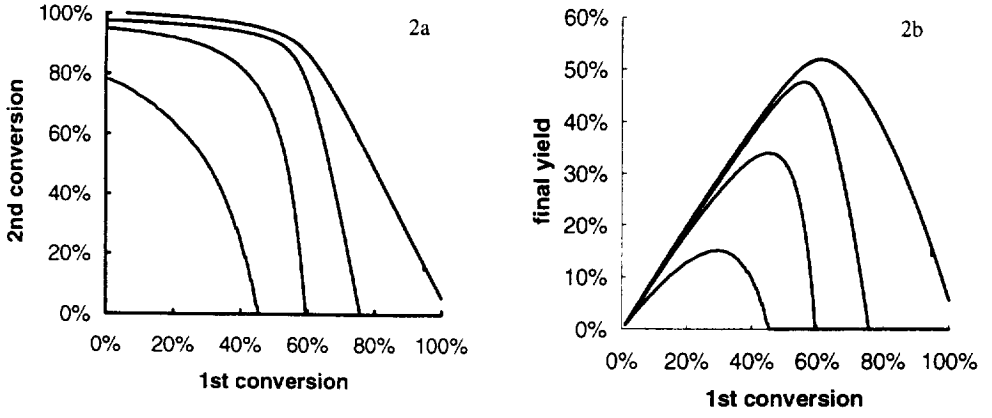


Figure 2. The termination conversion of the first resolution *vs.* termination conversion of the second resolution (**2a**) and *vs.* the final yield (**2b**). The curves correspond to $E_1=E_2=20$ and *ee*P=90, 95, 98 and 99% from top to bottom, respectively.

The final chemical yield can then be calculated. The plots of Figure 2 clearly reveal the existence of optimal termination conversions for the first and second resolution steps leading to the maximal final chemical yield of the product enantiomer at the desired enantiopurity. Accordingly, the demand for *ee*P=99% is achieved optimally with 29 and 51% conversions (Figure 2a) for the first and second resolution, respectively, the final chemical yield being 15% (Figure 2b). Higher enantiopurities are practically unattainable at the particular E value. On the other hand, if *ee*P=95% is acceptable the final yield of 48% will be obtained corresponding to 56% and 86% termination conversions for the 1st and 2nd resolution steps, respectively. Thus, the demand for high enantiopurity restricts the range of enantiomeric ratios usable in the double kinetic resolution strategy. Discontinuity near the x- and y-axis of the curve corresponding to desired *ee*P=90% is apparent in Figure 2. As an explanation, the required enantiopurity is too moderate in relation to E. Thus, at low conversion for the first resolution the second one will give the product at higher enantiopurity than desired with all conversion values. On the other hand, the first resolution can be allowed to proceed to 100% conversion and yet the second resolution step is able to give the product with required enantiopurity, the double kinetic resolution then being only formal.

Further informative plots are obtained when the optimal conversions and final yields are represented as the function of E (Figure 3). Accordingly, the demands for *ee*P=95% and 99% are fulfilled at the final yields of 48% and 15%, respectively with E=20 and that of 51% and 37%, respectively with E=30. This illustrates again the need for adjusting the desired *ee*P according to the enantiomeric ratio if high final yield is important. For obtaining comprehensibility in the graphs it was assumed that $E_1=E_2$, but it is equally possible to calculate the results for the cases of $E_1>E_2$ and $E_1<E_2$.

The different double kinetic resolution routes of Scheme 1 can now be considered for the practical enzymatic preparation of (*S*)-solketal with E of the order of 20 for both acylation and alcoholysis reactions (Tables 1 and 3). As seen in Figure 3, the maximal final yield in double resolution is obtained at above 50% conversion for the second step. For alcoholysis, the effect of equilibrium on enantiopurities will be noticeable at the required conversion range (Figure 1). Accordingly, the routes of Scheme 1 having deacylation as the 2nd resolution step are not usable for optimal double kinetic resolution, and the two first routes were chosen for the preparative scale double resolutions described in the experimental part. For the first route, the calculated optimal conversions of 51 and 82% for the 1st and 2nd enzymatic steps, respectively, should result in 42% final yield with *ee*P=97% and $E_1=E_2=20$ (Figure 3). In accordance with these theoretical values, the butyrate of (*S*)-solketal (31% isolated yield and 97% *ee*) was prepared by stopping the 1st and 2nd resolutions at 46 and 75% conversions, respectively. In the route consisting of the enzymatic alcoholysis of a solketal ester

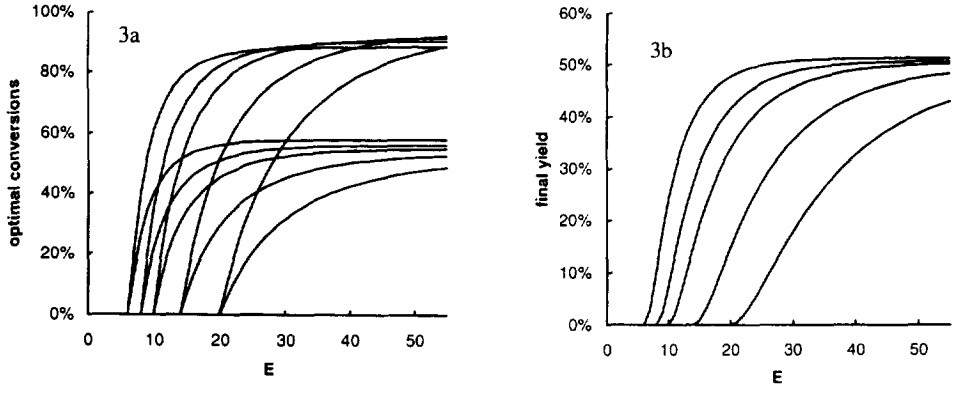


Figure 3. *E vs.* optimal termination conversion for the 1st (3a, lower curves) and the 2nd resolution (3a, upper curves) and *vs.* final yield (3b), when $E=E_1=E_2$ and ee_P=95, 97, 98, 99 and 99.5% from top to bottom, respectively.

followed by enzymatic acylation, 48% final yield and ee_p=95% should be achievable with 57 and 85% conversions. In practice, the butyrate of (*S*)-solketal (37% isolated yield and 95% *ee*) was prepared when the conversions for the first and second resolution were 46 and 85%, respectively.

Conclusions

The present work describes the usefulness of enzymatic double kinetic resolution for the preparation of the more reactive enantiomer at conditions of $[(E-1)/(E+1)] < ee_P < [(E_1E_2-1)/(E_1E_2+1)]$. In the case of $E=E_1=E_2=20$ the corresponding application range of double kinetic resolution in terms of desired ee_P is $90.5\% < ee_P < 99.5\%$. A basic program was used in predicting the termination conversions for the first and second resolution steps, leading to the maximal theoretical chemical yield of the product at desired ee_P at certain *E*. In a good agreement with the theoretical consideration (*S*)-solketal as a butyrate was prepared at 31% (97% *ee*) or 36% (95% *ee*) isolated yields starting with 283 g of racemic solketal or 464 g of racemic solketal hexanoate and using enzymatic butyrylation–chemical saponification–enzymatic butyrylation or enzymatic methanolysis–enzymatic butyrylation sequences, respectively (Scheme 1). Lipase-catalysed alcoholysis of racemic solketal esters when used as the 2nd enzymatic step are not recommended because the equilibrium leads to the lowering of *ee* at the critical conversion range.

In this work, the focus has been in the preparation of the more reactive (*S*)-enantiomer of solketal by lipase catalysis using double kinetic resolution methods. The less reactive counterpart (enriched with respect to the (*R*)-enantiomer) can be easily racemized and recycled as was previously described[16] or the first resolution of the isolated substrate can be continued in a normal manner as shown for solketal hexanoate in the experimental section.

Experimental

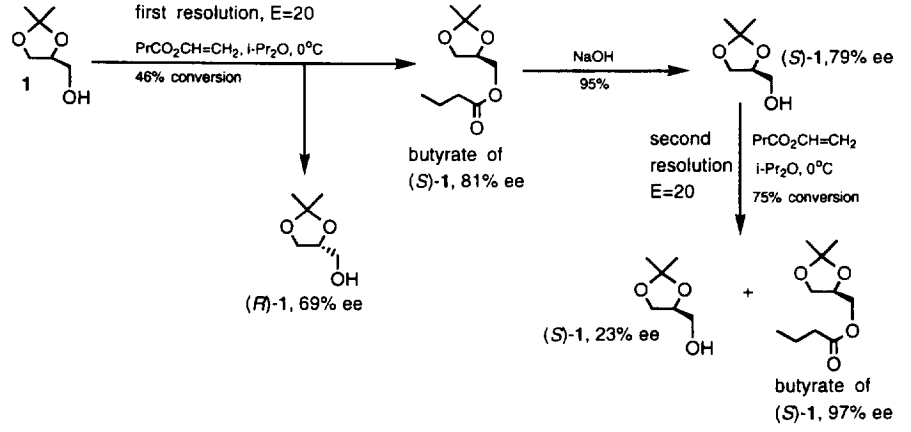
Lipase AK was from Amano Pharmaceuticals. Racemic solketal was from Aldrich and was purified by distillation. Vinyl butyrate and laurate were from Fluka. 2,2,2-Trifluoroethyl and racemic solketal esters were prepared from the corresponding alcohol and appropriate carboxylic acid anhydride or chloride by standard procedures. Initial screenings were performed in stoppered vials (reaction volume 3.00 ml) by shaking in an orbital shaker. The progress of the reactions was followed by taking 100 μl samples at intervals and filtering off the enzyme. The samples were derivatized with either acetic, propionic or butyric anhydride (10 μl anhydride and 10 μl of pyridine containing 1 mol-% 4-*N*,*N*-dimethylaminopyridine) followed by the *ee* determination of the substrate and product fractions on a permethylated β-cyclodextrin GLC-capillary column. In the case of enzymatic benzoylation, the product was analyzed with Chiralcel-OD HPLC column with hexane–isopropanol as an eluent. In the

case of enzymatic acylation with lauric or decanoic acid derivatives and for the enzymatic alcoholysis of solketal decanoate the determination of E was based on conversion (determination using internal standard) and either ee_S or ee_P. ^{1}H NMR spectra were measured on a Lambda GX 400 spectrometer in $CDCl_3$ (tetramethylsilane as an internal standard). Optical rotations were measured using a JASCO DIP-360 polarimeter.

Preparative scale double kinetic resolution

Butyrylation–saponification–butyrylation sequence (Scheme 4)

The first resolution was started by adding the lipase preparation (15 g, 10% of lipase AK immobilized on Celite with 5% of sucrose as an additive) to a solution of freshly distilled solketal (283 g, 2.14 mol) and vinyl butyrate (244 g, 2.14 mol) in diisopropyl ether (4.5 l) containing triethyl amine (1.5 g) at 0°C. The resolution was allowed to proceed under vigorous mechanical stirring. E=20 was determined from 7 samples taken during the progress of the resolution. The reaction was stopped after 37 h by filtering of the enzyme preparation at 46% conversion (69% *ee* for (*R*)-solketal and 81% *ee* for the produced butyrate of (*S*)-solketal). The solvent and remaining acylating agent were evaporated and the residue was distilled through a fractionating column giving (*R*)-solketal (89–91°C/19 mm Hg; 153.3 g; *ee* 69%; $[\alpha]_D^{25}=-7.43$; (c=4.04, MeOH) at 54% yield based on the racemate). The butyrate of (*S*)-solketal (193.7 g; 0.96 mol; *ee* 81%; yield 45% based on the racemate) was obtained as a distillation residue and contained 1–2% of the antipodal solketal as an impurity. The butyrate was saponified by heating with NaOH (41.4 g; 1.04 mol) in water (150 ml). After the vigorous reaction had subsided the cooled homogenous solution was extracted with ethyl acetate. The combined organic phases were evaporated and the residue distilled yielding the enantiomerically enriched (*S*)-solketal (120.0 g; 0.91 mol; *ee* 79%; yield 95% based on the butyrate). The isolated (*S*)-solketal was subjected to the second resolution step conducted at 0°C in the presence of vinyl butyrate (104.0 g, 0.91 mol), triethyl amine (1.0 g), diisopropyl ether (1.8 l) and the enzyme preparation (16 g). The resolution was stopped after 30 h at 75% conversion (23% *ee* for unreacted substrate and 97% *ee* for the produced butyrate). The unreacted substrate was extracted into water and discarded. The organic phase was concentrated and the residue distilled yielding the butyrate of (*S*)-solketal (92°C/7 mm Hg–110°C/11 mm Hg; 133.1 g; 0.66 mol; *ee* 97%; $[\alpha]_D^{25}=+13.3$; (c=1.0, hexane); $[\alpha]_D^{20}=-14.4$ for the antipode;[12] yield 72% based on the enantiomerically enriched solketal). ^{1}H NMR: ($CDCl_3$): δ 0.95 (t, 3H); 1.37 (s, 3H); 1.44 (s, 3H); 1.67 (m, 2H); 2.34 (t, 2H); 3.71–3.76 (dd, 1H); 4.06–4.11 (m, 2H); 4.16–4.20 (dd, 1H); 4.29–4.35 (m, 1H). The total isolated yield was 31% based on the original racemic substrate.

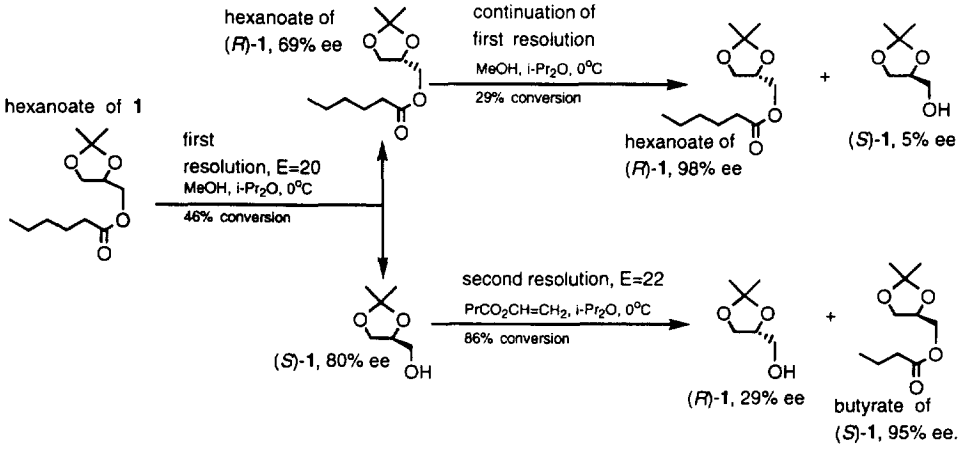


Scheme 4.

Preparative scale double kinetic resolution

Methanolysis–butyrylation sequence (Scheme 5)

The first resolution was started by adding the lipase preparation (50 g, 40% of lipase AK immobilized on Celite with 5% of sucrose as an additive) into the cold solution (0°C) of racemic solketal hexanoate (464.0 g, 2.01 mol) and methanol (516.0 g, 16.1 mol) in diisopropyl ether (4.1 l). The reaction proceeded under vigorous mechanical stirring (0°C; E=20) and was stopped after 83 h at 46% conversion by filtering of the enzyme preparation. Sample analysis revealed 69% *ee* for the unreacted hexanoate of (*R*)-solketal and 80% *ee* for the produced (*S*)-solketal. The solvent was evaporated and the residue was distilled giving methyl hexanoate (52–59°C/19–25 mm Hg; 102.8 g; yield 85%) and (*S*)-solketal (88–89°C/18–19 mm Hg; 112.9 g; 0.85 mol; *ee* 77%; yield 55% based on the racemate). The hexanoate of (*R*)-solketal was obtained as the distillation residue (254.1 g; 1.10 mol; *ee* 69%; yield 42% based on racemic substrate). The enantiomerically enriched (*S*)-solketal fraction was subjected to the next resolution step in the presence of vinyl butyrate (97 g, 0.85 mol), enzyme preparation (15 g), diisopropyl ether (1.7 l) and triethyl amine (0.8 g). The resolution was stopped after 22 h followed by the usual work up and extractive removal of unreacted solketal to yield the butyrate of (*S*)-solketal (145.0 g; 1.01 mol; *ee* 95%; $[\alpha]_D^{25}$=+12.9; (c=1.0, hexane); $[\alpha]_D^{20}$=−14.4 for the antipode;[12] yield 84% based on the enantiomerically enriched substrate). The ^{1}H NMR data was as described in the case of the butyrylation–saponification–butyrylation sequence The total isolated yield was 36% based on the racemic starting material.



Scheme 5.

The resolution of the hexanoate from the first resolution step was continued by adding methanol (283 g, 8.83 mol), diisopropyl ether (1.3 l) and the enzyme preparation (50 g, 40%). After 116 h of vigorous mechanical stirring (0°C) the methanolysis was stopped at 29% conversion by filtering of the catalyst (ee_S=98%, ee_P=5%). The concentrated filtrate was washed with water in order to remove the produced solketal. Finally fractional distillation through a Vigreux column afforded the hexanoate of (*R*)-solketal (130–135°C/11–12 mm Hg; 171.1 g; 0.74 mol; *ee* 98%; $[\alpha]_D^{25}$=−12.2; (c=1.2, hexane); yield 37% based on the racemate). ^{1}H NMR: ($CDCl_3$): δ 0.90 (t, 3H); 1.33 (m, 4H); 1.38 (s, 3H); 1.44 (s, 3H); 1.63 (m, 2H); 2.35 (t, 2H); 3.71–3.76 (dd, 1H); 4.06–4.12 (m, 2H); 4.16–4.20 (dd, 1H); 4.25–4.35 (m, 1H).

Calculation of optimal termination conversions in double kinetic resolution

A basic program for the calculation of optimal termination conversions in double kinetic resolution is based on the following schemes and relations. A and B refer to the concentrations of the fast and slow reacting enantiomers and C and D to the corresponding products. The subscript 0 refers to the

initial quantity and subscripts 1 and 2 to the 1st and 2nd resolution step. The allowed numerical ranges are $0<D_1<1$ and $0<D_2<D_1$. According to Chen[1] $E_1 = [\ln(A_1/A_0)] / [\ln(B_1/B_0)]$. Thus if $A_0=B_0=1$ the following relations are valid.

$$A_1 \xrightarrow{fast\ v_1} C_1 = A_2 \qquad B_1 \xrightarrow{slow\ v_2} D_1 = B_2, \qquad E_1 = \frac{v_1}{v_2} = \frac{\ln\frac{1-C_1}{A_0}}{\ln\frac{1-D_1}{B_0}}, \qquad ee_{1P} = \frac{1-(1-D_1)^{E_1}-D_1}{1-(1-D_1)^{E_1}+D_1}, c_1 = \frac{1-(1-D_1)^{E_1}+D_1}{2}$$

$$A_2 \xrightarrow{fast\ v_3} C_2 \qquad B_2 \xrightarrow{slow\ v_4} D_2, \quad E_2 = \frac{v_3}{v_4}, \qquad ee_{2P} = \frac{C_1 - \frac{C_1(D_1-D_2)^{E_2}}{D_2^{E_2}} - D_2}{C_1 - \frac{C_1(D_1-D_2)^{E_2}}{D_2^{E_2}} + D_2}, \qquad c_2 = \frac{C_1 - \frac{C_1(D_1-D_2)^{E_2}}{D_2^{E_2}} + D_2}{C_1 + D_1}$$

The program calculates the termination conversion for first and second resolution resulting in required ee_P and determines the conversion values that give the maximal final yield. The calculated data is stored in files which are easily accessible by a spreadsheet program for the graphical representation.

Program listing

```
10 CLS:CLEAR
20 PRINT"The program calculates the termination
conversions for 1st and 2nd resolution and the final yields
that will give the required product-ee. Calculated data is
stored in files:ayield, aconv1, aconv2"
50 PRINT "Input: 1) required product-ee (0 < ee < 1)"
60 PRINT"   2) E1, enantiomeric ratio of 1st resolution
(1<E1)"
70 PRINT"   3) E2, the enantiomeric ratio of 2nd
resolution (1<E2)"
80 INPUT"Enter when ready";A$:CLS
90 DIM CONVERSION1(1000):DIM
CONVERSION2(1000)
100 INPUT"Enantiomeric ratio for 1st resolution, E1=";E1
110 INPUT"Enantiomeric ratio for 2nd resolution,E2=";E2
120 INPUT"Required product-ee";EEREQUIRED
130 FOR D=.001 TO .999 STEP (.001)
140 C=1-((1-D)^E1)
150 CONVERSION1=(C+D)/2
160 D1=.00001:D3=D:D2=D/2
170 C1=C-C*(((D-D1)/D)^E2):C3=C-C*(((D-
D3)/D)^E2):C2=C-C*(((D-D2)/D)^E2)
180 EEPRODUCT2A=(C1-
D1)/(C1+D1):EEPRODUCT2B=(C3-
D3)/(C3+D3):EEPRODUCT2C=(C2-D2)/(C2+D2)
190 IF EEPRODUCT2A-EEPRODUCT2B<.00001 THEN
300
200 IF EEPRODUCT2A<EEREQUIRED THEN 290
210 IF EEPRODUCT2A>EEREQUIRED AND
EEPRODUCT2C<EEREQUIRED THEN 230
220 IF EEPRODUCT2C>EEREQUIRED AND
EEPRODUCT2B<EEREQUIRED THEN 260
230 D3=D2
240 D2=(D1+D3)/2
250 GOTO 170
260 D1=D2
270 D2=(D1+D3)/2
280 GOTO 170
290 C2=0:D2=0
300 X=X+1:T=X
310 CONVERSION2(X)=(C2+D2)/(C+D)
320 CONVERSION1(X)=CONVERSION1
330 IF YIELD<CONVERSION1(X)*CONVERSION2(X)
THEN G=X
340 IF YIELD<CONVERSION1(X)*CONVERSION2(X)
THEN YIELD=CONVERSION1(X)*CONVERSION2(X)
350 NEXT D
360 PRINT"Maximal final yield=";YIELD
370 PRINT"Conversion of 1st
resolution=";CONVERSION1(G)
380 PRINT"Conversion of 2nd
resolution=";CONVERSION2(G)
390 OPEN "aconv1" FOR OUTPUT AS #1
400 OPEN "aconv2" FOR OUTPUT AS #2
410 OPEN "ayield" FOR OUTPUT AS #3
420 PRINT#1,"Required optical purity=";EEREQUIRED
430 PRINT#1,"E1=";E1; " E2=";E2
440 PRINT#1,"Maximal final yield=";YIELD
450 PRINT#1,"Conversion of 1st
resolution=";CONVERSION1(G)
460 PRINT#1,"Conversion of 2nd
resolution=";CONVERSION2(G)
470 PRINT#1,"Conversion of 1st resolution"
480 PRINT#2,"Conversion of 2nd resolution"
490 PRINT#3,"Final yield"
500 FOR X=1 TO T
510 PRINT#1,CONVERSION1(X)
520 PRINT#2,CONVERSION2(X)
530 PRINT#3,CONVERSION1(X)*CONVERSION2(X)
540 NEXT X
550 CLOSE
```

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