Lipase-catalysed Transesterification in the Preparation of Optically Active Solketal

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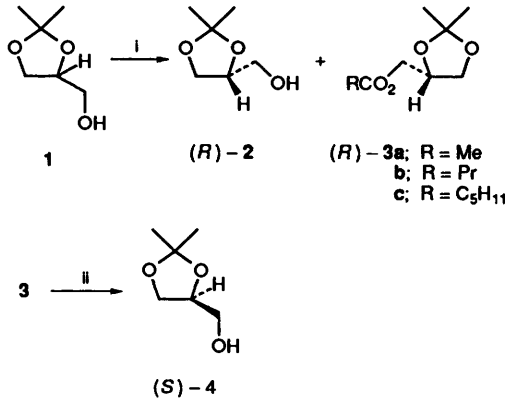
A lipase-catalysed method for a large-scale preparation of both (*R*)- (ee 99%) and (*S*)-solketal (ee 94% after double resolution) has been described. Separation of the reaction products in the resolution mixture was achieved by extraction/distillation and the unwanted enantiomer was racemized and recycled.

Natural products and pharmaceuticals are often optically active compounds, the synthesis of which usually begins with small optically active synthons. Glycerol derivatives such as solketal (2,2-dimethyl-1,3-dioxolane-4-methanol, **1**) and glycidol (2,3-epoxypropan-1-ol) with one asymmetric centre are inexpensive examples of useful chiral synthons. They have been used for the preparation of a wide variety of structurally different, enantiomerically pure and biologically active compounds such as bioactive phospholipids[1] and β-adrenergic-blocking propanolamines.[2] The use of the chiral pool, the Sharpless asymmetric epoxidation, and chemical or biocatalytic resolutions are common methods studied for the preparation of the enantiomers of solketal and glycidol.[3–14] It is noteworthy that solketal can be easily transformed into glycidol and *vice versa*.[3]

Although great attention has been paid to the enzymic resolution of racemic solketal **1** and glycidol, success has remained disappointingly modest. The porcine pancreatic lipase (PPL)-catalysed hydrolysis of glycidyl esters proceeds with moderate enantioselectivity, the enantiomeric ratio (*E*)† being between 12 and 16 for butyric or some higher carboxylic acid esters in aqueous biphasic media.[4,5] The hydrolysis of the corresponding esters of solketal by isolated enzymes, on the other hand, occurs with low enantioselectivity,[5–8] the best result being obtained for the hydrolysis of solketal butyrate with the proteinase from *Aspergillus oryzae* ($E = 9.0$).[8] To our knowledge, the hydrolysis of solketal esters by micro-organisms (the culture from *Streptomyces parvulus*) represents the only positive exception to the above rule.[14] In this patented system, (*S*)-solketal (ee 0.75)‡ and acetylated (*R*)-solketal (ee 0.98) were prepared.

In organic solvents, the enzymic resolution of racemic solketal **1** and glycidol by transesterification seems to be even less successful than by hydrolysis in water. For the PPL- or *Candida cylindracea* lipase (CCL)-catalysed acylation of glycidol and solketal with enol esters or 2,2,2-trifluoroethyl butyrate in anhydrous organic solvents, values of $E < 5$ have always resulted.[9,10] Similarly, the PPL-catalysed alcoholysis of glycidyl butyrate led to the low values of $E < 5$.[11] On the other hand, in the acylation of the alcohol **1** with oleic acid in the presence of the lipase from *Alcaligenes* sp., (*S*)-solketal with 11.4% ee at 36.2% conversion was prepared.[12] The best enantioselectivity reported concerns the lipase PS-catalysed esterification of solketal **1** with succinic anhydride in diethyl ether, with $E = 7$.[13]



Scheme 1 *Reagents:* i, lipase, organic solvent, RCO_2R' (– R'OH); ii, aq. NaOH

The present article describes a hundred-gram-scale resolution of solketal **1** by lipase catalysis in anhydrous organic solvents. The method is based on the asymmetric acylation of solketal **1** (Scheme 1). The lipase-catalysed deacylation of butyrate **5** in organic solvents has also been studied (Scheme 2).

Results and Discussion

The strategy used for the preparation of the enantiomers of alcohol **1** (Scheme 1) is based on enzyme and solvent screenings and the optimization of other reaction conditions.

Acylation of Soketal.—For the transesterification between isopropenyl acetate and solketal **1** in toluene five commercial lipases were screened. As is shown in Table 1, all of the lipases used catalyse the acylation reaction, but, in accord with the previous results,[9] no clear preference for the (*R*)- or (*S*)-isomer is observed in the cases of PPL and CCL catalyses. For the three lipases (SAM 2, lipase PS and lipase AK) from *Pseudomonas*, on the other hand, somewhat enhanced enantioselectivity is observed and the ester product enriched with respect to the (*R*)-enantiomer is obtained (Scheme 1).§ The absolute configurations of the products are based on chiral GLC and the acetylated derivative of commercial (*S*)-**4**. Lipase AK with the highest *E*-value (5.4) was used for further studies.

For enzyme-catalysed reactions in organic solvents the possibility of manipulating enzymic enantioselectivity[16–20] as

† Enantiomeric ratio, which equals the ratio of specificity constants (or, roughly, the ratio of initial rates) for the individual enantiomers, can be calculated from the degree of conversion, *c*, and the corresponding enantiomeric excess (ee)-values of the substrate, ee_s, by the equation $E = \ln[(1 - c)(1 - ee_s)]/[\ln(1 - c)(1 + ee_s)]$ where $c = ee_s/(ee_s + ee_p)$. For the reactions which stop at an equilibrium, the equilibrium constant must be inserted in the equation.[15]

‡ ee: enantiomeric excess.

§ Note that the priority order of the substituents at the asymmetric centre is changed when solketal is acylated and *vice versa*.

Table 1 Acylation of solketal with isopropenyl acetate in toluene in the presence of lipases[a]

Lipase	Time (t/h)	Conversion/%	E
PPL	41	2	1.5
PPL[b]	38	33	2.0
CCL	20	43	1.6
SAM 2[c]	17	18	3.1
Lipase PS	20	54	3.1
Lipase AK	6	35	5.4

[a] Conditions: 25 mg cm^{-3} lipase powder, 0.1 mol dm^{-3} solketal and 0.2 mol dm^{-3} isopropenyl acetate in toluene were shaken at 25 °C; E calculated according to footnote † on p. 3459 in text and ref. 15. [b] 0.2 mol dm^{-3} $PrCO_2CH{=}CH_2$ as an acyl donor in the presence of 6 mg cm^{-3} of PPL. [c] 2.5 mg cm^{-3} lipase.

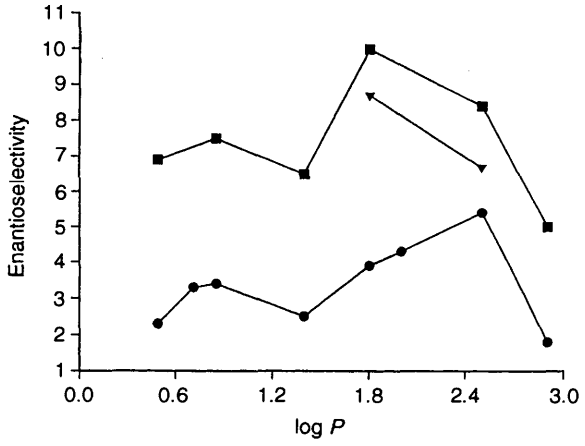


Fig. 1 The dependence of the enantioselectivity[15] of lipase AK in the acylation of solketal with isopropenyl acetate (●), and vinyl (▼) and 2,2,2-trifluoroethyl (■) butyrates on the hydrophobicity of the solvent. Solvents with increasing log P-values:[23] tetrahydrofuran, pyridine, diethyl ether, *tert*-amyl alcohol, benzene, diisopropyl ether, toluene and dibutyl ether.

well as other selectivities[21] by the proper choice of solvent has been among the most fundamental discoveries.[22] For the acylation of solketal the solvent clearly affects both the enantioselectivity and the catalytic efficiency of lipase AK (Table 2). Moreover, the acylating agent affects the choice of preferred solvent (Fig. 1). Thus, in the case of an acetic acid ester as an acyl donor, toluene (log P = 2.5)* is the best solvent (E = 5.4). In the case of 2,2,2-trifluoroethyl and vinyl butyrates, diisopropyl ether (log P = 1.9) provides a more valid medium (E = 10 and 8.7, respectively). According to the initial rate measurements for the butyrylation of **1** with 2,2,2-trifluoroethyl butyrate, decreased enantioselectivity in dibutyl ether (E = 5.0) as compared with that in diisopropyl ether (E = 10) is mainly explained by the increased reactivity of the less reactive (*R*)-alcohol. In tetrahydrofuran (THF) (E = 6.9) the reactivity of the (*S*)-alcohol, on the other hand, decreases more pronouncedly than does that of the (*R*)-alcohol.

For the resolution of solketal by lipase catalysis, enantiodiscrimination takes place when the acyl-enzyme intermediate†

* P is the partition coefficient of any solute between octan-1-ol and water. The value of log P reflects the hydrophobicity of the solute.[23]

† Lipase-catalysed reactions usually proceed by an acyl-enzyme mechanism where the acyl donor first forms an acyl-enzyme intermediate (the first product is released) which in the next step reacts with a nucleophile (the second product is released). The existing experimental evidence (generally the serine protease subtilisin as a model enzyme) predicates that the structure of the enzyme active site itself, as well as the mechanistic course of the reaction, be relatively independent of the solvent.[24]

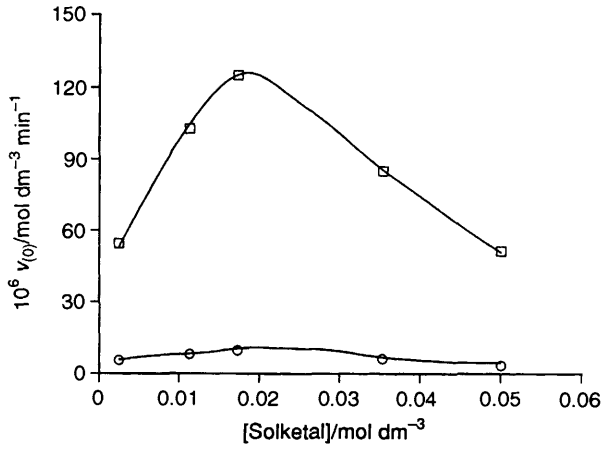


Fig. 2 Dependence of $v_0^{(S)}$ (○) and $v_0^{(R)}$ (□) on solketal concentration for the formation of solketal butyrate from racemic solketal (0.005–0.1 mol dm^{-3}, corresponding to 0.0025–0.05 mol dm^{-3} for both enantiomers) and 2,2,2-trifluoroethyl butyrate (0.2 mol dm^{-3}) in diisopropyl ether in the presence of 2.5 mg cm^{-3} of the enzyme preparation (8.6% lipase AK on Celite) at 25 °C

reacts with solketal. This enantiodiscrimination clearly depends on the chain length of the acyl group (Tables 2 and 3; Fig. 1). Thus, for the formation of esters **3a–c** from racemic solketal **1** (0.1 mol dm^{-3}) and the corresponding 2,2,2-trifluoroethyl ester (0.2 mol dm^{-3}) in the presence of the enzyme preparation (2.5 mg cm^{-3}; 8.6% lipase AK on Celite), the initial rates (μmol dm^{-3} min^{-1}) in diisopropyl ether at 25 °C have the values $v_0^{(S)}$ = 117, 49 and 54 and $v_0^{(R)}$ = 23, 3.5 and 4.0, respectively. These results are proposed to reflect increased enantioselectivity with increased steric hindrance in the butyryl (or hexanoyl)-enzyme over the acetyl-enzyme intermediate. Butyric acid derivatives were deemed as the most appropriate acyl donors for this study.

One of the basic demands for optimal enzymic resolution is that the reaction is irreversible. In an acylation reaction, this demand can be best fulfilled by a suitable choice of an acyl donor. As irreversible acyl donors we used butyric anhydride and vinyl esters which release butyric acid and unstable enols, respectively. Generally, 2,2,2-trifluoroethyl esters (2,2,2-trifluoroethanol is a very weak nucleophile for the reverse enzymic transesterification) are also believed to fulfil the demand. We found, however, that the reaction of compound **1** (0.1 mol dm^{-3}) with 2,2,2-trifluoroethyl butyrate (0.2 mol dm^{-3}) in diisopropyl ether reaches an equilibrium at 96–98% conversion. Accordingly, the optical purity of enantiomer (*R*)-**2** starts to decrease after 60% conversion, the highest ee obtainable being of the order of 95%. The equilibrium nature observed is not important at conversions < 50%.

Owing to our interest in the gram-scale preparation of the enantiomers **2** and **4**, resolution at high solketal concentrations is preferred. We found, however, that initial rates for the butyrylation of compound **1** do not increase asymptotically to the maximal velocity, V_{max}, with increasing solketal concentration (Fig. 2). Rather, v_0 decreases, and consequently the time needed for the resolution increases at higher levels of alcohol **1**. A possible explanation for the above behaviour is competitive substrate inhibition by solketal.[25] Fortunately enough, this inhibition does not affect enantioselectivity as is shown by the values of $v_0^{(S)}/v_0^{(R)}$ ~ 13 observed when 0.005–0.1 mol dm^{-3} solketal is used. However, when 0.6 mol dm^{-3} **1** is butyrylated there is a drop in E (Table 3). In this case, the medium contains 19% (w/w) of the reactants, and thus solvent effects on enantioselectivity at least partly explain the drop in E.

Butyric anhydride as the most effective and irreversible butyric acid derivative was used for the final optimization of the

Table 2 Acylation of solketal with isopropenyl acetate and 2,2,2-trifluoroethyl butyrate in organic solvents in the presence of lipase AK[a]

	$AcOC(Me)=CH_2$			$PrCO_2CH_2CF_3$		
Solvent	Time (t/h)	Conversion/%	E	Time (t/h)	Conversion/%	E
Bu_2O	5	78[b]	1.8	2	38[d]	5.0
PhMe–hexane (1:1)	5	24[b]	3.7			
PhMe	6	35[b]	5.4	5	29[d]	8.4
Pr^i_2O	1	40[b]	3.9	3	50[d]	10
PhH	22	40[b]	4.3			
tert-Amyl alcohol	25	83[c]	2.5	0.5	10[e]	6.5
Et_2O	2	32[b]	3.4	2	25[e]	7.5
Pyridine	14	38[b]	3.3			
THF	2	26[b]	2.3	2	24[e]	6.9

[a] Conditions: lipase AK powder, 0.1 mol dm^{-3} solketal and 0.2 mol dm^{-3} ester in an organic solvent were shaken at 25 °C; E calculated according to footnote † on p. 3459 in text and ref. 15. [b] 25 mg cm^{-3} lipase AK. [c] 3 mg cm^{-3} lipase AK. [d] 10 mg cm^{-3} lipase AK. [e] 5 mg cm^{-3} lipase AK.

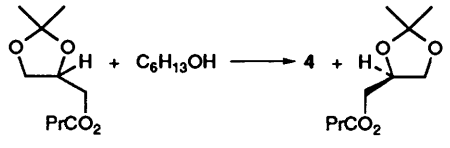
Table 3 The effect of an acyl donor on enantioselectivity for the acylation of solketal in toluene and diisopropyl ether in the presence of lipase AK[a]

	Toluene		Pr^iO			
Acyl donor	E[b] (25 °C)	E[b] (4 °C)	E[b] (25 °C)	E[c] (25 °C)	E[b] (4 °C)	E[c] (4 °C)
$AcOCH=CH_2$	5.3					
$AcOC(Me)=CH_2$	5.4	6.3	3.9			
$AcOCH_2CF_3$	4.0			5.1		
$PrCO_2Et$			5.2			
$PrCO_2CH=CH_2$	6.7	9.4	8.7		14	
$PrCO_2CH_2CF_3$	8.4	10	10	14	15	22/20[d]
$Me[CH_2]_4CO_2CH_2CF_3$	8.3	10		14		
$(PrCO)_2O$	10	12	13			24
$(PrCO)_2O$				14		24[e]/19[f]
$(PrCO)_2O$						29[g]/24[h]

[a] Conditions: lipase AK, 0.1 mol dm^{-3} solketal and 0.2 mol dm^{-3} acyl donor in an organic solvent were shaken at a given temperature; E calculated according to footnote † on p. 3459 in the text and ref. 15. [b] 2–25 mg cm^{-3} lipase AK powder. [c] 2–10 mg cm^{-3} enzyme preparation (8.6% lipase AK on Celite). [d] 0.6 mol dm^{-3} solketal and 0.8 mol dm^{-3} acyl donor. [e] 0.06 mol dm^{-3} acyl donor. [f] 0.64 mol dm^{-3} solketal and 0.41 mol dm^{-3} acyl donor. [g] Reaction temperature 0–1 °C; 0.06 mol dm^{-3} acyl donor. [h] 0.64 mol dm^{-3} solketal and 0.41 mol dm^{-3} acyl donor at 0–1 °C.

reaction conditions in the resolution of racemic solketal **1**. The highest enantioselectivity (E = 29 or 24 depending on the solketal concentration) was obtained by using lipase AK adsorbed on Celite in diisopropyl ether at 0 °C (Table 3). Under these conditions, a large-scale resolution of alcohol **1** was performed with the amount of butyric anhydride enough to stop the reaction at *ca.* 60% conversion. In accord with what was estimated,[15] optically pure (*R*)-**2** (ee = 98%) was obtained at 58% conversion after 28 h. To prepare (*S*)-solketal **4** with high optical purity, a double-resolution methodology was adopted. For that purpose, butyrate **3b** (64% ee) was first chemically saponified. The alcohol now enriched with respect to the faster reacting enantiomer was subjected to the second resolution with butyric anhydride. Saponification of the butyrate thus obtained resulted in (*S*)-solketal **4** with high optical and chemical yields. It is worth mentioning that enantioselectivity for the acylation of compound **1** was the same, independently of whether lipase AK was adsorbed on Celite from aqueous buffer at pH 7.8 or 9.0. On the other hand, the initial rates $v_0^{(S)}$ and $v_0^{(R)}$ were 3-fold higher when the enzyme was obtained from the pH optimum at pH 9.0. Under the resolution conditions, there is no reaction in the absence of the enzyme.

Deacylation of Solketal Butyrate.—For the deacylation of butyrate **5** with hexan-1-ol, lipase enantioselectivities follow the same pattern as for the corresponding acylation reactions above. Accordingly, E = 2 for the PPL- and CCL-catalysed deacylations of racemic compound **5** in diisopropyl ether at 25 °C. The *Pseudomonas* lipases in the same reaction give E-values of the order of 9 and enantioselectivity is improved (E up to 13–15) by lowering the temperature and by adsorbing the



5 (*S*)-**6**

Scheme 2 *Reagents:* Lipase, organic solvent (– $PrCO_2C_6H_{13}$)

enzyme on Celite. As is shown in Scheme 2, (*S*)-alcohol **4** is preferentially released in the deacylation of the corresponding carboxylic acid ester. In spite of the seemingly good enantioselectivity observed in the case of the *Pseudomonas* lipases, enzymic deacylation is not a method of choice for the preparation of (*R*)- or (*S*)-solketal. This is due to the lipase-catalysed acylation of the alcohol **4** with hexyl butyrate in the reverse reaction back to solketal butyrate. The equilibrium conversion is only 75% as measured by allowing 0.1 mol dm^{-3} solketal to react with 0.1 mol dm^{-3} hexyl butyrate and 0.1 mol dm^{-3} solketal butyrate with 0.1 mol dm^{-3} hexan-1-ol in diisopropyl ether. This equilibrium results in a gradual racemization of the resolution products **4** and **6** with time. In accordance, *e.g.*, for the lipase AK-catalysed hexanolysis of solketal butyrate in diisopropyl ether, E = 15 at 6% conversion at 4 °C drops to the value 10 at 30% conversion.

Conclusions.—In spite of numerous earlier efforts[5–9,13] the first successful resolution of solketal **1** with isolated enzymes is described herein. The method exploits a transesterification reaction and is based on the enantioselectivity of lipase AK

from *Pseudomonas*. From the two possible transesterification reactions [acylation (Scheme 1) and deacylation (Scheme 2)] deacylation is less practical because the resulting primary alcohol **4** is capable of competing with hexan-1-ol for the acyl–enzyme intermediate, resulting in a gradual decrease in the optical purity of the resolution products. Enantioselectivity of lipase AK for the acylation of solketal **1** strongly depends on the nature of the reaction medium and the acyl group of the acyl donor, butyrylation in diisopropyl ether providing the best combination in that respect (Tables 2 and 3). Adsorption of the enzyme on Celite and working at low temperatures (close to 0 °C) further improve enzymic enantioselectivity.

The lipase AK-catalysed asymmetric acylation of racemic **1** is an economical route for the preparation of the less reactive (*R*)-solketal **2** in diisopropyl ether. Thus, the enzyme (1 g, *ca.* $3) produces optically pure enantiomer **2** (35 g; ee 99%) and the enzyme, when adsorbed on Celite, can be reused several times without loss of enantioselectivity. The more reactive (*S*)-enantiomer **4** (ee 64%) is obtained through saponification of the other resolution product **3**. The (*S*)-enantiomer can then be racemized as is described in the Experimental section. Consequently, it is theoretically possible to convert racemic solketal **1** into optically pure enantiomer **2** with almost 100% yield. On the other hand, a double-resolution procedure, by subjecting the saponified ester **3** obtained as a result of the first resolution to another biocatalytic acylation, is a method for the preparation of optically pure enantiomer **4**.

Experimental

Materials.—Porcine pancreatic and *Candida cylindracea* lipases were purchased from Sigma Chemical Co. Lipases AK (*Pseudomonas* sp.) and PS (*Pseudomonas cepacia*) were the products of Amano Pharmaceuticals Co. and SAM 2 (*Pseudomonas fluorescens*) was obtained from Fluka. All the solvents were of the highest analytical grade and were used as received. Racemic and (*S*)-solketal, hexan-1-ol, vinyl and isopropenyl acetates, ethyl butyrate and butyric anhydride were the products of Aldrich. Vinyl butyrate was purchased from Tokyo Kasei Kogyo Co. 2,2,2-Trifluoroethyl acetate and butyrate as well as racemic solketal acetate, butyrate and hexanoate (for calibration of a gas chromatograph) were prepared from the corresponding alcohol and acid chloride or anhydride while 2,2,2-trifluoroethyl hexanoate was obtained from 2,2,2-trifluoroethanol, hexanoic acid and thionyl chloride by the usual procedures and work-up.

Assays.—The progress of the reaction and the ee-values of the reactants were followed by taking samples from the reaction mixture at intervals and analysing them gas chromatographically (Perkin-Elmer 8600) with a cyclodextrin-β capillary column (30 m, J & W Scientific). The free solketal enantiomer in the sample was derivatized with acetic anhydride (with propionic anhydride in the case of enzymic acetylation) in the presence of 4-(dimethylamino)pyridine and pyridine before being injected into the gas chromatograph. With butyric anhydride as acyl donor for an enzymic reaction, two injections were necessary: first directly from the sample to obtain the ee-value for compound **3b** and the second after the derivatization to obtain the ee-value for unchanged **2** as an acetate. Both enantiomers of the esters **3a–c** were excellently resolved to the base-line. Specific rotations $[\alpha]_D^{25}$ were determined with a JASCO Model DIP-360 digital polarimeter and their values are given in units of 10^{-1} deg cm^2 g^{-1}.

Adsorption of Lipase AK on Celite.—Sucrose (3.0 g) was dissolved in Tris-HCl buffer (20 mmol dm^{-3}; 250 cm^3; pH 7.8). Lipase AK (5.0 g) premixed with Celite (50 g) was added. The resulting slurry was evaporated under a hood to dryness, ground to a fine powder, and allowed to dry in the open air. Lipase AK was identically adsorbed on Celite using Tris-HCl buffer at pH 9.0. The enzyme preparation adsorbed on Celite at pH 7.8 was used throughout this work if not stated otherwise.

Enzymic Reactions.—The enantioselectivity studies (results in Tables 1–3) and initial rate measurements for the acylation of compound **1** with carboxylic acid derivatives as well as for the deacylation of butyrate **5** with hexan-1-ol were performed using an appropriate amount of a lipase suspended in an organic solvent. As a typical example, a solution of racemic solketal **1** (0.1 mol dm^{-3}) and 2,2,2-trifluoroethyl butyrate (0.2 mol dm^{-3}) in diisopropyl ether (3 cm^3) was added on the lipase AK preparation (7.5 mg; 8.6% lipase AK on Celite). The reaction mixture was shaken at 25 °C. Samples taken at intervals were analysed as described above with respect to the ee-values and the conversion and *E*-values were calculated according to Chen *et al.*[15] The initial rates for the formations of (*R*)- and (*S*)-solketal butyrate were measured by starting with 0.005–0.10 mol dm^{-3} racemic solketal **1** and 0.2 mol dm^{-3} 2,2,2-trifluoroethyl butyrate. In that case, GLC was calibrated with racemic butyrate **5**, and using decan-3-one as an internal standard.

Preparation of (R)-*Solketal* **2**. *Separation of Compound* **2** *and the* (R)-*Butyrate* **3b** *by Distillation.*—Racemic solketal **1** (147 g), butyric anhydride (109 g) and diisopropyl ether (1.5 dm^3) were added to a round-bottomed flask. The flask was placed in an ice-bath at 0–1 °C and the enzyme preparation (18.4 g; 8.6% lipase AK on Celite) was added. Resolution was allowed to proceed under vigorous stirring at 0–1 °C. Under these conditions, the estimated[15] optical purity of (*R*)-solketal **2** at 60% conversion and with $E = 24$ should correspond to 99% ee. At 59% conversion after 28 h, the enzyme was filtered off and the filtrate was stirred with aq. $NaHCO_3$ (60 g in 300 cm^3) overnight. Conc. ammonia (20 cm^3) and after a few hours NaCl (60 g) were added. The organic phase was separated and the water phase was extracted twice with EtOAc (250 cm^3). Combined organic phases were dried with Na_2SO_4 before evaporation of the mixture in a rotary evaporator. The residue was carefully fractionated through a 35 cm distillation column packed with glass balls. Distillation yielded compound (*R*)-**2** (54.9 g, 37%), b.p. 75–78 °C/10–11 mmHg; purity 93% by GLC; ee 98%; $[\alpha]_D^{25}$ −10.7 (*c* 3.8, MeOH); and further distillation gave compound (*R*)-**3b**, b.p. 105–106 °C/10–11 mmHg; ee 69%; purity 99% by GLC.

Preparation of (R)-*Solketal* **2**. *Separation of Compound* **2** *and the* (R)-*Butyrate* **3b** *by Extraction.*—The resolution of racemic solketal **1** (99.0 g) was performed with butyric anhydride (77.0 g) and the enzyme preparation (12.5 g) in diisopropyl ether (1 dm^3) at 0–1 °C as described above. The reaction was stopped at 62% conversion by filtering off the enzyme after 25 h and the solvent was evaporated off. Hexane (150 cm^3) was added and the resulting solution was extracted successively with water (150 cm^3) containing Na_2CO_3 (26 g) and then four times with water (100 cm^3). The hexane phase was evaporated, to leave butyrate (*R*)-**3b** (95.6 g, 63%): ee 59%; purity 95% by GLC. The water phases were combined, saturated with NaCl, and extracted four times with EtOAc (250 cm^3). The extracts were combined, and dried with Na_2SO_4. After evaporation off of the solvent, compound (*R*)-**2** (37.8 g, 38%) was obtained: ee > 99%; purity 88%; $[\alpha]_D^{25}$ −10.2 (*c* 3.9, MeOH).

Preparation of (S)-*Solketal* **4** *by Double Resolution.*—The butyrate (*R*)-**3b** (289 g; ee 64%), obtained by combination of the

products from several preparative-scale resolutions, was heated with aq. NaOH (63 g, in 200 cm^3) in a flask equipped with a reflux condenser. After the vigorous reaction had subsided, the homogeneous solution was extracted three times with EtOAc (300 cm^3). The combined extracts were dried with Na_2SO_4 and filtered through a thin layer of chromatography-grade silica. After evaporation off of the solvent the residue was distilled under reduced pressure through a Vigreux column, to yield title compound (*S*)-**4** (165 g, 87%): ee 64%; purity 97% by GLC; b.p. 77–80 °C/10–11 mmHg; $[\alpha]_D^{25}$ +6.9 (*c* 3.8, MeOH). The product **4** (100 g) was then subjected to a second resolution with butyric anhydride (93 g) and the enzyme preparation (17.8 g) in diisopropyl ether (1 dm^3) at 0–1 °C. After 8.5 h the reaction was stopped at 71% conversion by filtering off the enzyme. The solution was washed successively with aq. NaOH (25 g in 200 cm^3) and three times with water (250 cm^3) to remove butyric acid and unchanged solketal. The organic phase was evaporated, to leave compound (*R*)-**3b** (111 g) with ee 94%; it was estimated * that the second resolution should be stopped below 71% conversion in order to obtain a product with ee >95%. Saponification and distillation as above yielded compound **4** (63.2 g, 63%): ee 94%; b.p. 78–80 °C/10–11 mmHg; purity 95% by GLC; $[\alpha]_D^{25}$ +9.9 (*c* 3.7, MeOH).

Racemization of Optically Active Solketal.—Amberlyst 15 acid resin [1% (w/w)] was added to neat (*S*)-solketal **4** (10 g; ee 64%) and the mixture was stirred at room temperature. The product was practically racemic (ee 2%) within 3 h. The racemization was allowed to proceed overnight and the racemized solketal **1** was isolated by filtering off the resin. It is advisable to filter through Celite in order to eliminate all acidic material from the racemate.

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* Enantiomeric ratio, which equals the ratio of specificity constants (or, roughly, the ratio of initial rates) for the individual enantiomers, can be calculated from the degree of conversion, *c*, and the corresponding enantiomeric excess (ee)-values of the substrate, ee_s, by the equation $E = \ln[(1 - c)(1 - ee_s)]/[\ln(1 - c)(1 + ee_s)]$ where $c = ee_s/(ee_s + ee_p)$. For the reactions which stop at an equilibrium, the equilibrium constant must be inserted in the equation.[15]

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