Double Enantioselective Transesterification of Racemic Carboxylic Esters and Cyclic *meso*-Diols by Lipase Catalysis

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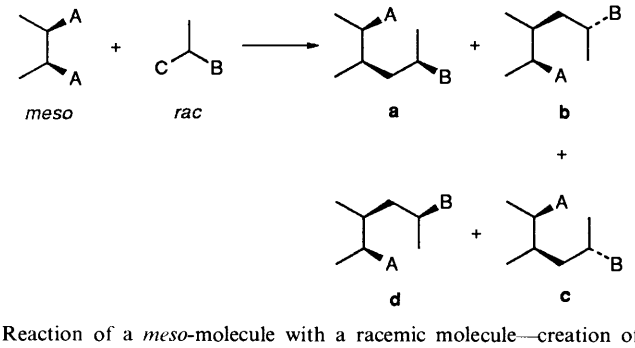
Lipase-catalysed double enantioselective transesterifications of racemic carboxylic esters and cyclic *meso*-diols to give the hydroxy esters **3**, **6**, **9**, **11** and **14** have been investigated. The selectivity of this process is determined by the structure of both substrates and the origin of the lipase. In four of the five cases investigated, lipase SP 382 shows the highest activity and selectivity. In the products, excepting the acyl part of compounds **3**, (*S*)-selectivity for both the alcohol and the acyl moiety has been observed. However, regarding the acyl part the selectivity is poor compared with that of the alcohol part. Application of this method allows us to prepare enantiomerically pure compounds with at least three asymmetric centres in one biocatalytic step if the reaction partners are matching and/or the products are easy to separate as found for compounds **9a**, **9c** and **11a** for instance. The X-ray molecular structures of compounds **9a** and **11a** are reported.

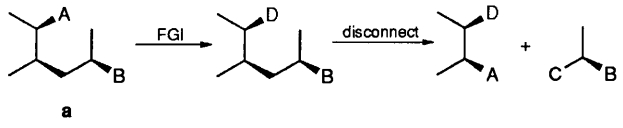
Lipases as chiral catalysts play an important role in the preparation of optically pure compounds by separation of racemates or asymmetrisation of prochiral compounds. Usually, lipase-catalysed esterifications, transesterifications, and interesterifications have been carried out between a racemic or prochiral hydroxy compound and an achiral acylating agent as well as *vice versa* to achieve a kinetic resolution or asymmetrisation of either the alcohol or the carboxylic acid.[1] On the other hand, enzymes are able to discriminate between diastereoisomers in hydrolyses.[2]

It was expected by Chen and Sih[1b] that 'the matching of appropriate racemic acids with racemic alcohols in a double kinetic resolution experiment is an exciting area that warrants systematic exploration in the future.' Until now, only a couple of efforts have been made to obtain a reaction between two racemic partners catalysed by lipases.[3] Two different binding sites for the alcohol and the carboxylic acid are believed to be responsible for chiral discrimination of both racemic partners.[3d] By application of a double enantioselective transesterification it is possible to synthesize molecules with more than one asymmetric centre in a single step using one biocatalyst. The formation of diastereoisomers in this process allows their separation. The separation of the initially formed molecule gives two enantiomerically pure molecules.



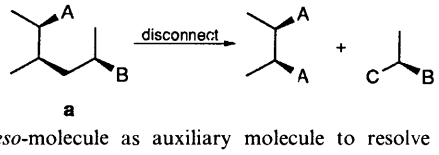
Reaction of a *meso*-molecule with a racemic molecule—creation of molecules with three asymmetric centres

It was our aim to use cyclic *meso*-diols and racemic carboxylic esters as substrates in a lipase-catalysed transesterification to give two diastereoisomeric pairs of enantiomers with at least three asymmetric centres in one step. Reaction of a *meso*- and a racemic (*rac*) compound between the functional groups A and C gives the four stereoisomers **a**–**d** in equal amounts. The isomers **a** and **d** as well as **b** and **c** are enantiomeric. The pairs **a** + **d** and **b** + **c** are diastereoisomeric. The proportions of the isomers **a**–**d** should be influenced in a chiral environment, *e.g.* in the presence of an enzyme if the reaction is enzyme-catalysed.



Creation of two chiral molecules *via* FGI and disconnection

If the reaction is highly selective to give only one stereoisomer, or if it is possible to isolate one of the isomers, for instance **a**, then after a functional-group interconversion (FGI) and a subsequent separation two chiral molecules are available. On the other hand, without FGI a single stereoisomer gives, after separation of the newly formed bond, one enantiomerically pure compound and the starting *meso*-compound which served in this case as an auxiliary compound to resolve the racemic partner in a chiral environment.



Use of *meso*-molecule as auxiliary molecule to resolve a racemic molecule

We recently published preliminary results of the double enantioselective, lipase-catalysed transesterification between the *meso*-diol **8** and the racemic carboxylic ester *rac*-**2**.[4] In order to obtain information on the scope and limitations of this type of reaction and to find matching partners, the structure of the *meso*-diol,[5] the acylating agent and the type of lipase and solvent have been altered. Owing to its reactivity the structure of the carboxylic ester is limited to compounds with electron-withdrawing substituents at the 2-position.[1b]

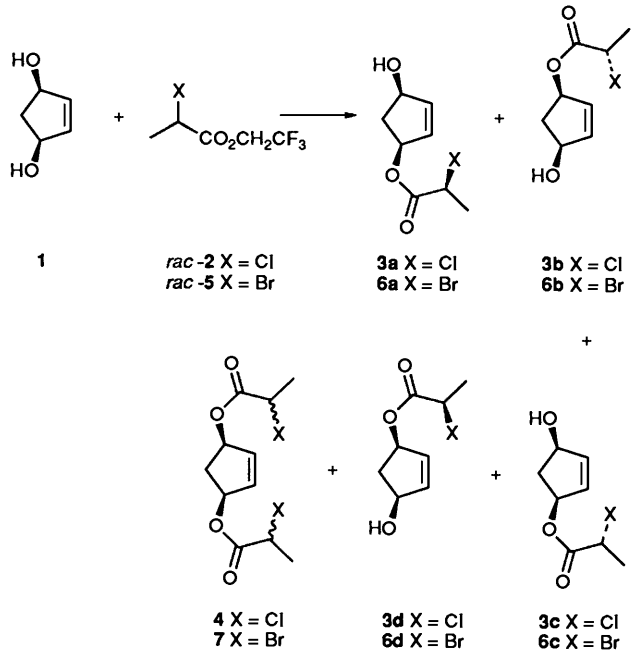
Results

First, we investigated the lipase-catalysed transesterification between the *meso*-diol **1** and 7 mole equivalents of the ester

Table 1 Lipase-catalysed transesterification of the *meso*-diol **1** and *rac*-**2**[a]

Lipase	Time (*t*/h)	Recovery of **1** (%)	Yield of **3a–d** (%)	Yield of **4** (%)	Proportions of **3a**	**3b**	**3c**	**3d**
SP 382[b]	25	0	59	41	35	10	35	20
Amano PS[b]	19	0	62	35	27	11	50	12
PPL[b]	50	65	35		19	19	30	32
Lipozyme[b]	23	60	24	n.d.[d]	32	25	26	17
CCL[b]	23	38	31	n.d.	35	26	26	13
Yarrowia lipolytica[c]	45	35	56	n.d.	41	13	36	10
Rhizopus sp.[c]	52	67	15	n.d.	25	26	26	23

[a] Reaction conditions: **1** (1 mmol), *rac*-**2** (7 mmol), THF (2.5 cm^3), lipase, room temp. [b] 50 mg. [c] 500 mg. [d] Not determined.



Scheme 1 *Reagents and conditions:* lipase, solvent

rac-**2*** in tetrahydrofuran (THF) to give the monoacylated compounds **3a–d**, the diester **4** and unchanged starting material **1** (Scheme 1).

In general, the seven lipases tested showed only very poor selectivity regarding the monoacylated products **3a–d**. The isomeric proportions were analysed by GLC on Lipodex E. The results are summarised in Table 1. Lipase Amano PS showed the highest selectivity of the lipases tested. 77% of the mixture represent the alcohols **3a** + **3c** formed by acylation of the (*S*)-hydroxy group of diol **1** and 23% represent the alcohols **3b** + **3d** formed by acylation of the (*R*)-hydroxy group of diol **1**. The analysis of this experiment regarding the selectivity of the carboxylic acid moiety incorporated in the monoacylated products **3a–d** showed that 62% represent (*R*)-2-chloropropanoic acid and 38% the corresponding (*S*)-acid. The enantiomeric pair **3a** + **3d** could not be separated on a preparative scale from the enantiomeric pair **3b** + **3c**, which pairs are diastereoisomeric to each other. The diester **4** is a *ca.* 1:1 mixture of the *meso*- and the *rac*-form as indicated by ^{13}C NMR spectroscopy.

Using other lipases, the stereochemistry of **4** was not investigated. Solvent variation, often used to enhance selectivity of lipase-catalysed reactions, did not improve the selectivity of the product ratio **3a–d** in the presence of lipase Amano PS as biocatalyst. Diisopropyl ether showed the same selectivity as THF whereas 1,4-dioxane, *tert*-butyl methyl ether, diethyl ether, toluene, and chloroform caused a decrease in selectivity. Replacement of *rac*-**2** by the corresponding 2-bromo ester *rac*-**5** (Scheme 1) in THF in the presence of lipase SP 382 caused a much higher selectivity (Table 2).

In this case, the isomeric ratio was analysed by HPLC on Chiralpak AD. The (*S*)-acylated monoester fraction **6a** + **6c** represents 97.3% and the (*R*)-acylated fraction **6b** + **6d** represents only 2.7% of the whole mixture. The selectivity regarding the carboxylic acid moiety shows 69.8% of the (*S*)-2-bromo acid in **6a** + **6b** and 30.2% of the corresponding (*R*)-enantiomer in **6c** + **6d**. The diastereoisomers **6a** and **6c** could not be separated on a preparative scale. The corresponding diester **7** represents a *ca.* 1:1 mixture of the *meso*- and *rac*-form as shown by ^{13}C NMR spectroscopy. Other lipases tested showed only poor selectivity and a lower rate of conversion.

As known from our earlier investigations[5] the bicyclic *meso*-diol **8** shows a much higher pro-(*S*) selectivity in lipase-catalysed transesterification with vinyl acetate in the presence of different lipases compared with the diol **1**. This high pro-(*S*) selectivity could be confirmed by the lipase-catalysed reaction of diol **8** and the racemic acylating agent *rac*-**2** (Scheme 2). Diester **10** could not be detected. The (*S*)-selectivity for acylation of the diol **8** represented by the mixture of **9a** + **9c** is for three of the lipases tested, very high (Table 3).

In the presence of SP 382,† compound **9a** is the main isomer, whereas in the presence of pancreatin a reversed selectivity, with dominating isomer **9c**, is observed. Whereas SP 382 prefers the (*S*)-enantiomer of the acylating agent, pancreatin prefers the corresponding (*R*)-enantiomer. Either monoester **9a** or **9c** can be prepared as the main product by appropriate choice of enzyme and could be isolated in pure crystalline form, because these diastereoisomers are separable by flash chromatography and/or crystallisation. By using diisopropyl ether, *tert*-butyl methyl ether and toluene as solvent instead of THF the selectivity is not influenced significantly, but in toluene the rate of conversion was decreased. Decrease of the reaction temperature from 25 to 0 °C does not influence the selectivity very much. On the other hand, diminution of the excess of the acylating agent *rac*-**2** is accompanied by a decrease of selectivity (Table 4).

In order to improve the selectivity *rac*-**2** was replaced by the corresponding bromo ester *rac*-**5**. The results for the transesterification of the *meso*-diol **8** and *rac*-**5** are shown in Table 5. Lipase SP 382 gave the diastereoisomers **11a** and **11c** in the

* The rate of conversion was lower, and the selectivity was poor as well, when methyl *rac*-2-chloropropanoate was used instead of *rac*-**2**. On the other hand, vinyl *rac*-2-chloropropanoate is able to acylate diol **1** in the absence of lipase and is therefore unusable in our work.

† Lipase SP 382 (from *Candida antarctica*) consists of components A and B. The selectivity in this reaction is determined by component B (called SP 435) whereas the activity of component A is suppressed in the presence of component B.[6]

Table 2 Lipase-catalysed transesterification of the *meso*-diol **1** and *rac*-**5**[a]

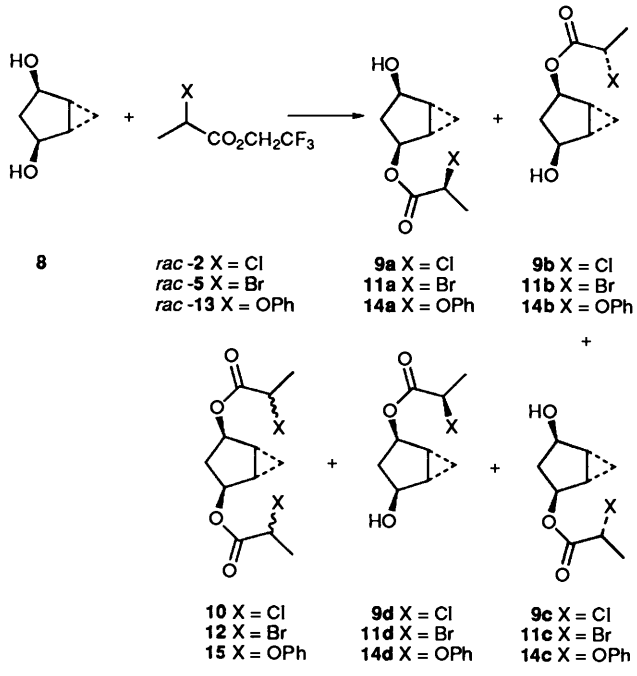
Lipase	Time (*t*/h)	Recovery of **1** (%)	Yield of **6a–d** (%)	Yield of **7** (%)	Proportions of **6a**	**6b**	**6c**	**6d**
SP 382[b]	1.83		68	32	68.2	1.6	29.1	1.1
Amano PS[b]	28		37	55	20.5	23.5	31.2	24.8
Pancreatin[c]	24	14	54	32	21.2	27.1	23.5	28.2
CCL[c]	28	25	75		40.7	14.0	34.1	11.2

[a] Reaction conditions: **1** (1 mmol), *rac*-**5** (7 mmol), THF (2.5 cm^3), lipase, room temp. [b] 50 mg. [c] 500 mg.

Table 3 Lipase-catalysed transesterification of the *meso*-diol **8** and *rac*-**2**[a]

Lipase	Time (*t*/h)	Recovery of **8** (%)	Yield of **9a–d** (%)	Yield of **10** (%)	Proportions of **9a**	**9b**	**9c**	**9d**
SP 382[b]	2.5		95		69.1	0	28.4	2.5
Amano PS[b]	23		92		47.1	1.9	49.9	1.1
Pancreatin[c]	24		92		25.2	0.3	74.5	
CCL[c]	4.5	19	68		47.7	9.0	33.7	9.6

[a] Reaction conditions: **8** (1 mmol), *rac*-**2** (7 mmol), THF (2.5 cm^3), lipase, room temp. [b] 50 mg. [c] 500 mg.



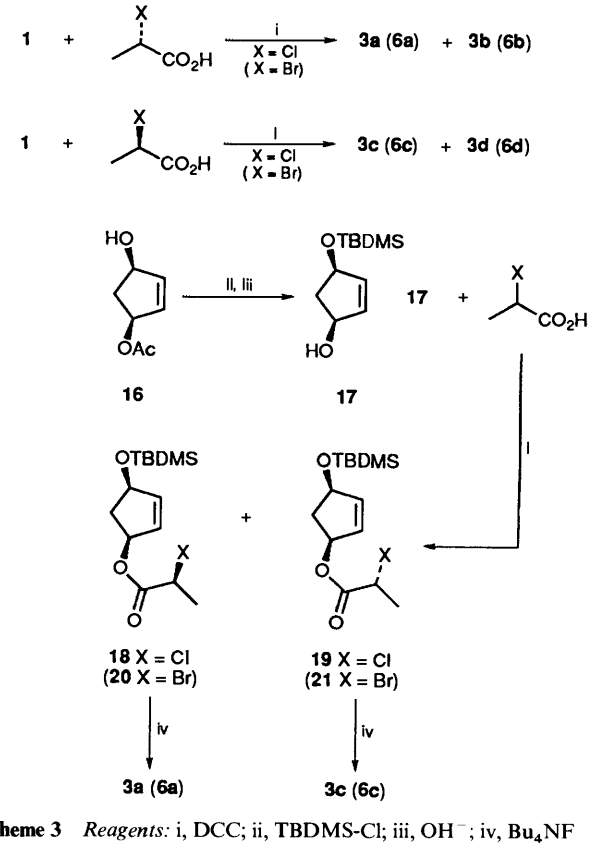
Scheme 2 *Reagent and conditions:* lipase, solvent

ratio 78 : 22 exclusively. The diacylated compound **12** was not formed. This is the highest selectivity observed in all examples investigated.

Both diastereoisomers **11a** and **11c** could be isolated in pure form by crystallisation, which yielded pure isomer **11a**. Subsequent flash chromatography of the mother liquor gave the minor isomer **11c**. Other lipases used as biocatalyst showed decreased selectivity as well as rate of conversion.

The transesterification of diol **8** with the 2-phenoxy ester *rac*-**13** (Scheme 2) in the presence of lipase SP 382 gave, as the main isomers, the (*S*)-acylated alcohols **14a** and **14c** in the ratio 59 : 38 and only traces of the (*R*)-acylated isomers **14b** and **14d**. The diester **15** was not formed. The diastereoisomers **14a** and **14c** could be separated by flash chromatography. Other lipases tested show decreased selectivity and a poor rate of conversion (Table 6). In the latter three cases the isomeric distribution was analysed as follows: analytical and preparative separation by HPLC of the corresponding diastereoisomeric pairs **a** + **d** and **b** + **c** on silica gel, followed by separation of the corresponding enantiomers **a** and **d** as well as **b** and **c** by HPLC on Chiralpak AD.

Assignment of the Structures of the Monoacylated Compounds.—Reaction of the *meso*-diol **1** with (*S*)- and (*R*)-2-chloropropanoic anhydride [prepared *in situ* by reaction of the acid with dicyclohexylcarbodiimide (DCC)] gave 1 : 1 mixtures of monoesters **3a** + **3b** and **3c** + **3d**, respectively. Transformation of the known, enantiomerically pure, monoacetate **16**[5] by silylation with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and subsequent deacetylation gave the alcohol **17**, which was acylated with *rac*-2-chloropropanoic anhydride to give a 1 : 1 mixture of siloxy esters **18** + **19**. Desilylation of the latter mixture gave a 1 : 1 mixture of monoesters **3a** + **3c** (Scheme 3).



Scheme 3 *Reagents:* i, DCC; ii, TBDMS-Cl; iii, OH^-; iv, Bu_4NF

Table 4 Lipase-catalysed transesterification of the *meso*-diol **8** and *rac*-**2** under modified reaction conditions[a]

Lipase	Time (*t*/h)	Temp. (*T*/°C)	Solvent	Equivalents of *rac*-**2**	Yield of **9a–d** (%)	Proportions of **9a**	**9b**	**9c**	**9d**
SP 382	2.5	20	THF	3	91	66.5		33.2	0.3
SP 382	4.25	20	THF	2	96	60.7	0.3	38.0	1.0
SP 382	7	0	THF	7	92	67.5	0.6	28.2	3.7
SP 382	3	20	Pr^i_2O	7	94	65.8	0.5	31.6	2.1
SP 382	3	20	Bu^tOMe	7	88	59.6	2.0	36.0	2.4
SP 382	31	20	Toluene	7	79[b]	62.7	1.4	33.8	2.1
Pancreatin	50	20	Pr^i_2O	7	50[c]	27.7	1.1	69.7	1.5
Pancreatin	48	20	Bu^tOMe	7	58[d]	28.4	2.2	67.4	2.0
Pancreatin	45	20	Toluene	7	12[e]	n.d.	n.d.	n.d.	n.d.

[a] **5** (1 mmol), SP 382 (50 mg) or Pancreatin (500 mg), respectively, solvent, (2.5 cm^3). [b] 15% recovered **8**. [c] 49% recovered **8**. [d] 7% recovered **8** and 32% of **10**. [e] 88% recovered **8**.

Table 5 Lipase-catalysed transesterification of the *meso*-diol **8** and *rac*-**5**[a]

Lipase	Time (*t*/h)	Recovery of **8** (%)	Yield of **11a–d** (%)	Yield of **12** (%)	Proportions of **11a**	**11b**	**11c**	**11d**
SP 382[b]	1.33		96		78.0		22.0	
Amano PS[b]	23	54	16[c]		39.6	1.3	56.2	2.9
Pancreatin[d]	28.5	67	29		44.7	1.3	52.9	1.1
CCL[d]	46	29	69		43.0	9.5	36.5	11.0

[a] Reaction conditions: **8** (1 mmol), *rac*-**5** (7 mmol), THF (2.5 cm^3), lipase, room temp. [b] 50 mg. [c] Unidentified by-products. [d] 500 mg.

Table 6 Lipase-catalysed transesterification of the *meso*-diol **8** and *rac*-**13**[a]

Lipase	Time (*t*/h)	Recovery of **8** (%)	Yield of **14a–d** (%)	Yield of **15** (%)	Proportions of **14a**	**14b**	**14c**	**14d**
SP 382[b]	64		89		59.3	0.9	38.2	1.6
Amano PS[b]	92	47	37		75.8	8.2	14.5	1.5
Pancreatin[c]	92	95						
CCL[d]	66	65	33		45.1	10.9	34.8	9.2

[a] Reaction conditions: **8** (1 mmol), *rac*-**13** (7 mmol), THF (2.5 cm^3), lipase, room temp. [b] 50 mg. [c] 500 mg.

Comparison of these pairs of compounds with the mixture **3a–d**, which was obtained by a lipase-catalysed reaction, by GLC on Lipodex E allowed the assignment of the structure to be made.

The analogous transformation was used to prepare mixtures of isomers **6a** + **6b**, **6c** + **6d** and **6a** + **6c**, respectively (Scheme 3).The mixture of **6a** + **6c** was prepared *via* the esters **20** and **21**. The assignment of the structures from the lipase-catalysed reaction was performed on the basis of comparison of the retention times in HPLC on Chiralpak AD.

Reaction of the *meso*-diol **8** with (*S*)- and (*R*)-2-chloropropanoic anhydride yielded a 1 : 1 mixture of monoesters **9a** + **9b** and **9c** + **9d**, respectively. Transformation of the known, enantiomerically pure, monoacetate **22**[5] *via* the alcohol **23** and the esters **24** and **25** gave a 1 : 1 mixture of products **9a** + **9c** (Scheme 4).

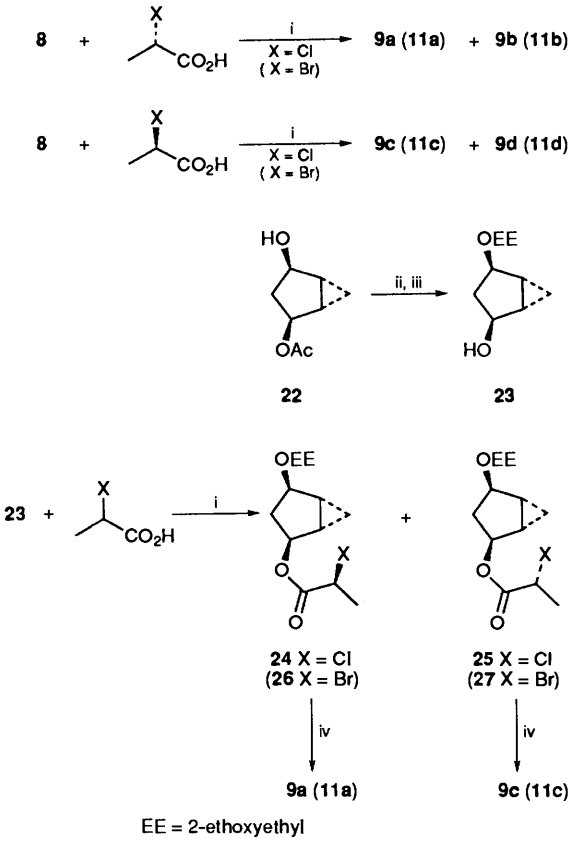
The same reaction sequences were used to prepare the corresponding bromo compounds **11a** + **11b**, **11c** + **11d** and **11a** + **11c**, respectively (Scheme 4). The latter mixture was obtained *via* the esters **26** and **27**. Comparison of the chromatographic behaviour of the above prepared mixtures with the mixtures obtained in the biocatalytic process by HPLC on silica gel and on Chiralpak AD allowed assignment of the structures to be made.

The structures of (*S*)-esters **9a** and **11a** were determined independently by X-ray analysis. In the case of bromopropanoate **11a** it was possible to determine the absolute configuration. X-ray molecular structures are presented in Figs. 1 (for **9a**) and 2 (for **11a**).

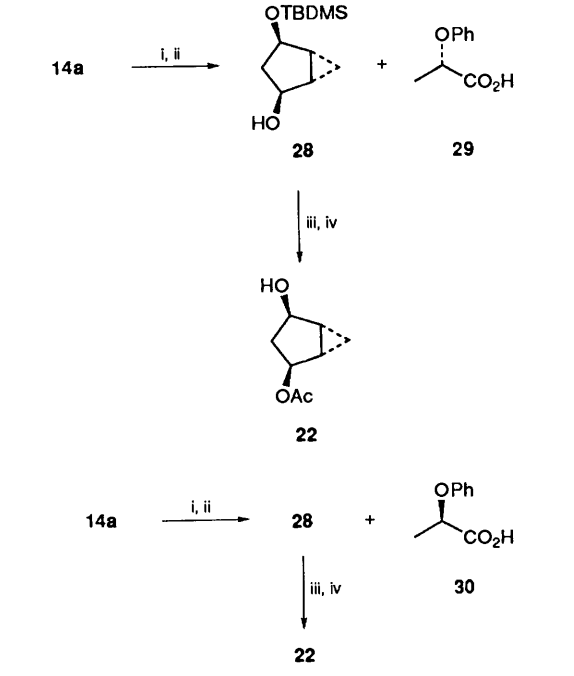
The absolute configuration of the (*S*)-phenoxypropanoate **14a** was determined by degradation according to Scheme 5 to give the known monoacetate **22** and (*S*)-2-phenoxypropanoic acid **29**.[11] The configuration of compound **14c** was determined in an analogous manner to give monoacetate **22** and (*R*)-2-phenoxypropanoic acid **30**.[11]

Discussion

The pathway of double enantioselective lipase-catalysed transesterifications between a racemic carboxylic ester and a *meso*-diol includes two coupled enantiodifferentiation steps. The first step in this transformation is the enantioselection between the enantiomers of the acylating agent to give two diastereoisomeric acyl–enzyme complexes. The second step represents the acyl transfer from the diastereoisomeric acyl–enzyme complexes to one of the prochiral hydroxy groups of the diol. If both the acylating agent and the diol for a given lipase are cooperating in a matching sense one of the four possible stereoisomers should be formed in a highly selective manner. Matching means highly enantioselective separation of the acylating agent and formation of a main acyl–enzyme complex which reacts with high selectivity with one of the prochiral hydroxy groups of the *meso*-diol.



Scheme 4 *Reagents:* i, DCC; ii, CH_2=CHOEt; iii, OH^-; iv, Bu_4NF



Scheme 5 *Reagents:* TBDMS-Cl; ii, OH^-; iii, Ac_2O; iv, Bu_4NF

The poorest selectivity was observed in the formation of compounds **3a–d**. The diol **1** could be acylated highly selectively with achiral acylating agents to give the corresponding (*S*)-acylated alcohols[5,8] with an enantiomeric excess (ee) of >99%. However, this high selectivity was realised by the formation of the corresponding diester from the 'wrong' enantiomer.[8] This diacylation using *rac*-**2** was observed as well but seemed to be not so fast. Therefore, the (*R*)-acylated alcohols **3b** + **3d** could be detected in the reaction mixture to a greater extent. However, replacement of *rac*-**2** by the corresponding bromo ester *rac*-**5** in the presence of SP 382 removed the corresponding (*R*)-acylated alcohols **6b** + **6d** by diacylation to give the corresponding diester **7** besides the monoesters **6a** + **6c**. This result is comparable with those obtained with achiral acylating agents.[5,8]

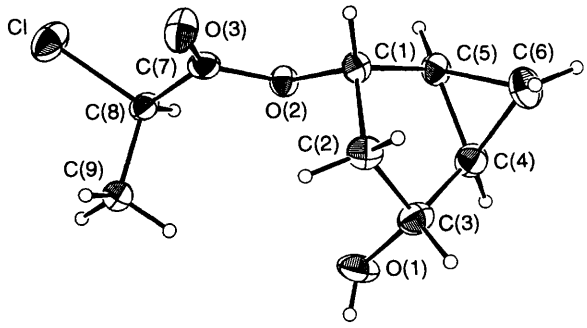


Fig. 1 ORTEP drawing of compound **9a** (50% probability thermal ellipsoids)[7]

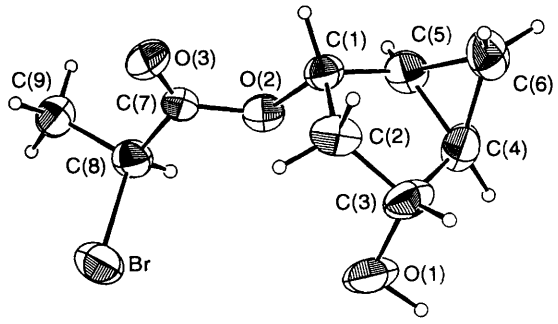


Fig. 2 ORTEP drawing of compound **11a** (50% probability thermal ellipsoids)

The lipase-catalysed acylation of the diol **8** with vinyl acetate gave the corresponding monoesters with ees between 90 and 99% depending on the lipase. In this case only very small amounts of the corresponding diacylated products were obtained. By use of the esters *rac*-**2**, *rac*-**5** and *rac*-**8** the *meso*-diol **8** could be converted into the corresponding (*S*)-acylated alcohols **9a** + **9c**, **11a** + **11c** and **14a** + **14c**, respectively.

Lipase SP 382 in all cases was the enzyme of choice regarding selectivity of both the alcohol and the acyl moiety as well as the rate of conversion. That means that SP 382 is able to accept a broad spectrum of 2-substituted propanoates with an electron-withdrawing group at this position. In the case of the synthesis of compounds **9a–d** the selectivity regarding the acyl moiety was reversed when using pancreatin as biocatalyst, which preferred the (*R*)-acid. However, this was an exception, showing that pancreatin is less flexible in accepting other acylation agents. The highest selectivity was observed in the reaction of diol **8** with the sterically crowded bromo ester *rac*-**5**.

In general, with lipase SP 382 high (*S*)-selectivity was observed for the diols used. On the other hand the selectivity of the incorporated acyl moiety is much lower. This fact may be explained on the assumption that either enantioselection of the acylating agent is poor or that the formed minor acyl–enzyme complex is more reactive towards the *meso*-diols, compensating for higher selectivity in the first step of this coupled double enantioselective process. Apart from some exceptions the other lipases tested were not able to catalyse this process in a comparable manner. In comparison with these facts, best results concerning the resolution of 2-halogeno and 2-phenoxy propanoates were obtained by using an esterification procedure catalysed by the lipase from *Candida cylindracea* (CCL). The

enantioselectivity and the rate of conversion strongly depend on the structure of the alcohol as well as the solvent.[1b,9] CCL is (*R*)-selective in these cases. Furthermore, the enantioselectivity of the lipase-catalysed hydrolysis of 2-phenoxypropanoates in the presence of CCL is poor.[10] The enzyme of choice for the resolution of these acids or their corresponding esters is CCL which, on the other hand, shows little selectivity and low rate of conversion in the double enantioselective process described above. Additionally, the strong dependency of the selectivity on the alcohol in the resolutions of these 2-substituted carboxylic acids does not allow us to predict the selectivity in double enantioselective transesterifications.

All reactions investigated in this paper indicate that it is not easy to predict the overall selectivity of the two coupled enantioselective reactions because the enantioselectivities in the separation of the acyl and the alcohol moiety are not only affected by their own structure, but also by the structure of their counterpart.[3d] However, in general, in the cases investigated regarding the alcohol moiety the selectivity is in accord with that observed for achiral acylating agents. Despite the fact that it is not easy to find matching partners in the lipase-catalysed double enantioselective transesterifications, useful applications could be demonstrated for the formation of compounds with at least three asymmetric centres in one step by using one biocatalyst. More understanding of this coupled process, including the two binding sites of lipases, should help to clarify such processes and to predict matching partners more easily.

Experimental

General.—The following lipases were used: lipase PS (from *Pseudomonas cepacia*, Amano Co., Japan), pancreatin (from porcine pancreas, Fa. Belger, Germany), PPL (from porcine pancreas, Serva), CCL (from *Candida cylindracea*, Serva), lipase from *Rhizopus sp.*, Serva), lipase from *Yarrowia lipolytica* (from the former Institute of Biotechnology of the Academy of Sciences of the GDR), SP 382 (from *Candida antarctica*, Novo Nordisk, A/S, Denmark), Lipozyme 20M (from *Mucor miehei*, Novo Nordisk, A/S, Denmark. Solvents were dried over sodium wire. All reactions were monitored by TLC on glass plates coated with a 0.25 mm layer of silica gel. Compounds were visualised with a 3.5% solution of molybdatophosphoric acid in ethanol. Flash chromatography was performed with silica gel 60 (0.063–0.040 mm). ^{1}H NMR spectra were recorded on a Bruker WP 200 SY instrument and ^{13}C NMR spectra were measured on a Varian Gemini 300 instrument. *J*-Values are given in Hz. EI mass spectra were measured at 70 eV on a GC/MS-Datensystem HP 5985 B. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Specord 75 IR spectrometer (Carl Zeiss).

Lipase-catalysed Transesterification of meso-*Diols and Racemic Carboxylic Esters. General Procedure.*—A solution of the *meso*-diol (1 mol equiv.) in the corresponding solvent (2.5 cm^3 mmol^{-1}) was treated with the racemic carboxylic ester (7 mol equiv.) and stirred with the corresponding lipase for the time indicated in the Tables 1–6 under monitoring by TLC. Then the reaction mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (3 ×). The combined filtrates were evaporated under reduced pressure. The excess of the acylating agent was removed by co-distillation with toluene under reduced pressure. The remaining residues were separated by flash chromatography on silica gel with mixtures of hexane–ethyl acetate as eluent.

Determination of the Isomeric Ratios of the Monoacylated Products.—The proportions of compounds **3a–d** were determined by GLC on Lipodex E (10 m) at 85 °C, using H_2 as carrier gas. The isomeric proportions of compounds **6a–d** were analysed by HPLC on Chiralpak AD (25 cm) with heptane–EtOH (9:1) as eluent. The proportions of isomers **9a–d** were analysed by analytical and preparative separation of the diastereoisomeric mixtures **9a** + **9d** and **9b** + **9c** by HPLC on silica gel 60 (14 cm) with heptane–propan-2-ol (97:3) as eluent. The enantiomers **9a** and **9d**, as well as **9b** and **9c**, were separated by HPLC (25 cm) on Chiralpak AD with heptane–propan-2-ol (8:2) as eluent. The diastereoisomeric proportions of compounds **11a–d** and **14a–d** were determined as for compounds **9a–d**. The enantiomeric proportions of isomers **11a** and **11d/11b** and **11c** as well as **14a** and **14d/14b** and **14c** were analysed as for compounds **9a–d**.

(1R,4S)-4-[(S)- *and* (R)-2-*Chloropropanoyloxy*]*cyclopent*-2-*enol* **3a** + **3c** *and* (1S,4R)-4-[(S)- *and* (R)-2-*Chloropropanoyloxy*]*cyclopent*-2-*enol* **3b** + **3d**.—Starting from diol **1** (0.500 g, 5 mmol) with lipase Amano PS (0.250 g) in THF (12.5 cm^3), monoesters **3a–d** (0.600 g, 62%) and diester **4** (0.497 g, 35%) were obtained. *Compounds* **3a–d**: b.p. 140 °C/1 Pa (bath temp., Kugelrohr). (Found: C, 49.4; H, 5.85. Calc. for $C_8H_{11}ClO_3$·0.25 H_2O requires C, 49.2; H, 5.9%); ν_{max}(film)/cm^{-1} 3370, 3050 and 1725; δ_H(200 MHz; $CDCl_3$) 1.50–1.70 (4 H, dt and d, overlapping, J_d 7), 2.46 (1 H, br s), 2.78 (1 H, dt, *J* 15 and 8), 4.32 (1 H, q, *J* 7), 4.69 (1 H, br s), 5.50 (1 H, m), 5.93 (1 H, m) and 6.10 (1 H, m); δ_C(75 MHz; $CDCl_3$) 21.30, 21.34, 40.16, 52.41, 52.48, 74.60, 78.76, 131.55, 131.60, 139.28, 139.33 and 169.78; *m/z* 173 (M^+ − OH), 134, 109, 99 and 83 (100).

cis-3,5-*Bis*(2-*chloropropanoyloxy*)*cyclopentene* **4** (*mixture of* meso- *and* rac-*form*): B.p. 140 °C/1 Pa (bath temp., Kugelrohr) (Found: C, 46.9; H, 5.1. $C_{11}H_{14}Cl_2O_4$ requires C, 47.0; H, 5.0%); ν_{max}(film)/cm^{-1} 3060 and 1740; δ_H(200 MHz; $CDCl_3$) 1.63 (6 H, d, *J* 7), 1.76 (1 H, dt, *J* 15 and 4), 2.87 (1 H, dt, *J* 15 and 7.5), 4.33 (2 H, q, *J* 7), 5.56 (2 H, dd, *J* 5 and 4) and 6.10 (2 H, s); δ_C(75 MHz; $CDCl_3$) 21.32, 21.38, 36.72, 36.78, 52.28, 52.38, 77.97, 134.60, 134.67 and 169.67 (*meso*:*rac* ratio ~ 1:1); *m/z* 173 [M^+ − MeCH(Cl)CO_2H], 91 (100), 83 and 82.

(1R,4S)-4-[(S)- *and* (R)-2-*Bromopropanoyloxy*]*cyclopent*-2-*enol* **6a** + **6c**.—Starting from diol **1** (0.500 g, 5 mmol) with lipase SP 382 (0.250 g) in THF (12.5 cm^3), products **6a–d** (0.797 g, 68%) and **7** (0.596 g, 32%) were obtained. *Compounds* **6a–d**: b.p. 160 °C/0.5 Pa (bath temp., Kugelrohr) (Found: C, 40.6; H, 4.8. $C_8H_{11}BrO_3$ requires C, 40.9; H, 4.7%); ν_{max}(film)/cm^{-1} 3350, 3070 and 1740; δ_H(200 MHz; $CDCl_3$) 1.50–1.90 (5 H, m and d, overlapping, J_d 7), 2.75 (1 H, dt *J* 15 and 8), 4.28 (1 H, q, *J* 7), 4.68 (1 H, m), 5.49 (1 H, m), 5.90 (1 H, d, *J* 6) and 6.11 (1 H, d, *J* 6); δ_C(75 MHz; $CDCl_3$) 21.47, 21.53, 40.08, 40.12, 40.18, 40.22, 74.74, 78.72, 131.69, 139.29, 139.37 and 169.90; *m/z* 219 + 217 (M^+ − OH), 155, 137 + 135, 109 + 107, 83, 82 and 55 (100).

cis-3,5-*Bis*(2-*bromopropanoyloxy*)*cyclopentene* **7** (*mixture of* meso- *and* rac-*form*): B.p. 160 °C/0.5 Pa (bath temp., Kugelrohr) (Found: C, 35.6; H, 3.8. $C_{11}H_{14}Br_2O_4$ requires C, 35.7; H, 3.8%); ν_{max}(film)/cm^{-1} 3065 and 1735; δ_H(200 MHz; $CDCl_3$) 1.65–1.85 (7 H, dt and d, overlapping, J_d 7), 2.86 (1 H, dt, *J* 15 and 8), 4.30 (2 H, q, *J* 7), 5.55 (2 H, dd, *J* 7 and 3.5) and 6.10 (2 H, s); δ_C(75 MHz; $CDCl_3$) 21.47, 21.54, 36.48, 36.63. 36.76, 39.85, 39.96, 77.89, 77.94, 134.21, 134.51, 134.58, 134.67 and 169.79 (*meso*:*rac* ratio ~ 1:1); *m/z* 219 + 217 [M^+ − MeCH(Br)CO_2H], 137 + 135, 109 + 107 and 82 (100).

(1R,2R,4S,5S)-4-[(2S)-2-*Chloropropanoyloxy*]*bicyclo*[3.1.0]-*hexan*-2-*ol* **9a**.—Starting from diol **8** (0.570 g, 5 mmol) and SP 382 (0.250 g) in THF (12.5 cm^3), monoesters **9a–d** (0.956 g, 95%) were obtained. Recrystallisation of the mixture from hexane–diethyl ether gave compound **9a** (0.420 g) in dia-

stereoisomerically and enantiomerically pure form, m.p. 54–55.5 °C; $[\alpha]_D^{20}$ −24.1 (*c* 1.0, $CHCl_3$) (Found: C, 52.9; H, 6.5. $C_9H_{13}ClO_3$ requires C, 52.8; H, 6.4%); ν_{max}(KBr)/cm^{-1} 3480, 3065, 3055 and 1750; δ_H(200 MHz; $CDCl_3$) −0.07 (1 H, m), 0.57 (1 H, m), 1.50–1.80 (8 H, m and d, overlapping, J_d 7), 4.14 (1 H, dd, *J* 10 and 3), 4.32 (1 H, q, *J* 7) and 5.19 (1 H, d, *J* 3); δ_C(75 MHz; $CDCl_3$) 6.71, 21.02, 21.27, 24.80, 38.06, 52.65, 73.44, 79.05 and 169.54; *m/z* 204 (M^+), 187, 160, 148, 96 (100), 79 and 67.

(1R,2R,4S,5S)-4-[(2R)-2-*Chloropropanoyloxy*]*bicyclo*[3.1.0]-*hexan*-2-*ol* **9c**.—Starting from diol **8** (0.570 g, 5 mmol) with pancreatin (2.500 g) in THF (12.5 cm^3), compounds **9a–d** (0.948 g, 92%) were obtained. Flash chromatography on silica gel (100 g) with hexane–diethyl ether (1:1) gave compound **9a** (0.033 g), a mixture (~1:1) of isomers **9a** + **9c** (0.210 g) and *title compound* **9c** (0.572 g). Recrystallisation of compound **9c** from hexane–diethyl ether gave diastereoisomerically and enantiomerically pure compound **9c** (0.420 g), m.p. 40.5–42.5 °C; $[\alpha]_D^{20}$ −15.2 (*c* 1.0, $CHCl_3$) (Found: C, 52.8; H, 6.45%); ν_{max}(KBr)/cm^{-1} 3450, 3060, 3050 and 1725; δ_H(200 MHz; $CDCl_3$) −0.07 (1 H, m), 0.59 (1 H, m), 1.50–1.90 (8 H, m and d, overlapping, J_d 7), 4.13 (1 H, br d, *J* 10), 4.32 (1 H, q, *J* 7) and 5.17 (1 H, d, *J* 2); δ_C(75 MHz; $CDCl_3$) 6.74, 21.02, 21.37, 24.76, 38.02, 52.78, 73.48, 79.04 and 169.63; *m/z* 204 (M^+), 187, 160, 148, 96, 79 and 67 (100).

(1R,2R,4S,5S)-4-[(2S)-2-*Bromopropanoyloxy*]*bicyclo*[3.1.0]-*hexan*-2-*ol* **11a** and (1R,2R,4S,5S)-4-[(2R)-2-*Bromopropanoyloxy*]*bicyclo*[3.1.0]*hexan*-2-*ol* **11c**.—Starting from diol **8** (0.570 g, 5 mmol) and SP 382 (0.250 g) in THF (12.5 cm^3), compounds **11a–d** (1.200 g, 96%) were obtained. Recrystallisation from hexane–diethyl ether yielded diastereoisomerically and enantiomerically pure compound **11a** (0.520 g). The remaining mother liquor was separated by flash chromatography on silica gel (120 g) with hexane–diethyl ether (1:1) to give a further crop of compound **11a** (0.370 g), a mixture of isomers **11a** + **11c** (0.034 g) and pure compound **11c** (0.196 g) as an oil. *Compound* **11a**: m.p. 64.5–66 °C; $[\alpha]_D^{20}$ −23.6 (*c* 1.0, $CHCl_3$) (Found: C, 43.2; H, 5.2. $C_9H_{13}BrO_3$ requires C, 43.4; H, 5.3%); ν_{max}(KBr)/cm^{-1} 3450, 3065, 3050 and 1750; δ_H(200 MHz; $CDCl_3$) −0.07 (1 H, m), 0.58 (1 H, m), 1.50–1.90 (8 H, m and d, overlapping, J_d 7), 4.15 (1 H, br s), 4.32 (1 H, q, *J* 7) and 5.19 (1 H, d, *J* 3); δ_C(75 MHz; $CDCl_3$) 6.68, 20.93, 21.41, 24.84, 38.01, 40.43, 73.47, 78.96 and 169.60; *m/z* 250 + 248 (M^+), 233 + 231, 206 + 204, 194 + 192, 137 + 135, 109 + 107, 96 (100), 79 and 67.

Compound **11c**: $[\alpha]_D^{20}$ −13.3 (*c* 1.0, $CHCl_3$) (Found: C, 42.9; H, 5.4%); ν_{max}(film)/cm^{-1} 3420, 3060, 3040 and 1730; δ_H(200 MHz; $CDCl_3$) −0.05 (1 H, m), 0.59 (1 H, m), 1.40–2.10 (7 H, m and d, overlapping, J_d 7), 2.48 (1 H, br s), 4.17 (1 H, m), 4.32 (1 H, q, *J* 7) and 5.18 (1 H, m); δ_C(75 MHz; $CDCl_3$) 6.70, 20.87, 21.50, 24.73, 37.89, 40.53, 73.41, 78.88 and 169.40; *m/z* 250 + 248 (M^+), 233 + 231, 206 + 204, 194 + 192, 137 + 135, 109 + 107, 96 (100), 79 and 67.

(1R,2R,4S,5S)-4-[(2S)-2-*Phenoxypropanoyloxy*]*bicyclo*-[3.1.0]*hexan*-2-*ol* **14a** and (1R,2R,4S,5S)-4-[(2R)-2-*Phenoxypropanoyloxy*]*bicyclo*[3.1.0]*hexan*-2-*ol* **14c**.—Starting from diol **8** (0.320 g, 2.8 mmol) and SP 382 (0.140 g) in THF (7 cm^3), compounds **14a–d** (0.730 g, 89%) were obtained. Flash chromatography on silica gel (100 g) with hexane–diethyl ether (1:1) yielded compound **14a** (0.275 g), a mixture of isomers **14a** + **14c** (0.122 g) and compound **14c** (0.243 g). Repeated chromatography (20 g) of the mixture gave a further crop of compound **14a** (0.070 g), a mixture of isomers **14a** + **14c** (0.012 g) and compound **14c** (0.040 g). The diastereoisomeric purity of compound **14a** was 97% and that of compound **14c** 98%. *Compound* **14a**: Oil, b.p. 240 °C/1 Pa (bath temp.; Kugelrohr); $[\alpha]_D^{20}$ −49.1 (*c* 1.0, $CHCl_3$) (Found: C, 68.4; H, 7.1. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); ν_{max}(film)/cm^{-1} 3450, 3060, 3040, 1740, 1600, 1590 and 1490; δ_H(200 MHz; $CDCl_3$) −0.14 (1 H, m), 0.49 (1 H, m), 1.30–1.80 (8 H, m and d, overlapping, J_d 7), 4.04 (1 H, m), 4.73 (1 H, q, *J* 7), 5.15 (1 H, d, *J* 4) and 6.80–7.66 (5 H, m); δ_C(75 MHz; $CDCl_3$) 6.63, 18.43, 21.09, 24.74, 38.15, 72.40, 73.20, 77.90, 114.86, 121.69, 129.67, 157.37 and 171.59; *m/z* 262 (M^+), 245, 220, 205, 192, 166, 121 (100), 107, 97, 95, 79, 77 and 67.

Compound **14c**: Oil; b.p. 240 °C/1 Pa (bath temp.; Kugelrohr); $[\alpha]_D^{20}$ +22.6 (*c* 1.0, $CHCl_3$) (Found: C, 67.5; H, 7.0. $C_{15}H_{18}O_4 \cdot 0.25\ H_2O$ requires C, 67.5; H, 7.0%); ν_{max}(film)/cm^{-1} 3450, 3060, 3040, 1740, 1600, 1585 and 1490; δ_H(200 MHz; $CDCl_3$) −0.12 (1 H, m), 0.54 (1 H, m), 1.35–1.80 (8 H, m and d, overlapping, J_d 7), 4.03 (1 H, br d, *J* 4), 4.73 (1 H, q, *J* 7), 5.21 (1 H, d, *J* 4) and 6.80–7.27 (5 H, m); δ_C(75 MHz; $CDCl_3$) 6.70, 18.47, 21.08, 24.30, 37.64, 72.30, 73.25, 78.17, 114.73, 121.61, 129.66, 157.35 and 171.72; *m/z* 262 (M^+), 245, 205, 179, 166, 121 (100), 107, 97, 95, 79, 77 and 67.

Preparation of the Compounds for Structural Assignment.—(a) *Preparation of the mixtures* **3a** + **3b** *and* **3c** + **3d**, *respectively*. A solution of (*S*)-2-chloropropanoic acid (0.434 g, 4 mmol) in CH_2Cl_2 (4 cm^3) was treated with DCC (0.412 g, 2 mmol) and stirred for 10 min at room temp. The resulting suspension was added at 0 °C to a solution of diol **1** (0.200 g, 2 mmol) in pyridine and the mixture was stirred for 50 min. The reaction was quenched by addition of MeOH (0.5 cm^3). The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel (10 g) with hexane–ethyl acetate (2:1) to give a 1:1 mixture of diastereoisomers **3a** + **3b** (0.250 g). The ^1H NMR spectrum was identical with that for the mixed products **3a–d** obtained by a lipase-catalysed reaction. In the same manner, using (*R*)-2-chloropropanoic acid, a 1:1 mixture of diastereoisomers **3c** + **3d** (0.280 g) was obtained.

(b) *Preparation of the mixture of isomers* **3a** + **3c**. A solution of enantiomerically pure monoacetate **16** (1.000 g) was silylated in the usual manner with TBDMS-Cl and imidazole in dimethylformamide (DMF) to give the corresponding silyl ether (1.73 g). The latter compound was deacetylated in the usual manner in the presence of the strongly basic ion-exchange resin Wofatit SBW (OH^-) in MeOH to give, after flash chromatography, the alcohol **17** (1.100 g). Acylation of compound **17** (0.428 g) with *rac*-2-chloropropanoic anhydride (prepared *in situ* by reaction of the corresponding acid with DCC) in the usual manner in pyridine gave, after flash chromatography, a 1:1 mixture of chloroacetates **18** + **19** (0.522 g). Desilylation of compounds **18** + **19** (0.480 g) gave a 1:1 mixture of the alcohols **3a** + **3c** (0.190 g) contaminated with their isomers **3b** + **3d** as by-products. The ^1H NMR spectrum of this mixture was identical with that of compounds **3a–d** obtained by lipase-catalysed reaction.

(c) *Preparation of mixtures of isomers* **6a** + **6b**, **6c** + **6d** *and* **6a** + **6c**, *respectively*. The above described procedures (a) and (b) with the corresponding (*S*)-, (*R*)- and *rac*-2-bromopropanoic acids, respectively, gave the title compounds as 1:1 mixtures.

(d) *Preparation of the mixtures of compounds* **9a** + **9b** *and* **9c** + **9d** *as well as bromopropanoates* **11a** + **11b** *and* **11c** + **11d**. These 1:1 mixtures were prepared in analogy to the above described procedure (a) by using the diol **8** and (*S*)- and (*R*)-2-chloropropanoic anhydrides and the corresponding 2-bromo anhydrides, respectively.

(e) *Preparation of the mixtures of compounds* **9a** + **9c** *and* **11a** + **11c**. Reaction of the enantiomerically pure monoacetate **22** (0.153 g) with ethyl vinyl ether gave the corresponding (2-ethoxy)ethyl ether (0.222 g), which was deacetylated with the strongly basic ion-exchange resin Wofatit SBW (OH^-) in

Table 7 Crystal data of compounds **9a** and **11a**

	9a	**11a**
Chemical formula	$C_9H_{13}ClO_3$	$C_9H_{13}BrO_3$
a (Å)	8.916 (3)	9.285 (3)
b (Å)	19.277 (7)	5.521 (1)
c (Å)	5.520 (1)	10.018 (2)
β (°)	90.0	100.24 (2)
V (Å^3)	948.8 (5)	505.4 (2)
Space group	$P2_12_12_1$	$P2_1$
Z	4	2
D_x (gcm^{-3})	1.43	1.68
μ (cm^{-1})	3.71	40.08
θ-range (°)	1.5, 28	1.5, 25
h_{min}, h_{max}	0, 7	−11, 11
k_{min}, k_{max}	0, 11	−6, 6
l_{min}, l_{max}	0, 25	0, 11
No. of reflections measured	1393	950
No. of observed reflections	940 [$F_o > 2\sigma(F_o)$]	799 [$F_o > 1\sigma(F_o)$]
Treatment of hydrogen atoms	calculated except for hydroxy hydrogen	calculated
No. of parameters refined	123	118
$R(R_w)$	0.051 (0.050)	0.041 (0.041)
$(\Delta\rho)_{max}$ (e Å^3)	0.357	0.439

MeOH in the usual manner to give compound **23** (0.200 g). Acylation of the alcohol **23** (0.180 g) with *rac*-2-chloropropanoic anhydride (prepared *in situ* by reaction of the corresponding acid with DCC) in the usual manner in pyridine gave, after flash chromatography, a 1:1 mixture of diastereoisomeric chloropropanoates **24** + **25** (0.163 g). The mixture was deprotected in the usual manner with the strongly acidic ion-exchange resin Wofatit KPS (H^+) in MeOH to give, after flash chromatography, a 1:1 mixture of compounds **9a** + **9c** (0.080 g). The ^{1}H NMR spectrum was identical with that of compounds **9a–d** obtained by a lipase-catalysed reaction. The corresponding mixture of bromopropanoates **11a** + **11c** was prepared in the analogous manner using *rac*-2-bromopropanoic anhydride.

(f) *Determination of the absolute configuration of compounds* **14a** *and* **14c**. Compound **14a** (0.100 g) was silylated in the usual manner with TBDMS-Cl and imidazole in DMF to give the corresponding silyl ether (0.137 g). A solution of the latter compound in MeOH (10 cm^3) was treated with 1 mol dm^{-3} aq. NaOH (0.5 cm^3) and stirred for 2.5 h at room temp. MeOH was removed under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with diethyl ether (3 ×). The organic extract was dried ($MgSO_4$) and the solvents were removed under reduced pressure to give crude siloxy alcohol **28** (0.055 g). The aqueous phase was acidified with acetic acid and extracted with $CHCl_3$ (3 ×). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (10 g) with ethyl acetate–hexane–acetic acid (7:3:0.1) to give (*S*)-2-phenoxypropanoic acid **29** (0.031 g), $[\alpha]_D^{20}$ −27.0 (*c* 2.1, EtOH) {lit.,[11] $[\alpha]_D^{20}$ −39.3 (*c* 2.2, EtOH)}; ee 89%: determined by HPLC on cellulose tris-(3,5-dimethylphenylcarbamate).

A solution of crude siloxy alcohol **28** was acetylated in the usual manner (Ac_2O, pyridine) and subsequently desilylated in the usual manner (Bu_4NF). Flash chromatography of the residue on silica gel with ethyl acetate–hexane (2:1) as eluent yielded monoacetate **22** (0.050 g), $[\alpha]_D^{20}$ −12.3 (*c* 1.5, $CHCl_3$) {lit.,[5] $[\alpha]_D^{20}$ −16.0 (*c* 1.0, $CHCl_3$)}.

The analogous reaction sequence starting with compound **14c** gave (*R*)-2-phenoxypropanoic acid **30** (0.033 g), $[\alpha]_D^{20}$ + 30.2 (*c* 1.9, EtOH) {lit.,[11] $[\alpha]_D^{20}$ +39.3 (*c* 2.5, EtOH)}; ee 91%: determined by HPLC on cellulose tris(3,5-dimethylphenylcarbamate); further elaboration of compound **28** as above gave the monoacetate **22** $[\alpha]_D^{20}$ −10.4 (*c* 1.0, $CHCl_3$).

X-Ray Structure Analysis.—Data were collected on a CAD-4 diffractometer using graphite-monochromatised Mo-Kα radiation (λ 0.710 37 Å). The cell dimensions were determined by least-squares refinement employing the setting angles of 25 reflections. The data were corrected for Lorentz and polarisation effects and extinction. The structures were solved by MULTAN11/82,[12] Fourier methods and were refined by full-matrix least-squares procedures which minimised the function $\Sigma w(\Delta F)^2$. Applied weighting scheme was $w(F) = 1/\sigma(F)^2$. The applied program system was Enraf-Nonius MolEN.[13] The absolute configuration of compound **11a** was determined by comparison of the *R*-values of the enantiomers. Compound **9a** decomposed at room temp. under X-rays. Therefore the structure was investigated at 213 K. Table 7 summarises details.

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