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Chemoenzymatic synthesis of enantiomerically enriched α-chiral 3-oxy-propionaldehydes by lipase-catalyzed kinetic resolution and desymmetrization

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Abstract—Enantiomerically enriched phenylalanine- and leucine aldehyde analogues have been prepared by lipase catalyzed desymmetrization or kinetic resolution of 1,3-propanediol derivatives as key steps. Observations of unusual enantioselectivity were made, and most notably, *Candida antarctica* lipase B showed an opposite enantiopreference from other lipases, which was exploited in the synthesis. A thorough evaluation of chemoenzymatic routes to both enantiomers of the target α-chiral 3-oxy-propionaldehydes resulted in simple, inexpensive, and efficient procedures that provide the products in up to 92% enantiomeric excess and 55% total yield in five steps from easily accessible starting materials.

1. Introduction

As part of our research program directed toward the development of peptidomimetics, access to amino acid equivalents in which the amino function is replaced by an aldehyde and the C-terminus is represented by a protected alcohol (e.g. **1a**–**b**, Fig. 1), is needed. This implies the preparation of 2-substituted 3-oxy-propionaldehydes with defined stereochemistry at the 2-position.

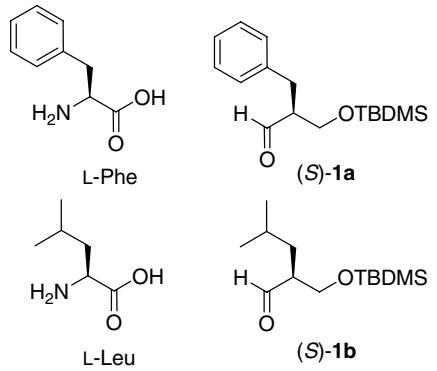

Figure 1. Optically active aldehyde equivalents **1a**–**b** of the amino acids phenylalanine and leucine, respectively.

α-Chiral propionaldehydes can be prepared by several procedures.[1,2] The most commonly employed protocol involves the use of oxazolidinones as chiral auxiliaries to introduce the desired stereochemistry at C-2.[2] Although such approaches have been successfully applied on several occasions, they are stoichiometric in auxiliary, and require several steps to prepare the diastereomeric adduct and finalize the aldehyde product. Recently, lipases (triacylglycerol ester hydrolases, EC 3.1.1.3)[3,4] were also used as asymmetric catalysts in the preparation α-chiral propionaldehydes as intermediates in syntheses of more complex compounds.[5] 2-Substituted 3-oxy-propionaldehydes are of great interest as building blocks within the fields of medicinal chemistry and peptidomimetics,[6,7] and in total synthesis.[8] In all the literature reports mentioned above, the aldehydes have been used immediately for subsequent transformations, usually without characterization.

Both enantiomers of the phenylalanine and leucine analogues **1a**–**b** (Fig. 1) were selected as our primary target aldehydes. Considering that the asymmetric center can be presumed to be stereochemically labile, the synthetic method must be designed to avoid racemization. We set out to develop a simple, expedient, and inexpensive route to these derivatives. In view of synthetic efficiency and

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yield, asymmetric catalysis by lipases stood out as the most promising procedure although extensive optimization may be required for good enantioselectivity. Two principal reaction modes may be utilized, kinetic resolution of racemates[9] or desymmetrization of prochiral or *meso* substrates.[10]

Herein, we report a full account of our efforts to find a lipase-based method for preparing both enantiomers of aldehydes **1a**–**b**. Observations of unusual stereoselectivity and substrate recognition of lipases are discussed and methods which allow the isolation of the target aldehydes in high yield and enantiomeric excess are presented.

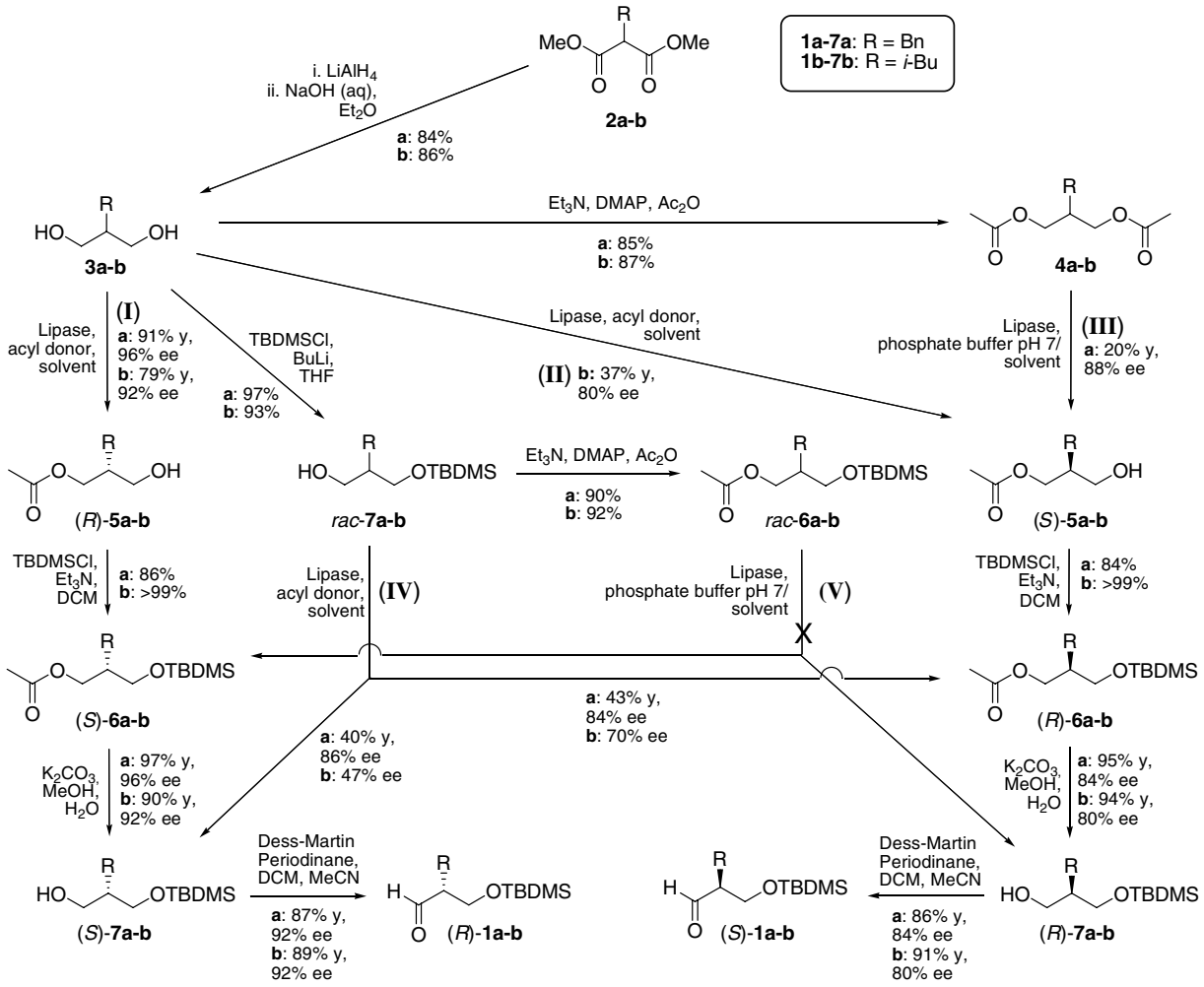
2. Results and discussion

2.1. Lipase-based synthetic routes to chiral aldehydes 1a–b

For maximum synthetic efficiency, we wanted to find a common precursor for both enantiomers of aldehyde **1a** or **1b**. Considering that a 1,3-propanediol motif is present in the target compounds, a lipase catalyzed desymmetrization step was considered most suitable for the introduction of asymmetry (Scheme 1, routes I and III).[10] Kinetic resolution may also be a viable alternative. Although this would decrease the maximum yield to 50%, it would confer added synthetic efficiency since fewer steps toward the aldehydes would involve enantiomerically enriched material (Scheme 1, routes IV and V). Enantioselectivity may be a limiting factor of such a strategy since lipases generally are less selective toward primary alcohols with high conformational flexibility.[9]

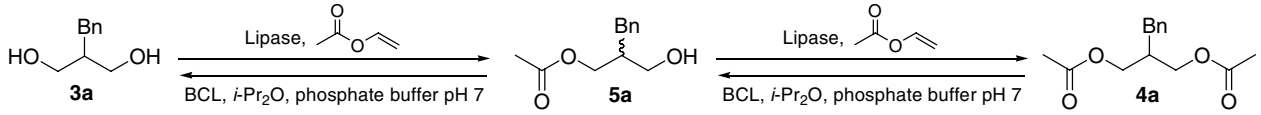
2.2. Introducing asymmetry by desymmetrization of the benzyl derivatives 3a and 4a

Benzyl derivatives **3a** and **4a** (Scheme 1) have been studied previously,[11–13] and BCL[14] has been reported to be a suitable catalyst for desymmetrization. Diol **3a** was treated with vinyl acetate in the presence of BCL, and the reaction was run to full conversion with no resymmetrization to diacetate **4a**, and monoacetate (*R*)-**5a** was isolated in 96% ee and 91% yield (Table 1, entry 1).



Scheme 1. An overview of synthetic routes to aldehydes **1a**–**b** via enzymatic desymmetrization or kinetic resolution. The indicated yields and enantiomeric purities are representative for larger scale reactions. For details of reaction conditions, yields, enantiopreference, and ee's, see: (I) **a**: Table 1, **b**: Table 5; (II) Tables 5 and 6; (III) **a**: Table 1 and Figure 2, **b**: Table 4; (IV) **a**: Table 2 and Figure 3, **b**: Table 3; (V) All reactions failed.

Table 1. Desymmetrization of **3a** and **4a** by lipase catalyzed acetylation and hydrolysis[a]



Entry	Lipase	Substrate	Product[b]	Time (h)	Catalyst loading (mg mmol^{-1})	Conversion[c] (%) **3a**:**5a**:**4a**	Isolated yield (%)	ee[d] (%)
1	BCL	**3a**	(*R*)-**5a**	2	66	0:100:0	91	96
2	BCL	**4a**	(*S*)-**5a**	40	60	32:34:34	30	62
3	BCL	**4a**	(*S*)-**5a**	22	60	45:28:26	20	88
4	CALB	**3a**	(*R*)-**5a**	0.5	17	74:26:0	[e]	18
5	CALB	**3a**	(*S*)-**5a**	2.25	17	0:41:59	[e]	22

[a] Reaction conditions: for acetylation, substrate (0.38 M), and lipase were stirred in vinyl acetate at rt; for hydrolysis, substrate (0.1 M) and BCL were vigorously stirred in *i*-Pr_2O/0.1 M phosphate buffer pH 7 (1:2) at rt.
[b] Absolute configuration was established by direct comparison of specific rotation, see Refs. 11–13.
[c] Determined by RP-HPLC.
[d] Determined by chiral GC after transformation into alcohol **7a** (Scheme 1), and/or chiral HPLC of the filtered reaction mixture.
[e] Product not isolated.

To obtain access also to monoacetate (*S*)-**5a**, desymmetrization of diacetate **4a** by hydrolysis was investigated. The BCL-mediated hydrolysis of **4a** was slow compared to the aforementioned acetylation reaction and the rate decreased as the reaction progressed. The formation of **5a** was accompanied by resymmetrization into diol **3a** at a comparable rate, leading to a decrease in enantiomeric purity of (*S*)-**5a** (Table 1, entries 2 and 3).[15] These results prompted us to investigate the stereochemical course of the hydrolysis reaction in detail, and to this end, the conversion and enantiomeric excess were monitored at intervals during BCL catalyzed hydrolysis of **4a**. From the results (Fig. 2), it is evident that high enantiomeric purity of (*S*)-**5a** is only attainable at low conversion. The first step of the hydrolysis reaction proceeds with reasonable stereoselectivity; however, resymmetrization to **3a** is accompanied with loss of stereochemical integrity, indicating that (i) the reactivity of (*S*)-**5a** is higher than (*R*)-**5a** in the second step, and/or (ii) the reaction is accompanied by a racemization process. The rate of conversion decreases as **3a** is formed and after 100 h, it essentially halts (Fig. 2). We took this as an indication that **3a** or **5a** may be inhibiting the enzyme, and left the reaction for an additional 70 h after which complete racemization had occurred. This suggests the presence of a secondary racemizing reaction since no conversion was evident during this period. To clarify if the racemization is a spontaneous process or if it can be attributed to the enzyme, a sample of (*R*)-**5a** was stirred in the reaction medium without lipase. No racemization was detected in 72 h, indicating that the enzyme preparation may facilitate racemization, or that an equilibrium between **3**–**5a** is established. Loss of enantioselectivity by product inhibition of lipases has been reported previously.[3,16]

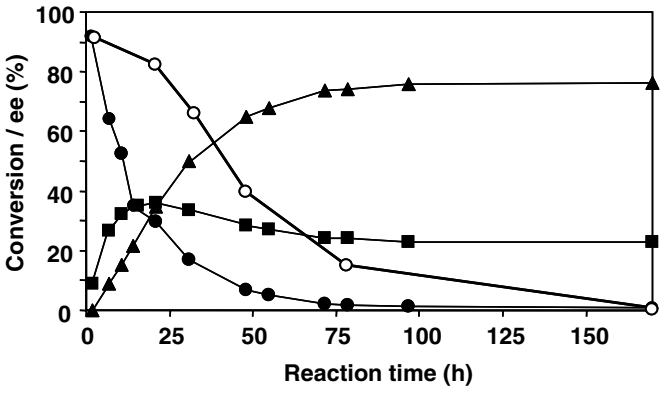


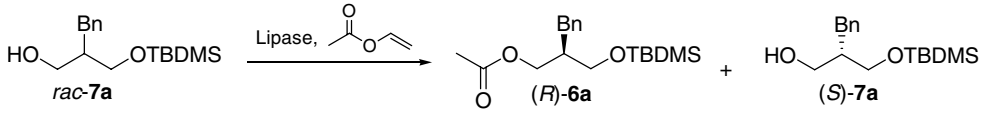
Figure 2. The dependence of the enantiomeric excess (○) on the degree of conversion for monoacetate (*S*)-**5a** during BCL catalyzed desymmetrization of diacetate **4a** (●) to **5a** (■) and subsequent resymmetrization to diol **3a** (▲) by hydrolysis. The parameters were monitored by chiral HPLC (○) and RP-HPLC (●, ■, ▲).

Desymmetrization of the benzyl derivative **3a** was a promising entry toward aldehyde (*R*)-**1a** (Scheme 1), but (*S*)-**1a** did not seem accessible in acceptable yield or enantiomeric purity by this route. Rather than trying to optimize the hydrolysis reaction we decided to try an alternative strategy involving the kinetic resolution of *rac*-**7a**.

2.3. Kinetic resolution of benzyl derivative 7a

Treatment of *rac*-**7a** with vinyl acetate in the presence of BCL did not give a satisfactory reaction rate, and the ee of alcohol (*S*)-**7a** was low (Table 2). Attempts with different solvents gave no improvement (data not shown). We then turned to other enzymes, among which PPL[14] was found to have the most promising characteristics in the screen, yielding both (*R*)-**6a** and (*S*)-**7a** in high ee (Table 2). The PPL catalyzed resolution reaction was investigated in detail to fully assess the relationship between the enantiomeric purity and the degree of conversion for both products (Fig. 3). The enantiomeric ratio (*E*)[17] was determined to be 38 ± 1 by linear regression analysis of the data for (*S*)-**7a**.[18] The same analysis of the data for (*R*)-**6a** was less consistent, indicating that *E* is dependent on conversion, which results in an inaccurate determination.[19] An explanation for this behavior may be that commercial PPL is contaminated by several other hydrolases.[3] A larger scale reaction was performed with the guidance of Figure 3 to produce both products in maximal yield and an acceptable

Table 2. Lipase screening for kinetic resolution of *rac*-**7a** (0.12 M) in vinyl acetate at rt (entries 1–5), and larger scale synthesis with PPL (entry 6)



Entry	Lipase	Catalyst loading (mg mmol^{-1})	Time	Conversion[a] (%)	Isolated yield (%)		ee[b] (%)		'*E*'[c]
					6a	**7a**	(*R*)-**6a**	(*S*)-**7a**	
1	BCL	40	34 d	42	36	37	n.d.	24	n.d.
2	ANL	280	26 h	6	n.d.	n.d.	n.d.	n.d.	n.d.
3	CALB	28	3 h	51	[d]	[d]	32	40	3
4	PPL	280	26 h	42	26	50	91	70	44
5[e]	PPL	280	39 h	47	44	43	86	86	37
6[f]	PPL	422	22 h	48	43	40	84	86	32

[a] Determined by RP-HPLC.
[b] Determined by chiral GC [for (*R*)-**6a** after hydrolysis to alcohol (*R*)-**7a**, Scheme 1], and/or chiral HPLC of the filtered reaction mixture. Absolute configurations were determined by chemical correlation (Scheme 1).
[c] The *E* values, designated as '*E*', are calculated based on the ee's at the conversion shown only, and are to be seen as estimates for relative comparisons of enantioselectivity, see Ref. 20.
[d] Products not separated.
[e] Performed at 32 °C.
[f] Larger scale reaction (16.6 mmol substrate).

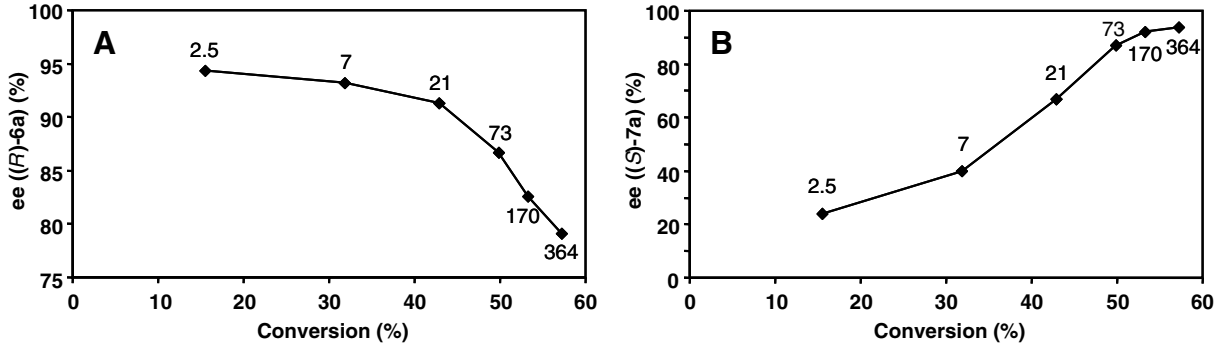


Figure 3. Enantiomeric excess as a function of conversion for (*R*)-**6a** (A) and (*S*)-**7a** (B) during PPL catalyzed kinetic resolution of *rac*-**7a** by acetylation. Reaction time (h) is indicated near the data points. Conversion and ee's were monitored by RP-HPLC and chiral HPLC of the reaction mixture.

enantiomeric excess (Table 2, entry 6). A higher catalyst loading increased the reaction rate in this experiment with no notable change in enantioselectivity.

2.4. Resolution of isobutyl derivatives 6b and 7b

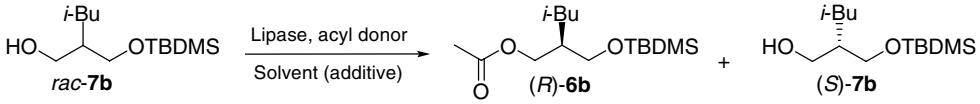
Since the kinetic resolution was useful for preparing the benzyl derivatives, it was considered first for the preparation of optically active precursors to aldehydes (*R*/*S*)-**1b** (Scheme 1). It was anticipated that good enantioselectivity could also be achieved in resolution of alcohol *rac*-**7b**, since it is similar to *rac*-**7a** in terms of substituent size and lipophilicity. Various lipases were screened in acetylation of *rac*-**7b** (Table 3). Remarkably, PPL had low catalytic efficiency and enantioselectivity. BCL was found to be the best catalyst of the lipases tested, albeit that the low reaction rate and enantioselectivity called for optimization. A variety of solvents were tried and modest increases in enantioselectivity were observed, although the reaction rate did not improve (Table 3). Amine additives have been reported to have a beneficial effect on rates and enantioselectivities in some lipase catalyzed reactions,[21] but in our hands, the addition of catalytic amounts of triethylamine or pyridine to the reaction medium had no significant effect.

The reverse reaction, the resolution of acetate *rac*-**6b** by hydrolysis was also tried (Scheme 1, route V). Rates were in all cases impractically low (data not shown), PFL[14] being the most reactive to give a conversion of 6% in 68 h (no background reaction could be detected in 360 h).

2.5. Desymmetrization of the isobutyl derivatives 3b and 4b—synthesis of (*R*)-5b

We then turned our attention to the desymmetrization of diol **3b** and diacetate **4b** as an entry toward aldehydes **1b** (Scheme 1). Asymmetric hydrolysis of **4b** was attempted with BCL in biphasic systems consisting of phosphate buffer and various immiscible solvents. Reaction rates were generally low (data not shown), but highest in diisopropyl

Table 3. Selected results of lipase screening (entries 1–5) and reaction optimization attempts (entries 6–11) of the kinetic resolution of *rac*-**7b**



Entry	Lipase	Solvent (additive)[a]	Acyl donor[b]	Catalyst loading (mg mmol^{-1})	Time (h)	Conversion[b] (%)	ee[c] (%)		'*E*'[d]
							(*R*)-**6b**	(*S*)-**7b**	
1	PPL	VA	VA	345	191	36	33	16	2
2	ANL	VA	VA	369	174	39	20	12	2
3	PFL	VA	VA	369	5	47	23	27	2
4	CALB	VA	VA	49	2	49	48	40	4
5	BCL	VA	VA	369	119	52	50	62	5
6	BCL	Toluene	VA	246	144	44	70	47	9
7	BCL	Toluene (Et_3N)	IPA	246	332	37	75	39	10
8	BCL	$CHCl_3$	VA	246	144	13	87	10	16
9	BCL	*i*-Hexane	VA	246	96	52	70	60	10
10	BCL	*i*-Hexane (pyridine)	VA	246	71	29	71	27	8
11	BCL	*i*-Hexane	IPA	246	71	14	83	11	12

Reaction conditions: Substrate (0.15 M) was shaken in solvent with 5 equiv of acyl donor in the presence of lipase and when applicable, 0.1 equiv of additive.

[a] VA = vinyl acetate, IPA = isopropenyl acetate.

[b] Determined by GC.

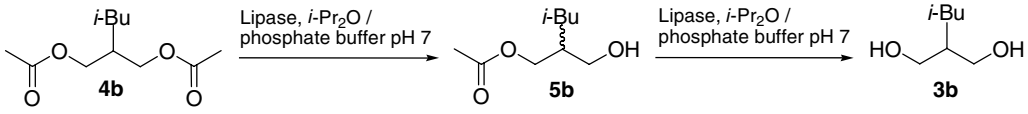
[c] Determined by chiral GC on a sample of filtered reaction mixture. Absolute configurations were determined by stereochemical correlation (Scheme 2).

[d] The *E* values, designated as '*E*', are calculated based on the ee's at the conversion shown only, and are to be seen as estimates for relative comparisons of enantioselectivity, see Ref. 20.

ether, which was used in the following screen. Heating the reaction had only a marginal effect on the rate. Four additional lipases were screened (Table 4), none had good enantioselectivity and in all cases the rate decreased considerably as the reaction progressed. Complete racemization resulted after prolonged reaction times (up to 30 days). As observed in the desymmetrization of the benzyl derivative **4a** (Fig. 3), these results indicate enzyme inhibition and/or deactivation in combination with a racemization process. Alcoholysis in ethanol also failed. Interestingly, CALB[14] had an opposite enantiopreference from the other lipases, albeit with modest selectivity (Table 4).

Five different lipases were evaluated in the asymmetric acetylation of diol **3b** and the results are summarized in Table 5. Assessment of the enantiomeric excess by chiral GC required purification and derivatization to **6b** (Scheme 1), which made a full analysis of the dependence of enantiomeric purity on the conversion impractical. By stopping the reaction at a low formation of diacetate **4b**, we could evaluate the enantioselectivity of the initial desymmetrization step (Table 5, entries 1–3, 5, and 8). Some highly interesting observations were made during the initial screen. PPL, BCL, CALB, and PFL were all efficient catalysts, the latter being most enantioselective. Interestingly, CALB showed an exceptional catalytic efficiency, and had opposite enantiopreference from that of all other lipases. The second resymmetrization step was evaluated for BCL, PFL, and CALB (Table 5, entries 4, 6, and 9). The enantiomeric purity of **5b** was improved in all cases. It was concluded that PFL was the best catalyst for the synthesis of (*R*)-**5b** but that high enantiomeric purity requires some resymmetrization. In a larger scale reaction, (*R*)-**5b** was isolated in 79% yield and 92% ee—a tolerable compromise

Table 4. Selected results of lipase screening for the desymmetrization of **4b**



Entry	Lipase	Product[a]	Time (h)	Catalyst loading (mg mmol^{-1})	Conversion[b] (%) **4b**:**5b**:**3b**	Isolated yield (%)	ee[c] (%)
1	ANL	(*S*)-**5b**	160	202	40:51:9	22	8
2	PPL	(*S*)-**5b**	160	200	33:62:5	28	54
3	BCL	(*S*)-**5b**	12	213	86:11:3	10	30
4	PFL	(*S*)-**5b**	160	204	26:64:10	22	10
5	CALB	(*R*)-**5b**	30	173	91:5:4	5	16

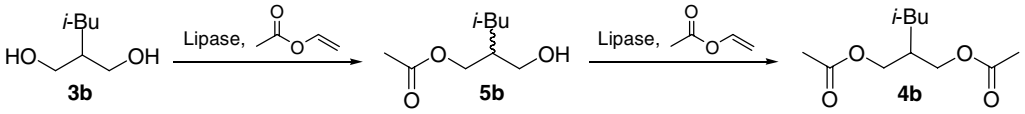
Reaction conditions: substrate (0.15 M) was shaken in *i*-Pr_2O/0.1 M phosphate buffer pH 7 (1:2) in the presence of lipase.

[a] Absolute configuration was determined by chemical correlation (Scheme 2).

[b] Determined by GC.

[c] Determined by chiral GC after purification and transformation into **6b** (Scheme 1).

Table 5. Results of lipase and conversion screening for the desymmetrization of **3b** and larger scale synthesis with PFL (entry 7)



Entry	Lipase	Product[a]	Time (h)	Catalyst loading (mg mmol^{-1})	Conversion[b] (%) **3b**:**5b**:**4b**	Isolated yield (%)	ee[c] (%)
1	ANL	(*R*)-**5b**	45	132	3:86:11	63	56
2	PPL	(*R*)-**5b**	1.5	132	1:88:11	77	84
3	BCL	(*R*)-**5b**	2.3	66	0:97:3	91	78
4	BCL	(*R*)-**5b**	110	129	0:11:89	10	92
5	PFL	(*R*)-**5b**	0.75	130	0:90:10	74	90
6	PFL	(*R*)-**5b**	11	176	0:13:87	10	96
7[d]	PFL	(*R*)-**5b**	4.7	26	0:80:20	79	92
8	CALB	(*S*)-**5b**	0.5	7	28:68:4	30	56
9	CALB	(*S*)-**5b**	0.75	128	0:17:83	14	92

Reaction conditions: substrate (0.3 M) was stirred in vinyl acetate in the presence of lipase at rt.
[a] Absolute configuration was determined by chemical correlation (Scheme 2).
[b] Determined by GC.
[c] Determined by chiral GC after purification and transformation into **6b** (Scheme 1).
[d] Larger scale reaction (4.4 mmol).

(Table 5, entry 7). Due to its opposite enantiopreference, CALB may be useful for the production of (*S*)-**5b** after reaction optimization.

2.6. Evaluation of the (*S*)-enantiopreference of CALB—synthesis of (*S*)-5b

The opposite enantiopreference of CALB from other lipases in the desymmetrization of diol **3b** and diacetate **4b** was surprising, and we resorted to a size based model derived from Kazlauskas rule for primary alcohols[22] (Fig. 4) to rationalize this observation. A literature survey of 75 lipase catalyzed reactions involving 2-alkyl or aryl 1,3-propanediol derivatives showed that while BCL, PPL, and PFL have been used extensively for desymmetrization of 1,3-propanediols, CALB has not gained as much interest for this type of transformation. With a few exceptions,[23] the overall enantiopreference of all lipases except the CALB was found to be that predicted by the model (Fig. 4). The 2-methyl analogue gives an (*S*)-configured product by acetylation and has a reversed alignment in the model,[12,24] while larger 2-substituents resulted in (*R*)-configured products.[12,25] The opposite interpretation is true for hydrolysis. Reports on ethyl derivatives are contradicting.[26] With regard to CALB, the enantiopreference seems highly dependent on the substrate structure and in some cases it matches that of other lipases,[13,27] while in some cases it does not.[28] Since CALB was found to have reversed enantiopreference in desymmetrization of the isobutyl substituted diol **3b** it was also employed to desymmetrize the benzyl analogue **3a**. Interestingly, the reaction gave a modest excess of the (*R*)-enantiomer of **5a** at low conversion (Table 1, entry 4), whereas the second resymmetrization step to **4a** left a slight excess of (*S*)-**5a** (Table 1, entry 5). We find it intriguing that the two structurally similar diols **3a** and **4a** are desymmetrized with opposite enantiopreference by CALB, and that resymmetrization of monoacetate **5a** to diacetate **4a** involves a switch in substrate alignment (Table 1, Fig. 4).

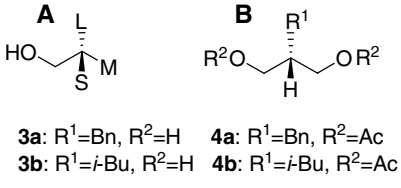


Figure 4. Lipase enantiopreference model for the substrates **3**–**4a**–**b**. (A) The preferred orientation of a primary alcohol in the active site of BCL, with the relative directions of the small (S), medium (M), and large (L) substituents;[22] (B) Spatial alignment of prochiral diols **3a**–**b** and diacetates **4a**–**b**. The active site is situated to the left.

Desymmetrization of diol **3b** with CALB was studied under various conditions (Table 6). Resymmetrization to diacetate **4b** is required for high enantiomeric purity as indicated in Table 5. We aimed for the evaluation of the enantiomeric excess when the substrate was converted to approximately equal amounts of **5b** and **4b**. The main difference between the conditions tried (Table 6, entries 1–5) was the rates. The reaction was fastest in isohexane in which the substrate was insoluble. A slight increase in enantioselectivity was noticed when the reaction was run at 0 °C instead of 20 °C in vinyl acetate. The data also indicated that more than 50% resymmetrization to **4b** was needed to achieve high enantiomeric purity. A larger scale reaction was run in isohexane at 0 °C and by allowing 60% formation of **4b**, (*S*)-**5b** could be isolated in 37% yield and 80% ee (entry Table 6, entry 6).

2.7. Synthesis of aldehydes 1a–b

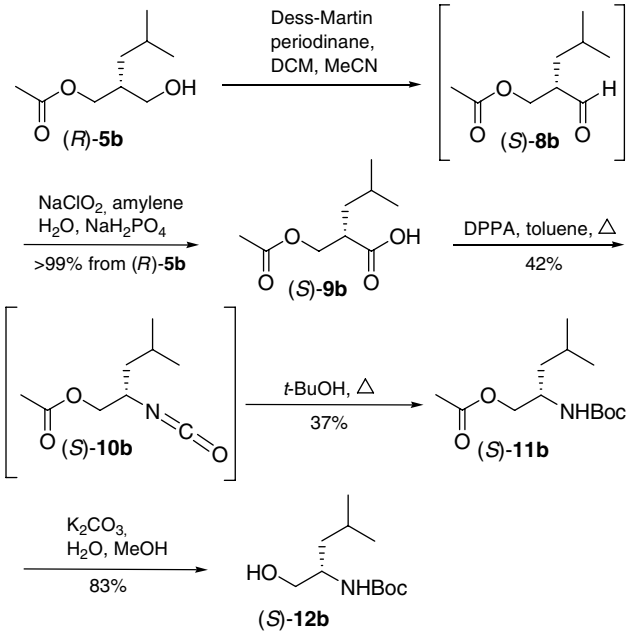
With suitable conditions for the production of chiral precursors to both enantiomers of aldehydes **1a**–**b** at hand, we set out to complete the synthesis (Scheme 1). The monoacetate products of desymmetrization (*R*)-**5a**, (*S*)-**5a**, and (*S*)-**5b** were protected with TBDMSCl to **6a**–**b** and hydro-

Table 6. Results of optimization of the desymmetrization of diol **3b** (0.3 M) to monoacetate (*S*)-**5b** catalyzed by CALB (entries 1–5) and larger scale synthesis (entry 6)

Entry	Solvent[a]	Acyl donor (equiv)[a]	*T* (°C)	Catalyst loading (mg mmol^{-1})	Time (h)	Conversion[b] (%) **3b**:**5b**:**4b**	Isolated yield (%)	ee[c] (%)
1	VA	VA	20	15[d]	5	0:47:53	33	76
2	VA	VA	0	15[d]	5	0:57:43	36	73
3	Toluene	IPA (6)	20	15[d]	5	0:51:49	38	75
4	THF	IPA (3)	0	20[d]	5	14:79:7	51	36
5[e]	*i*-Hexane	VA (2)	20	10[d]	4.75	0:44:56	35	76
6[e,f]	*i*-Hexane	VA (3)	0	20	6.5	0:40:60	37	80

See also Table 5, entries 8 and 9.
[a] VA = vinyl acetate, IPA = isopropenyl acetate.
[b] Determined by GC.
[c] Determined by chiral GC after purification and transformation into **6b** (Scheme 1).
[d] Enzyme was added in portions during the first hour of reaction until a suitable rate was reached.
[e] The reaction mixture was an emulsion initially since the substrate was insoluble.
[f] Larger scale reaction (8.8 mmol).

lysis furnished alcohols **7a**–**b**. Both transformations proceeded without incident and no racemization was detected. Acetate (*R*)-**6a** was obtained by kinetic resolution and then treated accordingly. Racemization was of concern when performing the oxidation to aldehydes **1a**–**b**. The Dess–Martin reagent was chosen for its mildness and the nearly neutral conditions that can be employed.[29] Aldehydes **1a**–**b** were formed in good yield and no racemization was detected for **1b**. Minor racemization (1–2%) was observed during some oxidation runs to **1a**. The entire synthetic sequence only required purification after two steps when run on a larger scale, after the desymmetrization or resolution, and for isolation of the final product. In summary, aldehydes (*R*)-**1a**, (*S*)-**1a**, (*R*)-**1b**, and (*S*)-**1b** could be isolated in 92%, 84%, 92%, and 80% enantiomeric excess and 55%, 29%, 54%, and 27% total yield, respectively, starting from dimethyl malonates **2a**–**b** in five steps. Fair comparison with other methods is difficult since the enantiomeric excess and yield of the final product are rarely reported. Compound (*S*)-**1b** has been prepared in 50% crude yield over five steps,[6] starting from a chiral oxazolidinone. Aldehydes **1a** and **1b** were stored at −18 °C for several months and were found to be completely stereochemically stable under these conditions.



Scheme 2. Stereochemical correlation of monoacetate (*R*)-**5b** with L-Boc leucinol ((*S*)-**12b**).

2.8. Establishment of absolute configuration by stereochemical correlation

Monoacetates (*R*)- and (*S*)-**5a** are known compounds,[11–13] and the absolute configurations of the benzyl series **1a**, **5a**–**7a** (Scheme 1) were assigned by correlation with specific rotations and chiral chromatography. For the isobutyl series, **1b** and **5b**–**7b** (Scheme 1), a stereochemical correlation between monoacetate (*R*)-**5b** and L-Boc leucinol (*S*)-**12b**[30,31] was undertaken (Scheme 2). (*R*)-**5b** in 88% ee was oxidized to acid (*S*)-**9b** by Dess–Martin–$NaClO_2$ tandem oxidation via aldehyde (*S*)-**8b** in quantitative yield. A Curtius reaction furnished isocyanate (*S*)-**10b**, which reacted sluggishly with *tert*-butyl alcohol to form (*S*)-**11b** in 37% yield. Hydrolysis afforded (*S*)-**12b** and its optical rotation (ee ⩽88%, $[\alpha]_D^{20} = -22$) was in good agreement with that reported ($[\alpha]_D^{24} = -26.8$).[30] The synthesis allowed the absolute configuration of all isobutyl derivatives to be assigned with reference to (*R*)-**5b**. It also gives an indication that a broad range of synthetically useful chiral compounds can be derived from monoacetates **5a**–**b**.

3. Conclusions

As indicated in the tables above, a thorough evaluation has been made of lipase-based routes to both enantiomers of aldehydes **1a**–**b**. Suitable conditions involving four different lipases for the synthesis of enantiomerically enriched precursors to aldehydes **1a**–**b** (Scheme 1) were identified, and efficient, simple, and inexpensive routes were devised.

The (*R*)-enantiomers of aldehydes **1a**–**b** were more easily accessible for both the benzyl series **1**–**7a** (Scheme 1) and the isobutyl derivatives **1**–**7b** (Scheme 1). In both cases this

Table 7. Chiral GC methods and retention times

Method	Temperature program	t_R (min)
A	120 °C isothermal	(*S*)-**7a** = 121.1; (*R*)-**7a** = 125.0
B	117 °C isothermal	(*R*)-**1a** = 76.6; (*S*)-**1a** = 79.5
C	95 °C isothermal	(*R*)-**6b** = 49.4; (*S*)-**6b** = 50.8
D	110 °C isothermal	(*S*)-**7b** = 22.4; (*R*)-**7b** = 23.4
E	90 °C for 73 min, then 2 °C min^{-1} increase	(*R*)-**6b** = 65.0; (*S*)-**6b** = 67.2; (*S*)-**7b** = 79.9; (*R*)-**7b** = 82.1
F	90 °C isothermal	(*R*)-**1b** = 32.7; (*S*)-**1b** = 33.7

Table 8. Chiral HPLC methods and retention times, flow was in all cases 1 mL min^{-1}

Method	Column, eluent	t_R (min)
G	Chiralpak AD-H, 5% *i*-PrOH/*n*-hexane	**4a** = 8.3; (*R*)-**5a** = 20.3; (*S*)-**5a** = 21.3; **3** = 33.6
H	Chiralcel OD-H, 5% *i*-PrOH/*n*-hexane	(*R*/*S*)-**6a** = 3.8;[a] (*S*)-**7a** = 5.6; (*R*)-**7a** = 6.1
I	Chiralcel OD-H, 100% *n*-hexane	(*S*)-**6a** = 14.4; (*R*)-**6a** = 15.6

[a] Enantiomers not resolved.

Table 9. Specific rotation of compounds **1**–**7a**–**b** in $CHCl_3$

Compound	ee (%)	*c* (g dL^{-1})	$[\alpha]_D^{20}$
(*R*)-**1a**	92	0.80	−54
(*S*)-**1a**	88	0.94	+52
(*R*)-**1b**	92	0.83	−22
(*S*)-**1b**	80	0.84	+19
(*R*)-**5a**[a]	96	0.90	+29
(*S*)-**5a**	96	1.0	−29
(*R*)-**5b**	96	0.99	+17
(*S*)-**5b**	92	1.1	−12
(*R*)-**6a**	88	0.91	−5.1
(*S*)-**6a**[b]	96	1.2	+5.2
(*R*)-**6b**	92	1.1	+0.6
(*S*)-**6b**	96	1.0	−0.5
(*R*)-**7a**	88	0.92	+15
(*S*)-**7a**[c]	96	1.1	−16
(*R*)-**7b**[d]	80	0.75	+12
(*S*)-**7b**	92	0.76	−17

[a] Lit. $[\alpha]_D^{20}$ = +27.7 (97% ee, *c* 1.3, $CHCl_3$, Ref. 11).
[b] Lit. $[\alpha]_D$ = +1 (97% ee, *c* 1.39, C_6H_6, Ref. 35).
[c] Lit. $[\alpha]_D$ = −18 (97% ee, *c* 1.08, MeOH, Ref. 35).
[d] Lit. $[\alpha]_D^{23}$ = +10.3 (*c* 1.02, $CHCl_3$, Ref. 6).

can be attributed to differences in enantioselectivity of the lipases used for the various substrates. Desymmetrization by acetylation was found to be useful as the key step toward (*R*)-**1a**–**b** and also (*S*)-**1b** since CALB was found to have opposite enantiopreference from the other lipases used. The results concerning the desymmetrization of 1,3-propanediols **3a** and **3b** with CALB (Tables 1, 5, and 6) indicate that isobutyl and benzyl closely touch upon the size or shape requirements for enantiotopic discrimination of this enzyme. Kinetic resolution was employed as the key step to prepare (*S*)-**1a** where PPL was found to have unique catalytic properties.

4. Experimental

4.1. General

Optical rotations were measured on a Perkin Elmer 341 LC polarimeter (wavelength 589 nm), values for compounds **1**–**7a**–**b** are listed in Table 9. ^1H and ^{13}C NMR spectra were recorded on a JEOL Eclipse 400 FT NMR spectrometer in $CDCl_3$ at 20 °C and 400 and 100 MHz, respectively. Chemical shifts are reported in ppm with the following references: ^1H–residual $CHCl_3$ (δ^H 7.26); ^{13}C–$CDCl_3$ (δ^C 77.0). Coupling constants (*J*) are given in hertz. 2D COSY, HMQC, and HMBC NMR spectroscopy was used to validate structural assignments of the signals. TLC was performed on MERCK silica gel plates, grade 60 F_{254} and the spots were visualized by UV light (254 nm) and/or treatment with phosphomolybdic acid in ethanol, alkaline aq $KMnO_4$ or anisaldehyde/acetic acid/H_2SO_4 in ethanol and heating. Flash chromatography was performed on Geduran silica SI-60 (0.063–0.2 mm). IR spectra were recorded on a Perkin–Elmer 16PC FT-IR with neat samples and only the major peaks are listed. All compounds were analyzed by NMR and HPLC or GC to be >95% pure. Elemental analyses were conducted by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany or MikroKemi AB, Uppsala, Sweden.

4.2. Materials

THF and Et_2O were dried and stored over 3 Å molecular sieves that had been thoroughly washed with H_2O and acetone and activated at 300 °C in high vacuum for 8 h. *i*-Pr_2O was stored in the dark in a firmly closed container and was checked with Merckoquant peroxide test-strips before use. Butyllithium was titrated with diphenyl acetic acid as indicator. All other solvents and reagents were used as received. The lipases used in this study were: ANL = *Aspergillus niger* lipase (Amano lipase A); BCL = *Burkholderia cepacia* lipase (formerly known as *Pseudomonas cepacia*, Amano lipase PS); CALB = *Candida antarctica* lipase B (Novozym 435); PFL = *Pseudomonas fluorescens* lipase (Amano lipase AK); PPL = Pig pancreatic lipase (Lipase from hog pancreas, Fluka). Compound **2a** was prepared according to literature procedures.[32]

4.3. Chromatography methods

Analytical RP-HPLC for compounds **1**–**7a** was performed on a Waters diode array system fitted with a 50 × 4.6 mm Genesis C8 4 μm column. A 0.1 M NH_4OAc buffer 0–100% acetonitrile 7 min gradient at 2 mL min^{-1} flow was used for elution. Samples of reaction mixtures for RP-HPLC was prepared by diluting 20 μL of reaction mixture (well stirred or shaken to give a homogenous suspension or emulsion) in 1 mL of acetonitrile and filtration through a 0.45 μm syringe filter. Analytical GC (for compounds **1**–**7b**) was performed on a Varian 3400 chromatograph fitted with a CPWAX 25 m × 2.5 mm column with H_2 as carrier gas (2 mL min^{-1}). Injector and detector temperatures were 225 and 250 °C, respectively. A 200 °C isothermal 6 min program was used for reaction monitoring. For purity analyses, a 95–200 °C 26 min program was used. Samples of reaction mixtures were prepared by dilution with Et_2O,

and in the case of mixtures containing water, extraction with satd aq NH_4Cl, and filtration as mentioned above.

Chiral GC analysis was performed with the same apparatus, parameters, and sample preparation as achiral analyses. A CP-Chirasil-DEX CB, 25 m × 0.32 mm column was used. Methods and retention times are given in Table 7. Chiral HPLC analysis was performed on a Varian system (9010 pump, flow 1 mL min^{-1}; 9050 detector at 254 nm). All columns were 250 × 4.6 mm. Samples of non-aqueous reaction mixtures were prepared by dilution in DCM and filtration through a 0.45 μm syringe filter followed by evaporation in vacuo and dilution with mobile phase. For mixtures containing water, the diluted sample was extracted with water and the DCM phase was treated as above. Methods and retention times are given in Table 8.

4.4. Synthesis of prochiral and racemic compounds; representative procedures

The prochiral starting materials were used for desymmetrization experiments; racemic compounds were used for kinetic resolution and for development of chiral chromatography methods.

4.4.1. Diols 3a–b. $LiAlH_4$ (5.89 g, 155 mmol) was suspended in dry Et_2O (225 mL) under N_2 at 0 °C. Isobutyl dimethyl malonate **2b** (9.73 g, 51.6 mmol) in dry Et_2O (10 mL) was carefully added dropwise during constant stirring. The reaction was allowed to warm to room temperature and stirred for 6 h. Quenching was performed at 0 °C with constant stirring by careful dropwise addition of 6 mL H_2O, 6 mL 2 M NaOH and 18 mL H_2O in sequence. The resulting precipitate was filtered off and washed with EtOAc (150 mL). The solvent volume was reduced to half by rotary evaporation, and washed with brine (150 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated to afford 2-isobutyl-propane-1,3-diol **3b** (5.85 g, 86%) as a colorless oil. ^{1}H NMR δ 3.76 (dd, $J = 3.7$, 10.6, 2H, CH_2^aO), 3.57 (dd, $J = 7.7$, 10.6, 2H, CH_2^bO), 3.20 (s, 2H, O*H*), 1.89–1.78 (m, 1H, H-2), 1.52–1.65 (m, 1H, H-2′), 1.04 (t, $J = 7.1$, 2H, H-1′), 0.86 (d, $J = 6.6$, 6H, 2 × Me); ^{13}C δ 66.6 (2C, C-1, C-3), 39.5 (C-2), 36.8 (C-1′), 25.3 (C-2′), 22.7 (2C, Me); IR $\nu = 3336$, 2956, 1468, 1032 cm^{-1}. Anal. Calcd for $C_7H_{16}O_2$: C 63.60, H 12.2. Found: C 63.3, H 11.9. 2-Benzyl-propane-1,3-diol **3a** was prepared analogously in 84% yield and the spectral data were in agreement with those reported.[33]

4.4.2. Diacetates 4a–b. Diol **3b** (1.18 g, 8.94 mmol) was dissolved in Et_3N (3.0 mL, 23 mmol). DMAP was added (0.20 g, 1.6 mmol) followed by dropwise addition of acetic anhydride (3.2 mL, 34 mmol). The reaction was stirred at rt for 2 h after which the mixture was diluted with Et_2O (40 mL) and 1 M HCl (30 mL) and the phases were separated. The organic phase was washed with 1 M HCl (30 mL), satd aq $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 2-(acetyloxymethyl)-4-methylpentyl acetate **4b** (1.69 g, 87%) as a colorless oil, which was used as such without further purification. A small analytical sample was prepared by flash chromatography (EtOAc/hexanes 1:20). ^{1}H NMR δ 4.05 (dd, $J = 4.8$, 11.0, 2H, CH_2^aO), 3.99 (dd, $J = 6.2$, 11.0, 2H, CH_2^bO), 2.08–2.00 (m, 1H, H-2), 2.03 (s, 6H, Ac), 1.69–1.59 (m, 1H, H-4), 1.18 (t, $J = 7.1$, 2H, H-3), 0.88 (d, $J = 6.6$, 6H, Me); ^{13}C NMR δ 171.0 (2C, *C*O), 64.4 (2C, *C*H_2O), 37.3 (C-3), 34.9 (C-2), 25.1 (C-4), 22.6 (2C, Me), 20.8 (2C, Ac); IR $\nu = 2959$, 1742, 1470, 1369, 1232 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C 61.09, H 9.32. Found: C 60.8, H 9.3. 2-(Acetyloxymethyl)-3-phenylpropyl acetate **4a** was prepared analogously in 85% yield and the spectral data were in agreement with those reported.[34]

4.4.3. Alcohols *rac*-7a–b. Diol **3a** (0.62 g, 3.7 mmol) was dissolved in dry THF (16 mL) under N_2 and the stirred solution was cooled to −78 °C in a $CO_{2(s)}$/acetone bath. Butyllithium (1.6 M, 2.45 mL, 3.9 mmol) was added dropwise, and the mixture was allowed to warm to rt and was again cooled to −78 °C over 1 h. TBDMSCl (0.59 g, 3.9 mmol) was dissolved in THF (2.5 mL) and added dropwise. The excess $CO_{2(s)}$ was removed from the cooling bath and replaced with a magnetic stirrer bar. The reaction was stirred for 3 h during which it slowly warmed to rt. The reaction was quenched by addition of 10 mL satd aq NH_4Cl and the phases were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic phases were washed with brine (20 mL). Drying ($MgSO_4$), filtration, and concentration yielded *rac*-2-benzyl-3-((*tert*-butyl-dimethylsilyl)oxy)-propanol[32] **7a** (1.01 g, 97%). An equivalent procedure afforded *rac*-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylpentanol[6] **7b** in 93% yield. The spectral data were in both cases in agreement with those reported.

4.4.4. Aldehydes *rac*-1a–b. Dess–Martin periodinane (15% wt in DCM, 2.58 g, 0.913 mmol) was cooled to 0 °C. Alcohol *rac*-**7b** (150 mg, 0.608 mmol) was dissolved in acetonitrile (3 mL) and the solution was added dropwise. The reaction was stirred for 1 h after which it was allowed to reach rt and stirring was continued for 2 h. When no starting material remained according to TLC, the solvent volume was reduced to half by rotary evaporation. Et_2O (20 mL) and satd aq $Na_2S_2O_3$ (15 mL) were added and the mixture was stirred vigorously for 15 min. The phases were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic phases were washed with satd aq $NaHCO_3$ (2 × 15 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (100% hexanes—1:100 EtOAc/hexanes) to yield *rac*-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylpentanal **1b** (106 mg, 71%). ^{1}H NMR δ 9.64 (d, $J = 2.6$, 1H, C*H*O), 3.81–3.76 (m, 2H, CH_2O), 2.52–2.44 (m, 1H, H-2), 1.64–1.51 (m, 2H, CH_2^a-3, H-4), 1.32–1.22 (m, 1H, CH_2^b-3), 0.91–0.83 (m, 6H, 2 × Me), 0.86 (s, 9H, *t*-Bu), 0.04 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR δ 205.0 (*C*HO), 62.4 (*C*H_2O), 52.4 (C-2), 34.4 (C-3), 25.8 (3C, *t*-Bu), 25.7 (C-4), 22.7 (Me^a), 22.6 (Me^b), 18.2 (Si*C*), −5.55 (2C, Si(*C*H_3)$_2$); IR $\nu = 2930$, 1732, 1472, 1386, 1258, 1111, 838 cm^{-1}. Anal. Calcd for $C_{13}H_{28}O_2$: C 63.88, H 11.55. Found: C 63.8, H 11.5. *rac*-2-Benzyl-3((*tert*-butyldimethylsilyl)oxy)propanal **1a** was prepared analogously in 86% yield and the spectral data were in agreement with those reported.[32]

4.4.5. Acetates *rac*-6a–b. Alcohol *rac*-**7b** (1.00 g, 4.06 mmol) and DMAP (50 mg, 0.40 mmol) were dissolved in Et_3N (0.68 mL, 5.3 mmol) at rt. Acetic anhydride (0.77 mL, 8.1 mmol) was added dropwise and the mixture stirred for 1.5 h. Et_2O (40 mL) and 1 M HCl (20 mL) were added and the phases were separated. The organic phase was washed with 1 M HCl (20 mL), satd aq $NaHCO_3$ (2×20 mL), and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to yield *rac*-4-methyl-2-(((*tert*-butyldimethylsilyl)oxy)-methyl)-pentyl acetate **6b** (1.08 g, 92%). The product was used as such without further purification. A small analytical sample was prepared by flash chromatography (EtOAc/hexanes 50:1) ^{1}H NMR δ 4.03 (d, $J = 5.9$, 2H, H-1), 3.57 (dd, $J = 4.4$, 9.9, 1H, CH_2^aOSi), 3.52 (dd, $J = 6.2$, 10.3, 1H, CH_2^bOSi), 2.04 (s, 3H, Ac), 1.86 (sep, $J = 5.9$, 1H, H-2), 1.68–1.60 (m, 1H, H-4), 1.24–1.08 (m, 2H, H-3), 0.92–0.86 (m, 6H, $2 \times$ Me), 0.88 (s, 9H, *t*-Bu), 0.03 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR δ 171.4 (*C*O), 65.1 (C-1), 63.0 (*C*H$_2$OSi), 38.1 (C-2), 37.4 (C-3), 26.1 (3C, *t*-Bu), 25.5 (C-4), 23.0 (2C, $2 \times$ Me), 18.5 (Si*C*), −3.3 (2C, Si(*C*H$_3$)$_2$); IR $\nu = 2957$, 1745, 1472, 1252, 1094, 874 cm^{-1}. Anal. Calcd for $C_{15}H_{32}O_3Si$: C 62.45, H 11.18. Found: C 62.3, H 11.1. *rac*-2-Benzyl-3-((*tert*-butyldimethylsilyl)oxy)-propyl acetate **6a** was prepared analogously in 90% yield and the spectral data were in agreement with those reported.[35]

4.4.6. Monoacetate *rac*-5a. Compound *rac*-**6a** (85 mg, 0.26 mmol) and TBAF (1 M in THF, 0.40 mL, 0.40 mmol) were stirred in THF (1 mL) at rt for 1 h. The mixture was diluted with Et_2O (10 mL) and 1 M aq HCl (10 mL) and the phases were separated. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Gradient flash chromatography (EtOAc/hexanes 1:10–1:2) yielded *rac*-2-hydroxymethyl-3-phenyl-propyl acetate **5a** (39 mg, 71%). The spectral data were in agreement with those reported.[34]

4.5. General procedures for lipase-catalyzed reactions

4.5.1. Desymmetrization of diols 3a–b, lipase screening. Substrate **3a** or **3b** (approx 150 mg, 0.9 mmol) was stirred in solvent and acyl donor (total volume 5 mL) in the presence of lipase at the temperature specified in Tables 1, 5, and 6, where reaction times can also be found. Conversion was monitored by RP-HPLC (**3**–**5a**) or GC (**3**–**5b**). The reactions were quenched by addition of THF (5 mL), filtration, and evaporation of the solvent and acyl donor. The monoacetate products **5a**–**b** where isolated by flash gradient chromatography on a short silica column (EtOAc/hexanes 1:15—100% EtOAc) and the intermediates **3a**–**b** and **4a**–**b** were also collected for recycling. Data for 2-hydroxymethyl-4-methylpentyl acetate **5b**: ^{1}H NMR δ 4.21 (dd, $J = 4.4$, 11.4, 1H, H-1^a), 4.05 (dd, $J = 6.6$, 11.0, 1H, H-1^b), 3.58 (dd, $J = 4.4$, 11.4, 1H, CH_2^aOH), 3.48 (dd, $J = 6.6$, 11.4, 1H, CH_2^bOH), 2.14 (s, 1H, O*H*), 2.06 (s, 3H, Ac), 1.88 (m, 1H, H-2), 1.71–1.60 (m, 1H, H-4,), 1.22–1.09 (m, 2H, H-3,), 0.89 (d, $J = 6.6$, 6H, $2 \times$ Me); ^{13}C NMR δ 171.7 (*C*O), 64.8 (C-1), 62.8 (*C*H$_2$OH), 38.1 (C-2), 36.9 (C-3), 25.2 (C-4), 22.7 (2C, Me), 20.9 (Ac); IR $\nu = 3426$, 2957, 1738, 1368, 1234, 1036 cm^{-1}. Anal. Calcd for $C_9H_{18}O_3$: C 62.04, H 10.41. Found: C 61.9, H 10.5. The enantiomeric purity of **5a** was assessed by chiral HPLC (method G, Table 8) or silylation to give **6a** followed by hydrolysis to alcohol **7a**, which was analyzed by chiral GC (method A, Table 7). The enantiomeric purity of **5b** was determined after silylation to **6b**, which was analyzed by chiral GC (method C, Table 7).

4.5.2. Desymmetrization of diacetates 4a–b, lipase screening. Substrate **4a** or **4b** (approx 200 mg, 0.9 mmol) was vigorously shaken or stirred in solvent (2.5 mL) and 0.1 M phosphate buffer pH 7 (5 mL) in the presence of lipase as specified in Tables 1, and 4. The reactions were quenched by filtration, followed by extraction of the aqueous phase with Et_2O, drying over $MgSO_4$, filtration, and concentration. The conversion was monitored and the enantiomeric purity of **5a**–**b** was determined as described in the preceding section.

4.5.3. Kinetic resolution of alcohols *rac*-7a–b, lipase screening. Substrate *rac*-**7a** or *rac*-**7b** (approx 100 mg, 0.4 mmol) was vigorously stirred in solvent and acyl donor (total volume 2.5 mL) in the presence of lipase as specified in Tables 2 and 3. The reactions were quenched by the addition of THF (5 mL), filtration, and evaporation of the solvent and acyl donor. The enantiomeric purity of (*S*)-**7a** was determined by chiral GC (method A, Table 7, after purification by gradient flash chromatography (EtOAc/hexanes 1:50–1:10)), or chiral HPLC (method H, Table 8). The enantiomeric excess of (*R*)-**6a** was determined by chiral HPLC (method I, Table 8), or by chiral GC after purification and hydrolysis to (*R*)-**7a** (method A, Table 7). The enantiomeric purities of (*S*)-**7b** and (*R*)-**6b** were determined by chiral GC of the crude filtered product mixture (method E, Table 7).

4.6. Larger scale synthesis of aldehydes 1a–b

4.6.1. (*R*)-1a. Diol **3a** (0.92 g, 5.5 mmol) was dissolved in vinyl acetate (12 mL) and BCL (0.55 g) was added. The suspension was stirred vigorously for 2 h at which full conversion was reached. The reaction was diluted with THF (15 mL) and the solids were filtered off. Evaporation yielded an oily residue, which was purified by gradient flash chromatography (EtOAc/hexanes 1:5–1:3) to give monoacetate (*R*)-**5a** as a transparent oil (1.05 g, 91%). (*R*)-**5a** (0.54 g, 2.59 mmol) was dissolved in DCM (8 mL) and TBDMSCl (0.47 g, 3.11 mmol) and Et_3N (0.83 mL, 6.48 mmol) were added. The mixture was stirred for 24 h, and quenched by addition of Et_2O (30 mL) and 1 M HCl (20 mL) and the layers were separated. The organic phase was washed with 1 M HCl (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and evaporated to yield acetate (*S*)-**6a** as a transparent oil (0.74 g, 89%). The product was dissolved in MeOH (40 mL) and H_2O (4 mL), and K_2CO_3 (1.59 g, 11.5 mmol) was added and the mixture stirred for 1.5 h. The mixture was diluted with brine (40 mL) and Et_2O (40 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (2×40 mL) and the combined organic phases washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated to yield alcohol

(*S*)-**7a** as a transparent oil (0.57 g, 89%). The ee of the product was 96% according to chiral HPLC (method H, Table 8). Dess–Martin oxidation of (*S*)-**7a** and purification as described for *rac*-**1a**–**b** afforded aldehyde (*S*)-**1a** in 89% yield and 92% enantiomeric purity according to chiral GC (method B, Table 7).

4.6.2. (*R*)-1b. A similar procedure to that for obtaining (*R*)-**1a** was employed to prepare (*R*)-**1b**. Diol **3b** (0.58 g, 4.39 mmol) was treated with PFL (116 mg) in vinyl acetate (12 mL) for 4.7 h to yield monoacetate (*R*)-**5b** in 79% yield after gradient flash chromatography (EtOAc/hexanes 10:1–4:1). Silylation as described for (*R*)-**1a** afforded (*S*)-**6b** in quantitative yield and the enantiomeric excess was 92% according to chiral GC (method C, Table 7). Hydrolysis as described for (*R*)-**1a** afforded alcohol (*S*)-**7b** in 90% yield. Dess–Martin oxidation and purification as described for *rac*-**1a**–**b** afforded (*R*)-**1b** in 89% yield and the enantiomeric purity was 92% according to chiral GC (method F, Table 7).

4.6.3. (*S*)-1a. *rac*-**7a** (4.67 g, 16.6 mmol) was dissolved in vinyl acetate (140 mL), and PPL (7.0 g) was added. The suspension was stirred for 22 h and the reaction stopped at 48% conversion. The solids were filtered off and washed with THF (100 mL). The combined filtrates were evaporated to yield a crude oil, which was chromatographed on silica (EtOAc/hexanes 1:50–1:10) to afford acetate (*R*)-**6a** (2.16 g, 40%) and alcohol (*S*)-**7a** (2.02 g, 43% yield, 86% ee, chiral HPLC (method H, Table 8)). (*R*)-**6a** was subjected to hydrolysis as described for (*R*)-**1a** to give (*R*)-**7a** in 95% yield and 84% ee according to chiral HPLC (method H, Table 8). (*R*)-**7a** was subjected to Dess–Martin oxidation and subsequent purification as described for *rac*-**1a**–**b** to give aldehyde (*S*)-**1a** in 86% yield and 84% ee as determined by chiral GC (method B, Table 7).

4.6.4. (*S*)-1b. Diol **3b** (1.16 g, 8.77 mmol) was suspended in isohexane (23 mL) and cooled to 0 °C. Vinyl acetate (2.43 mL, 26.3 mmol) and CALB (174 mg) were added and the mixture was stirred for 6.5 h at which the product distribution was 0:40:60 (**3b**:**5b**:**4b**) according to GC. THF (20 mL) was added and the solids were filtered off and the filtrate was concentrated. Gradient flash chromatography (EtOAc/hexanes 1:10–1:4) gave monoacetate (*S*)-**5b** (0.57 g, 37%). Silylation as described for (*R*)-**1a** afforded (*R*)-**6b** in quantitative yield and the enantiomeric excess was 80% according to chiral GC (method C, Table 7). Hydrolysis as described for (*R*)-**1a** gave alcohol (*R*)-**7b** in 94% yield. Dess–Martin oxidation and subsequent purification as described for *rac*-**1a**–**b** afforded aldehyde (*S*)-**1b** in 91% yield and the enantiomeric purity was 80% according to chiral GC (method F, Table 7).

4.7. Stereochemical correlation of monoacetate (*R*)-5b with L-Boc leucinol ((*S*)-12b)

4.7.1. (*S*)-2-(Acetyloxymethyl)-4-methylpentanoic acid ((*S*)-9b). Monoacetate (*R*)-**5b** (88% ee, 1.03 g, 5.91 mmol) was oxidized with the Dess–Martin periodinane and the reaction was worked up as described for *rac*-**1a**–**b** to give (*S*)-2-formyl-4-methylpentyl acetate (*S*)-**8b** with some minor impurities as a light yellow oil (1.02 g). The product was used as such without further purification. $[\alpha]_D^{20} = +4$ (*c* 1, $CHCl_3$, crude product); ^{1}H NMR δ 9.64 (d, $J = 1.5$, 1H, C*H*O), 4.26 (d, $J = 5.9$, 2H, H-1), 2.72–2.63 (m, 1H, H-2), 2.04 (s, 3H, Ac), 1.66–1.61 (m, 1H, H-4), 1.61–1.54 (m, 1H, H-3^a), 1.32–1.27 (m, 1H, H-3^b), 0.92–0.87 (m, 6H, 2 × Me); ^{13}C NMR δ 202.4 (*C*HO), 170.8 (*C*OO), 62.5 (C-1), 49.1 (C-2), 34.6 (C-3), 25.6 (C-4), 22.5 (Me^a), 22.4 (Me^b), 20.7 (Ac); IR $\nu = 2959$, 2359, 1742, 1470, 1237, 1037 cm^{-1}.

Aldehyde (*S*)-**8b** (960 mg, 5.57 mmol) and amylene (5.9 mL, 56 mmol) were dissolved in THF (80 mL) and the mixture stirred and cooled to 0 °C. $NaH_2PO_4{\cdot}2H_2O$ (1.74 g, 11.2 mmol) was dissolved in H_2O (40 mL) and $NaClO_2$ (80% pure, 1.89 g, 16.7 mmol) was added carefully. The aqueous solution was added dropwise to the reaction mixture. The reaction was stirred for 4 h after which a 1:1 mixture of brine and 1 M HCl (80 mL) was added carefully and stirring was continued for 5 min. The reaction mixture was extracted with EtOAc (2 × 100 mL) and the combined organic phases were washed with a 1:1 mixture of brine and 1 M HCl (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by gradient flash chromatography (EtOAc/hexanes 1:10–1:1 with 1% AcOH) afforded the title compound (1.05 g, >99% from (*R*)-**5b**). $[\alpha]_D^{20} = +4.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 4.22 (dd, $J = 4.8$, 11.0, 1H, CH_2^aO), 4.16 (dd, $J = 8.8$, 11.0, 1H, CH_2^bO), 2.85–2.77 (m, 1H, H-2), 2.05 (s, 3H, Ac), 1.66–1.63 (m, 1H, H-4), 1.63–1.58 (m, 1H, H-3^a), 1.36–1.30 (m, 1H, H-3^b), 0.93 (d, $J = 2.6$, 3H, Me^a), 0.92 (d, $J = 2.9$, 3H, Me^b); ^{13}C NMR δ 179.8 (*C*OOH), 170.8 (CH_3CO), 64.7 (CH_2O), 42.8 (C-2), 37.6 (C-3), 25.8 (C-4), 22.6 (Me^a), 22.1 (Me^b), 20.8 (Ac); IR $\nu = 2960$, 1746, 1715, 1369, 1240, 1039 cm^{-1}. Anal. Calcd for $C_9H_{16}O_4$: C 57.43, H 8.57. Found: C 57.3, H 8.5.

4.7.2. (*S*)-2-(*tert*-Butoxycarbonylamino)-4-methylpentyl acetate (*S*)-11b. A reflux apparatus was charged with carboxylic acid (*S*)-**9b** (115 mg, 0.608 mmol) and toluene (7.5 mL) under a N_2 atmosphere. Et_3N (0.42 mL, 3.3 mmol) and diphenyl phosphoryl azide (0.14 mL, 0.66 mmol) were added and the mixture was stirred for 25 min at rt, after which it was refluxed for 6 h. The reaction was allowed to cool and Et_2O (20 mL) and satd aq Na_2CO_3 (20 mL) were added. After 5 min of stirring, the layers were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was filtered through a silica column (eluent EtOAc/hexanes 1:30) to give (*S*)-2-isocyanato-4-methylpentyl acetate (*S*)-**10b** (48 mg, 42%). ^{1}H NMR δ 4.14 (dd, $J = 3.7$, 11.4, 1H, H-1^a), 3.96 (dd, $J = 7.7$, 11.0, 1H, H-1^b), 3.81–3.74 (m, 1H, H-2), 2.11 (s, 3H, Ac), 1.83–1.74 (m, 1H, H-4), 1.51–1.43 (m, 1H, H-3^a), 1.27–1.20 (m, 1H, H-3^b), 0.95 (d, $J = 6.6$, 3H, Me^a), 0.91 (d, $J = 6.6$, 3H, Me^b); ^{13}C NMR δ 170.6 (CH_3CO), 124.3 (N*C*O), 67.1 (C-1), 52.8 (C-2), 41.6 (C-3), 24.8 (C-4), 23.1 (Me^a), 21.3 (Me^b), 20.7 (Ac); IR $\nu = 2960$, 2262, 1749, 1369, 1236 cm^{-1}. The product was used as such without further purification or characterization.

Isocyanate (*S*)-**10b** (19 mg, 0.10 mmol) was dissolved in *t*-BuOH (2 mL) in a screw-cap tube and the mixture heated to 100 °C for 14 h. The reaction was allowed to cool after which DCM (10 mL) and H_2O (5 mL) were added and the phases were separated. The organic phase was dried over $MgSO_4$, filtered, and evaporated. Gradient flash chromatography on a short column (EtOAc/hexanes 1:20–1:4) afforded the title compound (10 mg, 37%). The procedure was repeated to prepare 36 mg of (*S*)-**11b**. $[\alpha]_D^{20} = -28$ (*c* 1.0, $CHCl_3$);^{1}H NMR δ 4.45 (d, $J = 8.4$, 1H, N*H*), 4.04–4.00 (m, 2H, H-1), 4.00–3.89 (m, 1H, H-2), 2.06 (s, 3H, Ac), 1.71–1.60 (m, 1H, H-4), 1.43 (s, 9H, *t*-Bu), 1.32–1.21 (m, 2H, H-3), 0.92 (d, $J = 2.6$, 3H, Me[a]), 0.91 (d, $J = 2.2$, 3H, Me[b]); ^{13}C NMR δ 171.0 (CH_3COO), 155.4 (NH*C*OO), 79.3 (^{q}C), 66.8 (C-1), 47.7 (C-2), 40.9 (C-3), 28.3 (3C, *t*-Bu), 24.7 (Me[a]), 23.0 (C-4), 22.2 (Me[b]), 20.8 (Ac); IR $\nu = 2959$, 1745, 1716, 1524, 1519, 1367, 1239, 1171 cm^{-1}. Anal. Calcd for $C_{13}H_{25}NO_4$: C 60.21, H 9.72, N 5.40. Found: C 60.4, H 9.8, N 5.3.

4.7.3. (*S*)-2-(*tert*-Butoxycarbonylamino)-4-methylpentanol (*S*)-12b. Compound (*S*)-**11b** (27 mg, 0.10 mmol) was dissolved in MeOH (1.7 mL) and H_2O (0.17 mL), and K_2CO_3 (72 mg, 0.52 mmol) was added. The reaction was stirred for 2 h, after which H_2O (10 mL) and Et_2O (10 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (10 mL) and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give the title compound (19 mg, 83%). $[\alpha]_D^{20} = -22$ (ee $\leqslant$ 88%, *c* 0.95, $CHCl_3$) {lit.[30] $[\alpha]_D^{24} = -26.8$ (*c* 0.8, $CHCl_3$)}. The ^{1}H and ^{13}C NMR data were identical with those reported.[31]

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